INTRODUCTION

This document is the *Manual of Operations* (*MOO*) for the Type 1 Diabetes Genetics Consortium (T1DGC) study. The T1DGC study is an international effort to identify the genes that affect the risk of Type 1 diabetes, and is funded by the National Institute of Diabetes, Digestive and Kidney Diseases (NIDDK) in the National Institutes of Health, Department of Health and Human Services. Additional sponsors of this international effort include: the Juvenile Diabetes Research Foundation (JDRF); National Institute of Allergy and Infectious Diseases (NIAID); and National Human Genome Research Institute (NHGRI).

The Consortium is comprised of four networks (Asia-Pacific, European, North American and the United Kingdom) and a Coordinating Center at Wake Forest University School of Medicine that oversees the operations of the networks.

Within each network, there exists an infrastructure consisting of a Regional Network Center and individual clinics. The Regional Network Center is responsible for maintaining and supporting the every day operations of the clinics. The Regional Network Center staff sends label sets to the clinic and data enters the information obtained from the clinics. Clinics are in close contact with the Regional Network Center and are responsible for the recruitment and examination (*i.e.*, questionnaires and blood collection) of families that meet the study criteria. Any problems or questions that arise that cannot be dealt with at the clinic level are brought to the attention of the Regional Network Center. In turn, the Coordinating Center is in close contact with the Regional Network Centers. Any problems or questions that the Regional Network Centers cannot resolve are brought to the attention of the Coordinating Center. Both the Coordinating Center and the Regional Network Centers monitor recruitment and overall operations. (See Figure 1 for an overview of the T1DGC study structure.)

Due to the diverse nature of this study, the *Manual of Operations* is web-based in design. When necessary, this document is updated and all revisions are posted on the T1DGC web site. The Regional Network Centers are notified of changes via e-mail,

and they are responsible for notifying the clinics. Regional Network Centers are responsible for ensuring that the most current version is used in each clinic, verifying this by noting the date shown on all pages of the document. The Coordinating Center encourages Regional Network Centers to provide hard copies of this document to the individual clinics for their reference, especially if a clinic does not have access to the Internet.

For questions related to this manual that cannot be answered by the Regional Network Centers, contact the Coordinating Center at:

T1DGC Coordinating Center c/o Teresa Harnish
Wake Forest University Health Sciences
Medical Center Boulevard
WC-22
Winston-Salem NC, 27157

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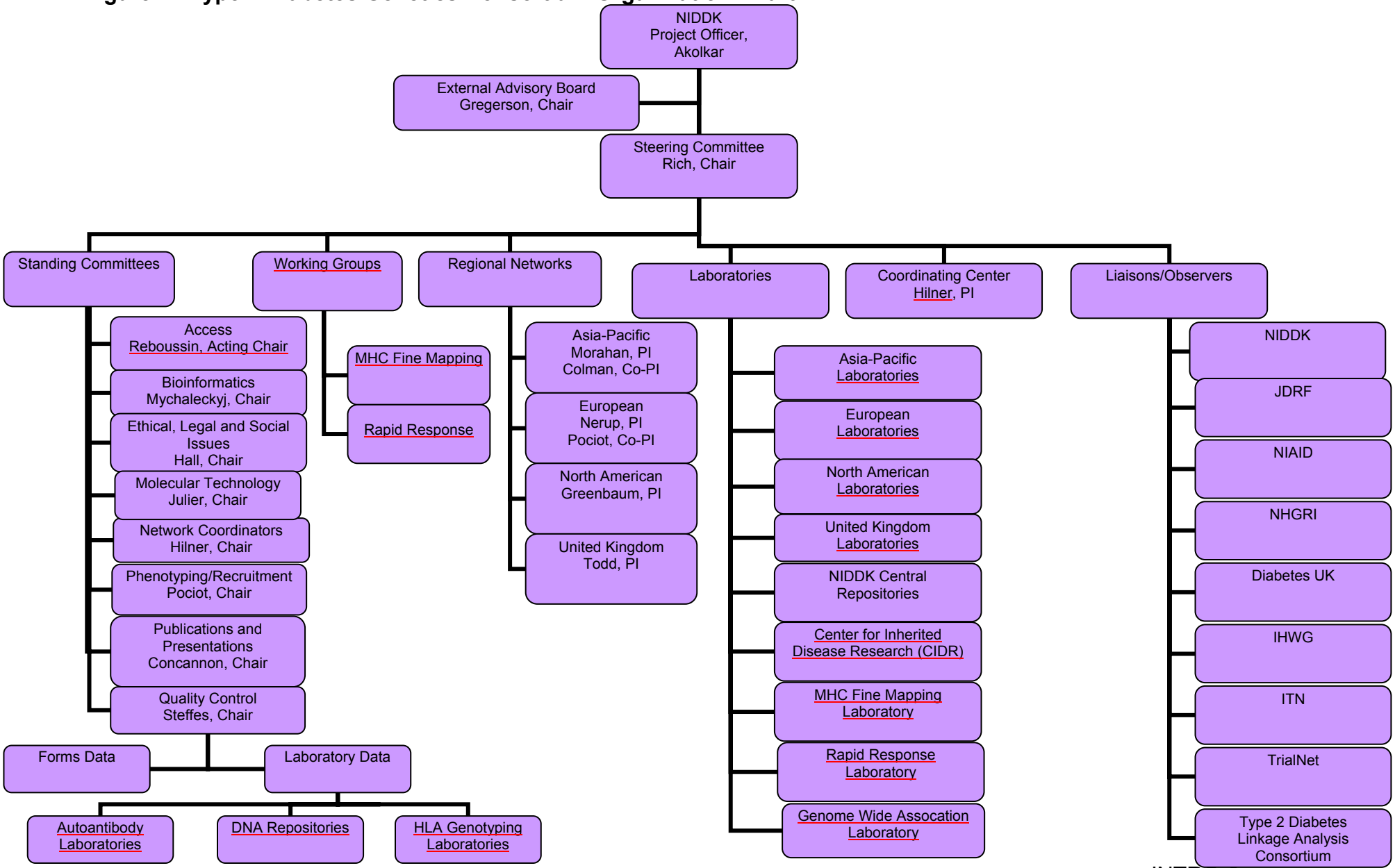
Figure 1. Type 1 Diabetes Genetics Consortium Organization Chart



GUIDELINES

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I. INTRODUCTION

This chapter provides general guidelines for recruitment and data collection in the Type 1 Diabetes Genetic Consortium (T1DGC) Study. This information serves as a general reference for questions that may arise in the conduct of this project. Refer to the *T1DGC Data Collection Flow Chart* for the model containing the basic components of data collection (Appendix A); this may vary somewhat between networks or regions.

II. PARTICIPANT IDENTIFIERS

The T1DGC uses a consortium-wide scheme for unique participant identification. (See Appendix B for a complete description of this scheme.) For ASP and trio families, the seven-digit ID structure includes 1 character for the network (*i.e.*, 1 for Asia-Pacific; 2 for European; 4 for North American; and 5 for United Kingdom). This network identifier is followed by 4 characters for the family (0001-9999) and 2 characters for the individual within a family (*i.e.*, 01 for father; 02 for mother; 03 for the proband or affected sibling 1; 04 for affected sibling 2; 05 for unaffected sibling 1; 06 for unaffected sibling 2). All IDs are bar-coded, with the numeric version of the ID (X-XXXX-XX) also on each label.

For the Case/Control study the unique participant identifier is also a seven-digit ID structure. The first character indicates the network (*i.e.*, 1 for Asia-Pacific; 2 for European; and 4 for North American). The second character identifies whether this is a case or a control (7 = case, 8 = control). The last five characters are the unique identifier for the participant. These IDs are also bar-coded with the numeric version on each label (X-X-XXXXX).

Another level of individual identifiers is recorded on all forms by clinic staff in the designated data field. These 2 or 3 character Secondary Identifiers are FA for father, MO for mother, AS1 for affected sibling 1 (proband), AS2 for affected sibling 2, UN1 for unaffected sibling 1, and UN2 for unaffected sibling 2. For the Case/Control study there are two individual identifiers: CAS for the case and CON for the control participant.

III. FORM AND LABEL SETS

A. Data Collection Forms

Forms are created and revised at the Coordinating Center, with the most current version of each form posted on the T1DGC web site. Forms are printed by the clinic from the T1DGC web site as needed, or by the Regional Network Center for distribution to those clinics without Internet access.

A form set is composed of all required data forms necessary for an entire family recruited into the T1DGC study. An entire ASP form set consists of the following forms: one *T1DGC ASP Eligibility Form*, (either administered to the proband or administered to a guardian of the proband); one *T1DGC ASP Family Contact Sheet*; one *T1DGC ASP Consent Summary Form*; six *T1DGC ASP Exam Forms* (one for each potential member of the family); and six *T1DGC Blood Collection Form*s (one for each potential member of the family). For each ASP family, one *T1DGC ASP Eligibility Form* (proband or guardian version) and one *T1DGC Consent Summary Form* must be printed. For each member of the family, the appropriate *T1DGC ASP Exam Form* and *T1DGC Blood Collection Form* must be printed. A copy of the local informed consent must be completed.

Clinics in the Asia-Pacific, European and North American Networks are also collecting trio families (*i.e.*, proband, father and mother). Separate form sets exist for trios, comprised of the same types of forms as in the affected sib-pair families (ASP) but for the proband, father and mother only. The *T1DGC North American Trio Pre-Eligibility Form* identifies eligible trios in the North American Network and **must** be completed in addition to the trio form set.

Three networks (Asia-Pacific, European and North American) are participating in the Case/Control study. Separate form sets exist for this study, comprised of the same types of forms as in the ASP and trio collections, but for the case (person with T1DGC-defined Type 1 diabetes) and control (ethnically-matched person without Type 1 diabetes).

B. Label Sets

Label sets are produced at the Coordinating Center and are distributed to the Regional Network Centers in batches for data collection over an approximate three-month period. Regional Network Centers are responsible for subsequent distribution to individual clinics. The Regional Network Center staff must notify the Coordinating Center at least two weeks in advance when additional label sets are needed. An e-mail should be sent to the designated project manager and Teresa Harnish (tharnish@wfubmc.edu).

For ASP and trio families, label sets are pre-packaged as a family unit for, at maximum, a six-member family. Each family is assigned a unique family ID with corresponding individual ID labels for each family member. A standard label set consists of all labels necessary for an entire family; a unique bar-coded family ID label appears on the outside of the envelope containing the label set. There are both large and small labels in each packet.

Label sets for the Case/Control study will be packaged individually. Each case and control is assigned a unique ID and a standard set of labels containing all labels necessary (both large and small labels) is contained in the packet.

1. Large Labels

The large labels are used on each page of the data forms and each of the blood collection tubes. The ASP and trio label packet includes the following sheets of large labels:

Family ID: 1 sheet of plain white labels

Father ID: 1 sheet of blue striped labels

Mother ID: 1 sheet of pink striped labels

Proband ID: 1 sheet of purple striped labels

Affected Sibling ID: 1 sheet of green striped labels

Unaffected Sibling IDs: 2 sheets of yellow striped labels (one for each of up to two unaffected siblings)

The case or control label packet will include one sheet of orange-striped (case) or one sheet of gray-striped (control) labels.

Each large label sheet contains thirty labels; however, not all labels are used during the exam. Extra labels may be used for locally produced forms (*e.g.*, regional logs), and those not used are kept in the clinic file for each participant. These are used if a blood re-collection is necessary. Table 1 outlines the use and number of large labels to be used for data collection.

Table 1. Large Label Specifications for T1DGC Data Collection

Label Sheet (30/sheet)	Color	Number of Labels for Data Collection Forms and Samples	Total Number of Labels Needed
Family ID	White	ASP Eligibility Form – 8 ASP Consent Summary Form – 5 Trio Eligibility Form (4 or 5) Trio Consent Summary Form - 3 North American Trio Pre-Eligibility Form – 3 Participant Identification Form – 1 (ASP and trios)	14 (Trios – 8-9; dependent on the proband's age; 11-12 North American Network trios)
Father ID	Blue	Informed Consent Form – 1 Consent Summary Form – 1 Exam Form – 7 Blood Collection Form – 5 One for each blood collection tube – 5 One for each shipping form – 2 Participant Identification Form – 1 Participant and QC Selection Log – 1	23
Mother ID	Pink	Informed Consent Form – 1 Consent Summary Form – 1 Exam Form – 7 Blood Collection Form – 5 One for each blood collection tube – 5 One for each shipping form – 2 Participant Identification Form – 1 Participant and QC Selection Log – 1	23
Proband ID	Purple	Informed Consent Form – 1 Consent Summary Form – 1 Exam Form – 10 (Trios - 8) Blood Collection Form – 5 One for each blood collection tube – 4 or 5 One for each shipping form – 2 Participant Identification Form – 1 Participant and QC Selection Log – 1	25 – 26; dependent on the proband's age (Trios – 23-24; dependent on the proband's age)

Label Sheet (30/sheet)	Color	Number of Labels for Data Collection Forms and Samples	Total Number of Labels Needed
Affected Sibling ID (ASP Family only)	Green	Informed Consent Form – 1 Consent Summary Form – 1 Exam Form – 4 Blood Collection Form – 5 One for each blood collection tube – 4 or 5 One for each shipping form – 2 Participant Identification Form – 1 Participant and QC Selection Log – 1	19 – 20; dependent on the affected sibling's age
Unaffected Sibling ID (ASP Family only)	Yellow	Informed Consent Form – 1 Consent Summary Form – 1 Exam Form – 5 Blood Collection Form – 5 One for each blood collection tube – 4 or 5 One for each shipping form – 2 Participant Identification Form – 1 Participant and QC Selection Log – 1	20 – 21; dependent on the unaffected sibling's age
Case ID	Orange	Eligibility Form - 4 Informed Consent Form – 1 Exam Form – 9 Blood Collection Form – 5 One for each blood collection tube – 4 or 5 One for each shipping form – 2 Participant and QC Selection Log – 1	26 – 27; dependent on the case's age
Control ID	Gray	Eligibility Form - 4 Informed Consent Form – 1 Blood Collection Form – 5 One for each blood collection tube – 4 or 5 One for each shipping form – 2 Participant and QC Selection Log – 1	17 – 18; dependent on the control's age

2. Small Labels

The small labels can tolerate -70°C and are used for the storage aliquots for each family member. The ASP and trio label packets contain one sheet of small labels for each family; on each sheet, there is a column of 20 labels for each family member. These labels follow the same color scheme for each family member as the large labels {*i.e.,* blue for father, pink for mother, purple for proband, green for affected sibling, and yellow for unaffected sibling(s). Each column contains more labels than needed. Case and control label packets contain only 1 sheet for the appropriate participant (orange for cases and grey for controls). Extra labels are kept in the participants' clinic file for future use if needed.

Table 2 outlines the number and type of labels to be used for the individual aliquots.

Table 2. Small Label (Aliquot) Specifications for T1DGC Data Collection

Small Labels (20 / family member)			
	Color	Intended Use	Labels Needed
Father ID	Blue	Serum samples – 5 Plasma samples – 4 Top of storage box – 1 Potential re-collection – 10	20
Mother ID	Pink	Serum samples – 5 Plasma samples – 4 Top of storage box – 1 Potential re-collection – 10	20
Proband ID	Purple	Serum samples – 5 Plasma samples – 4 Top of storage box – 1 Potential re-collection – 10	20
Affected Sibling ID (ASP Family only)	Green	Serum samples – 5 Plasma samples – 4 Top of storage box – 1 Potential re-collection – 10	20
Unaffected Sibling(s) ID (ASP Family only)	Yellow	Serum samples – 5 Plasma samples – 4 Top of storage box – 1 Potential re-collection – 10	20
Case ID	Orange	Serum samples – 5 Plasma samples – 4 Top of storage box – 1 Potential re-collection – 10	20
Control ID	Gray	Serum samples – 5 Plasma samples – 4 Top of storage box – 1 Potential re-collection – 10	20

3. Labels for Trio Families

Special label sets are not produced for trio families. The standard label sets produced for the ASP families are used, discarding the labels for affected and unaffected siblings.

4. Labels for Case/Control Study

Special label sets are produced for the cases and controls because the ID structure is unique. These can be distinguished from the ASP and trio label sets by the color striped label on the outside of the label set envelope.

5. Labels for Additional Affected Siblings

Under special circumstances, families with more than the standard number of members may be approved for study inclusion and the clinic will be sent the additional unique participant ID labels. The Coordinating Center has produced such label sets and sent these to the Regional Network Centers which will send them to clinics.

6. Quality Control Labels

In addition to the pre-packaged label sets for family members, quality control (QC) labels are sent to the clinics. QC label sets are separate from the general exam label sets and are specified as "QC-Red" or "QC-Purple" on a label on the outside of the envelope. The QC label sets contain large labels for use on the *T1DGC Blood Collection Form* and QC blood collection tubes as well as small labels for laboratory (aliquot) use. The QC label sheets contain an additional row of labels printed with "Quality Control" to aid the clinics in identifying these labels and to prevent confusion. See **Chapter VIII,** *Quality Control*, for details regarding the QC scheme. Table 3 outlines the use, number and type of labels (large and small) to be used for QC-Red and QC-Purple participants. For the Case/Control Study, separate sets of "QC-Red" and "QC-Purple" will be used. These can be distinguished by the label on the outside of the envelope, "Case QC-Red" or "Control QC-Purple."

Table 3. Label Specifications for Quality Control Data Collection

QC-Red	Number of Labels for Data Collection Forms and Samples	Total Number of Labels Needed
Large Label Sheet (3 labels/individual) Age Eligible Probands, Affected Siblings, Cases	Blood Collection Form – 1 Blood Collection Tube – 1 Shipping Form – 1	3/individual
Small Label Sheet (6 labels/individual)	Serum samples – 5 Top of Storage Box – 1	6/individual

QC-Purple	Number of Labels for Data Collection Forms and Samples	Total Number of Labels Needed
Large Label Sheet (6/family member) Any Age Eligible Family Member, Control	Blood Collection Form – 1 Blood Collection Tube – 2 (1 for re-labeling EDTA tube after processing, if needed) Shipping Form – 1 for plasma sample shipment and 1 for cell pack shipment	5/individual
Small Label Sheet (5/individual)	Plasma samples – 4 Top of Storage Box – 1	5/individual

IV. RECRUITMENT

Chapter III, *Recruitment,* of the *Manual of Operations (MOO)* contains specific recruitment guidelines for this study. Participants are recruited based on individual network, regional and clinic strategies and goals. Recruitment strategies may include flyers, brochures and referrals from physicians or other healthcare professionals. Once an individual or family is contacted, eligibility of each individual and family must be ascertained.

V. ELIGIBILITY

An ASP family is deemed eligible if at least the proband **and** an affected full sibling are available and willing to participate; without these two individuals, the family itself is ineligible. The larger family unit is preferred, and the emphasis in the clinics must be to recruit and examine as many eligible family members as possible.

Trio families are eligible only if the affected child **and** both biological parents are available and willing to participate. No additional members of the trio family are eligible to participate. In the North American Network, trio families are eligible **only** if the biological parents self-identify as African American or Mexican American.

Case/Control participants are eligible only in designated clinics in the Asia-Pacific, European, and North American networks.

The *T1DGC Eligibility Form* identifies family members who are eligible and willing to participate in this study and is required to determine inclusion of a family and its members in the T1DGC. There are two versions of the eligibility form, one that is administered to the proband/case **OR** the other form for the parent/guardian of the proband/case if the proband/case is not old enough to consent. Additional eligibility forms for the Case/Control Study include two versions of the eligibility form for the control participant, one that is administered to the control **OR** the other form for the parent/guardian of the control if the control is not old enough to consent. The appendices of **Chapter IV**, *Eligibility* contain specific line-by-line instructions (Q x Qs) that guide the interviewer through each question of the eligibility form(s).

In the North American Network, the *T1DGC North American Trio Pre-Eligibility Form* is administered to the biological mother and father prior to the *T1DGC Eligibility Form.* This is to ascertain that the trio meets initial eligibility requirements. Appendix E of **Chapter IV** *Eligibility* contains specific line-by-line instructions (Q x Qs) that guide the interviewer through each question of the pre-eligibility form.

For ASP and trio families, once initial eligibility of the family is established, a family ID is assigned and contact with additional family members may proceed to determine other potential participants. The *T1DGC Family Contact Sheet* was developed to aid in tracking members of the family and provides room for contact information. It is intended for use by clinic personnel to help organize information as it is collected. This form is never data entered since it contains personal identifiers. Thus,

this form is **never** forwarded to the Regional Network Center or to the Coordinating Center. In the Case/Control Study, only individuals are recruited so there will be no enrollment of other family members. Once eligibility of the individual is established, the case or control ID is assigned.

During completion of the *T1DGC Eligibility Form,* it is possible that the clinic will identify a participant whose Type 1 diabetes status is questionable based on information obtained from this questionnaire (*e.g.*, Type 1 diabetes not yet treated with insulin). At this point, eligibility is in question and a clinic staff member must complete the *T1DGC Application to Eligibility Committee*. (See **Chapter IV**, *Eligibility*, for detailed instructions in the use of this form.) All available information is included to aid the committee members in making a decision. If the application is for the proband and/or the affected sibling, only after the committee approves the application does the clinic continue the data collection with this family. The family is considered "PENDING" until that time. If a family is deemed ineligible, the clinic staff explains the reasons for ineligibility. **Chapter IV,** *Eligibility,* provides the interviewer with a response to questions regarding reasons for ineligibility that may arise during an interview. The same criteria apply to cases in the Case/Control Study in terms of completing an eligibility application. There is a separate *T1DGC Application to Eligibility Committee* for cases.

Up to three additional affected siblings may participate in an ASP family (for a total of five affected siblings). However, an *Application for Additional Affected Sibling* must be completed for approval of inclusion for each additional sibling. This form is completed at the clinic and forwarded to the Regional Network Center. Staff members at the Regional Network Center are responsible for approving inclusion of each sibling.

Upon approval, the Coordinating Center is notified and labels for the additional affected sibling are generated and sent to the Regional Network Center. Each Regional Network Center has also been provided several label packets that contain extra labels for families with additional affected siblings. If a clinic discovers that a family has potential additional affected siblings prior to assigning the family ID and label sets, they

can request a set of labels that already include the additional labels and not have to wait for additional labels to be printed. The additional affected siblings are given participant identifiers (*i.e.,* 07 for affected sibling 3; 08 for affected sibling 4; 09 for affected sibling 5), and secondary identifiers (*i.e.,* AS3 for affected sibling 3; AS4 for affected sibling 4 and; AS5 for affected sibling 5).

In the event that a Family ID or a case or control ID has been assigned and the family, case or control subsequently is deemed ineligible or withdraws from the study before the exam, the assigned ID is discarded. The *T1DGC Discarded ID Log* was created to track such IDs and is located on the T1DGC web site. This log, in conjunction with other software, assists in tracking all IDs that have been sent to each network and clinic. The Regional Network Center or Coordinating Center may request to see the *Discarded ID Log* from individual clinics to verify missing IDs; however, it is not data entered. Once an ID (family, participant, case or control) has been discarded, the remainder of the label set and any incomplete forms with those labels affixed must be destroyed. This will prevent that ID from being used mistakenly in the future.

VI. INFORMED CONSENT

A. Obtaining Consent

The following information contains guidelines for consenting individuals to participate in the T1DGC, and is set forth by the study investigators to ensure that good research practice is conducted and correct information is disseminated to the potential participant(s). Each institution's Internal Review Board (IRB) or Ethics Committee (EC) requires that the document being used by that particular clinic reflect the clinic-specific rules for written informed consent. Therefore, the following guidelines are general, and while they should be met to the best of each clinic's ability, there may be some variation among clinics and across networks.

The process of consenting individuals to participate in this study begins once potential participants have been asked if they are willing to participate in the T1DGC. For some institutions, this may be required prior to completing the *T1DGC Eligibility*

Form, and for some this process begins once the participant is deemed eligible based on the *T1DGC Eligibility Form*. Again, this is determined by the requirements of the local IRB or EC.

Once the participant agrees to participate, or to learn more about the study, a copy of the *Informed Consent* is provided to the potential participant or the parent/guardian of the participant. The most current version of the *Informed Consent* approved by the IRB or EC must be used. A template for each version of the informed consent (*i.e.*, adult, teenager, and child*)* for the T1DGC is maintained on the web site as a guide for the elements of consent required by the study. Separate consent forms for cases and controls are required and templates for each are maintained on the T1DGC web site. However, it is recognized that each clinic will need to modify the templates according to the specific requirements of the local IRB or EC.

Consent forms must be translated into the participant's native language. All translated forms must be back-translated into English.

A copy of the IRB or EC approval and the most current approved consent form must be provided to the Regional Network Center as soon as approval is obtained. The Regional Network Center will forward these on a monthly basis to the Coordinating Center. The approval documents should contain the date of approval and the date that the approval expires. Clinics will need to renew this approval prior to the expiration date for the years that the clinic is participating in the study.

A brief description of the study is written on a cue card and may be used to aid the interviewer in describing the study. However, the participant is required to read or have the *Informed Consent* read to him/her (if he/she is incapable of reading the document). The participant must be adequately informed of the purpose, methods, personal involvement in the study, direct benefit (or lack thereof), potential risks, and his/her rights. All questions that the potential participant/family has regarding the study

must be answered thoroughly. Once the *Informed Consent* is provided to and read by the participant and/or parent/guardian, it must be signed. In the case of a minor, the legal guardian signs the form. Once a signature is obtained, a unique individual ID is assigned.

Because this study involves children, special guidelines/considerations may be required by the institution's IRB or EC. Each clinic's study coordinators or recruiters must be familiar with all requirements that the institution has regarding the informed consent process with studies involving children. For example, certain institutions may require that young participants give their assent to participate in the study in addition to consent given by the parent or guardian of the child (ren). Assent is a child's oral or written affirmative agreement to participate in research (*i.e.*, a child says "yes" when asked if he/she would like to participate in the study). In addition, the age requirement for written consent may vary depending on the network, region and/or institution.

Once informed consent forms have been completed, copies are made. Certain local IRBs or ECs may require that the original be kept in the IRB/EC office. A copy must be maintained in the clinic and a copy **must** be provided to the participant.

A copy of the page on which the layered consent for various aspects of the exam is obtained is labeled with the participant's ID and sent to the Regional Network Center for entry into the informed consent database. Regional Network Centers and/or clinics may choose to include an ID label box on this layered portion of the consent form for the participant's ID label. The copy of the informed consent page that is forwarded to the Regional Network Center must be free of personal identifiers and participant signatures. In the event that a participant is re-consented or withdraws their consent, the Regional Network Center is notified and the informed consent database is updated.

For ASP and trio families, as informed consent forms for family members are signed and completed, the *T1DGC Consent Summary Form* is completed. Details on completion of this form are located in the Question by Question instructions (Q x Qs) in

Appendices of **Chapter V**, *Interviewing Instructions*. No consent summary form is completed for the Case/Control study.

B. Withdrawing Consent

The consent form for the Type 1 study indicates that participants who change their mind about participating in the study may withdraw consent at any time by notifying the clinic/institution where they gave consent. Withdrawal of consent will require that their data be removed from the Data Entry System, and that their data forms, blood samples, and genetic material be destroyed.

As clinics begin to plan for close-out, the Clinic Coordinator should contact the local IRB/Ethics Committee to receive specific instructions and information about the local requirements for handling withdrawal of consent after the clinic, Regional Network Center and Coordinating Center are closed. The Clinic Coordinator and/or Clinic Principal Investigator should develop a long-term plan for handling withdrawal of consent. This may include providing the IRB/Ethics Committee with the list that contains the link of the participant and study IDs as well as the contact information for the network repositories.

1. Withdrawal of Consent by ASP Family Participant

a. Proband or Affected Sibling Withdraws Consent

If either the proband (AS1, -03) or the affected sibling (AS2, -04) withdraws consent, then the family is no longer eligible, unless there is an additional affected sibling (so that there are still two siblings who have type 1 diabetes).

Clinic:

i. Notify the Regional Network Center (RNC) in writing that this participant has withdrawn consent and no longer wants to be enrolled in the study. The RNC should only be supplied participant ID; they should never be given a participant's name. Include the participant IDs for all family members originally enrolled in the study.

ii. Place a statement in the family's file indicating the date that the clinic was contacted by the participant and the date the RNC was notified that the participant had withdrawn consent and the family was no longer eligible.

iii. To ensure that this participant is not contacted again, clearly note the withdrawal of consent in a highly visible way in the participant's file and on the *ASP Family Contact Sheet*.

iv. Use the method that meets the local institution's IRB or Ethics Committee requirements to destroy the set of data forms collected for this participant and all family members. Retain only the statement regarding withdrawal of consent and RNC notification.

v. If needed, the Coordinating Center will send the *Notification to Destroy Samples* form(s) for each family member. If samples are still at the clinic, the clinic should complete the clinic sections, send completed forms to the Coordinating Center and retain a copy of the form(s) in the clinic file.

Regional Network Center:

i. Notify the Coordinating Center of this participant's withdrawal of consent in writing and request that a *Notification to Destroy Samples* form be initiated, if needed. The form will need to be requested for each family member. Include participant IDs, the number and location of samples.

ii. Promptly complete the RNC portion of the *Notification to Destroy Samples* form when it is received from the Coordinating Center and forward it to the Coordinating Center.

iii. When a completed copy of the *Notification to Destroy Samples* form (if required) is received, place it in this participant's file.

iv. Using the method that meets the RNC's IRB or Ethics Committee requirements, destroy the set of data forms on file for this participant. Retain the statement from the clinic regarding withdrawal of consent and the RNC copy of the *Notification to Destroy Samples* form.

Coordinating Center:

i. Initiate the *Notification to Destroy Samples* for the participant and all family members.

ii. Send a copy of the completed *Notification to Destroy Samples* to the RNC for their files.

iii. Data previously entered in the Data Entry System will be marked as "withdrew consent," and these data will be deleted from the system and removed from reports.

iv. Determine if this family's forms were entered during double data entry and if so, those data should be deleted.

b. Father, Mother, Unaffected Sibling, and/or Additional Affected Sibling Withdraws Consent

If any other family member withdraws consent, the remaining family members' consents are valid and they are still eligible to participate in the study. If the father, mother, unaffected sibling, or an additional affected sibling notifies the Clinic Coordinator or Clinic Principal Investigator that they want to withdraw from the study, this does not affect the eligibility of the remaining family members. The following procedures should be implemented:

Clinic:

i. Notify the Regional Network Center in writing that this participant has withdrawn consent and no longer wants to be enrolled in the study. The RNC should only be supplied participant ID; they should never be given a participant's name.

ii. Place a statement in the family's file indicating the date that the clinic was contacted by the participant and the date that the RNC was notified.

iii. To ensure that this participant is not contacted again, clearly note the withdrawal of consent in a highly visible way in the participant's file and on the *ASP Family Contact Sheet.*

iv. If needed, the Coordinating Center will send the *Notification to Destroy Samples* form(s) for each family member. If samples are still at the clinic, the clinic should complete the clinic sections, send completed forms to the Coordinating Center and retain a copy of the form(s) in the clinic file.

v. Use the method that meets the local institution's IRB or Ethics Committee requirements to destroy the set of data forms collected for this participant.

Regional Network Center:

i. Notify the Coordinating Center of this participant's withdrawal of consent in writing and request that a *Notification to Destroy Samples* form be initiated, if it is needed.

ii. Promptly complete the RNC portion of the *Notification to Destroy Samples* form when it is received from the Coordinating Center and forward it back to the Coordinating Center.

iii. When a completed copy of the *Notification to Destroy Samples* (if required) is received, place it in this participant's file.

iv. Using the method that meets the RNC's IRB or Ethics Committee requirements, destroy the set of data forms on file for this participant. Retain the statement from the clinic regarding withdrawal of consent and the RNC copy of the *Notification to Destroy Samples* form.

Coordinating Center:

i. Initiate the *Notification to Destroy Samples* for the participant, if needed.

ii. Send a copy of the completed *Notification to Destroy Samples* to the RNC for their files.

iii. Data previously entered in the Data Entry System will be marked as "withdrew consent," and these data will be deleted from the system and removed from reports.

iv. Determine if this participant's forms were entered during double data entry and if so, those data should be deleted.

2. Withdrawal of Consent by Participant in Trio Family

If any member of a trio family withdraws consent, the trio is no longer eligible and the following procedures should be completed.

Clinic:

i. Notify the Regional Network Center in writing that a member of this trio has withdrawn consent and no longer wants to be enrolled in the study. The RNC should only be supplied participant ID; they should never be given a participant's name. Include the participant IDs for all family members originally enrolled in the study

ii. Place a statement in the family's file indicating the date that the clinic was contacted by the participant and the date that the RNC was notified that participant had withdrawn consent and the trio was no longer eligible.

iii. To ensure that this participant is not contacted again, clearly note the withdrawal of consent in a highly visible way in the participant's file and on the *Trio Family Contact Sheet*.

iv. Use the method that meets the local institution's IRB or Ethics Committee requirements to destroy the set of data forms collected for this participant and all trio members. Retain only the statement regarding withdrawal of consent and RNC notification.

Regional Network Center:

i. Notify the Coordinating Center of this participant's withdrawal of consent in writing and request that a *Notification to Destroy Samples* form be initiated, if samples were collected. The form should be requested for each trio family member who had samples collected.

ii. Promptly complete the RNC portion of the *Notification to Destroy Samples* form when it is received from the Coordinating Center and forward it to the Coordinating Center.

iii. When a completed copy of the *Notification to Destroy Samples* form (if required) is received, place it in the family's file.

iv. Using the method that meets the RNC's IRB or ethics committee requirements, destroy the set of data forms on file for the participant. Retain the statement from the clinic regarding withdrawal of consent and the RNC copy of the *Notification to Destroy Samples* form.

Coordinating Center:

i. Initiate the *Notification to Destroy Samples* for any family member who had samples collected.

ii. Send a copy of the completed *Notification to Destroy Samples* to the RNC for their files.

iii. Data previously entered in the Data Entry System will be marked as "withdrew consent," and these data will be deleted from the system and removed from reports.

iv. Determine if this family's forms were entered during double data entry and if so, those data should be deleted.

3. Withdrawal of Consent by Case or Control Participant

If a case or control participant withdraws consent, the individual is no longer eligible and his/her data be removed from the Data Entry System, and data forms, blood samples, and genetic material be destroyed.

Clinic:

i. Notify the Regional Network Center in writing that this participant has withdrawn consent and no longer wants to be enrolled in the study. The RNC should only be supplied participant ID; they should never be given a participant's name.

ii. Place a statement in the individual's file indicating the date that the clinic was contacted by the participant and the date the RNC was notified that the participant had withdrawn consent and was no longer eligible.

iii. To ensure that this participant is not contacted again, clearly note the withdrawal of consent in a highly visible way in the participant's file.

iv. Use the method that meets the local institution's IRB or Ethics Committee requirements to destroy the set of data forms collected for this participant. Retain only the statement regarding withdrawal of consent and RNC notification.

Regional Network Center:

i. Notify the Coordinating Center of this participant's withdrawal of consent in writing and request that a *Notification to Destroy Samples* form be initiated, if needed. Include participant ID, the number and location of samples.

ii. Promptly complete the RNC portion of the *Notification to Destroy Samples* form when it is received from the Coordinating Center and forward it to the Coordinating Center.

iii. When a completed copy of the *Notification to Destroy Samples* form (if required) is received, place it in this participant's file.

iv. Using the method that meets the RNC's IRB or Ethics Committee requirements, destroy the set of data forms on file for this participant. Retain the statement from the clinic regarding withdrawal of consent and the RNC copy of the *Notification to Destroy Samples* form.

Coordinating Center:

i. Initiate the *Notification to Destroy Samples* for the participant. Send a copy of the completed *Notification to Destroy Samples* form to the RNC for their files.

ii. Data previously entered in the Data Entry System will be marked as "withdrew consent," and these data will be deleted from the system and removed from reports.

iii. Determine if this participant's forms were entered during double data entry and if so, those data should be deleted.

VII. HEALTH INSURANCE PORTABILITY AND ACCOUNTABILITY ACT OF 1996 (HIPAA)

HIPAA was passed in 1996 as a means for the United States Congress to strive for incremental health care reform in the country. This act encompasses many components and is quite complex. For research purposes, we are concerned with a subsection called the Privacy Rule. This rule was established to protect individually identifiable health information by putting limits on the use and disclosure of an individual's protected health information (PHI).

On April 14, 2003, all institutions with access to PHI were required to be in compliance with these regulations. Health information included in this rule is anything oral or recorded in any form that is created or received by a health care worker, health plan, public health authority, employer, life insurer, school, university or health care clearinghouse. The information can pertain to a person's physical or mental health or condition, health care provided to that person, or payment for the provision of health care in the past, present or future. Data collected from research is included as PHI, and thus is subject to the rules and regulations of HIPAA.

For research practice to continue within an entity that is covered by HIPAA, there are certain rules that must be followed. This includes the transmission of data within the T1DGC study. Under HIPAA regulations, data that are transmitted must be de-identified (*i.e.,* removal of eighteen identifiers from all forms of PHI). However, there are several ways in which PHI can be used and transmitted for research purposes that permit inclusion of certain data elements. For additional information regarding HIPPA regulations, visit http://www.hhs.gov/ocr/hipaa/.

For the T1DGC, a *Data Use Agreement for a Limited Data Set* is established by the Coordinating Center with each of the Regional Network Centers. This agreement essentially permits a limited number of identifiers to be released with health information including: age, full elements of dates (*e.g.,* birth date) and geocoding data to the level of

city (*e.g.,* town/city, state, and full zip code). Copies of all data use agreements are maintained at the Coordinating Center and the Regional Network Centers.

All participants in the United States who sign an informed consent **must** sign a *Written Authorization* that authorizes the T1DGC to disclose certain elements of their PHI for research purposes. The *Written Authorization* is a document, either independent of the informed consent or embedded within the informed consent, that authorizes the entity to disclose that person's protected health information to other entities described in the document. Simply stated, this allows data/information to flow between all participating clinics, regions and networks to carry out the goals of the T1DGC. A potential participant who refuses to sign the *Written Authorization* cannot participate in the study. Refer to Appendix C for templates of the *Data Use Agreement* and *Written Authorization*. The template for the *Written Authorization* is a guide for all elements important for this study.

In addition to the *Written Authorization*, each participant in the United States must be offered the Notice of Privacy Practices brochure. This brochure explains the privacy policy of the institution and is provided by the institution itself, and must be available for each potential participant of the T1DGC. Appendix C contains an example of this privacy notice, but this may not be used by any clinic. All clinics must obtain this material from their local IRB or EC.

For Regional Network Centers outside the United States, the rules of HIPAA apply only as it pertains to participant's data that are transmitted to the Coordinating Center at Wake Forest University School of Medicine. That is, all data must be de-identified, and contain only those few identifiers allowed by the terms of the *Data Use Agreement for a Limited Data Set*. Participants outside the United States sign only an informed consent and do **not** sign a *Written Authorization*.

The Coordinating Center at Wake Forest University practices strict procedures to maintain privacy and confidentiality of all research participants and the subsequent

generated data. Data are released and exchanged only with entities with which a *Data Use Agreement for a Limited Data Set* exists. The Coordinating Center takes every precaution necessary to protect the privacy of all participants who have volunteered their time, and expects that all clinics, regions and networks uphold these same standards. It is expected that individual clinics maintain all participant files in locked cabinets accessible **only** to the study staff. In addition, information that is considered a personal identifier (*e.g.,* participant name) is kept only by the clinic staff and is **never** transmitted to the Regional Network Center or Coordinating Center.

VIII. EXAM (PARTICIPANT VISIT)

Once the participant has signed an informed consent, their exam consists of two required components: an interview to complete a brief questionnaire (the *T1DGC Exam Form*) and a blood collection for each consented participant (using the *Blood Collection Form)*. The exam form is completed before the blood is collected. (See **Chapter V**, *Interviewing Instructions,* for general interviewing guidelines and the Question by Question (QxQs) instructions for administering each form.) In the Case/Control study, only the case will complete the *T1DGC Exam Form*, there will not be an exam form for the control participant.

A. Scheduling Visits

Family members may attend a single clinic visit together or each member may come on a separate day. Thus, the length of time required to complete examination of an entire family varies. Clinics must be flexible in scheduling visits and every effort should be made to accommodate participant schedules.

Family members may be seen at different clinics within the same network. The clinic IDs recorded on the forms must correspond to the clinic where the information was collected for that particular family member.

B. Identification Form, Participant and QC Selection Log

A *T1DGC Participant Identification Form* was created to establish a link between participant names and the T1DGC Family and Participant IDs. This form is available on the T1DGC web site, and it, or a similar one developed in the clinic, must be used for each unique ASP and trio family which participates in the T1DGC. The form is kept with the family's files, is **never** forwarded to the Regional Network Center or Coordinating Center, and is **never** data entered. If a problem arises and the participant must be identified (*e.g.,* the participant wishes to withdraw their blood sample) and the ID must be linked back to him/her, this form will provide a mechanism to do so. Each clinic is responsible for linking the family names and their respective IDs. There is no *Participant Identification Form* for the Case/Control study. Clinics should be able to identify the participants in cases where the participant needs to be re-contacted.

In addition to the *T1DGC Participant Identification Form,* a *T1DGC Participant and QC Selection Log* was created as a method to track all participants seen in the clinic and to determine when a quality control (QC) sample needs to be collected and on which individual. The clinic staff member places a participant ID label on the log for each person participating in the study. Details on the use and completion of this form as well as quality control procedures are outlined in **Chapter VIII**, *Quality Control*. Although this form is not automatically sent to the Regional Network Center, the Regional Network Center may request these forms from a clinic.

C. Blood Collection

Once the exam form is completed (or the eligibility form for the control participant), the participant has blood collected. Prior to the exam, the participant should be informed of the procedures. This includes reiterating to the participant the amount of blood to be collected (approximately 2-3 tablespoons) and the importance of being well hydrated for the blood collection. Detailed procedures for blood collection, handling, and shipment to the various laboratories are outlined in **Chapter VI**, *Blood Collection and Processing* and **Chapter VII**, *Sample Storage and Shipping*.

D. Completed Forms

Completed forms are sent weekly from the clinics to the Regional Network Center by regular postal service for data entry and subsequent transmission to the Coordinating Center. **Original forms are maintained at the clinics with copies forwarded to the Regional Network Center for data entry.**

1. ASP Families

For ASP families, forms are sent **only** when both the proband and affected sibling have been recruited and examined. When the affected sib pair exams are completed, copies of the *T1DGC ASP Eligibility Form*, the *T1DGC ASP Consent Summary Form*, the layered portion of the consent form, the *T1DGC Blood Collection Form* for both individuals, and their respective *T1DGC ASP Exam Form* are sent to the Regional Network Center. As other members of the family are recruited, consented and blood collected, copies of the remainder of the *T1DGC ASP Exam Forms* and *T1DGC Blood Collection Forms* are sent. The most current version of the *T1DGC ASP Consent Summary Form* is sent each time new members of a family are examined, and the exam and blood collection forms are sent to the Regional Network Center for entry. If desired, forms can be held until all family members are consented.

2. Trio Families

In trio families, all three members (*i.e.*, proband, father and mother) must be available and recruited for a family to participate. No forms are sent to the Regional Network Center unless all three are eligible, all have been interviewed, and all have had blood collected. When all are completed, the *T1DGC Trio Eligibility Form*, the *T1DGC Trio Consent Summary Form*, the layered portion of the consent form, the *T1DGC Trio Exam Forms*, and the *T1DGC Blood Collection Forms* are forwarded to the Regional Network Center.

In the North American Network, the *T1DGC North American Trio Pre-Eligibility Form* should be forwarded to the Regional Network Center with all other completed forms.

3. Case/Control Participants

In the Case/Control Study, forms are sent to the Regional Network Center as soon as eligibility has been determined and the participant has been interviewed, their blood has been collected, and the forms for that particular individual are completed. For cases, the *T1DGC Case Eligibility Form*, the layered portion of the consent form, the T*1DGC Case Exam Form*, and the *T1DGC Blood Collection Form* are forwarded to the Regional Network Center on a weekly basis. For controls, the *T1DGC Control Eligibility form,* the layered portion of the consent form, and the *T1DGC Blood Collection* Form are forwarded to the Regional Network Center.

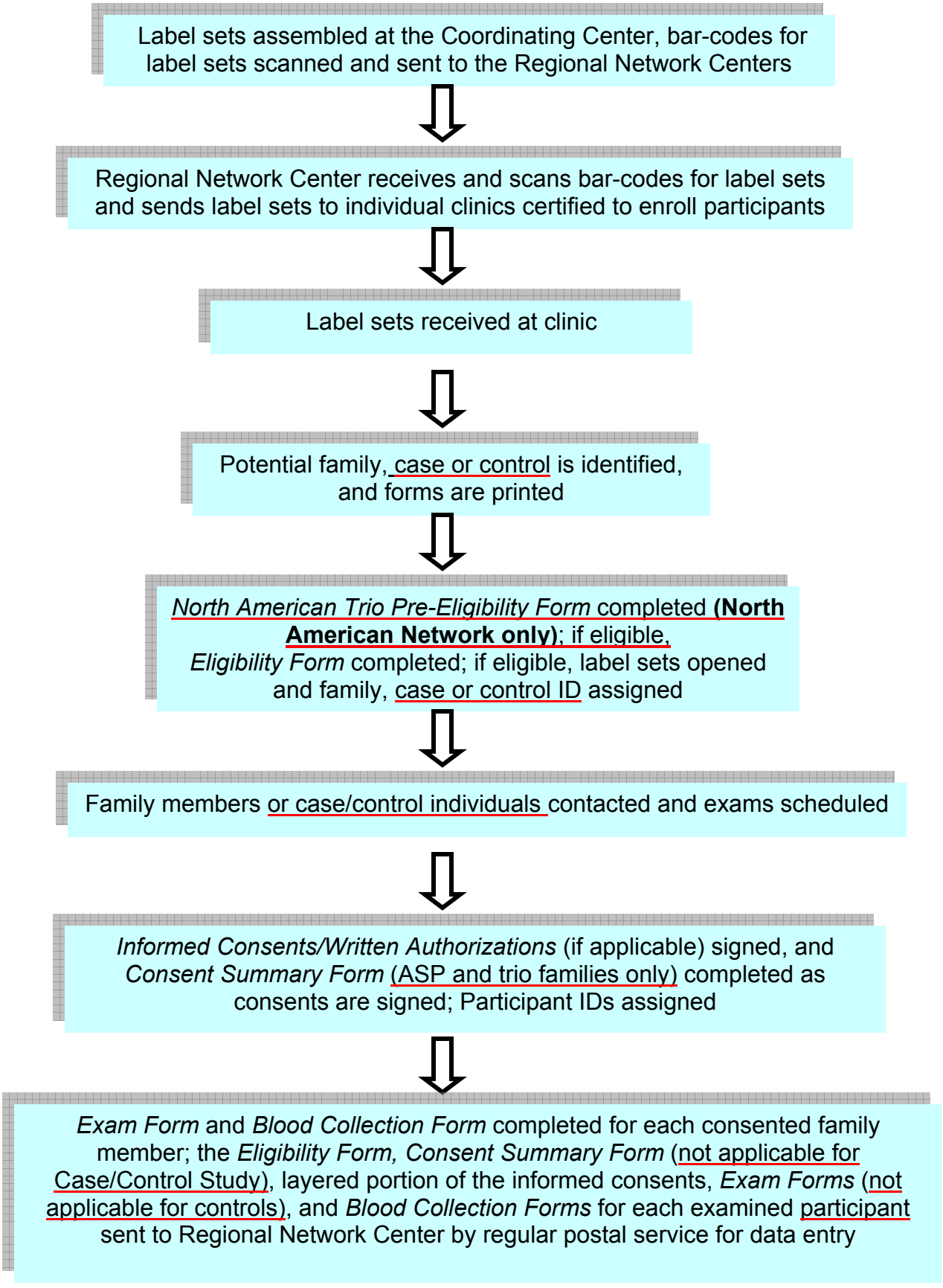
E. Incomplete Forms/Data

Incomplete questionnaires/data are not sent to the Regional Network Centers. This includes a participant/family that is "PENDING" for varying reasons. Only at the time that the "PENDING" status is resolved and eligibility is confirmed can the completed forms be sent. No forms for an ASP family can be sent unless both the proband and affected sibling are recruited and examined. Likewise, forms for a family and/or participant deemed ineligible are **not** sent to the Regional Network Centers for data entry. Locally produced forms may be forwarded to the Regional Network Center for monitoring purposes, but are not entered into the primary T1DGC database. Figure 1 illustrates the sequence of events from distribution of label sets by the Coordinating Center through completion of exam and return of completed forms to the Regional Network Center for data entry.

IX. DESTRUCTION OF SAMPLES

All T1DGC samples should be retained until the clinic and/or laboratories receive a completed *T1DGC Notification to Destroy Samples* form from the Coordinating Center at Wake Forest University. The Coordinating Center will confirm the list of samples to be destroyed with the Network Center prior to forwarding the form to the appropriate clinic or laboratory. Only after receipt of this form can the listed samples be destroyed. (See **Chapter VII**, *Sample Shipping and Storage,* for detailed instruction regarding destruction of samples.)

Figure 1. Sequence of Events in T1DGC Data Collection



X. CLINIC PREPARATION, TRAINING AND CERTIFICATION

Prior to participant recruitment and data collection, each clinic must be formally trained by the Regional Network Center staff and certified by the Coordinating Center to begin the study. Centers may not begin enrollment until they have received notification of successful completion of these requirements.

A. Clinic Preparation

Prior to the beginning of recruitment, there are requirements for conducting the study that must be made. First, the clinic's institution must have Office of Human Subjects Protections (OHRP) approval. This office is part of the US Department of Health and Human Services and has the responsibility of assuring that research with human subjects is done ethically and safely. If the institution already has approval, the clinic forwards the FWA number to the Regional Network Center. If it does not, this process needs to begin immediately. The OHRP website (http://www.hhs.gov/ohrp) provides detailed information on how to apply and obtain approval from this office for a study center as well as a listing of the institutions that have this approval. Local IRB and EC offices are a good resource for determining if a center has an FWA number or for additional assistance in this process. As soon as approval is obtained, the clinic should notify the Regional Network Center of the FWA number.

The T1DGC study must be approved by the institution's IRB or EC. This includes the Protocol, MOO, Forms, the informed consent document(s), and any posters or recruitment brochures. The informed consent templates are available on the T1DGC web site (https://www.t1dgc.org) and should be modified to satisfy the local institution's IRB or EC requirements and should include local contact information. If needed, the informed consent must be translated and then back translated into English.

Once the IRB or EC has approved the study, a copy of the approved informed consent and the IRB/EC approval letter is forwarded to the Regional Network Center which forwards copies of each to the Coordinating Center. The approval letter must clearly state the date of the approval and the expiration date of the approval. For IRB or

EC approval letters in foreign languages, the clinic must provide these dates when the letter is forwarded to the Regional Network Center.

Clinics will need to order supplies for blood collection and shipping. The Regional Network Center can provide further guidance about this part of the clinic preparation.

B. Training

Training is provided by the Regional Network Center staff and can be conducted as a centralized group training or with an individualized training session at the clinic site, depending on the needs and timing of the clinic joining the study. Training can occur while the clinic preparation is in process. It must occur prior to the pilot study.

C. Certification

Certification consists of successful completion of a pilot study, including data forms, blood collection (including a quality control sample for plasma) and laboratory shipments. The pilot study is intended to assess the readiness of the clinic to begin data collection for the T1DGC; as such, poor performance during the pilot signals a need to re-train prior to initiating data collection. Volunteers for the pilot study should not be T1DGC participants; use of “mock families”, consisting of staff or family volunteers, is encouraged.

The Regional Network Center will work with the new clinic to ascertain that the pilot study was completed correctly by reviewing forms submitted and asking the clinic to correct any errors. The Regional Network Center will data enter the forms for the pilot study and notify the Coordinating Center that the pilot study is completed.

Once the data are entered, and the Regional Network Center has notified the Coordinating Center that the blood shipments arrived at the laboratories, the Coordinating Center will review the pilot study data and must indicate successful completion of the pilot prior to a clinic beginning actual participant recruitment. This

requires data entry of all forms at the Regional Network Center and successful specimen shipments to the Autoantibody and Storage Laboratory and the DNA Repository (including data entry of shipping forms at the laboratory).

The Coordinating Center will notify the Regional Network Center when a clinic has successfully completed the pilot study. If all other requirements are met, then the clinic can be certified to begin enrollment of participants.

BEFORE PARTICIPANT RECRUITMENT CAN BEGIN: In addition to the successful completion of the pilot study, all appropriate documentation (*i.e.*, copy of the clinic's approved informed consent, IRB/EC approval letter and OHRP approval) must be on file at the Regional Network Center and the Coordinating Center before actual data collection begins.

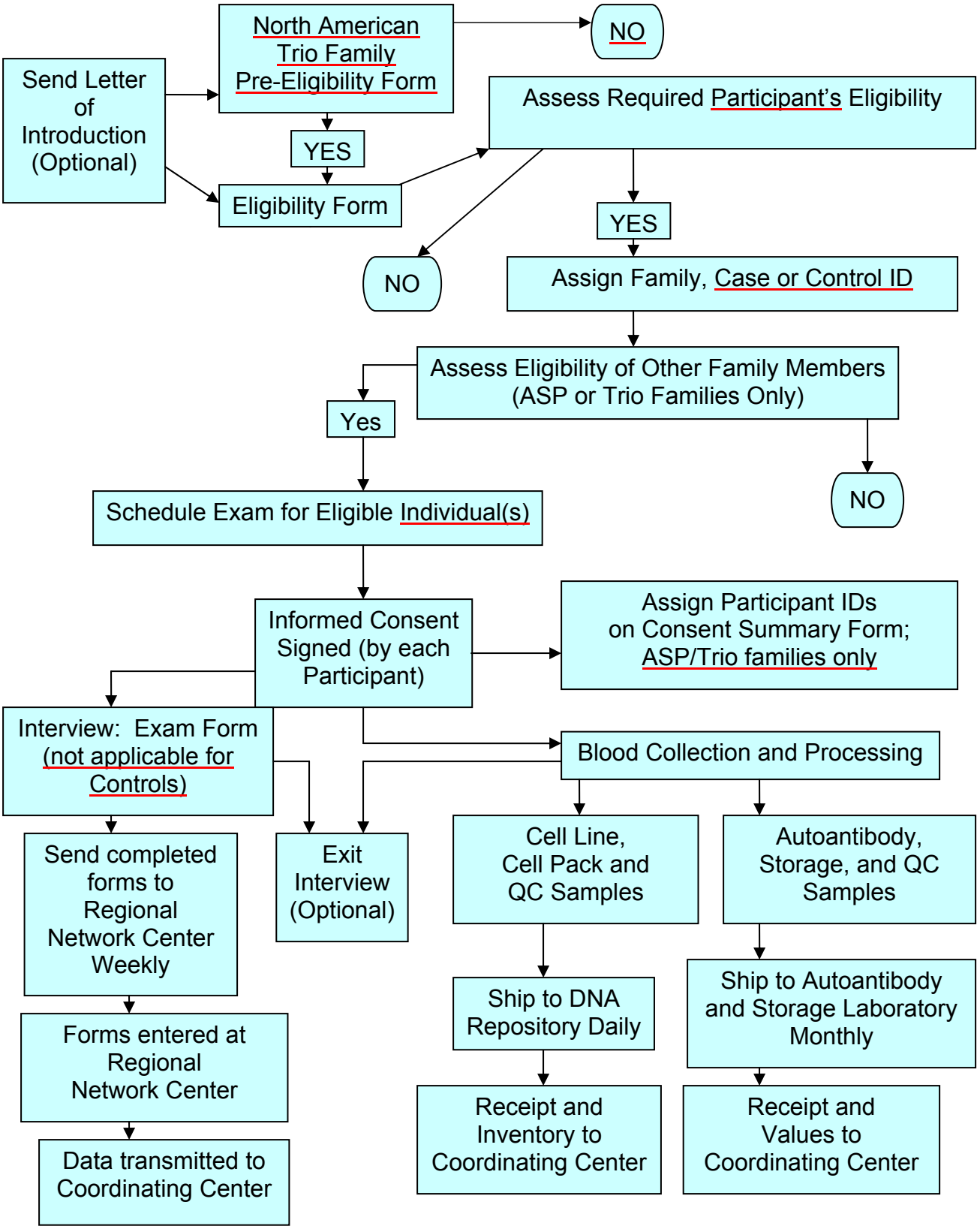
XI. SUMMARY OF STUDY FORMS

Table 4 summarizes the T1DGC forms, when each form is used and who is interviewed. The most current versions of the study forms are located on the T1DGC web site (http://www.t1dgc.org).

Table 4. Summary of T1DGC Study Forms

Form	Administered/ Used When	Participant Interviewed	Notes
North American Trio Pre-Eligibility	First contact with participant	Mother **AND** Father	One form completed per family; only for North American trios
Eligibility	First contact with participant	Proband/Case/ Control **OR** Guardian	One form completed per family/per case/per control
Family Contact Sheet	As eligibility is determined	Proband **OR** Guardian	Not data entered; ASP/trio families only
Consent Summary	As family members are consented	Each participating family member	One form per family ; ASP/trio families only
Exam	Exam visit	Each participating individual	Administered to the guardian for children too young to complete for themselves. (Not applicable for Control)
Blood Collection (Original Collection)	Exam visit, at blood collection	Each participating individual	
Blood Collection (Re-collection)	As needed, at re-collection	Each participating individual	Only if errors or problems in the original collection or samples are lost or damaged during shipping
Application to Eligibility Committee	As needed, to determine eligibility	Proband, Affected Sibling, or Case	Only if Type 1 diagnosis is in question
Application for Additional Affected Siblings	As needed	Proband **OR** Guardian	Only if more than 2 affected siblings in family; ASP families only. Sent to Regional Network Center for approval.
Adverse Event Report	As needed	Not applicable	If adverse event occurs
Clinic Shipping Form: Face Sheet and Contents Sheet	As needed	Not applicable	Completed with every shipment
Data Editing Log	As needed	Not applicable	Not data entered
Discarded ID Log	As needed	Not applicable	Not data entered
Daily Freezer Temperature Log	Recorded daily	Not applicable	Not data entered
Participant Identification	As needed	Not applicable	ASP/trio families only. Not data entered
Participant and QC Selection Log	As needed; each new participant added	Not applicable	Not data entered

APPENDIX A
T1DGC DATA COLLECTION FLOW CHART



APPENDIX B
IDENTIFIERS FOR T1DGC FAMILIES AND INDIVIDUALS

I. OVERVIEW

In a multi-center, international consortium that is as complex and diverse as the Type 1 Diabetes Genetics Consortium (T1DGC), there is great potential for confusion over participant specimens and forms. This confusion can compromise the integrity of data collected and overall study quality control. A consistent consortium-wide scheme for identification of participants and data that are collected from them can minimize these problems. While the consortium recognizes that it is highly unlikely that any clinic or lab currently uses the same identification scheme for clinical or research purposes, and therefore an added burden is placed upon them, the benefits of a consortium-wide system outweighs the costs in familiarization and training.

II. REQUIREMENTS

The major requirements for the consortium identification scheme are:

A. Utilize a single identifier for all study data collected or derived for an individual participant in the consortium.

B. Ensure the identifier format chosen can be encoded within a bar-code label that can be attached to forms, large vacutainer tubes, or small 2-ml aliquot cryovials.

C. Identify any family within any network within the consortium.

D. Identify any individual within any network within the consortium.

E. Provide an easy mechanism for clinics or labs to identify forms or specimens that belong to the same individual, or the same family.

III. IDENTIFICATION SCHEME

A. Implementation

The requirements discussed above (Section II) are met by using a labeling system to label all paper forms and specimens. Each label has a bar-code and a numeric version of the identifier (ID) printed underneath the bar-code on the same label. Scanning the bar-code will show the numeric version of the ID on data entry screens. The numeric version of the bar-code ID (the participant ID) is the unique identifier for an individual participating in the T1DGC. All communications between clinics, Regional Network Centers, laboratories, and the Coordinating Center regarding the forms and specimens for individuals and families in the study will refer to the participant ID. Clinics use one set of bar-coded labels per family, attaching them to paper copies of forms and blood collection tubes for each individual. Laboratories will scan the bar-codes on blood collection and storage tubes received from clinics or from the Network DNA Repository.

After eligibility has been determined, the clinic staff selects a set of labels from the available sets, attaches these labels to forms and blood collection tubes; thus this family and/or participant ID is assigned to this specific individual. Labels not used at the initial visit are kept in the participant's files so that if a blood recollection is necessary, the forms and blood collection tubes are labeled with the same participant ID as previous forms and tubes. Should the family (or participant) choose to withdraw from the study, the ID is **not** reassigned to another family or participant.

B. Technical Specifications

The specifications have been created using a Code 39 + mod 43 checksum bar-code format, with a numeric version of the ID printed underneath the bar-code on the same label. The vertical lines in the bar-code are the encoding of the ID that can be read by a bar-code scanner.

The separate components of the bar-code are discussed below. The actual bar-code lines do not encode the '-' (hyphen) separators; for example, the numeric ID 1-

1001-01 is actually read by a scanner as 1100101; the hyphens are automatically included in the numeric form on labels and in reports.

1. Network Code

Each network in the consortium has been assigned a single digit Regional Network Center code. The digits are assigned alphabetically:

Asia Pacific	1
European	2
North American	4
United Kingdom	5
Existing Samples	7
Pilot Studies	8 (Reserved for pilot studies in all networks)
Coordinating Center	9 (Reserved for testing and Coordinating Center use)

If other networks join the T1DGC, their codes will start at 6.

2. ASP and Trio Participant IDs

a. Finalized bar-code format for ASP and trio families is:

Attribute	Size	Allowed Value Range
Network Code	char(1)	1 - 9
Family Code	char(4)	0001 – 9999
Individual Code	char(2)	01 – 99

The numeric version of the bar-code for the ASP and trio families, printed on labels will be:

X-XXXX-XX for example: 1-1001-01

b. Family Code

Within each network, the family code numbering begins at 0001 with a maximum of 9999; allowing for 9999 maximum families that can be recruited in a single network.

Since the same range of family codes is used within each network, the unique ID for a family in the study is a combination of network code + family code.

Family codes will not necessarily be sequential across families seen in a clinic. For example: family "A" is assigned family ID 2-0012 and then family "B" enters the clinic for their exam immediately after family "A," ***does not have to be assigned*** ID 2-0013. The available label sets may be split across multiple clinics in a network. Certain codes within each network will be reserved for special purposes such as quality control and internal checking. Clinics do not need to be concerned with these reserved family IDs and should use the next available label set as directed.

c. Participant Identifier

The individuals within an eligible participating family are assigned participant identifiers according to their relationship. The following list provides the standard codes for each family member:

Participant Identifier	**Relationship**
01	Father
02	Mother
03	Affected Sib1 (Proband)
04	Affected Sib 2
05	Unaffected Sib 1
06	Unaffected Sib 2
07	Affected Sib 3
08	Affected Sib 4
09	Affected Sib 5

Each father in every network will have a participant identifier of 01, each mother 02 and so on. ***The unique ID for an ASP or trio family individual in the study is a combination of network code + family code + individual code.***

In addition to the individual code within the overall bar-code, the individual members of a family can easily be identified from the colored stripes on the labels. The following list provides the standard bar-code color stripes for individual family members:

Bar-code Color Stripe	Relationship
Blue	Father
Pink	Mother
Purple	Affected Sib1 (Proband)
Green	Affected Sib 2
Yellow	Unaffected Sib 1
Yellow	Unaffected Sib 2
Green	Affected Sib 3
Green	Affected Sib 4
Green	Affected Sib 5

There will be some repetition in label stripe color. In these cases, such as multiple affected siblings or unaffected siblings, each individual will have a different participant identifier, but the same label color.

A third level of individual identifiers, the Secondary IDs, are recorded on forms by clinic staff. The corresponding Secondary IDs are shown below.

Secondary IDs	Relationship
FA	Father
MO	Mother
AS1	Affected Sib 1 (Proband)
AS2	Affected Sib 2
UN1	Unaffected Sib 1
UN2	Unaffected Sib 2
AS3	Affected Sib 3
AS4	Affected Sib 4

AS5 Affected Sib 5

The Secondary IDs have 2 or 3 characters – for example father is FA, while unaffected sibling 1 is UN1. When recording the Secondary ID on forms, for FA and MO, clinics leave one box blank in the three digit field.

The label's bar-code contains the full individual ID (X-XXXX-XX). The label also has the colored stripe and personal identifier that indicates the specific family member. The Secondary ID is recorded by clinic staff on all forms except the *Eligibility Form* and the *Consent Summary Form* (which both require only the overall family ID).

3. Case and Control Participant IDs

a. Finalized bar-code format for cases and controls is:

Attribute	**Size**	**Allowed Value Range**
Network Code	char(1)	1 - 9
Case/Control Code	char(1)	7 (Case) or 8 (Control)
Individual Code	char(4)	0001 – 9999

The numeric version of the bar-code for the Case/Control Study, printed on labels will be:

X-X-XXXXX for example: 1-7-40001

b. Participant Code

Within each network, the case and control code numbering each begins at 0001 with a maximum of 9999; allowing for 9999 maximum cases and 9999 controls that can be recruited in a single network. ***Since the same range of individual codes is used within each network, the unique ID for a case or control participant in the study is a combination of the network code + the participant code.***

Codes for these individuals will not necessarily be sequential as assigned to each clinic because these label sets also may be split across multiple clinics in a network. Clinics should use the next available label set for the case or control as directed.

c. Participant Identifier

Each case in every network will have a participant identifier of 7, each control 8. The unique ID for a case or control is a combination of network code + individual code:

In addition to the individual code within the overall bar-code, the individual can easily be identified from the colored stripes on the labels. The following list provides the standard bar-code color stripes for individuals in the Case/Control study.

Bar-code Color Stripe	**Relationship**
Orange	Case
Grey	Control

A third level of individual identifiers, the Secondary IDs, are recorded on forms by clinic staff. The corresponding Secondary IDs are shown below.

Secondary IDs	**Relationship**
CAS	Case
CON	Control

In the Case/Control study all forms will include the individual participant ID in addition to the Secondary ID that will either be pre-recorded on the forms that are unique to the case and the control, or it will be completed by the clinic coordinator. The label's bar-code contains the full individual ID (X-X-XXXXX) as well as the colored stripe and the participant identifier that indicates that the person is a case or a control.

C. Examples

This section shows examples demonstrating the use of the identification scheme for different family (pedigree) structures.

Example 1:

ASP Family 0034 in Europe with participating father, mother, 2 affected siblings and 1 unaffected sibling.

Family ID = 2-0034

Individual	Full Bar-code ID	Secondary ID
Father	2-0034-01	FA
Mother	2-0034-02	MO
Affected Sib1 (Proband)	2-0034-03	AS1
Affected Sib2	2-0034-04	AS2
Unaffected Sib1	2-0034-05	UN1

Example 2:

*ASP Family 0034 in North America, participating father, mother, 4 affected siblings and 1 unaffected sibling.

Family ID = 4-0034

Individual	Full Bar-code ID	Secondary ID
Father	4-0034-01	FA
Mother	4-0034-02	MO
Affected Sib1 (Proband)	4-0034-03	AS1
Affected Sib2	4-0034-04	AS2
Unaffected Sib1	4-0034-05	UN1
Affected Sib3	4-0034-07	AS3
Affected Sib4	4-0034-08	AS4

* Notes:

1. 4-0034-06 is not used here since there is only 1 unaffected sibling in the family
2. Families in different networks may have the same family code, but the combination of network code + family code is unique study-wide, and constitutes the family ID.

Example 3:

Trio Family 1-0114 in Asia-Pacific, participating father, mother, 1 affected sibling.

Family ID = 1-0114

Individual	Full Bar-code ID	Secondary ID
Father	1-0114-01	FA
Mother	1-0114-02	MO
Affected Sib1 (Proband)	1-0114-03	AS1

Example 4:

*Case 4-7-00080 in the North American Network is an individual participating as a case.

Individual	Full Bar-code ID	Secondary ID
Case	4-7-00080	CAS

Note:

1. Cases and controls in different networks may have the same participant identifier, but the combination of network code + participant code + participant identifier is unique study-wide, and constitutes the individual's ID.

D. Rationale

The bar-code and participant ID format strikes a balance between having a long confusing string of redundantly encoded information with the need for being able to perform a quick visual check for source network and family on a blood sample or form. Since clinics generally manage and ship family specimens as a unit in the same box, this ID provides a quick way to identify and count family specimens without the need for constant cross-referencing of random single code identifiers. A visual check of family ID can help clinics prepare the boxes appropriately. Similarly, receiving laboratories will benefit from having a visual way to recognize family specimens since they will typically be stored in freezers, in boxes or racks with adjacent freezer addresses.

The network is encoded in the Participant ID to create the unique key for a family across all networks. This scheme of network code + family (or participant) code in the

identifier enables the Coordinating Center, Central Repositories, and other laboratories to quickly identify the source network for an individual/family.

APPENDIX C
HIPAA-RELATED DOCUMENTS

DATA USE AGREEMENT TEMPLATE

WRITTEN AUTHORIZATION TEMPLATE

EXAMPLE OF NOTICE OF PRIVACY PRACTICES

DATA USE AGREEMENT

This **DATA USE AGREEMENT ("the Agreement")** is effective the____day of _____, 2003, by and between **Wake Forest University Health Sciences ("Wake Forest"),** and _____ **("Participant").**

R E C I T A L S:

WHEREAS, Wake Forest and Participant are part of the Type 1 Diabetes Genetics Consortium (the "**Consortium**"), whose general purpose is to identify genes that determine an individual's risk of type 1 diabetes;

WHEREAS, the Consortium requires the transfer, sharing, analysis, and other uses of various types of medical data among the many institutions that are participating internationally;

WHEREAS, medical data is regulated by various laws, regulations, protocols, and guidelines in both the United States and in other countries that are part of the Consortium, which the parties to this agreement wish to comply with;

NOW, THEREFORE, in consideration of the mutual agreements, covenants, terms and conditions herein contained, Wake Forest and Participant agree as follows:

I. TRANSFER AND USE OF LIMITED DATA

Section 1.1 **Activities.** Wake Forest and Participant will use and transfer data under this agreement only for the research purposes of the Consortium, specified in its Consortium Agreement, its Statement of Purposes, and its Specific Aims, as they may be modified from time to time.

Section 1.2 **Limited Data.** Wake Forest and Participant will transfer to each other data that is collected through the forms and protocols established by the Consortium, as they may be amended from time to time. Wake Forest and Participant acknowledge that these data elements are the minimum necessary for accomplishing the research purposes of the Consortium. Data that are transferred between Wake Forest and Participant will not contain any of the following information that can be used to identify the research participant or their relatives, household members or employers: names, telephone numbers, fax numbers, street addresses, electronic mail addresses, social security numbers, medical record numbers, insurance identification numbers, account numbers, certificate/license numbers, vehicle identifiers and serial numbers (including license plate numbers) device identifiers and serial numbers, Web Universal Resource Locators (URLs); Internet Protocol (IP) address numbers, biometric identifiers, full face photographic images and comparable images. Data without these personal identifiers shall be known as "**Limited Data**."

Section 1.3. **Use of Limited Data.** Wake Forest and Participant may use and disclose the Limited Data only as permitted under the terms of this Agreement or required by law, but shall not otherwise use or disclose the Limited Data and shall ensure that its directors, officers, employees, contractors and agents do not use or disclose the Limited Data in any manner that would constitute a violation of this Agreement or applicable law. Wake Forest and Participant agree not to use the Limited Data in such a way as to identify any individual and further agree not to contact any individual who might be identified using this data. Data User shall limit the use or receipt of the Limited Data to the individuals who reasonably need the Limited Data for the performance of the Consortium's Activities. Wake Forest and Participant shall use appropriate safeguards to prevent use or disclosure of the Limited Data other than as permitted under this Agreement.

Section 1.4. **Reporting of Disclosures of Protected Health Information.** Wake Forest or Participant shall, within thirty (30) days of becoming aware of any use or disclosure of the Limited Data in violation of this Agreement, report any such use or disclosure to the other party to this Agreement.

Section 1.5. **Notice of Request for Data**. Wake Forest and Participant agree to notify the other party within (7) business days if it receives an official request or legal subpoena for any Limited Data. To the extent that one party decides to challenge the validity of such request, the other party shall cooperate fully in such challenge.

Section 1.6. **Agreements by Third Parties.** Wake Forest and Participant shall obtain and maintain an agreement with each agent or subcontractor that has or will have access to the Limited Data, which requires such agent or subcontractor to be bound by the same restrictions, terms and conditions that apply to the Limited Data under this Agreement.

II. GENERAL PROVISIONS

Section 2.1. **Termination Upon Breach.** Any other provision of this Agreement notwithstanding, this Agreement may be terminated by either party upon fifteen (15) days written notice (including e-mail) to the other party in the event that the second party breaches any provision contained in this Agreement and such breach is not cured within such fifteen (15) day period. Wake Forest and Participant acknowledge and agree that in the event the other's efforts to cure any breach are unsuccessful, the first party has a duty to discontinue use of the Limited Data, notwithstanding any other provision of this Agreement to the contrary.

Section 2.2. **Return or Destruction of Data upon Termination.** If this Agreement is terminated due to breach of the Agreement, the breaching party shall either return or destroy all data received from the other party that the breaching party maintains in any form. The breaching party shall not retain any copies of such data. Notwithstanding the foregoing, to the extent that the non-breaching party agrees that it is not feasible to return or destroy such data, the terms and provisions of this Agreement shall survive termination of the Agreement and such data shall be used or disclosed solely as required by the reasons that prevented their return or destruction.

Section 2.3 **Injunction.** Wake Forest and Participant each acknowledge and agree that the other party will suffer irreparable damage if it breaches this Agreement and that damages from such breach shall be difficult to quantify. Therefore, Wake Forest and Participant acknowledge and agree that an action for an injunction may be filed to enforce the terms of this Agreement, in addition to any other remedy the law may provide.

Section 2.4. **Effect.** The terms and provisions of this Agreement shall supercede any other conflicting or inconsistent agreements between Wake Forest and Participant, including all exhibits or other attachments thereto and all documents incorporated therein by reference.

IN WITNESS WHEREOF, the parties have caused this Agreement to be executed as of the day and year first written above.

Wake Forest:	**Participant:**
By: _____	By: _____
Title: _____	Title: _____
Date: _____	Date: _____

Wake Forest University Health Sciences
North Carolina Baptist Hospital
Authorization for Use or Disclosure of Protected Health Information for Research

Study Title
First Name Last Name, Degree, Principle Investigator

You have already agreed to take part in the research study with the title listed above. The purpose of this study is *[insert purpose of study as it appears in the informed consent]*. In deciding whether or not to take part you have read the informed consent, been able to ask questions about this research study, have had your questions answered, signed the informed consent and been given a copy. This form gives you some more information about how health information collected about you for this research study will be used by the researchers and disclosed to others involved in the research study.

Taking part in this research study may involve collecting health information that you consider confidential or private and that directly identifies you. As described in the research informed consent for this study, information from study-related visits, procedures, test, interventions, interactions, questionnaires, or surveys will be collected. In addition, information in your medical/health records may be reviewed and collected. The researchers may also need to discuss your health information with individuals responsible for treating you such as your physician. All the collected information will be used and possible disclosed and re-disclosed to monitor your health status, to measure effects of drugs/devices/procedures/interventions, to determine research results and outcomes, and possibly to develop new drugs/devices/tests/procedures and commercial products.

Your health information may be used by, disclosed to and re-disclosed for research, quality assurance, or regulatory purposes by members, agents or successors of the research team such as the principal investigator, co-investigators, and members of their research staff; other researchers and their staff involved with this study at other medical centers, institutions, hospitals, central laboratories or study related sites such as data monitoring committees, coordinating centers, data management centers, or data reading centers; the sponsor of the study, [Insert Sponsor Name]; the U.S. Food and Drug Administration (FDA) and similar governmental agencies in other countries; the Department of Health and Human Services (DHHS) agencies; the Federal Office of Human Research Protection; North Carolina Baptist Hospitals;, and Wake Forest University Health Sciences. *[Add any other individuals, organizations, agencies, etc. to this list as applicable for the particular study]* All or part of your research related health information may be used or disclosed for treatment, operations or payment related to providing you healthcare. If this research study involves the treatment or diagnosis of a medical condition research related health information may be placed in your medical record and discussed with individual not involved with the study who are caring for you. This will allow the individuals caring for you to have information about what drugs, tests or procedures you are receiving in the study and treat you appropriately, if you have other health problems or needs. Your research related health information may be disclosed if required by state or federal law. The results of this research study may be presented at meetings or in publications. Your identity will not be disclosed in those presentations.

Although every effort will be made to keep your research-related information private, absolute confidentiality and protection of your information cannot be guaranteed. If your information is disclosed to a person or entity that is not covered by the federal privacy regulations it may be re-disclosed. Your research-related information may be used or disclosed until the end of the research study. If your research-related information is included in a research database or repository there is no scheduled date at which this information will be destroyed or no longer used. This is because research information continues to be analyzed for many years and it is not possible to determine when this will be complete. You agree to waive access to or review of your research-related information for the period of the conduct of the research and of the use of the research findings for regulatory purposes. You can access or review your information after this time.

Taking part in this research study is voluntary and you have the right to choose to not sign this form. If you decide not to sign, you cannot participate in this study. You may decide to revoke this authorization at any time by providing written notification of your decision. If you decide at any time to revoke your authorization any information already collected will continue to be used to the extent that it has already been relied on for the study, as necessary to maintain the integrity of the research study or as required by law. You will also not be able to continue to take part in the study if you revoke this authorization. Refusing to sign this authorization or deciding to revoke this authorization will not affect you ability to obtain treatment, or payment or eligibility for benefits to which you are entitled. This Authorization has no expiration date.

You will be given a signed copy of this authorization form.

Signatures

I agree to authorize the use and disclosure of my health information as described above. By signing this form I have not given up any legal rights that I am entitled to. If I have not already received a copy of the Privacy Notice, I may request one. If I have any question or concerns about my privacy or for information about where to write to revoke this Authorization I should contact the Privacy Officer at (336) 713-2320.

_____

Subject Name (Printed)

_____ _____

Subject Signature Date

_____

Legally Authorized Representative Name (Print)

The above named Legally Authorized Representative has authority to act for the research subject based upon:

[ ] The Legally Authorized Representative holds the subject's health care power of attorney

[ ] The Legally Authorized Representative is the subject's spouse

[ ] The subject is a minor and the Legally Authorized Representative is the subject's parent

[ ] The subject is a minor and the Legally Authorized Representative is the subject's guardian who is authorized under North Carolina state law to consent on behalf of the minor for general medical care.

[ ] Other: (specify) _____

_____ _____

Legally Authorized Representative Signature Date

Wake Forest University Health Sciences
North Carolina Baptist Hospital
Authorization for Use or Disclosure of Protected Health Information for Research

Study Title
BG#____-_____
First Name Last Name, Degree, Principle Investigator

You have already agreed to take part in the research study with the title listed above. The purpose of this study is *[insert purpose of study as it appears in the informed consent]*. In deciding whether or not to take part, you have read the informed consent, been able to ask questions about this research study, have had your questions answered, signed the informed consent and been given a copy. This form gives you additional information about how health information collected about you for this research study will be used by the researchers and disclosed to others involved in the research study.

Taking part in this research study may involve collecting health information that you consider confidential or private and that directly identifies you. As described in the research informed consent for this study, information from study-related visits, procedures, test, interventions, interactions, questionnaires, or surveys will be collected. In addition, information in your medical/health records may be reviewed and collected. The researchers may also need to discuss your health information with individuals responsible for treating you such as your physician. All the collected information will be used and possibly disclosed and re-disclosed to monitor your health status, to measure effects of drugs/devices/procedures/interventions, to determine research results and outcomes, and possibly to develop new drugs/devices/tests/procedures and commercial products.

Your health information may be used by, disclosed to and re-disclosed for research, quality assurance, or regulatory purposes by members, agents or successors of the research team such as the principal investigator, co-investigators, and members of their research staff; other researchers and their staff involved with this study at other medical centers, institutions, hospitals, central laboratories or study related sites such as data monitoring committees, coordinating centers, data management centers, or data reading centers; the sponsor of the study, [Insert Sponsor Name]; the U.S. Food and Drug Administration (FDA) and similar governmental agencies in other countries; the Department of Health and Human Services (DHHS) agencies; the Federal Office of Human Research Protection; North Carolina Baptist Hospitals;, and Wake Forest University Health Sciences. *[Add any other individuals, organizations, agencies, etc. to this list as applicable for the particular study]* All or part of your research related health information may be used or disclosed for treatment, operations or payment related to providing you healthcare. If this research study involves the treatment or diagnosis of a medical condition, research related health information may be placed in your medical record and discussed with individuals not involved with the study who are caring for you. This will allow the individuals caring for you to have information about what drugs, tests, or procedures you are receiving in the study and treat you appropriately if you have other health problems or needs. Your research related health information may be disclosed if required by state or federal law. The results of this research

study may be presented at meetings or in publications. Your identity will not be disclosed in those presentations.

Although every effort will be made to keep your research-related information private, absolute confidentiality and protection of your information cannot be guaranteed. If your information is disclosed to a person or entity that is not covered by the federal privacy regulations, it may be re-disclosed. Your research-related information may be used or disclosed until the end of the research study. If your research-related information is included in a research database or repository there is no scheduled date at which this information will be destroyed or no longer used. This is because research information continues to be analyzed for many years and it is not possible to determine when this will be complete. You agree to waive access to or review of your research-related information for the period of the conduct of the research and of the use of the research findings for regulatory purposes. You can access or review your information after this time.

Taking part in this research study is voluntary and you have the right to choose not to sign this form. If you decide not to sign, you cannot participate in this study. You may decide to revoke this authorization at any time by providing written notification of your decision. If you decide at any time to revoke your authorization, any information already collected will continue to be used to the extent that it has already been relied on for the study, as necessary to maintain the integrity of the research study, or as required by law. You will also not be able to continue to take part in the study if you revoke this authorization. Refusing to sign this authorization or deciding to revoke this authorization will not affect your ability to obtain treatment, or payment, or eligibility for benefits to which you are entitled. This Authorization has no expiration date.

You will be given a signed copy of this authorization form.

Signatures

I agree to authorize the use and disclosure of my health information as described above. By signing this form, I have not given up any legal rights that I am entitled to. If I have not already received a copy of the Privacy Notice, I may request one. If I have any question or concerns about my privacy or for information about where to write to revoke this Authorization, I should contact the Privacy Officer at (336) 713-2320.

_____

Subject Name (Printed)

_____ _____

Subject Signature Date

_____

Legally Authorized Representative Name (Print)

The above named Legally Authorized Representative has authority to act for the research subject based upon:

[ ] The Legally Authorized Representative holds the subject's health care power of attorney

[ ] The Legally Authorized Representative is the subject's spouse

[ ] The subject is a minor and the Legally Authorized Representative is the subject's parent

[ ] The subject is a minor and the Legally Authorized Representative is the subject's guardian who is authorized under North Carolina state law to consent on behalf of the minor for general medical care.

[ ] Other: (specify) _____

_____ _____

Legally Authorized Representative Signature Date

NORTH CAROLINA BAPTIST HOSPITAL

WAKE FOREST UNIVERSITY HEALTH SCIENCES

PRIVACY NOTICE

THIS NOTICE DESCRIBES HOW MEDICAL INFORMATION ABOUT YOU MAY BE USED AND DISCLOSED AND HOW YOU CAN GET ACCESS TO THIS INFORMATION.

PLEASE REVIEW IT CAREFULLY.

WHO WILL FOLLOW THIS NOTICE

This Notice describes the privacy practices of North Carolina Baptist Hospital (Hospital) and Wake Forest University Health Sciences, which includes Wake Forest University Physicians (Clinic) and:

- Any health care professional authorized to enter information into your Hospital and/or Clinic chart;
- All departments and units of the Hospital or Clinic (including the pharmacy);
- Any member of a volunteer group we allow to help you while you are in the Hospital or Clinic; and
- All employees, staff and other Hospital and/or Clinic personnel.

These entities, sites and locations will follow the terms of this Notice. In addition, these entities, sites and locations may share medical information with each other for treatment, payment or Hospital operations purposes described in this Notice.

OUR PLEDGE REGARDING MEDICAL INFORMATION

We understand that medical information about you and your health is personal. We are committed to protecting medical information about you. We create a record of the care and services you receive at the Hospital and/or Clinic. We need this record to provide you with quality care and to comply with certain legal requirements. This Notice applies to all of your health information communicated by you or generated by the Hospital and/or the Clinic, whether made by Hospital personnel or your personal doctor. A doctor or Hospital not associated with our facilities may have different policies or notices regarding the doctor's use and disclosure of your medical information created in the doctor's office or Clinic. A notice of their privacy practices may be obtained directly from them.

This Notice will tell you about the ways in which we may use and disclose medical information about you. This Notice also describes your rights and certain obligations we have regarding the use and disclosure of medical information.

We are required by law to:

- make sure that medical information that identifies you is kept private;
- give you this Notice of our legal duties and privacy practices with respect to medical information about you; and
- follow the terms of the Notice that is currently in effect.

HOW WE MAY USE AND DISCLOSE MEDICAL INFORMATION ABOUT YOU

The following categories describe different ways that we use and disclose medical information. For each category of uses or disclosures we will explain what we mean and try to give some examples. Not every use or disclosure in a category will be listed. However, all of the ways we are permitted to use and disclose information will fall within one of the categories.

For Treatment: We may use your medical information to provide you with medical treatment or services. We may disclose your medical information to doctors, nurses, technicians, medical students, or other Hospital personnel who are involved in taking care of you. For example, a doctor treating you for a broken leg may need to know if you have diabetes because diabetes may slow the healing process. In addition, the doctor may need to tell the dietitian if you have diabetes so that we can arrange for appropriate meals. Different departments of the Hospital and/or Clinics also may share medical information about you in order to coordinate the different things you need, such as prescriptions, lab work and x-rays. We also may disclose medical information about you to people outside the Hospital or Clinic who will be involved in your medical care after you leave the Hospital or Clinic, such as caregivers or others we use to provide services that are part of your care.

For Payment: We may use and disclose medical information about you so that the treatment and services you receive at the Hospital and/or Clinic may be billed to and payment may be collected from you, an insurance company or a third party (including collection agencies). For example, we may need to give your health plan information about surgery you received at the Hospital so your health plan will pay us or reimburse you for the surgery. We may also tell your health plan about a treatment you are going to receive to obtain prior approval or to determine whether your plan will cover the treatment.

For Health Care Operations: We may use and disclose medical information about you for Hospital and/or Clinic operations. We may disclose medical information to "business associates" who provide business services on behalf of the Hospital and/or Clinic. These uses and disclosures are necessary to run the Hospital and Clinics and make sure that all of our patients receive quality care. For example, we may use medical information to review our treatment and services and to evaluate the performance of our staff in caring for you. We may also combine medical information about many Hospital patients to decide what additional services the Hospital or Clinic should offer, what services are not needed, and whether certain new treatments are effective. We may also disclose information to doctors, nurses, technicians, medical students, and other

Hospital or Clinic personnel for review and learning purposes. We may also combine the medical information we have with medical information from other health care entities to compare how we are doing and see where we can make improvements in the care and services we offer. We may remove information that identifies you from this set of medical information so others may use it to study health care and health care delivery without learning who you are. For example, your information may be used for purposes of quality assurance and quality improvement by either/or the Hospital or its physicians.

Appointment Reminders: We may use and disclose medical information to contact you as a reminder that you have an appointment for treatment or medical care at the Hospital or Clinic.

Treatment Alternatives: We may use and disclose medical information to tell you about or recommend possible treatment options or alternatives that may be of interest to you.

Health-Related Benefits and Services: We may use and disclose medical information to tell you about health-related benefits or services that may be of interest to you.

Fundraising Activities: We may use certain information (such as your name, address, telephone number, dates of service) to contact you in the future to seek donations for community service programs, patient care, medical research, and education.

Hospital Directory: We may include certain limited information about you in the Hospital directory while you are a patient at the Hospital. This information may include your name, location in the Hospital, your general condition (e.g., fair, stable, etc.) and your religious affiliation. The directory information, except for your religious affiliation, may also be released to people who ask for you by name. Your religious affiliation may be given to a member of the clergy, such as a priest or rabbi, even if they don't ask for you by name. This is so your family, friends, and clergy can visit you in the Hospital and generally know how you are doing.

Individuals Involved in Your Care or Payment for Your Care: We may release medical information about you to a friend or family member who is involved in your medical care. We may also give information to someone who helps pay for your care. We may also tell your family or friends your condition and that you are in the Hospital. In addition, we may disclose medical information about you to an entity assisting in a disaster relief effort so that your family can be notified about your condition, status and location.

Research: Under certain circumstances, we may use and disclose medical information about you for research purposes. For example, a research project may involve comparing the health and recovery of all patients who received one medication to those who received another, for the same condition. All research projects, however, are subject to a special approval process. This process evaluates a proposed research project and the use of medical information pursuant to the project, trying to balance the research needs with patients' need for privacy of their medical information. Before we use or disclose medical information for research, the project will have been approved through this research approval process; however, we may disclose medical information about you to people preparing to conduct a research project, for example, to help them look for patients with specific medical needs, so long as the medical information they review does not leave the facility, and so long as the information sought is necessary for the research purpose. We will almost always ask for your specific permission if the research involves treatment. If you are asked for such permission, you have the right to refuse.

As Required by Law: We will disclose medical information about you when required to do so by federal, state or local law.

To Avert a Serious Threat to Health or Safety: We may use and disclose medical information about you when necessary to prevent a serious threat to your health and safety or the health and safety of the public or another person.

SPECIAL SITUATIONS

As Required by State or Federal Law: We will disclose medical information about you when necessary to do so by federal, state, or local law or other judicial or administrative proceeding.

Organ and Tissue Donation: If you are an organ donor, we may release medical information to organizations that handle organ procurement or organ, eye or tissue transplantation or to an organ donation bank, as necessary to facilitate organ or tissue donation and transplantation.

Military and Veterans: If you are a member of the armed forces, we may release medical information about you as required by military command authorities. We may also release medical information about foreign military personnel to the appropriate foreign military authority.

Workers' Compensation: We may release medical information about you for workers' compensation or similar programs. These programs provide benefits for work-related injuries or illness.

Public Health Risks: We may disclose medical information about you for public health activities. These activities generally include the following:

- to prevent or control disease, injury or disability;
- to report births and deaths;
- to report child abuse or neglect;

- to report reactions to medications or problems with products;
- to notify people of recalls of products they may be using;
- to notify a person who may have been exposed to a disease or may be at risk for contracting or spreading a disease or condition; and
- to notify the appropriate government authority if we believe a patient has been the victim of abuse, neglect or domestic violence. We will only make this disclosure if you agree or when required or authorized by law.

Health Oversight Activities: We may disclose medical information to a health oversight agency for activities authorized by law. These oversight activities include, for example, audits, investigations, inspections, and licensure. These activities are necessary for the government to monitor the health care system, government programs, and compliance with civil rights laws.

Lawsuits and Disputes: If you are involved in a lawsuit or a dispute, we may disclose medical information about you in response to a court or administrative order. We may also disclose medical information about you in response to a subpoena, discovery request, or other lawful process by someone else involved in the dispute, but only if efforts have been made to tell you about the request or to obtain an order protecting the information requested.

Law Enforcement: We may release medical information if asked to do so by a law enforcement official:

- in response to a court order, subpoena, warrant, summons or similar process;
- to identify or locate a suspect, fugitive, material witness, or missing person;
- about the victim of a crime if, under certain limited circumstances, we are unable to obtain the person's agreement;
- about a death we believe may be the result of criminal conduct;
- about criminal conduct at the Hospital or Clinic or on medical center property; and
- in emergency circumstances to report a crime; the location of the crime or victims; or the identity, description or location of the person who committed the crime.

Coroners, Medical Examiners and Funeral Directors: We may release medical information to a coroner or medical examiners. This may be necessary, for example, to identify a deceased person or determine the cause of death. We may also release medical information about patients of the Hospital to funeral directors as necessary to carry out their duties.

National Security and Intelligence Activities: We may release medical information about you to authorized federal officials for intelligence, counterintelligence, and other national security activities authorized by law.

Protective Services for the President and Others: We may disclose medical information about you to authorized federal officials so they may provide protection to the President, other authorized persons or foreign heads of state, or to conduct special investigations.

Inmates: If you are an inmate of a correctional institution or under the custody of a law enforcement official, we may release medical information about you to the correctional institution or law enforcement official. This release would be necessary (1) for the institution to provide you with health care; (2) to protect your health and safety or the health and safety of others; or (3) for the safety and security of the correctional institution.

YOUR RIGHTS REGARDING MEDICAL INFORMATION ABOUT YOU
You have the following rights regarding medical information we maintain about you:

Right to Inspect and Copy: You have the right to inspect and copy medical information that may be used to make decisions about your care. Usually, this includes medical and billing records, but does not include psychotherapy notes.

If you request a copy of the information, we may charge a fee for the costs of copying, mailing or other supplies associated with your request.

We may deny your request to inspect and copy in certain very limited circumstances. If you are denied access to medical information, you may request that the denial be reviewed. Another licensed health care professional chosen by the Hospital or Clinic, as applicable, will review your request and the denial. The person conducting the review will not be the person who denied your request. We will comply with the outcome of the review.

Right to Amend: If you feel that medical information we have about you is incorrect or incomplete, you may ask us to amend the information. You have the right to request an amendment for as long as the information is kept by or for the Hospital or Clinic.

We may deny your request for an amendment if it is not in writing or does not include a reason to support the request. In addition, we may deny your request if you ask us to amend information that:

- was not created by us, unless the person or entity that created the information is no longer available to make the amendment;
- is not part of the medical information kept by or for the Hospital or Clinic;
- is not part of the information which you would be permitted to inspect and copy; or
- is accurate and complete.

Right to an Accounting of Disclosures: You have the right to request an "accounting of disclosures." This is a list of certain disclosures we made of medical information about you. This accounting does not include disclosures that are made to carry out treatment, payment, or health care operations, or information that has already been delivered to you or your health care representative, or information disclosed pursuant to an authorization.

Your request must state a time period which may not be longer than six years and may not include dates before April 14, 2003. Your request should indicate in what form you want the list (for example, on paper, electronically). The first list you request within a 12 month period will be free. For additional lists, we may charge you for the costs of providing the list. We will notify you of the cost involved and you may choose to withdraw or modify your request at that time before any costs are incurred.

Right to Request Restrictions: You have the right to request a restriction or limitation on the medical information we use or disclose about you for treatment, payment or health care operations. You also have the right to request a limit on the medical information we disclose about you to someone who is involved in your care or the payment for your care, like a family member or friend.
We are not required to agree to your request. If we do agree, we will comply with your request unless the information is needed to provide you emergency treatment.

In your request, you must tell us (1) what information you want to limit; (2) whether you want to limit our use, disclosure or both; and (3) to whom you want the limits to apply, for example, disclosures to your spouse.

Right to Request Confidential Communications: You have the right to request that we communicate with you about medical matters in a certain way or at a certain location. For example, you can ask that we only contact you at work or by mail.

We will not ask you the reason for your request. We will accommodate all reasonable requests. Your request must specify how and where you wish to be contacted.

Right to a Paper Copy of This Notice: You have the right to a paper copy of this Notice. You may ask us to give you a copy of this Notice at any time. Even if you have agreed to receive this Notice electronically, you are still entitled to a paper copy of this Notice.

You may obtain a copy of this Notice at our web site, www.Privacy@wfubmc.edu.
To obtain a paper copy of this Notice, contact (336) 713-HIPA (4472) (Privacy Office).

CHANGES TO THIS NOTICE

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EFFECTIVE DATE: April 14, 2003

NCBH Department of Legal Affairs Review Date: April 1, 2003
WFUHS University Counsel Review Date: April 1, 2003

Reference: AHA Regulatory Advisory (2/13/01) 42 C.F.R. Parts 160 and 164 (2003)

RECRUITMENT
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I. INTRODUCTION

The recruitment goal for the Type 1 Diabetes Genetics Consortium (T1DGC) is 2,800 affected sib-pair families, 1,600 trio families, 2,050 cases and 2,050 ethnically matched controls. While each network has different strategies for recruiting families, all networks share the same eligibility criteria (see **Chapter IV**, *Eligibility*).

The optimal affected-sib pair (ASP) family structure is two affected siblings, both biological parents and (up to) two unaffected siblings. Up to five affected siblings per family are allowed to participate, but this requires advance notification and permission. The optimal trio family is an affected child and both biological parents. In the North American network, only African American and Mexican American trio families are eligible. In the Case/Control study, individuals will be recruited and cases and controls will be frequency matched on primary ethnic group, gender and region.

Recruitment of families requires the parents who provide genetic material be the biological (full) parents of the affected and unaffected siblings, and similarly, the siblings be full (not half-, step-, or adopted) siblings, having the same biological mother and same biological father. Details of study-wide recruitment are provided below.

II. RECRUITMENT GOALS AND TIMELINES

A. Asia-Pacific Network

The Asia-Pacific Network goal is to recruit 340 ASP families. In addition, the Asia-Pacific Network will recruit 1,150 trio families from ethnic groups other than Caucasian. China, India, and Thailand will recruit 1,000 cases and 1,000 ethnically matched controls.

B. European Network

The European Network goal is to recruit 1,200 ASP families. In addition, 50 trios from ethnic groups other than Caucasian will be recruited. Cameroon will recruit 150 cases and 150 ethnically matched controls.

C. North American Network

The North American Network goal is to recruit 1,100 ASP families. In addition, 400 trios will be collected simultaneously in Mexican American and African American populations. The North American Network will recruit 900 cases and 900 ethnically matched controls from Mexican American and African American populations as well.

D. United Kingdom Network

The United Kingdom Network goal to recruit 160 ASP families was accomplished and the network closed in December 2005.

III. ETHNIC- AND GENDER-SPECIFIC GOALS

The National Institutes of Health (NIH) is the funding agency for the T1DGC and requires quarterly reporting of enrollment by ethnicity, race and gender. For these purposes, ethnicity is reported as either Hispanic or Latino ***OR*** Not Hispanic or Latino. Race is reported to the NIH as American Indian/Alaskan Native; Asian; Native Hawaiian or Other Pacific Islander; Black or African American; and/or White. However, race will be collected in network-specific categories. Participants are permitted to report up to three race categories, but must specify a primary category to be reported to the NIH.

Table 1 represents the targeted enrollment of individual ASP family members as submitted to NIH. This table is based on having an average of 6 members per family. Equal numbers of male and female participants are expected in each racial and ethnic category.

Table 1. Targeted ASP Enrollment

Network	Ethnicity		Race		**Network Total**
	Hispanic	Not Hispanic	White	Black	
Asia-Pacific	0	2,040	2,040	0	**2,040**
European	0	7,200	7,200	0	**7,200**
North American	600	6,000	6,000	600	**6,600**
United Kingdom	0	960	960	0	**960**
Ethnicity and Race Totals	**600**	**16,200**	**16,200**	**600**	**16,800**

NOTE: Totals for ethnicity and race are mutually exclusive. The total number of targeted individuals is 16,800.

IV. MINIMAL ACCEPTABLE STRUCTURE

A. Affected Sib-Pair (ASP) Families

Recognizing the difficulty in recruiting two affected siblings, both biological parents and two unaffected siblings, the Steering Committee established the following minimum data collection standards that define recruitment of an ASP family (thereby constituting reimbursement): ***completion of data forms (T1DGC ASP Eligibility Form, T1DGC ASP Consent Summary Form, layered portion of the informed consent, T1DGC ASP Exam Form and T1DGC Blood Collection Form) and collection of blood samples for both affected siblings.***

Additional reimbursement is provided for completion of questionnaires and collection of blood samples for each parent, and up to two unaffected siblings. As many as three additional affected siblings per family can also be included if approved by the Regional Network Center.

B. Trio Families

In families where only one affected child is available for participation, the inclusion of both the biological mother and biological father of this child is required. The Steering Committee established the following minimum data collection standards that define recruitment of a trio family (thereby constituting reimbursement): ***completion of data forms (T1DGC Trio Consent Summary Form, layered portion of informed consent, T1DGC Trio Eligibility Form, T1DGC Trio Exam Form, and T1DGC Blood Collection Form) and collection of blood samples for the affected child and both biological parents.*** In the North American Network, the *T1DGC North American Trio Pre-Eligibility Form* must also be completed to meet minimum data collection standards. No reimbursement is provided for any additional family members. Only approved networks and clinics are reimbursed for the collection of trio families.

In the North American Network, a trio family is eligible only if both biological parents are African American or Mexican American. The specific criteria for these low-prevalence trios are:

Mexican American -- defined as any individual of **Mexican** descent living in North America (US or Canada). The proband does not need to be born in North America. While the primary goal of this collection is to ascertain Mexican American individuals, individuals can be recruited and examined if born in Central America: Belize, Costa Rica, El Salvador, Guatemala, Honduras, Nicaragua, or Panama.

African American -- defined as any individual of **non-Caucasian of African** descent living in North America (US or Canada). This includes (but is not limited to) descent from Egypt and Somalia. The proband does not need to be born in North America. No Caucasians of African descent qualify (e.g., white South African) and cannot be included as trio families due to the sufficient number of Caucasian trios from previous collections.

C. Case/Control Study

The Case/Control study will be conducted in low prevalence populations and will be in addition to the ASP and trio family collections. Cases with Type 1 diabetes that meet the T1DGC definition will be enrolled. Controls will be selected from the same populations and will be individuals unrelated to the cases who do not have any form of diabetes and do not have any biological relatives – father, mother, brother(s), sister(s), or children – who have been diagnosed with any form of diabetes. The Steering Committee established the following minimum data collection standards for the case (thereby constituting reimbursement): ***completion of data forms (layered portion of informed consent, T1DGC Case/Control Eligibility Form, T1DGC Case Exam Form, and T1DGC Blood Collection Form) and collection of blood samples for the individual.*** The minimum data collection standards for the control (constituting reimbursement) are: ***completion of data forms (layered portion of informed consent, T1DGC Case/Control Eligibility Form, and T1DGC Blood Collection Form) and collection of blood samples for the individual.*** No reimbursement is provided for any additional family members. Only approved networks and clinics are reimbursed for the collection of cases and controls.

Three countries in the Asia-Pacific Network will participate in collection of cases and controls: China, India, and Thailand.

In the European Network, only Cameroon will participate in the collection of cases and controls.

In the North American Network, a case must be a person with Type 1 diabetes who is African American or Mexican American. A control must be a person without Type 1 diabetes who is African American or Mexican American. The specific criteria for these low-prevalence participants are:

Mexican American -- defined as any individual of **Mexican** descent living in North America (US or Canada). The case or control does not need to be born in North

America. While the primary goal of this collection is to ascertain Mexican American individuals, individuals can be recruited and examined if born in Central America: Belize, Costa Rica, El Salvador, Guatemala, Honduras, Nicaragua, or Panama.

African American -- defined as any individual of **non-Caucasian of African** descent living in North America (US or Canada). This includes (but is not limited to) descent from Egypt and Somalia. The case or control does not need to be born in North America. No Caucasians of African descent (e.g., white South African) can be included.

D. Reimbursement

Reimbursement is provided to the clinics to be used for personnel support, supplies, and/or incentives or remuneration for participating family members. Regional Network Centers invoice the Coordinating Center for recruitment on a monthly basis and reimburse the clinics based on family recruitment.

V. RECRUITMENT STRATEGIES

This section describes the planned recruitment strategies for each of the four networks.

A. Asia-Pacific

Network Coordinating Center: Walter and Eliza Hall Institute of Medical Research; Melbourne, Australia
Network Principal Investigators: Grant Morahan, Ph.D. and Peter Colman, M.D.
Network Coordinator: Amanda Loth, R.N.

The Asia-Pacific Network aims to recruit primarily via clinics and patients at collaborating institutions. It is expected that each collaborating clinic develops its own contacts regionally to increase the number of families it is able to recruit. This regional recruitment is the responsibility of each institution.

Regular contact with the clinics is made by the Network Coordinator to facilitate the process of getting blood samples to Melbourne. This is accomplished via regular conference calls and e-mail contact.

Each participating country has identified the anticipated number of families to be recruited. Recruitment goals for this network are 340 ASP families, along with 1,150 trio families and 1,000 cases and 1,000 controls. A plan has been negotiated with each clinic for timing of recruitment and is monitored by the Network Coordinator.

B. European Network

Network Coordinating Center: Steno Diabetes Center; Gentofte, Denmark
Network Principal Investigators: Jorn Nerup, M.D., D.M.Sc. and Flemming Pociot, M.D., D.M.Sc.
Project Managers: Ana Wagner, M.D., Ph.D. and Lotte Albret, B.A.

The recruitment strategy for Europe follows various approaches. The majority of clinics/regions/countries have registries from which probands can be identified. At least two-thirds of the families are likely to be identified by this approach. The remainder of the families will either be recruited through existing clinical networks for Type 1 diabetes (*e.g.,* ENDIT) or by general recruitment strategies. The latter includes announcements at professional meetings, patient organizations' meetings, and advertisements in lay journals.

This network has over 100 clinics in 28 participating countries. The European Network is targeted to collect 1,200 ASP families. In addition to the ASP collection, Cameroon is expected to recruit 50 trio families, 150 cases and 150 controls.

The European Network contains a number of previously genome-screened families in the Scandinavian countries. In Sweden, there is a registry-based system to ensure that families are not double-ascertained. In Denmark and Norway, primary focus is on newly eligible families since the last collection. Because most families collected in

Denmark are coordinated from one clinic, it is possible to validate their ascertainment as "new." This is not an option in Norway and thus may reduce the number of families available there. Participants are queried about previous participation in these studies on the *T1DGC Eligibility Form*.

C. North American Network

Network Coordinating Center: Benaroya Research Institute; Seattle, Washington, USA
Network Principal Investigator: Carla Greenbaum, M.D.
Network Coordinator: Alan Aldrich, M.S.

The North American Network will recruit 1,100 ASP families. First, approximately half of designated clinics are responsible for collection of approximately 60% of the ASP families (n=660). Second, approximately 30% of families (n=330) are expected to be recruited through interactions with existing clinical networks for Type 1 diabetes (*e.g.,* TrialNet, EDIC, SEARCH, etc.). Third, 10% of families (n=110) will be recruited through general recruitment strategies. These include announcements at relevant professional meetings (*e.g.,* ADA, CDA, CDE), notices and articles in lay journals directed towards people with Type 1 diabetes (*e.g.,* Diabetes Forecast, JDRF Countdown), and directed mailings (*e.g.,* JDRF or ADA members, Certified Diabetes Educators and school nurses). Recruitment of low-prevalence trios will be completed simultaneously with recruitment of ASP families with a goal of 400 trio families. Case/control recruitment will include 900 cases and 900 controls in the North American Network.

Recruitment materials include flyers, posters, brochures, small items with TIDGC logos, an 800 phone number, web site, and dedicated e-mail address. Incentive items may include small items such as hats, T-shirts, or similar. Participants and families are compensated for their time and effort to participate in the study.

D. United Kingdom Network

Network Coordinating Center: University of Cambridge; Cambridge, United Kingdom
Network Principal Investigator: John Todd, Ph.D.

Network Coordinator: Heather Withers, BA, MSC

Multiplex families are identified using the existing UK GRID infrastructure, and samples and data are collected using regionally organized, clinic-based recruitment. Affected sibling pairs, unaffected siblings and parents are approached by field workers for DNA and antibody samples. Samples and family histories are collected from parents at the interview. The majority of affected siblings in this network are younger than 16 years.

A number of samples that are suitable for developing cell lines are already available from certain probands and affected siblings. These families will be re-contacted to obtain phenotypic data and other blood samples. The United Kingdom Network completed its recruitment in December 2005 with a total of 163 ASP families.

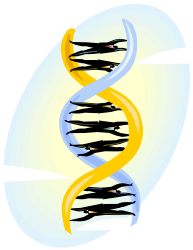
VI. PREVIOUSLY GENOME-SCREENED FAMILIES

No "double ascertainment" of families is permitted. These may include participants in the United States, United Kingdom, and Scandinavian countries (*e.g.,* HBDI, BDA/Warren I, and SCAND). Individuals also are ineligible if a member of their family has previously participated in the Type 1 Diabetes Genetics Consortium. Attempts to identify such individuals are made by asking a question about participation in genetic studies as part of the eligibility screening process on the *T1DGC Eligibility Form*.

VII. RECRUITMENT MATERIALS

Each network can assist the clinics in developing clinic-specific recruitment materials. However, local Internal Review Board (IRB) or Ethics Committee approval must be obtained to use such materials. Regional Network Centers may require copies of approved recruitment materials from each clinic. Examples of recruitment flyers and brochures for ASP families are available in Appendix A.

APPENDIX A
EXAMPLES OF RECRUITMENT MATERIALS



Type 1 Diabetes Study

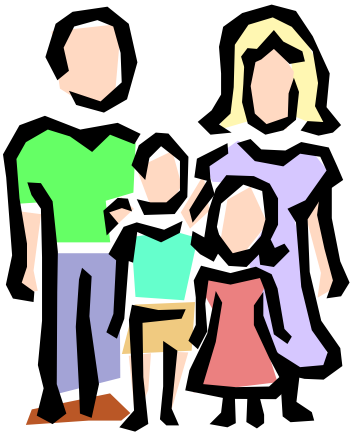
Type 1 Diabetes Genetics Consortium

In your family, are there two siblings (brothers or sisters) **with Type 1 diabetes?**

If so, your family may be eligible to help researchers understand the genetic causes of Type 1 diabetes.

If eligible, some members of your family will have a **small** amount of blood collected and will be asked questions about their health. There is no cost to you.

If you are interested in participating or would like to learn more about this study, please contact:



Name of Clinic Coordinator
Name of Clinic
Contact Information

Or get more information on our web site:
http://www.t1dgc.org

National Institute of Diabetes and Digestive and Kidney Diseases
Juvenile Diabetes Research Foundation
National Institute of Allergy and Infectious Diseases
National Human Genome Research Institute

What is the Type 1 diabetes genetic consortium?

The consortium is a group of diabetes researchers from around the world who have come together to collect samples and information from families with Type 1 diabetes.

What is the consortium trying to do?

We are trying to discover how differences in the genes that we inherit from our parents contribute to the risk for development of Type 1 diabetes. Genes are the 'blue prints' in our bodies which we get from our parents at birth, that decide our characteristics like the color of our hair, our eyes and the shape of our bodies. Some genes are also involved in whether you have diabetes or not. If we find out more about these genes, we may be able to prevent diabetes in the future.

Who can participate?

We are looking for families in which there are at least two siblings (brothers or sisters) with Type 1 diabetes. In these families, we would like the participation of the people with diabetes, other siblings without diabetes, and their parents.

What you will need to do:

If you want to help us, we will take some blood and ask you some questions about your diabetes and your health.

What is being done with my blood?

The blood will go to XXXXX where scientists will study the genes in the cells of the blood. The blood will be prepared in such a way that you do not need to come back in the future.

What do I do next?

After you have read this brochure, think about it and talk with other family members. If you have any more questions or want more information, please ask XXXXXXXXX or visit our web site at http://www.t1dgc.org. If interested, you will receive more information and an appointment will be scheduled. If you have e-mail, you can send your questions to the Clinic Coordinator in XXXXXXX at the address given.

Contact Information

Clinic Coordinator:

Phone:

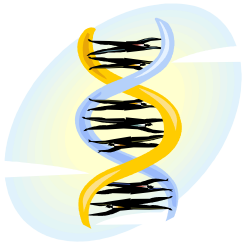
e-mail:

XXXXXX Network:

Network Principal Investigator:

Network Coordinator:

The Type 1 Diabetes Genetic Consortium



National Institute of Diabetes and Digestive and Kidney Diseases
Juvenile Diabetes Research Foundation
National Institute of Allergy and Infectious Diseases
National Human Genome Research Institute

Enter local hospital details

ELIGIBILITY

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I. INTRODUCTION

The purpose of the Type 1 Diabetes Genetics Consortium (T1DGC) is to organize international efforts to identify genes that determine an individual's risk of Type 1 diabetes. This will be facilitated by the creation of a resource-base of well-characterized families from multiple ethnic groups. In specified populations there will be a Case/Control study that will include individuals with Type 1 diabetes and ethnically matched controls without any type of diabetes.

The diagnosis of Type 1 diabetes must be firmly established according to study criteria including: age at onset; use of insulin; and absence of a concomitant disease or disorder causing the diabetes. Comprehensive questionnaires have been developed to ensure correct ascertainment.

In the North American Network, the *T1DGC North American Trio Pre-Eligibility Form* must be completed prior to completion of the *T1DGC Trio Eligibility Form* to determine the trio's eligibility. Comprehensive instructions (Q x Qs) for the pre-eligibility form are provided in Appendix A.

There are two versions of the *T1DGC Eligibility Form*. One eligibility form is completed per family, case or control either by the proband, case or control, **or** by the guardian if the proband, case or control is not old enough to provide consent. **The proband is the first child/person diagnosed with Type 1 diabetes in a family.** The age at which an individual can provide consent varies from network to network. The *T1DGC Eligibility Form* is completed by the proband, the case or the control, if this individual is of legal age to give consent and it is determined by the clinic staff that the individual is able to understand and answer all questions. Regardless of which *T1DGC Eligibility Form* is completed, only one member of the family is interviewed.

Comprehensive instructions (Q x Qs) for the eligibility forms are provided in Appendix B and C (for ASP families), Appendix D and E (for trio families), Appendix F and G (for Cases) and Appendix H and I (for Controls).

II. STUDY ELIGIBILITY CRITERIA

A. ASP Family Structure

The ideal family structure needed for establishing this resource is: two Type 1 diabetes-affected full siblings, both biological parents, and (up to) two unaffected full siblings. This family is referred to as an affected-sib pair (ASP) family. The minimum requirement is the inclusion of the affected sibling pair. The full family provides the **optimal information** and attempts should be made to include all family members as listed above.

The affected siblings cannot be identical twins. Only one individual of an identical twin pair can participate as an affected sibling. If the participants are unsure if they are identical or fraternal twins, both can be included. Both affected sibling and unaffected sibling who are identical twins can be included.

B. Trio Family Structure

The Asia-Pacific, European and North American Networks are collecting trio families in addition to ASP families. The ideal family structure is one Type 1 diabetes-affected child and both biological parents. This is both the minimum and the maximum requirement. In the North American Network, a trio family is eligible if: both parents self-identify as African American, **or** both parents self-identify as Mexican American, **or** one parent self-identifies as African American and the other self-identifies as Mexican American.

C. Case/Control Study

Specific clinics in the Asia-Pacific, European and North American Networks are participating in a Case/Control study in addition to the ASP and trio collections. For the Case/Control study, only individuals are collected; no families are collected. Cases and controls may not be biologically related to each other. In the Asia-Pacific Network, case and control participants will be collected in India, China, and Thailand. In the European Network, only Cameroon will participate in the Case/Control study. In the North

American Network, a case or a control participant is eligible if the participant self-identifies as African American, or Mexican American, or both.

D. Age at Diagnosis

Age at diagnosis of Type 1 diabetes must be less than 35 years. This minimizes the participation of persons with other types of diabetes

E. Current Age

There are no exclusions based on current upper age. However, infants who have not reached their first birthday are ineligible. Individuals less than 12 months are prohibited from the required venous blood collection. Once a child passes their first birthday, they are considered eligible; given all other study criteria are met. The participant's status is "PENDING" until this time.

F. Insulin Use

Insulin use is required within six months of diagnosis. Continuous use of insulin with the exception of short insulin-free periods (no longer than six months) is required. These criteria minimize the participation of persons with other types of diabetes. More than one interruption is permitted if each is within the allotted time period of six months.

G. Medical Conditions

Participants with the following genetic disorders or diseases are excluded. It is important that a medical professional has told the participant that he/she has one of these disorders or diseases before he/she is excluded from participation.

1. *Maturity onset diabetes of youth (MODY):* A heterogeneous clinical entity characterized by early onset and autosomal dominant inheritance. Some are non-insulin dependent, whereas others may require insulin from onset.

2. *Mitochondrial DNA 3243 mutation*: The best-characterized and most common mutation of the mitochondrial gene. It may cause diabetes and deafness.

3. *Type A insulin resistance*: A syndrome characterized by insulin resistance and acanthosis nigricans (and hyperandrogenism in women).

4. *Leprechaunism*: A syndrome of severe insulin resistance.

5. *Rabson-Mendelhall syndrome*: A syndrome of moderate to severe insulin resistance; often associated with dysmorphic features.

6. *Lipoathrophic diabetes*: A heterogeneous group of disorders of lipid storage characterized by lipodystrophy; insulin resistance is a feature of this disorder.

7. *Wolfram's syndrome*: An autosomal recessive, rare, non-autoimmune syndrome characterized by insulin-dependent diabetes due to loss of beta cells, also known as DIDMOAD.

These are all rare medical conditions and are known to be associated with non-classical insulin-dependent diabetes. They represent genetic subtypes of diabetes and are often diagnosed at birth or in early infancy. The presence of any one of these conditions is an exclusion criterion.

H. Previous Participation in Genetic Studies

Participants or immediate family members who have previously participated in genetic studies such as HBDI, BDA-Warren I, SCAND, or in the T1DGC are ineligible for inclusion in the T1DGC. The T1DGC already has genetic information from participants in these studies and does not want to recruit the same participants. Following is a brief description of the studies to be used if participants are unsure if they have participated in one of these studies.

Type 1 Diabetes Genetics Consortium (T1DGC): An international study taking place in Asia-Pacific, Europe, North America, and the United Kingdom. T1DGC will

collect samples for creation of cell lines as well as plasma and serum samples from 2,800 ASP families; 1,600 trio families; 2,050 cases; and 2,050 controls throughout the world.

HBDI (Human Biological Data Interchange): A repository that houses family collections of DNA used in genetic studies. The HBDI repository holds serum samples, immortalized cell lines and DNA from over 500 multiplex families with Type 1 diabetes.

BDA-Warren I: Founded in 1989 and collected DNA samples from over 450 families with children with Type 1 diabetes. These families had to have two or more children with Type 1 diabetes and living parents.

SCAND: Study performed in Scandinavia (Denmark, Sweden, and Norway), which included more than 400 multiplex families (at least two affected individuals other than parent-child pairs) on whom a genome-wide search for Type 1 diabetes susceptibility genes was performed.

III. REQUIRED ELEMENTS ON ELIGIBILITY FORM

There are several questions on the *T1DGC Eligibility Form* that must be answered before a participant can be included in the study. If one such answer is unknown at the time of initial screening, the participant's status is marked "PENDING" until the clinic can follow-up with the appropriate individuals to collect the information. All "PENDING" responses refer to eligibility criteria and must be resolved before the form is forwarded to the Regional Network Center or samples are collected. Participants may need to contact physicians or other family members to obtain information. Table 1 outlines the questions that must be answered for the essential family members in order for a family's eligibility to be determined. Other questions that are non-essential should be followed-up, but forms may be sent to the Regional Network Center when it has become apparent this information will not be found. In addition, for North American trio families, all questions on the *North American Trio Pre-Eligibility Form* must be completed in its entirety.

Table 1. Eligibility Questions for Inclusion in the T1DGC Study

Question Asked	Question # on ASP Proband Form	Question # on ASP Guardian Form	Question # on Trio Proband Form	Question # on Trio Guardian Form	Question # on the Case Form	Question # on the Case Guardian Form	Question # on the Control Form	Question # on the Control Guardian Form
Diagnosis with Type 1 diabetes, Type 2 diabetes or MODY	4	5	4	5	3	4	3	4
Previous participation in a genetic study	3	4	3	4	5	6	5	6
Birth origin, primary ethnic origin	N/A	N/A	N/A	N/A	4	5	4	5
Age of diagnosis	5, 13	7, 14	5	6	6	7	N/A	N/A
Insulin use within first 6 months of diagnosis	6, 14	8, 15	6	7	7	8	N/A	N/A
Continuous use of insulin for 6 months	7, 15	9, 16	7	8	8	9	N/A	N/A
Current age	9, 17	11, 18	9	10	10	11	10	11
Genetic disorders or diseases present	10, 18	12, 19	10	11	11	12	N/A	N/A
Willing to participate	11	13, 20	11	12	12	13	8	9
Biological father living/willing to participate	N/A	N/A	12	13a, 13b	N/A	N/A	N/A	N/A
Biological mother living/willing to participate	N/A	N/A	13	14a, 14b	N/A	N/A	N/A	N/A

IV. ELIGIBILITY COMMITTEE

Clinics may occasionally identify a proband, an affected sibling, or a case with Type 1 diabetes who does not fit the study criteria. For example, the sibling of a proband may not yet require insulin but meets typical autoantibody criteria according to a physician, may have been diagnosed after age 35 or may have stopped using insulin for longer than six months. Other reasons may exist and the clinic staff is responsible for deciding if an application is necessary. The clinic may submit information about this possible "affected" participant to the Eligibility Committee for review and decision about eligibility. In this case, the clinic completes the *T1DGC Application to Eligibility Committee.* (For instructions on completing this form, see Q x Qs in Appendix J.) There is a separate *T1DGC Application to Eligibility Committee* for the Case/Control Study. (For instructions on completing this form, see Q x Qs in Appendix K.)

The clinic FAXes the completed form to the Regional Network Center where a staff member completes a section of the form and FAXes it to the Coordinating Center for data entry. The Coordinating Center sends a copy of the application form and the *T1DGC Eligibility Committee Adjudication Form* (Q x Qs in Appendix L) to each Eligibility Committee member. The Phenotyping Committee operates as the *ad hoc* Eligibility Committee and reviews these cases.

Each member of the Eligibility Committee reviews the application form and completes the *T1DGC Eligibility Committee Adjudication Form*. The completed adjudication form is faxed to the Coordinating Center within two weeks of receipt and responses are compiled. Four of the six members must agree on eligibility in order for a decision to be made. If there is a major discrepancy among the members, a conference call is initiated to discuss the participant's eligibility. The Coordinating Center completes a section of the application and sends the final decision to the Regional Network Center; the network staff notifies the clinic staff. Clinic staff then completes the questions at the end of the *T1DGC Eligibility Form* regarding the Eligibility Committee decision and modifies the question regarding eligibility status from "Pending" to "Yes."

V. ADDITIONAL AFFECTED SIBLINGS

Clinics may identify a family with more than two affected siblings. In this event, the *T1DGC ASP Application for Additional Affected Sibling* (Q x Qs in Appendix M) for each sibling must be completed and sent to the Regional Network Center for approval prior to the sibling's inclusion in the study. This form asks the same information about this affected sibling as is asked about the proband and the affected sibling on the *T1DGC ASP Eligibility Form.* Upon approval, the Regional Network Center notifies the Coordinating Center to create and send additional labels for each additional sibling.

VI. INELIGIBILITY EXPLANATION

When a participant is deemed ineligible, the individual or family may have questions about ineligiblility, their diagnosis or other issues. If a participant inquires about ineligibility, the best answer is "You do not meet the study criteria for a Type 1 diabetic. I am not disagreeing with your doctor's opinion, but you do not meet the criteria for this study. If you have any questions about your diabetes, I will try to help, or you can talk to your physician."

APPENDIX A
NORTH AMERICAN TRIO PRE-ELIGIBILITY FORM
QUESTION BY QUESTION INSTRUCTIONS

These instructions are meant to assist the interviewer and provide answers to any questions from a participant or clinic staff member.

This form is administered to both the biological mother and biological father of the proband to determine pre-eligibility of a trio. Each parent will answer questions about him/herself. The interviewer reads the questions to the participant and marks or records appropriate answers.

The definitions for the low-prevalence trio families are as follows:

Mexican American -- defined as any individual of **Mexican** descent living in North America (US or Canada). The proband does not need to be born in North America. While the primary goal of this collection is to ascertain Mexican American individuals, individuals can be recruited and examined if born in Central America: Belize, Costa Rica, El Salvador, Guatemala, Honduras, Nicaragua, or Panama.

African American -- defined as any individual of **non-Caucasian of African** descent living in North America (US or Canada). This includes (but is not limited to) descent from Egypt and Somalia. The proband does not need to be born in North America. No Caucasians of African descent qualify (e.g., white South African) can be included as trio families due to the sufficient number of Caucasian trios from previous collections.

Information in all capital letters is an instruction to the interviewer and is not read to the participant.

All dates are written as day first, month second, and year third. The day is recorded numerically. If the day is a single-digit number, a "0" is recorded in the first box. The month is written out in its entirety (*e.g.,* January, February). The year is recorded numerically with all four digits of the year included (*e.g.,* 1950).

Question by Question Instructions

The interviewer does not affix the Family ID label until it has been determined that this family meets the pre-eligibility criteria. Once pre-eligibility has been determined, the interviewers affixes the Family ID Label in the box in the upper right hand corner on each page of the form.

The interviewer records the clinic ID for his/her individual clinic. The number is assigned by the Regional Network Center and is recorded on every page of the form.

QUESTIONS 1 – 4 ARE ADDRESSED TO MOTHER OF PROBAND.

1. Interview Date

This is the date the interview takes place. Record the date of the interview in the appropriate boxes.

2. How was this section completed? MARK ALL THAT APPLY.

The interviewer marks all methods used to gather information about the participant. If information is obtained by calling a participant before she comes into the clinic, mark "Phone interview." If the participant comes into the clinic and is interviewed in person, the interviewer marks "Face-to-face interview." The interviewer marks all applicable answers.

3a. How would you describe your race or ethnic origin? IF MORE THAN ONE APPLIES, MARK 'Other.'

This question can be read differently depending on the clinic, either the word "race" or "ethnic origin" may be used due to cultural sensitivity. The interviewer hands (or reads) the participant the cue card containing a list of races (or ethnic origins) to

choose from. The participant responds with her race (or ethnic origin). If the participant indicates that more than one race or ethnic origin applies, or responds with a race (or ethnic origin) other than Mexican American or African American, mark "Other," and stop completing this form, this family is ineligible.

3b. How would you describe your mother's race or ethnic origin? READ CUE CARD AND RECORD PARTICIPANT'S RESPONSES.

This question can be read differently depending on the clinic, either the word "race" or "ethnic origin" may be used due to cultural sensitivity. The interviewer hands (or reads) the participant the cue card containing a list of races (or ethnic origins) to choose from. The participant chooses up to three responses that best describe her mother's race (or ethnic origin). If the participant does not feel that any race (or ethnic origin) describes her mother's race (or ethnic origin), the entire list found in the **Chapter V,** *Interviewing Instructions,* Appendix K, should be shown to the participant and choices should be made from this list. Record the appropriate code(s) in the boxes. At least one set of boxes must be completed. If a participant chooses more than one category, the interviewer asks which race (or ethnic origin) the participant most identifies her mother with and records that choice in the first set of boxes with the word 'Primary' beside it. The use of 810 "North American, no further designation" should be avoided as it does not provide adequate information for the trio collection in terms of race or ethnic origin. The interviewer should make every effort to obtain specific codes regarding race (or ethnic origin) that include: 831 Mexican, 832 Nicaraguan, 833 Salvadoran, 839 Central American, not elsewhere classified (includes Belizean, Costa Rican, Mayan), 811 African American, and 816 Mexican American.

3c. How would you describe your father's race or ethnic origin? READ CUE CARD AND RECORD PARTICIPANT'S RESPONSES.

This question can be read differently depending on the clinic, either the word "race" or "ethnic origin" may be used due to cultural sensitivity. The interviewer hands (or reads) the participant the cue card containing a list of races (or ethnic origins) to choose from. The participant chooses up to three responses that best describe her father's race (or ethnic origin). If the participant does not feel that any race (or ethnic

origin) describes her father's race (or ethnic origin), the entire list found in **Chapter V,** *Interviewing Instructions,* Appendix K, should be shown to the participant and choices should be made from this list. Record the appropriate code(s) in the boxes. At least one set of boxes must be completed. If a participant chooses more than one category, the interviewer asks which race (or ethnic origin) the participant most identifies her father with and records that choice in the first set of boxes with the word 'Primary' beside it. The use of 810 "North American, no further designation" should be avoided as it does not provide adequate information for the trio collection in terms of race or ethnic origin. The interviewer should make every effort to obtain specific codes regarding race (or ethnic origin) that include: 831 Mexican, 832 Nicaraguan, 833 Salvadoran, 839 Central American, not elsewhere classified (includes Belizean, Costa Rican, Mayan), 811 African American, and 816 Mexican American.

4. Interviewer ID

The interviewer records his/her five-digit assigned code in the appropriate boxes after completion of this section of the *T1DGC North American Trio Pre-Eligibility Form.*

QUESTIONS 5 – 8 ARE ADDRESSED TO FATHER OF PROBAND.

5. Interview Date

This is the date the interview takes place. Record the date of the interview in the appropriate boxes.

6. How was this section completed? MARK ALL THAT APPLY.

The interviewer marks all methods used to gather information about the participant. If information is obtained by calling a participant before he comes into the clinic, mark "Phone interview." If the participant comes into the clinic and is interviewed in person, the interviewer marks "Face-to-face interview." The interviewer marks all applicable answers.

7a. How would you describe your race or ethnic origin? IF MORE THAN ONE APPLIES, MARK 'Other.'

This question can be read differently depending on the clinic, either the word "race" or "ethnic origin" may be used due to cultural sensitivity. The interviewer hands (or reads) the participant the cue card containing a list of races (or ethnic origins) to choose from. The participant responds with her race (or ethnic origin). If the participant indicates that more than one race or ethnic origin applies, or responds with a race (or ethnic origin) other than Mexican American or African American, mark "Other," and stop completing this form, this family is ineligible.

7b. How would you describe your mother's race or ethnic origin? READ CUE CARD AND RECORD PARTICIPANT'S RESPONSES.

This question can be read differently depending on the clinic, either the word "race" or "ethnic origin" may be used due to cultural sensitivity. The interviewer hands (or reads) the participant the cue card containing a list of races (or ethnic origins) to choose from. The participant chooses up to three responses that best describe her mother's race (or ethnic origin). If the participant does not feel that any race (or ethnic origin) describes her mother's race (or ethnic origin), the entire list found in the **Chapter V,** *Interviewing Instructions,* Appendix K, should be shown to the participant and choices should be made from this list. Record the appropriate code(s) in the boxes. At least one set of boxes must be completed. If a participant chooses more than one category, the interviewer asks which race (or ethnic origin) the participant most identifies her mother with and records that choice in the first set of boxes with the word 'Primary' beside it. The use of 810 "North American, no further designation" should be avoided as it does not provide adequate information for the trio collection in terms of race or ethnic origin. The interviewer should make every effort to obtain specific codes regarding race (or ethnic origin) that include: 831 Mexican, 832 Nicaraguan, 833 Salvadoran, 839 Central American, not elsewhere classified (includes Belizean, Costa Rican, Mayan), 811 African American, and 816 Mexican American.

7c. How would you describe your father's race or ethnic origin? READ CUE CARD AND RECORD PARTICIPANT'S RESPONSES.

This question can be read differently depending on the clinic, either the word "race" or "ethnic origin" may be used due to cultural sensitivity. The interviewer hands (or reads) the participant the cue card containing a list of races (or ethnic origins) to choose from. The participant chooses up to three responses that best describe her father's race (or ethnic origin). If the participant does not feel that any race (or ethnic origin) describes her father's race (or ethnic origin), the entire list found in **Chapter V,** *Interviewing Instructions,* Appendix K, should be shown to the participant and choices should be made from this list. Record the appropriate code(s) in the boxes. At least one set of boxes must be completed. If a participant chooses more than one category, the interviewer asks which race (or ethnic origin) the participant most identifies her father with and records that choice in the first set of boxes with the word 'Primary' beside it. The use of 810 "North American, no further designation" should be avoided as it does not provide adequate information for the trio collection in terms of race or ethnic origin. The interviewer should make every effort to obtain specific codes regarding race (or ethnic origin) that include: 831 Mexican, 832 Nicaraguan, 833 Salvadoran, 839 Central American, not elsewhere classified (includes Belizean, Costa Rican, Mayan), 811 African American, and 816 Mexican American.

8. Interviewer ID

The interviewer records his/her five-digit assigned code in the appropriate boxes after completion of this section of the *T1DGC North American Trio Pre-Eligibility Form.*

INTERVIEWER COMPLETED

9. Does the trio meet the eligibility criteria?

The interviewer reviews the questions to ensure this family meets pre-eligibility requirements. The interviewer marks "Yes" if this family meets all pre-eligibility requirements. The mother and father must both self-identify as African American, **or** the mother and father must both identify as Mexican American, **or** one parent must identify as African American and the other parent as Mexican American. The

interviewer marks “No” if at one point during either interview he/she came to a “STOP – INELIGIBLE” statement.

10. ID of person editing this form.

This is not completed until a clinic staff member reviews the form to ensure completion and accuracy. The person editing and reviewing the form records his/her five-digit assigned code in the appropriate boxes.

APPENDIX B
ASP ELIGIBILITY FORM (PROBAND):
QUESTION BY QUESTION INSTRUCTIONS

These instructions are meant to assist the interviewer and to provide answers to any questions from a participant or clinic staff member.

This form is administered to the proband. The proband is the first child diagnosed with Type 1 diabetes in the family. **This form is used if the proband is of legal age to give consent and it is determined by clinic staff that the proband is able to understand and answer all of the questions.** Only the proband answers questions; however, the legal guardians of the proband can be present at the interview. The interviewer reads the questions to the proband and marks or records appropriate answers.

Information in all capital letters is an instruction to the interviewer and is not read to the participant.

If at any point during the screening process, the interviewer marks a shaded box, the prospective family is deemed ineligible.

For eligible participants, please complete all parts of the form. Note that certain individual items may be marked “Don’t know” and with an asterisk. In these cases, continue completing the form and contact the appropriate individuals within 10 days in order to collect information not known at the time of the initial screening. The participant may need to contact his/her physician or other family members in order to obtain information. All “PENDING” responses refer to eligibility criteria and must be resolved before the form is forwarded to the Regional Network Center. Items without a “PENDING” status should be followed-up, but forms should be forwarded to the Regional Network Center when it has become apparent that this information will not be found. There may also be situations in which a participant diagnosed with Type 1

diabetes does not meet the Type 1 Diabetes Genetics Consortium (T1DGC) criteria for Type 1 diabetes. In this case the interviewer completes a *T1DGC Application to Eligibility Committee*.

All dates are written as day first, month second, and year third. The day is recorded numerically. If the day is a single-digit number, a "0" is recorded in the first box. The month is written out in its entirety (*e.g.,* January, February). The year is recorded numerically, with all four digits of the year included (*e.g.,* 1950). All single digit numerical responses are recorded with a leading "0" (*e.g.,* if participant is 5 years old, record "05").

Question by Question Instructions

The interviewer does not affix the Family ID Label until it has been determined that this family is eligible or the eligibility status is "PENDING." Once eligibility has been determined, the interviewer affixes the Family ID Label in the box shown in the upper right hand corner. A label is affixed on every page.

The interviewer records the clinic ID for his/her individual clinic. This number is assigned by the Regional Network Center and it is recorded on every page.

1. Interview date

This is the date the interview takes place. Record the date of the interview in the appropriate boxes. For some clinics, the information on the form is abstracted from other sources and transferred onto this form. In this case, the interviewer records the date the information is abstracted and the form is completed.

2. How was this form completed? MARK ALL THAT APPLY.

The interviewer marks all sources from which information is gathered about the participants. If information is obtained by calling a participant before he/she comes into the clinic, mark "Phone interview." If the participant comes into the clinic and is interviewed in person, the interviewer marks "Face-to-face interview." If information is

abstracted from other sources (*e.g.,* other forms, pulling medical records), the interviewer marks "From existing records." The interviewer marks all applicable answers.

3. Have you or any of your immediate family members previously participated in any of the following genetic studies? READ/SHOW PARTICIPANT CUE CARD.

The interviewer reads or shows the participant the cue card that includes the list of previously conducted genetic studies the T1DGC has genetic data from. The participant responds "Yes" if he/she or member(s) of their immediate family (*i.e.,* the participant, the participant's full biological siblings and/or the participant's biological parents) has participated in any of the genetic studies listed on the card. If the participant answers "Yes," stop completing this form; this family is ineligible. If the participant does not know this information, the interviewer marks "Don't know" and continues completing the form. This family's eligibility is "PENDING." If the participant answers "No," the interviewer continues completing the form.

Questions 4-11 relate to the proband. If in answering any of these questions it is determined that this person is not eligible for participation in this study, the interviewer asks the participant if he/she has two siblings diagnosed with Type 1 diabetes and these questions are completed for that child. It is required for a family to have two affected siblings and for both of these siblings to participate in this study.

4. Have you been diagnosed with Type 1 diabetes?

The participant answers "Yes" if he/she has been diagnosed with Type 1 diabetes, Insulin Dependent diabetes, Youth Onset diabetes, or Juvenile Onset diabetes. If the participant answers "No," stop completing this form; this participant is ineligible.

5. At what age were you diagnosed with Type 1 diabetes?

The participant gives the age he/she was diagnosed with Type 1 diabetes. If he/she cannot recall their age, an attempt is made to guess, or tell the interviewer in what year they were diagnosed. The age of diagnosis is calculated from the year of diagnosis. If the age of diagnosis is 35 years or older, stop completing this form; this participant is ineligible. The participant's age is recorded in years. If the participant was less than 1 year old, record "00."

6. Did you use insulin within six months of being diagnosed?

The participant answers "Yes" if insulin was used at any point during the first six months after he/she was diagnosed with Type 1 diabetes. This excludes nasal or inhaled insulin. If the participant answers "Yes," skip to Question 7. If the participant answers "No," the interviewer continues to Question 6a.

6a. Is there any other information to suggest you have Type 1 (insulin dependent) diabetes?

If the participant answers "Yes," the interviewer applies to the Eligibility Committee who reviews the information submitted on possible affected participants (*e.g.,* the participant was diagnosed early in the natural history via autoantibodies and/or OGTT and thus is not on insulin). The interviewer completes the *T1DGC Application to Eligibility Committee* and sends it to the Regional Network Center. The interviewer continues completing the form. This participant's eligibility is "PENDING." If the participant answers "No," stop completing this form; this participant is ineligible.

7. Once you started using insulin, did you ever stop using insulin for a period of six months or more for reasons other than a pancreas transplant?

The participant answers "Yes" if insulin use was started but discontinued for 6 months or longer. More than one interruption is permitted if each is within the allotted time frame. If a participant has had a pancreas transplant and has stopped insulin use for more than 6 months because of the transplant, they are not excluded from participating in the T1DGC. If the participant answers "Yes," stop completing this form;

this participant is ineligible. The participant answers "No" if insulin use was never disrupted after starting on insulin, or if any insulin was stopped for periods within 6 months. If the participant has not been diagnosed for six months, the "Not applicable" box is marked. However, this does not make the participant ineligible, continue with the form.

8. What is your date of birth?

Record the date of birth in the appropriate boxes. For some clinics, this information is considered an identifier and thus cannot be collected. In this case, the interviewer marks the "Can not collect" box, but must answer Question 9. If clinics are able to collect a portion of the date of birth, the year is recorded in the appropriate boxes.

9. What is your current age?

The participant responds by giving his/her current age at the time of the interview. If the information is abstracted from other sources and transferred onto this form, the interviewer determines the participant's current age. The participant's age is recorded in years.

10. Do you have a specific genetic disorder or disease that caused your diabetes? This would include maturity onset diabetes of youth (MODY). IF YES OR DON'T KNOW, READ/SHOW PARTICIPANT CUE CARD.

The participant answers "Yes" if he/she has been diagnosed with another genetic disease that is known to be associated with non-classical insulin dependent diabetes. If the participant answers "Yes" or "Don't know" show or read the participant the cue card listing the genetic disorders and diseases that exclude a person from participating in the T1DGC. If the participant answers "Yes," stop completing this form; this participant is ineligible. If the participant answers "No," continue completing the form. If the participant still does not know, mark the "Don't know" box and continue completing the form. This participant's eligibility is "PENDING."

11. Are you willing to participate in this study? READ BRIEF DESCRIPTION OF THE STUDY TO PARTICIPANT FROM CUE CARD.

The participant now has the option to participate in the T1DGC. Participant involvement in the study is discussed. The interviewer reads the cue card containing a brief description of the study. The participant answers "Yes" if he/she is interested in learning more about the study and participating. If the participant answers "No," stop completing this form; this participant is ineligible. If the participant has already given his/her consent to participate in the study prior to completing the eligibility form, mark the "Has signed consent" box and continue with the form. If the participant answers "Don't know," continue completing the form and follow-up at a later date for a definitive answer. This participant's eligibility is "PENDING."

Questions 12-18 relate to the proband's sibling who was next diagnosed with Type 1 diabetes. If in gathering information it is determined that this sibling is not eligible for participation in this study, the interviewer asks the proband if there is another sibling diagnosed with Type 1 diabetes. The questions are then completed using this affected sibling. The affected sibling must have the same biological mother and same biological father as the proband.

These questions refer to your sibling who was next diagnosed with Type 1 diabetes in your family.

12. Do you have a living full brother or sister who is not your identical twin who has been diagnosed with Type 1 diabetes? Full brothers and sisters are those that have the same biological mother and same biological father.

The participant answers "Yes" if he/she has a full brother or sister diagnosed with Type 1 diabetes, Insulin Dependent diabetes, Youth Onset diabetes, or Juvenile Onset diabetes. This sibling cannot be the proband's identical twin, however a fraternal twin is eligible to participate. Only one individual of an identical twin pair may participate. If the participant is unsure if their twin is fraternal or identical, both should participate. If the

participant answers “No” or “Don’t know,” stop completing this form; this family is ineligible.

13. At what age was your brother/sister diagnosed with Type 1 diabetes?

The participant gives his/her brother/sister’s age when diagnosed with Type 1 diabetes. If they cannot recall their sibling’s age, an attempt is made to guess or tell the interviewer in what year their sibling was diagnosed. The age of diagnosis is calculated using the year of diagnosis. If the participant has no recollection of their sibling’s age at diagnosis or the year of diagnosis, mark the “Don’t know” box, continue completing the form. This participant’s eligibility is “PENDING.” If the affected sibling’s age of diagnosis is 35 years or older, stop completing this form; this participant is ineligible. The sibling’s age is recorded in years. If the sibling was less than 1 year old, record “00.”

14. Did your brother/sister use insulin within six months of being diagnosed?

The participant answers “Yes” if insulin was used at any point during the first six months after their brother/sister was diagnosed with Type 1 diabetes. This excludes nasal or inhaled insulin. If the participant answers “Yes,” skip to Question 15. If the participant answers “No,” the interviewer continues to Question 14a. If the participant does not know this information, mark the “Don’t know” box and continue completing the form. This participant’s eligibility is “PENDING.”

14a. Is there any other information to suggest that your brother/sister has Type 1 (insulin dependent) diabetes?

If the participant answers “Yes,” the interviewer applies to the Eligibility Committee who reviews information submitted on possible affected participants (*e.g.,* the participant was diagnosed early in the natural history via autoantibodies and/or OGTT and thus is not on insulin). The interviewer completes the *T1DGC Application to Eligibility Committee* and sends it to the Regional Network Center. The interviewer continues completing the form. This participant’s eligibility is “PENDING.” If the participant answers “No,” stop completing this form; this participant is ineligible.

15. Once your brother/sister started using insulin, did he/she ever stop using insulin for a period of six months or more for reasons other than a pancreas transplant?

The participant answers "Yes" if insulin use was started but discontinued for six months or longer. More than one interruption is permitted as long as each is within the allotted time frame. If a participant has had a pancreas transplant and has stopped insulin use for more than six months because of the transplant, they are not excluded from participating in the T1DGC. If the participant answers "Yes," stop completing this form; this participant is ineligible. The participant answers "No" if insulin use was never disrupted after starting on insulin, or if any insulin was stopped for periods within 6 months. If the participant has not been diagnosed for six months, the "Not applicable" box is marked. However, this does not make this participant ineligible, continue with the form. If the participant answers "Don't know," continue with the form; this participant's eligibility is "PENDING."

16. What is your brother/sister's date of birth?

Record the date of birth in the appropriate boxes. For some clinics, this information is considered an identifier and thus cannot be collected. In this case, the interviewer marks the "Can not collect" box, but must answer Question 17. If clinics are able to collect a portion of the date of birth, the year is recorded in the appropriate boxes. If the participant doesn't know this information, mark the "Don't know" box and continue with the form.

17. What is your brother/sister's current age? CHILDREN LESS THAN 12 MONTHS CAN BE INCLUDED AFTER FIRST BIRTHDAY.

The participant responds by giving the current age of their sibling at the time of the interview. If the information is abstracted from other sources and transferred onto this form, the interviewer determines the sibling's current age. The sibling's age is recorded in years. If the sibling is less than 12 months old, mark the "Less than 12 months" box and continue completing the form. This participant's eligibility is "PENDING;" however, the participant's family is re-contacted after the sibling has had

his/her first birthday. If the participant does not know their sibling's current age mark the "Don't know" box and continue with the form.

18. Does your brother/sister have a specific genetic disorder or disease that caused his/her diabetes? This would include maturity onset diabetes of youth (MODY). IF YES OR DON'T KNOW, READ/SHOW PARTICIPANT CUE CARD.

The participant answers "Yes" if their brother/sister has been diagnosed with another genetic disease that is known to be associated with non-classical insulin dependent diabetes. If the participant answers "Yes" or "Don't know," show or read the participant the cue card listing the genetic disorders and diseases that exclude a person from participating in the T1DGC. If the participant answers "Yes," stop completing this form; this participant is ineligible. If the participant answers "No," continue completing the form. If the participant still does not know, mark the "Don't know" box and continue completing the form. This participant's eligibility is "PENDING."

Questions 19-20 relate to the biological parents of both siblings described above. It is not required for the biological parents to participate in this study.

19. Is your biological father living?

The participant answers "Yes" if he/she knows their biological father is living. If the participant answers "No" or "Don't know," continue with the form.

20. Is your biological mother living?

The participant answers "Yes" if he/she knows their biological mother is living. If the participant answers "No" or "Don't know," continue with this form.

Questions 21-23 relate to two unaffected full siblings of the proband and affected sibling described above. These are the eldest available siblings not diagnosed with any form of diabetes. If in gathering information it is determined that one or both of these siblings are not eligible or available for participation in this study, the interviewer asks the participant if there is another sibling not diagnosed with

any form of diabetes. The questions are then completed using this unaffected sibling. The unaffected siblings described below must have the same biological mother and same biological father as both the proband and the affected sibling. It is not required for a family to have any unaffected siblings, or for any unaffected siblings to participate in this study.

These final questions refer to the two oldest siblings in your family who have not been diagnosed with any type of diabetes.

21. Do you have any living full brother/sisters who do not have diabetes? This includes Type 1, Type 2 and MODY. Full brothers and sisters are those that have the same biological mother and same biological father.

The participant answers "Yes" if he/she has at least one brother or sister without diabetes who has the same biological mother and same biological father. These siblings cannot have been diagnosed with any form of diabetes including, but not limited to, Type 1 diabetes, Type 2 diabetes, and MODY. If the participant answers "No" or "Don't know," skip to Question 24.

22. What is the current age of your oldest brother/sister who does not have diabetes? CHILDREN LESS THAN 12 MONTHS CAN BE INCLUDED AFTER FIRST BIRTHDAY.

The participant responds by giving the age of the eldest available sibling not diagnosed with any form of diabetes at the time of the interview. If the eldest sibling is not available, the next eldest available unaffected sibling is used. If the information is abstracted from other sources and transferred onto this form, the interviewer determines the sibling's current age. The sibling's age is recorded in years. If the sibling is less than 12 months old, mark the "Less than 12 months" box and skip to Question 24; this participant's eligibility is "PENDING." However, since unaffected siblings are not necessary for the minimum family requirement, this family may still be eligible. This family may be re-contacted after the sibling's first birthday. However, the clinic continues collecting data and lab samples on members of the family over 12 months

old. The family's status is **not** "PENDING." If the participant does not know the sibling's current age, mark the "Don't know" box and continue with the form.

23. What is the current age of your next oldest brother/sister who does not have diabetes? CHILDREN LESS THAN 12 MONTHS CAN BE INCLUDED AFTER FIRST BIRTHDAY.

The participant responds by giving the age of their next eldest available sibling not diagnosed with any form of diabetes at the time of the interview. If the information is abstracted from other sources and transferred onto this form, the interviewer determines the sibling's current age. The sibling's age is recorded in years. If the sibling is less than 12 months old, mark the "Less than 12 months" box. This participant's eligibility is "PENDING." However, since unaffected siblings are not necessary for the minimum family requirement, this family may still be eligible. If an unaffected sibling is less than 12 months old, this family may be re-contacted after the sibling's first birthday. However, the clinic continues collecting data and lab samples on members of the family over 12 months old. This family's status is **not** "PENDING." If the participant does not have another sibling not diagnosed with any form of diabetes, mark the "Don't have one" box. If the participant does not know his/her sibling's current age mark the "Don't know" box and continue with the form.

Questions 24-29 are directed toward clinic staff and are completed as the activity occurs (*i.e.,* after interviewing, after editing, and after receiving the *T1DGC Application to Eligibility Committee*).

INTERVIEWER COMPLETED

24. Is this family eligible to participate in this study?

The interviewer reviews the questions to ensure this family meets eligibility requirements. The interviewer marks "Yes" if this family meets all eligibility requirements, and skips to Question 26. This family must consist at minimum of two affected siblings. The biological father, mother, and up to two unaffected siblings are

included if possible. The interviewer marks “No” if at one point during the interview he/she came to a “STOP-INELIGIBLE” statement, and skips to Question 26. The interviewer marks “PENDING” if one or more questions regarding the proband or affected sibling were marked as “Don’t know,” or the interviewer is in the process of applying to the Eligibility Committee. If “PENDING” is marked, the interviewer re-contacts the appropriate individuals within 10 days in order to determine eligibility or waits until a decision is made by the Eligibility Committee.

25. Is an application to the Eligibility Committee required?

The interviewer marks “Yes” if one of the participants appears to have Type 1 diabetes, but does not meet the T1DGC definition of diabetes. The interviewer completes the *T1DGC Application to Eligibility Committee* and sends it to the Regional Network Center. The interviewer continues completing the form. If the interviewer does not need to apply to the Eligibility Committee, the interviewer marks “No” and skips to Question 26.

25a. Is this for the proband, affected sibling or both?

The interviewer marks “Proband” or “Affected Sibling” if the *T1DGC Application to Eligibility Committee* is completed for that specific individual. The interviewer marks “Both” if the interviewer completes two *T1DGC Application to Eligibility Committee* forms.

26. Interviewer ID

The interviewer records his/her five-digit assigned code in the appropriate boxes after completion of the *T1DGC ASP Eligibility Form*.

27. ID of person editing

This is not completed until a clinic staff member reviews the form to ensure completion and accuracy. The person editing and reviewing the form records his/her five-digit assigned code in the appropriate boxes.

COMPLETED ONLY IF APPLICATION TO ELIGIBILITY COMMITTEE REQUIRED.

28. Did the Eligibility Committee approve inclusion in the study?

The interviewer completes this section **only** if a *T1DGC Application to Eligibility Committee* was sent to and a decision was made by the Eligibility Committee. The interviewer marks "Yes" if the Eligibility Committee decided the participant(s) is (are) eligible to participate, or marks "No" if the Eligibility Committee decided this participant is ineligible to participate in the T1DGC. If the interviewer marks "No," the interviewer skips to Question 29. If the application was completed for both the proband and the affected sibling, the interviewer marks "Yes" if approval is received on one or both of the participants.

28a. Was approval received for the proband, affected sibling or both?

The interviewer marks "Proband" if the *T1DGC Application to Eligibility Committee* is approved for the proband. The interviewer marks "Affected Sibling" if the *T1DGC Application to Eligibility Committee* is approved for the affected sibling. The interviewer marks "Both" if the interviewer completed two *T1DGC Application to Eligibility Committee* forms and each of these applications is approved.

29. Date Eligibility Committee decision received by clinic

The interviewer records the date the application is returned to the clinic with a decision regarding the eligibility of the proband and/or the affected sibling. Once information is received regarding the eligibility status of the participant(s), the clinic corrects Question 24 regarding eligibility status.

APPENDIX C
ASP ELIGIBILITY FORM (GUARDIAN):
QUESTION BY QUESTION INSTRUCTIONS

These instructions are meant to assist the interviewer and to provide answers to any questions from a participant or clinic staff member.

This form is administered to a guardian (*i.e.,* biological mother, biological father or other legal guardian) of the proband. The proband is the first child diagnosed with Type 1 diabetes in the family. **This form is used if the proband is under the legal age to give consent and it is determined by clinic staff that the proband is unable to understand and answer all of the questions.** Only one guardian answers the questions; however, more than one can be present at the interview. The interviewer reads the questions to the guardian and marks or records appropriate answers.

Information in all capital letters is an instruction to the interviewer and is not read to the participant.

If at any point during the screening process, the interviewer marks a shaded box, the prospective family is deemed ineligible.

For eligible participants, please complete all parts of the form. Note that certain individual items may be marked "Don't know" and with an asterisk. In these cases, continue completing the form and contact the appropriate individuals within 10 days in order to collect information not known at the time of the initial screening. The participant may need to contact his/her physician or other family members in order to obtain information. All "PENDING" responses refer to eligibility criteria and must be resolved before the form is forwarded to the Regional Network Center. Items without a "PENDING" status should be followed-up, but forms should be forwarded to the Regional Network Center when it has become apparent that this information will not be found. There may also be situations in which a participant diagnosed with Type 1

diabetes does not meet the Type 1 Diabetes Genetics Consortium (T1DGC) criteria for Type 1 diabetes. In this case the interviewer completes a *T1DGC Application to Eligibility Committee*.

All dates are written as day first, month second, and year third. The day is recorded numerically. If the day is a single-digit number, a "0" is recorded in the first box. The month is written out in its entirety (*e.g.,* January, February). The year is recorded numerically, with all four digits of the year included (*e.g.,* 1950). All single digit numerical responses are recorded with a leading "0" (*e.g.,* if participant is 5 years old, record "05").

Question by Question Instructions

The interviewer does not affix the Family ID Label until it has been determined that this family is eligible or the eligibility status is "PENDING." Once eligibility has been determined, the interviewer affixes the Family ID Label in the box shown in the upper right hand corner. A label is affixed on every page.

The interviewer records the clinic ID for his/her individual clinic. This number is assigned by the Regional Network Center and it is recorded on every page.

1. Interview date

This is the date the interview takes place. Record the date of the interview in the appropriate boxes. For some clinics, the information on the form is abstracted from other sources and transferred onto this form. In this case, the interviewer records the date the information is abstracted and the form is completed.

2. How was this form completed? MARK ALL THAT APPLY.

The interviewer marks all sources from which information is gathered about the participants. If information is obtained by calling a participant before he/she comes into the clinic, mark "Phone interview." If the participant comes into the clinic and is interviewed in person, the interviewer marks "Face-to-face interview." If information is

abstracted from other sources (*e.g.,* other forms, pulling medical records), the interviewer marks "From existing records." The interviewer marks all applicable answers.

3. Who is completing this form? ONLY ONE GUARDIAN IS INTERVIEWED.

The interviewer determines the relationship the guardian has with the proband and affected sibling. The interviewer may ask the participant his/her relationship to the children, if it is not already known. The interviewer marks "Biological Father" if the man completing the interview believes himself to be the biological father of both the proband and the affected sibling. The interviewer marks "Biological Mother" if the woman completing the interview gave birth to both the proband and the affected sibling. The interviewer marks "Other Guardian" if the person completing this form is neither biological parent of the proband and the affected sibling. The interviewer should be aware of the relationship the guardian has to the children while administering this questionnaire. Versions of questions may differ based upon the guardian's relationship to the proband and affected sibling.

4. Have you or any of your immediate family members previously participated in any of the following genetic studies? READ/SHOW PARTICIPANT CUE CARD.

The interviewer reads or shows the participant the cue card that includes the list of previously conducted genetic studies the T1DGC has genetic data from. The participant responds "Yes" if he/she or member(s) of their immediate family (*i.e.,* the proband, the proband's full biological siblings and/or the proband's biological parents) has participated in any of the genetic studies listed on the card. If the participant answers "Yes," stop completing this form; this family is ineligible. If the participant does not know this information, the interviewer marks "Don't know" and continues completing the form. This family's eligibility is "PENDING." If the participant answers "No," the interviewer continues completing the form.

5. Have two or more of your children who are not identical twins been diagnosed with Type 1 diabetes?

The participant answers "Yes" if two or more of his/her children have been diagnosed with Type 1 diabetes, Insulin Dependent diabetes, Youth Onset diabetes, or Juvenile Onset diabetes. These children cannot be identical twins; however fraternal twins are eligible to participate. Only one individual of an identical twin pair may participate. If the participant is unsure if their twin is fraternal or identical, both should participate. If the participant answers "No," stop completing this form; this family is ineligible.

6. Do both of these children have the same parents (that is, the same biological mother and same biological father)?

The participant answers "Yes" if two or more of the children with Type 1 diabetes have the same biological mother and the same biological father. If the participant answers "No," stop completing this form; this family is ineligible.

Questions 7-13 relate to the proband. The proband is the first child diagnosed with Type 1 diabetes. If in answering any of these questions it is determined that this child is not eligible for participation in this study, the interviewer asks the guardian if there is another child diagnosed with Type 1 diabetes and these questions are completed for that child. It is required for a family to have two affected siblings and for both of these siblings to participate in this study.

The next questions refer to the first child diagnosed with Type 1 diabetes in your family.

7. How old was this child when he/she was diagnosed with Type 1 diabetes?

The participant gives the age the proband was diagnosed with Type 1 diabetes. If he/she cannot recall the child's age, an attempt is made to guess, or tell the interviewer in what year the child was diagnosed. The age of diagnosis is calculated from the year of diagnosis. If the age of diagnosis is 35 years or older, stop completing

this form; this participant is ineligible. The child's age is recorded in years. If the child was less than 1 year old, record "00."

8. Did this child use insulin within six months of being diagnosed?

The participant answers "Yes" if insulin was used at any point during the first six months after the proband was diagnosed with Type 1 diabetes. This excludes nasal or inhaled insulin. If the participant answers "Yes," skip to Question 9. If the participant answers "No," the interviewer continues to Question 8a.

8a. Is there any other information to suggest that this child has Type 1 (insulin dependent) diabetes?

If the participant answers "Yes," the interviewer applies to the Eligibility Committee who reviews the information submitted on possible affected participants (*e.g.,* the participant was diagnosed early in the natural history via autoantibodies and/or OGTT and thus is not on insulin). The interviewer completes the *T1DGC Application to Eligibility Committee* and sends it to the Regional Network Center. The interviewer continues completing the form. This participant's eligibility is "PENDING." If the participant answers "No," stop completing this form; this participant is ineligible.

9. Once this child started using insulin, did he/she ever stop using insulin for a period of six months or more for reasons other than a pancreas transplant?

The participant answers "Yes" if the proband's insulin use was started but discontinued for six months or longer. More than one interruption is permitted if each is within the allotted time frame. If the proband has had a pancreas transplant and has stopped using insulin for more than six months because of the transplant, they are not excluded from participating in the T1DGC. If the participant answers "Yes," stop completing this form; this participant is ineligible. The participant answers "No" if insulin use was never disrupted after starting on insulin, or if any insulin was stopped for periods within six months. If the participant has not been diagnosed for six months, the "Not applicable" box is marked. However, this does not make this participant ineligible, continue with the form.

10. What is this child's date of birth?

Record the date of birth in the appropriate boxes. For some clinics, this information is considered an identifier and thus cannot be collected. In this case, the interviewer marks the "Can not collect" box, but must answer Question 11. If clinics are able to collect a portion of the date of birth, the year is recorded in the appropriate boxes.

11. What is this child's current age? CHILDREN LESS THAN 12 MONTHS CAN BE INCLUDED AFTER FIRST BIRTHDAY.

The participant responds by giving the current age of the proband at the time of the interview. If the information is abstracted from other sources and transferred onto this form, the interviewer determines the proband's current age. The proband's age is recorded in years. If the child is less than 12 months old, mark the "Less than 12 months" box and continue completing this form. This participant's eligibility is "PENDING." However, the child's family is re-contacted after the child has had his/her first birthday.

12. Does this child have a specific genetic disorder or disease that caused his/her diabetes? This would include maturity onset diabetes of youth (MODY). IF YES OR DON'T KNOW, READ/SHOW PARTICIPANT CUE CARD.

The participant answers "Yes" if the proband has been diagnosed with another genetic disease that is known to be associated with non-classical insulin dependent diabetes. If the participant answers "Yes" or "Don't know," show or read the participant the cue card listing the genetic disorders and diseases that exclude a person from participating in the T1DGC. If the participant answers "Yes," stop completing this form; this participant is ineligible. If the participant answers "No," continue completing the form. If the participant still does not know, mark the "Don't know" box and continue completing the form. This participant's eligibility is "PENDING."

13. Are you willing to have this child participate in this study? READ BRIEF DESCRIPTION OF THE STUDY TO PARTICIPANT FROM CUE CARD.

The participant now has the option to allow this child to participate in the T1DGC. Participant involvement in the study is discussed. The interviewer reads the cue card containing a brief description of the study. The participant answers "Yes" if he/she is interested in learning more about the study and allowing this child to participate. If the participant answers "No," stop completing this form; this participant is ineligible. If the participant has already given their consent for this child to participate in the study prior to completing the eligibility form, mark the "Has signed consent" box and continue with the form. If the participant answers "Don't know," continue completing the form and follow-up at a later date for a definitive answer. This participant's eligibility is "PENDING."

Questions 14-20 relate to the second child diagnosed with Type 1 diabetes. If in gathering information it is determined that this child is not eligible for participation in this study, the interviewer asks the guardian if there is another child diagnosed with Type 1 diabetes. The questions are then completed using this affected sibling. The affected sibling must have the same biological mother and same biological father as the proband.

The next questions refer to the second child diagnosed with Type 1 diabetes in your family.

14. How old was this child when he/she was diagnosed with Type 1 diabetes?

The participant gives the age of the affected sibling when diagnosed with Type 1 diabetes. If they cannot recall the child's age, an attempt is made to guess or tell the interviewer in what year the child was diagnosed. The age of diagnosis is calculated using the year of diagnosis. If the child's age of diagnosis is 35 years or older, stop completing this form; this participant is ineligible. The child's age is recorded in years. If the child was less than 1 year old, record "00."

15. Did this child use insulin within six months of being diagnosed?

The participant answers "Yes" if insulin was used at any point during the first six months after the child was diagnosed with Type 1 diabetes. This excludes nasal or inhaled insulin. If the participant answers "Yes," skip to Question 16. If the participant answers "No," the interviewer continues to Question 15a.

15a. Is there any other information to suggest that this child has Type 1 (insulin dependent) diabetes?

If the participant answers "Yes," the interviewer applies to the Eligibility Committee who reviews information submitted on possible affected participants (*e.g.,* the participant was diagnosed early in the natural history via autoantibodies and/or OGTT and thus is not on insulin). The interviewer completes the *T1DGC Application to Eligibility Committee* and sends it to the Regional Network Center. The interviewer continues completing the form. This participant's eligibility is "PENDING." If the participant answers "No," stop completing this form; this participant is ineligible.

16. Once this child started using insulin, did he/she ever stop using insulin for a period of six months or more for reasons other than a pancreas transplant?

The participant answers "Yes" if the affected sibling's insulin use was started but discontinued for six months or longer. More than one interruption is permitted as long as each is within the allotted time frame. If the affected sibling has had a pancreas transplant and has stopped using insulin for more than six months because of the transplant, they are not excluded from participating in the T1DGC. If the participant answers "Yes," stop completing this form; this participant is ineligible. The participant answers "No" if insulin use was never disrupted after starting on insulin, or if any insulin was stopped for periods within six months. If the participant has not been diagnosed for six months, the "Not applicable" box is marked. However, this does not make this participant ineligible, continue with the form.

17. What is this child's date of birth?

Record the date of birth in the appropriate boxes. For some clinics, this information is considered an identifier and thus cannot be collected. In this case, the interviewer marks the "Can not collect" box, but must answer Question 18. If clinics are able to collect a portion of the date of birth, the year is recorded in the appropriate boxes.

18. What is this child's current age? CHILDREN LESS THAN 12 MONTHS CAN BE INCLUDED AFTER FIRST BIRTHDAY.

The participant responds by giving the current age of the affected sibling at the time of the interview. If the information is abstracted from other sources and transferred onto this form, the interviewer determines the affected sibling's current age. The affected sibling's age is recorded in years. If the child is less than 12 months old, mark the "Less than 12 months" box and continue completing the form. This participant's eligibility is "PENDING." However, the child's family is re-contacted after the child has had his/her first birthday.

19. Does this child have a specific genetic disorder or disease that caused his/her diabetes? This would include maturity onset diabetes of youth (MODY). IF YES OR DON'T KNOW, READ/SHOW PARTICIPANT CUE CARD.

The participant answers "Yes" if the affected sibling has been diagnosed with another genetic disease that is known to be associated with non-classical insulin dependent diabetes. If the participant answers "Yes" or "Don't know," show or read the participant the cue card listing the genetic disorders and diseases that exclude a person from participating in the T1DGC. If the participant answers "Yes," stop completing this form; this participant is ineligible. If the participant answers "No," continue completing the form. If the participant still does not know, mark the "Don't know" box and continue completing the form. This participant's eligibility is "PENDING."

20. Are you willing to have this child participate in this study?

The participant now has the option to allow this child to participate in the T1DGC. Participant involvement in the study is discussed. The interviewer reads the cue card containing a brief description of the study. The participant answers "Yes" if he/she is interested in learning more about the study and allowing ths child to participate. If the participant answers "No," stop completing this form; this participant is ineligible. If the participant has already given their consent for this child to participate in the study prior to completing the eligibility form, mark the "Has signed consent" box and continue with the form. If the participant answers "Don't know," continue completing the form and follow-up at a later date for a definitive answer. This participant's eligibility is "PENDING."

Questions 21-22 relate to the biological parents of both children described above. There are two versions of each question depending on who is completing the interview. Be sure to ask the participant the correct version of the question. It is not required for the biological parents to participate in this study.

IF BIOLOGICAL FATHER COMPLETING FORM: 21a. Are you willing to participate in this study?

If the biological father is completing the form, this question is asked of the participant. He now has the option to participate in the T1DGC. Participant involvement in the study is discussed. The interviewer reads the cue card containing a brief description of the study. The father answers "Yes" if he is interested in learning more about the study and participating in the T1DGC. If he answers "No," continue with this form. If he has already given his consent to participate in the study prior to completing the eligibility form, mark the "Has signed consent" box and continue with the form. If the father answers "Don't know," continue completing the form and follow-up at a later date for a definitive answer.

IF BIOLOGICAL MOTHER OR OTHER GUARDIAN COMPLETING FORM: 21b. Is the biological father of these children living?

If the biological mother or other guardian is completing the form, this question is asked of the participant. The participant answers "Yes" if he/she knows the biological father of the children described above is living. If the participant answers "No" or "Don't know," continue with the form.

IF BIOLOGICAL MOTHER COMPLETING FORM: 22a. Are you willing to participate in this study?

If the biological mother is completing the form, this question is asked of the participant. She now has the option to participate in the T1DGC. Participant involvement in the study is discussed. The interviewer reads the cue card containing a brief description of the study. The mother answers "Yes" if she is interested in learning more about the study and participating in the T1DGC. If she answers "No," continue with this form. If she has already given her consent to participate in the study prior to completing the eligibility form, mark the "Has signed consent" box and continue with the form. If the mother answers "Don't know," continue completing the form and follow-up at a later date for a definitive answer.

IF BIOLOGICAL FATHER OR OTHER GUARDIAN COMPLETING FORM: 22b. Is the biological mother of these children living?

If the biological father or other guardian is completing the form, this question is asked of the participant. The participant answers "Yes" if he/she knows the biological mother of the children described above is living. If the participant answers "No" or "Don't know," continue with the form.

Questions 23-27 relate to two unaffected full siblings of the children described above. These are the eldest available siblings not diagnosed with any form of diabetes. If in gathering information it is determined that one or both of these siblings are not eligible or available for participation in this study, the interviewer asks the participant if there is another sibling not diagnosed with any form of

diabetes. The questions are then completed using this unaffected child. The unaffected siblings described below must have the same biological mother and same biological father as both the proband and the affected sibling. It is not required for a family to have any unaffected siblings, or for any unaffected siblings to participate in this study.

These final questions refer to the two oldest children in your family who have not been diagnosed with any type of diabetes.

23. Do these children with diabetes have a full brother or sister who does not have diabetes? This includes Type 1, Type 2, and MODY. Full brothers and sisters are those that have the same biological mother and same biological father.

The participant answers "Yes" if there is at least one child without diabetes who has the same biological mother and same biological father as the proband and the affected sibling. These siblings cannot have been diagnosed with any form of diabetes including, but not limited to, Type 1 diabetes, Type 2 diabetes, and MODY. If the participant answers "No," skip to Question 28.

24. What is the current age of the oldest child who does not have diabetes? CHILDREN LESS THAN 12 MONTHS CAN BE INCLUDED AFTER FIRST BIRTHDAY.

The participant responds by giving the age of the eldest available sibling not diagnosed with any form of diabetes at the time of the interview. If the eldest sibling is not available, the next eldest available unaffected sibling is used. If the information is abstracted from other sources and transferred onto this form, the interviewer determines the child's current age. The child's age is recorded in years. If the child is less than 12 months old, mark the "Less than 12 months" box and skip to Question 28; this participant's eligibility is "PENDING." However, since unaffected siblings are not necessary for the minimum family requirement, this family may still be eligible. This family may be re-contacted after the sibling's first birthday. However, the clinic

continues collecting data and lab samples on members of the family over 12 months old. This family's status is **not** "PENDING."

25. Are you willing to have this child participate in this study?

The participant now has the option to allow this child to participate in the T1DGC. Participant involvement in the study is discussed. The interviewer reads the cue card containing a brief description of the study. The participant answers "Yes" if he/she is interested in learning more about the study and allowing this child to participate. If the participant answers "No," continue with this form. This participant is ineligible. However, since unaffected siblings are not necessary for the minimum family requirement, this family may still be eligible. If the participant has already given their consent for this child to participate in the study prior to completing the eligibility form, mark the "Has signed consent" box and continue with the form. If the participant answers "Don't know," continue completing the form and follow-up at a later date for a definitive answer.

26. What is the current age of the next oldest child who does not have diabetes? CHILDREN LESS THAN 12 MONTHS CAN BE INCLUDED AFTER FIRST BIRTHDAY.

The participant responds by giving the age of the next eldest available sibling not diagnosed with any form of diabetes at the time of the interview. If the next eldest sibling is not available, and another unaffected sibling exists, he/she is used. If the information is abstracted from other sources and transferred onto this form, the interviewer determines the child's current age. The child's age is recorded in years. If the child is less than 12 months old, mark the "Less than 12 months" box and skip to Question 28; this participant's eligibility is "PENDING." However, since unaffected siblings are not necessary for the minimum family requirement, this family may still be eligible. This family may be re-contacted after the sibling's first birthday. However, the clinic continues collecting data and lab samples on members of the family over 12 months old. This family's status is **not** "PENDING." If the participant does not have

another child not diagnosed with any form of diabetes, mark the "Don't have one" box and skip to Question 28.

27. Are you willing to have this child participate in this study?

The participant now has the option to allow this child to participate in the T1DGC. Participant involvement in the study is discussed. The interviewer reads the cue card containing a brief description of the study. The participant answers "Yes" if he/she is interested in learning more about the study and allowing this child to participate. If the participant answers "No," continue with this form; this participant is ineligible. However, since unaffected siblings are not necessary for the minimum family requirement, this family may still be eligible. If the participant has already given their consent for this child to participate in the study prior to completing the eligibility form, mark the "Has signed consent" box and continue with the form. If the participant answers "Don't know," continue completing the form and follow-up with the participant at a later date for a definitive answer.

Questions 28-33 are directed toward clinic staff and are completed as the activity occurs (*i.e.,* after interviewing, after editing, and after receiving the *T1DGC Application to Eligibility Committee*).

INTERVIEWER COMPLETED

28. Is this family eligible to participate in this study?

The interviewer reviews the questions to ensure this family meets eligibility requirements. The interviewer marks "Yes" if this family meets all eligibility requirements, and skips to Question 30. This family must consist at minimum of two affected siblings. The biological father, mother, and up to two unaffected siblings are included if possible. The interviewer marks "No" if at one point during the interview he/she came to a "STOP-INELIGIBLE" statement, and skips to Question 30. The interviewer marks "PENDING" if one or more questions regarding the proband or affected sibling were marked as "Don't know," or the interviewer is in the process of

applying to the Eligibility Committee. If "PENDING" is marked, the interviewer re-contacts the appropriate individuals within 10 days in order to determine eligibility or waits until a decision is made by the Eligibility Committee.

29. Is an application to the Eligibility Committee required?

The interviewer marks "Yes" if one of the participants appears to have Type 1 diabetes, but does not meet the T1DGC definition of diabetes. The interviewer completes the *T1DGC Application to Eligibility Committee* and sends it to the Regional Network Center. The interviewer continues completing the form. If the interviewer does not need to apply to the Eligibility Committee, the interviewer marks "No" and skips to Question 30.

29a. Is this for the proband, affected sibling or both?

The interviewer marks "Proband" or "Affected Sibling" if the *T1DGC Application to Eligibility Committee* is completed for that specific individual. The interviewer marks "Both" if the interviewer completes two *T1DGC Application to Eligibility Committee* forms.

30. Interviewer ID

The interviewer records his/her five-digit assigned code in the appropriate boxes after completion of the *T1DGC ASP Eligibility Form*.

31. ID of person editing

This is not completed until a clinic staff member reviews the form to ensure completion and accuracy. The person editing and reviewing the form records his/her five-digit assigned code in the appropriate boxes.

COMPLETED ONLY IF APPLICATION TO ELIGIBILITY COMMITTEE REQUIRED.

32. Did the Eligibility Committee approve inclusion in the study?

The interviewer completes this section **only** if a *T1DGC Application to Eligibility Committee* was sent to and a decision was made by the Eligibility Committee. The interviewer marks "Yes" if the Eligibility Committee decided the participant(s) is (are) eligible to participate, or marks "No" if the Eligibility Committee decided this participant is ineligible to participate in the T1DGC. If the interviewer marks "No," the interviewer skips to Question 33. If the application was completed for both the proband and the affected sibling, the interviewer marks "Yes" if approval is received on one or both of the participants.

32a. Was approval received for the proband, affected sibling or both?

The interviewer marks "Proband" if the *T1DGC Application to Eligibility Committee* is approved for the proband. The interviewer marks "Affected Sibling" if the *T1DGC Application to Eligibility Committee* is approved for the affected sibling. The interviewer marks "Both" if the interviewer completed two *T1DGC Application to Eligibility Committee* forms and each of these applications is approved.

33. Date Eligibility Committee decision received by clinic

The interviewer records the date the application is returned to the clinic with a decision regarding the eligibility of the proband and/or the affected sibling. Once information is received regarding the eligibility status of the participant(s), the clinic corrects Question 28 regarding eligibility status.

APPENDIX D
TRIO ELIGIBILITY FORM (PROBAND):
QUESTION BY QUESTION INSTRUCTIONS

These instructions are meant to assist the interviewer and to provide answers to any questions from a participant or clinic staff member.

This form is administered to the proband. **This form is used if the proband is of legal age to give consent and it is determined by clinic staff that the proband is able to understand and answer all of the questions.** Only the proband answers the questions; however, the legal guardians of the proband can be present at the interview. The interviewer reads the questions to the proband and marks or records appropriate answers.

Information in all capital letters is an instruction to the interviewer and is not read to the participant.

If at any point during the screening process, the interviewer marks a shaded box, the prospective family is deemed ineligible.

For eligible participants, please complete all parts of the form. Note that certain individual items may be marked “Don’t know” and with an asterisk. In these cases, continue completing the form and contact the appropriate individuals within 10 days in order to collect information not known at the time of the initial screening. The participant may need to contact his/her physician or other family members in order to obtain information. All “PENDING” responses refer to eligibility criteria and must be resolved before the form is forwarded to the Regional Network Center. Items without a “PENDING” status should be followed-up, but forms should be forwarded to the Regional Network Center when it has become apparent that this information will not be found. There may also be situations in which a participant diagnosed with Type 1 diabetes does not meet the Type 1 Diabetes Genetics Consortium (T1DGC) criteria for

Type 1 diabetes. In this case the interviewer completes a *T1DGC Application to Eligibility Committee*.

All dates are written as day first, month second, and year third. The day is recorded numerically. If the day is a single-digit number, a "0" is recorded in the first box. The month is written out in its entirety (*e.g.,* January, February). The year is recorded numerically, with all four digits of the year included (*e.g.,* 1950). All single digit numerical responses are recorded with a leading "0" (*e.g.,* if participant is 5 years old, record "05").

Question by Question Instructions

The interviewer does not affix the Family ID Label until it has been determined that this family is eligible or the eligibility status is "PENDING." Once eligibility has been determined, the interviewer affixes the Family ID Label in the box shown in the upper right hand corner. A label is affixed on every page.

The interviewer records the clinic ID for his/her individual clinic. This number is assigned by the Regional Network Center and it is recorded on every page.

1. Interview date

This is the date the interview takes place. Record the date of the interview in the appropriate boxes. For some clinics, the information on the form is abstracted from other sources and transferred onto this form. In this case, the interviewer records the date the information is abstracted and the form is completed.

2. How was this form completed? MARK ALL THAT APPLY.

The interviewer marks all sources from which information is gathered about the participants. If information is obtained by calling a participant before he/she comes into the clinic, mark "Phone interview." If the participant comes into the clinic and is interviewed in person, the interviewer marks "Face-to-face interview." If information is abstracted from other sources (*e.g.,* other forms, pulling medical records), the

interviewer marks “From existing records.” The interviewer marks all applicable answers.

3. Have you or any of your immediate family members previously participated in a genetic study? READ/SHOW PARTICIPANT CUE CARD.

The interviewer reads or show the participant the cue card that includes the list of previously conducted genetic studies the T1DGC has genetic data from. The participant responds “Yes” if he/she or member(s) of their immediate family (*i.e.,* the participant and/or the participant’s biological parents) has participated in any of the genetic studies listed on the card. If the participant answers “Yes,” stop completing this form; this family is ineligible. If the participant does not know this information, the interviewer marks “Don’t know” and continues completing the form. This family’s eligibility is “PENDING.” If the participant answers “No,” the interviewer continues completing the form.

Questions 4-11 relate to the proband, a participant who has been diagnosed with Type 1 diabetes. It is required for the proband to participate in this study.

4. Have you been diagnosed with Type 1 diabetes?

The participant answers “Yes” if he/she has been diagnosed with Type 1 diabetes, Insulin Dependent diabetes, Youth Onset diabetes, or Juvenile Onset diabetes. If the participant answers “No,” stop completing this form; this family is ineligible.

5. At what age were you diagnosed with Type 1 diabetes?

The participant gives the age he/she was diagnosed with Type 1 diabetes. If he/she cannot recall their age, an attempt is made to guess, or tell the interviewer in what year they were diagnosed. The age at diagnosis is calculated from the year of diagnosis. If the age of diagnosis is 35 years or older, stop completing this form; this family is ineligible. The participant’s age is recorded in years. If the participant was less than 1 year old, record “00.”

6. Did you use insulin within six months of being diagnosed?

The participant answers "Yes" if insulin was used at any point during the first six months after he/she was diagnosed with Type 1 diabetes. This excludes nasal or inhaled insulin. If the participant answers "Yes," skip to Question 7. If the participant answers "No," the interviewer continues to Question 6a.

6a. Is there any other information to suggest you have Type 1 (insulin dependent) diabetes?

If the participant answers "Yes," the interviewer applies to the Eligibility Committee who reviews the information submitted on possible affected participants (*e.g.,* the participant was diagnosed early in the natural history via autoantibodies and/or OGTT and thus is not on insulin). The interviewer completes the *T1DGC Application to Eligibility Committee* and sends it to the Regional Network Center. The interviewer continues completing the form. This family's eligibility is "PENDING." If the participant answers "No," stop completing this form; this family is ineligible.

7. Once you started using insulin, did you ever stop using insulin for a period of six months or more for reason other than a pancreas transplant?

The participant answers "Yes" if insulin use was started but discontinued for 6 months or longer. More than one interruption is permitted if each is within the allotted time frame. If a participant has had a pancreas transplant and has stopped insulin use for more than six months because of the transplant, they are not excluded from participating in the T1DGC. If the participant answers "Yes," stop completing this form; this family is ineligible. The participant answers "No" if insulin use was never disrupted after starting on insulin, or if any insulin was stopped for periods within six months. If the participant has not been diagnosed for six months, the "Not applicable" box is marked. However, this does not make the participant ineligible, continue with the form.

8. What is your date of birth?

Record the date of birth in the appropriate boxes. For some clinics, this information is considered an identifier and thus cannot be collected. In this case, the

interviewer marks the “Can not collect” box, but must answer Question 9. If clinics are able to collect a portion of the date of birth, the year is recorded in the appropriate boxes.

9. What is your current age?

The participant responds by giving his/her current age at the time of the interview. If the information is abstracted from other sources and transferred onto this form, the interviewer determines the participant’s current age. The participant’s age is recorded in years.

10. Do you have a specific genetic disorder or disease that caused your diabetes? This would include maturity onset diabetes of youth (MODY). IF YES OR DON’T KNOW, READ/SHOW PARTICIPANT CUE CARD.

The participant answers “Yes” if he/she has been diagnosed with another genetic disease that is known to be associated with non-classical insulin-dependent diabetes. If the participant answers “Yes” or “Don’t know,” show or read the participant the cue card listing the genetic disorders and diseases that exclude a person from participating in the T1DGC. If the participant answers “Yes,” stop completing this form; this family is ineligible. If the participant answers “No,” continue completing the form. If the participant still does not know, mark the “Don’t know” box and continue completing the form. This family’s eligibility is “PENDING.”

11. Are you willing to participate in this study? READ BRIEF DESCRIPTION OF THE STUDY TO PARTICIPANT FROM CUE CARD.

The participant now has the option to participate in the T1DGC. Participant involvement in the study is discussed. The interviewer reads the cue card containing a brief description of the study. The participant answers “Yes” if he/she is interested in learning more about the study and participating. If the participant answers “No,” stop completing this form; this family is ineligible. If the participant has already given his/her consent to participate in the study prior to completing the eligibility form, mark the “Has signed consent” box and continue with the form. If the participant answers “Don’t

know," continue completing the form and follow-up at a later date for a definitive answer. This family's eligibility is "PENDING."

Questions 12-13 relate to the biological parents of the proband described above. It is required for both biological parents to participate in this study.

12. Is your biological father living?

The participant answers "Yes" if he/she knows their biological father is living. If the participant answers "No," stop completing this form; this family is ineligible. If the participant answers "Don't know," continue completing the form; this family's eligibility is "PENDING."

13. Is your biological mother living?

The participant answers "Yes" if he/she knows their biological mother is living. If the participant answers "No," stop completing this form; this family is ineligible. If the participant answers "Don't know," continue completing the form; this family's eligibility is "PENDING."

Questions 14-19 are directed toward clinic staff and are completed as the activity occurs (*i.e.,* after interviewing, after editing, and after receiving the *T1DGC Application to Eligibility Committee*).

INTERVIEWER COMPLETED

14. Is this family eligible to participate in this study?

The interviewer reviews the questions to ensure this family meets eligibility requirements. The interviewer marks "Yes" if this family meets all eligibility requirements, and skips to Question 16. This family must consist of a proband and both biological parents. The interviewer marks "No" if at one point during the interview he/she came to a "STOP-INELIGIBLE" statement, and skips to Question 16. The interviewer marks "PENDING" if one or more questions about the proband or biological

parents were marked as “Don’t know” or the interviewer is in the process of applying to the Eligibility Committee. If “PENDING” is marked, the interviewer re-contacts the appropriate individuals within 10 days in order to determine eligibility or waits until a decision is made by the Eligibility Committee.

15. Is an application to the Eligibility Committee required?

The interviewer marks “Yes” if the proband appears to have Type 1 diabetes, but does not meet the T1DGC definition of diabetes. The interviewer completes the *T1DGC Application to Eligibility Committee* and sends it to the Regional Network Center. The interviewer continues completing the form. If the interviewer does not need to apply to the Eligibility Committee, the interviewer marks “No” and continues completing the form.

16. Interviewer ID

The interviewer records his/her five-digit assigned code in the appropriate boxes after completion of the *T1DGC Trio Eligibility Form*.

17. ID of person editing

This is not completed until a clinic staff member reviews the form to ensure completion and accuracy. The person editing and reviewing the form records his/her five-digit assigned code in the appropriate boxes.

COMPLETED ONLY IF APPLICATION TO ELIGIBILITY COMMITTEE REQUIRED.

18. Did the Eligibility Committee approve inclusion in the study?

The interviewer completes this section **only** if a *T1DGC Application to Eligibility Committee* was sent to and a decision was made by the Eligibility Committee. The interviewer marks “Yes” if the Eligibility Committee decided the participant is eligible to participate, or marks “No” if the Eligibility Committee decided this participant is ineligible to participate in the T1DGC.

19. Date Eligibility Committee decision received by clinic

The interviewer records the date the application is returned to the clinic with a decision regarding the eligibility of the proband. Once information is received regarding the eligibility status of the proband, the clinic corrects Question 14 regarding eligibility status.

APPENDIX E
TRIO ELIGIBILITY FORM (GUARDIAN): QUESTION BY QUESTION INSTRUCTIONS

These instructions are meant to assist the interviewer and to provide answers to any questions from a participant or clinic staff member.

This form is administered to a guardian (*i.e.,* biological mother, biological father or other legal guardian) of the proband. **This form is used if the proband is under the legal age to give consent and it is determined by clinic staff that the proband is unable to understand and answer all of the questions.** Only one guardian answers the questions; however, more than one can be present at the interview. The interviewer reads the questions to the guardian and marks or records appropriate answers.

Information in all capital letters is an instruction to the interviewer and is not read to the participant.

If at any point during the screening process, the interviewer marks a shaded box, the prospective family is determined to be ineligible.

For eligible participants, please complete all parts of the form. Note that certain individual items may be marked "Don't know" and with an asterisk. In these cases, continue completing the form and contact the appropriate individuals within 10 days in order to collect information not known at the time of the initial screening. The participant may need to contact his/her physician or other family members in order to obtain information. All "PENDING" responses refer to eligibility criteria and must be resolved before the form is forwarded to the Regional Network Center. Items without a "PENDING" status should be followed-up, but forms should be forwarded to the Regional Network Center when it has become apparent that this information will not be found. There may also be situations in which a participant diagnosed with Type 1

diabetes does not meet the Type 1 Diabetes Genetics Consortium (T1DGC) criteria for Type 1 diabetes. In this case the interviewer completes a *T1DGC Application to Eligibility Committee*.

All dates are written as day first, month second, and year third. The day is recorded numerically. If the day is a single-digit number, a "0" is recorded in the first box. The month is written out in its entirety (*e.g.,* January, February). The year is recorded numerically, with all four digits of the year included (*e.g.,* 1950). All single digit numerical responses are recorded with a leading "0" (*e.g.,* if participant is 5 years old, record "05").

Question by Question Instructions

The interviewer does not affix the Family ID Label until it has been determined that this family is eligible or the eligibility status is "PENDING." Once eligibility has been determined, the interviewer affixes the Family ID Label in the box shown in the upper right hand corner. A label is affixed on every page.

The interviewer records the clinic ID for his/her individual clinic. This number is assigned by the Regional Network Center and it is recorded on every page.

1. Interview date

This is the date the interview takes place. Record the date of the interview in the appropriate boxes. For some clinics, the information on the form is abstracted from other sources and transferred onto this form. In this case, the interviewer records the date the information is abstracted and the form is completed.

2. How was this form completed? MARK ALL THAT APPLY.

The interviewer marks all sources from which information is gathered about the participants. If information is obtained by calling a participant before he/she comes into the clinic, mark "Phone interview." If the participant comes into the clinic and is interviewed in person, the interviewer marks "Face-to-face interview." If information is

abstracted from other sources (*e.g.,* other forms, pulling medical records), the interviewer marks "From existing records." The interviewer marks all applicable answers.

3. Who is completing this form? ONLY ONE GUARDIAN IS INTERVIEWED.

The interviewer determines the relationship the guardian has with the proband. The interviewer may ask the participant his/her relationship to the children, if it is not already known. The interviewer marks "Biological Father" if the man completing the interview believes himself to be the biological father of the proband. The interviewer marks "Biological Mother" if the woman completing the interview gave birth to the proband. The interviewer marks "Other Guardian" if the person completing this form is neither biological parent of the proband. The interviewer should be aware of the relationship the guardian has to the child while administering this questionnaire. Versions of questions may differ based upon the guardian's relationship to the proband.

4. Have you or any of your immediate family members previously participated in any of the following genetic studies? READ/SHOW PARTICIPANT CUE CARD.

The interviewer reads or shows the participant the cue card that includes the list of previously conducted genetic studies the T1DGC has genetic data from. The participant responds "Yes" if he/she or member(s) of their immediate family (*i.e.,* the proband and/or the proband's biological parents) has participated in any of the genetic studies listed on the card. If the participant answers "Yes," stop completing this form; this family is ineligible. If the participant does not know this information, the interviewer marks "Don't know" and continues completing the form. This family's eligibility is "PENDING." If the participant answers "No," the interviewer continues completing the form.

5. Do you have a child who has been diagnosed with Type 1 diabetes?

The participant answers "Yes" if one of his/her children has been diagnosed with Type 1 diabetes, Insulin Dependent diabetes, Youth Onset diabetes, or Juvenile Onset

diabetes. If the participant answers "No," stop completing this form; this family is ineligible.

6. How old was this child when he/she was diagnosed with Type 1 diabetes?

The participant gives the age the proband was diagnosed with Type 1 diabetes. If he/she cannot recall the child's age, an attempt is made to guess, or tell the interviewer in what year the child was diagnosed. The age of diagnosis is calculated from the year of diagnosis. If the age of diagnosis is 35 years or older, stop completing this form; this family is ineligible. The child's age is recorded in years. If the child was less than 1 year old, record "00."

7. Did this child use insulin within six months of being diagnosed?

The participant answers "Yes" if insulin was used at any point during the first six months after the proband was diagnosed with Type 1 diabetes. This excludes nasal or inhaled insulin. If the participant answers "Yes," skip to Question 8. If the participant answers "No," the interviewer continues to Question 7a.

7a. Is there any other information to suggest that this child has Type 1 (insulin dependent) diabetes?

If the participant answers "Yes," the interviewer applies to the Eligibility Committee who reviews the information submitted on possible affected participants (*e.g.,* the participant was diagnosed early in the natural history via autoantibodies and/or OGTT and thus is not on insulin). The interviewer completes the *T1DGC Application to Eligibility Committee* and sends it to the Regional Network Center. The interviewer continues completing the form. This family's eligibility is "PENDING." If the participant answers "No," stop completing this form; this family is ineligible.

8. Once this child started using insulin, did he/she ever stop using insulin for a period of six months or more for reasons other than a pancreas transplant?

The participant answers "Yes" if the proband's insulin use was started but discontinued for six months or longer. More than one interruption is permitted if each is

within the allotted time frame. If the proband has had a pancreas transplant and has stopped insulin use for more than six months because of the transplant, they are not excluded from participating in the T1DGC. If the participant answers "Yes," stop completing this form; this family is ineligible. The participant answers "No" if insulin use was never disrupted after starting on insulin, or if any insulin was stopped for periods within six months. If the participant has not been diagnosed for six months, the "Not applicable" box is marked. However, this does not make this participant ineligible, continue with the form.

9. What is this child's date of birth?

Record the date of birth in the appropriate boxes. For some clinics, this information is considered an identifier and thus cannot be collected. In this case, the interviewer marks the "Can not collect" box, but must answer Question 10. If clinics are able to collect a portion of the date of birth, the year is recorded in the appropriate boxes.

10. What is this child's current age? CHILDREN LESS THAN 12 MONTHS CAN BE INCLUDED AFTER FIRST BIRTHDAY.

The participant responds by giving the current age of the proband at the time of the interview. If the information is abstracted from other sources and transferred onto this form, the interviewer determines the proband's current age. The proband's age is recorded in years. If the child is less than 12 months old, mark the "Less than 12 months" box and continue completing this form. This family's eligibility is "PENDING." However, the child's family is re-contacted after the child has had his/her first birthday.

11. Does this child have a specific genetic disorder or disease that caused his/her diabetes? This would include maturity onset diabetes of youth (MODY). IF YES OR DON'T KNOW, READ/SHOW PARTICIPANT CUE CARD.

The participant answers "Yes" if the proband has been diagnosed with another genetic disease that is known to be associated with non-classical insulin dependent diabetes. If the participant answers "Yes" or "Don't know," show or read the participant

the cue card listing the genetic disorders and diseases that exclude a person from participating in the T1DGC. If the participant answers "Yes," stop completing this form; this family is ineligible. If the participant answers "No," continue completing the form. If the participant still does not know, mark the "Don't know" box and continue completing the form. This family's eligibility is "PENDING."

12. Are you willing to have this child participate in this study? READ BRIEF DESCRIPTION OF THE STUDY TO PARTICIPANT FROM CUE CARD.

The participant now has the option to allow this child to participate in the T1DGC. Participant involvement in the study is discussed. The interviewer reads the cue card containing a brief description of the study. The participant answers "Yes" if he/she is interested in learning more about the study and allowing their child to participate. If the participant answers "No," stop completing this form; this family is ineligible. If the participant has already given their consent for this child to participate in the study prior to completing the eligibility form, mark the "Has signed consent" box and continue with the form. If the participant answers "Don't know," continue completing the form and follow-up at a later date for a definitive answer. This family's eligibility is "PENDING."

Questions 13-14 relate to the biological parents of the child described above. There are two versions of each question depending on who is completing the interview. Be sure to ask the participant the correct version of the question. It is required for both biological parents to participate in this study.

IF BIOLOGICAL FATHER COMPLETING FORM: 13a. Are you willing to participate in this study?

If the biological father is completing the form, this question is asked of the participant. He now has the option to participate in the T1DGC. Participant involvement in the study is discussed. The interviewer reads the cue card containing a brief description of the study if necessary. The father answers "Yes" if he is interested in learning more about the study and participating in the T1DGC. If he answers "No," stop completing this form; this family is ineligible. If he has already given his consent to

participate in the study prior to completing this eligibility form, mark the "Has signed consent" box and continue with the form. If the father answers "Don't know," continue completing the form and follow-up at a later date for a definitive answer. This family's eligibility is "PENDING."

IF BIOLOGICAL MOTHER OR OTHER GUARDIAN COMPLETING FORM: 13b. Is the biological father of these children living?

If the biological mother or other guardian is completing the form, this question is asked of the participant. The participant answers "Yes" if he/she knows the biological father of the child described above is living. If the participant answers "No," stop completing this form; this family is ineligible. If the participant answers "Don't know," continue completing the form; this family's eligibility is "PENDING."

IF BIOLOGICAL MOTHER COMPLETING FORM: 14a. Are you willing to participate in this study?

If the biological mother is completing the form, this question is asked of the participant. She now has the option to participate in the T1DGC. Participant involvement in the study is discussed. The interviewer reads the cue card containing a brief description of the study. The mother answers "Yes" if she is interested in learning more about the study and participating in the T1DGC. If she answers "No," stop completing this form; this family is ineligible. If she has already given her consent to participate in the study prior to completing the eligibility form, mark the "Has signed consent" box and continue with the form. If the mother answers "Don't know," continue completing the form and follow-up at a later date for a definitive answer. This family's eligibility is "PENDING."

IF BIOLOGICAL FATHER OR OTHER GUARDIAN COMPLETING FORM: 14b. Is the biological mother of these children living?

If the biological father or other guardian is completing the form, this question is asked of the participant. The participant answers "Yes" if he/she knows the biological mother of the child described above is living. If the participant answers "No," stop

completing this form; this family is ineligible. If the participant answers "Don't know," continue completing the form; this family's eligibility is "PENDING."

Questions 15-20 are directed toward clinic staff and are completed as the activity occurs (*i.e.,* after interviewing, after editing, and after receiving the *T1DGC Application to Eligibility Committee*).

INTERVIEWER COMPLETED

15. Is this family eligible to participate in this study?

The interviewer reviews the questions to ensure this family meets eligibility requirements. The interviewer marks "Yes" if this family meets all eligibility requirements, and skips to Question 17. This family must consist of a proband and both biological parents. The interviewer marks "No" if at one point during the interview he/she came to a "STOP-INELIGIBLE" statement, and skips to Question 17. The interviewer marks "PENDING" if one or more questions about the proband or biological parents were marked as "Don't know" or the interviewer is in the process of applying to the Eligibility Committee. If "PENDING" is marked, the interviewer re-contacts the appropriate individuals within 10 days in order to determine eligibility or waits until a decision is made by the Eligibility Committee.

16. Is an application to the Eligibility Committee required?

The interviewer marks "Yes" if the proband appears to have Type 1 diabetes, but does not meet the T1DGC definition of diabetes. The interviewer completes the *T1DGC Application to Eligibility Committee* and sends it to the Regional Network Center. The interviewer continues completing the form. If the interviewer does not need to apply to the Eligibility Committee, the interviewer marks "No" and continues completing the form.

17. Interviewer ID

The interviewer records his/her five-digit assigned code in the appropriate boxes after completion of the *T1DGC Trio Eligibility Form*.

18. ID of person editing

This is not completed until a clinic staff member reviews the form to ensure completion and accuracy. The person editing and reviewing the form records his/her five-digit assigned code in the appropriate boxes.

COMPLETED ONLY IF APPLICATION TO ELIGIBILITY COMMITTEE REQUIRED.

19. Did the Eligibility Committee approve inclusion in the study?

The interviewer completes this section **only** if a *T1DGC Application to Eligibility Committee* was sent to and a decision was made by the Eligibility Committee. The interviewer marks "Yes" if the Eligibility Committee decided the participant is eligible to participate, or marks "No" if the Eligibility Committee decided this participant is ineligible to participate in the T1DGC.

20. Date Eligibility Committee decision received by clinic

The interviewer records the date the application is returned to the clinic with a decision regarding the eligibility of the proband. Once information is received regarding the eligibility status of the proband, the clinic corrects Question 15 regarding eligibility status.

APPENDIX F
CASE ELIGIBILITY FORM (CASE):
QUESTION BY QUESTION INSTRUCTIONS

These instructions are meant to assist the interviewer and to provide answers to any questions from a participant or clinic staff member.

This form is administered to the case. The case is an individual diagnosed with Type 1 diabetes. **This form is used if the case is of legal age to give consent and it is determined by clinic staff that the case is able to understand and answer all of the questions.** Only the case answers questions; however, the legal guardians of the case can be present at the interview. The interviewer reads the questions to the case and marks or records appropriate answers.

Information in all capital letters is an instruction to the interviewer and is not read to the participant.

If at any point during the screening process, the interviewer marks a shaded box, the prospective participant is deemed ineligible.

For eligible participants, please complete all parts of the form. Note that certain individual items may be marked "Don't know" and with an asterisk. In these cases, continue completing the form and contact the appropriate individuals within 10 days in order to collect information not known at the time of the initial screening. The participant may need to contact his/her physician or other family members in order to obtain information. All "PENDING" responses refer to eligibility criteria and must be resolved before the form is forwarded to the Regional Network Center. Items without a "PENDING" status should be followed-up, but forms should be forwarded to the Regional Network Center when it has become apparent that this information will not be found. There may also be situations in which a participant diagnosed with Type 1 diabetes does not meet the Type 1 Diabetes Genetics Consortium (T1DGC) criteria for

Type 1 diabetes. In this case the interviewer completes a *T1DGC Application to Eligibility Committee*.

All dates are written as day first, month second, and year third. The day is recorded numerically. If the day is a single-digit number, a "0" is recorded in the first box. The month is written out in its entirety (*e.g.,* January, February). The year is recorded numerically, with all four digits of the year included (*e.g.,* 1950). All single digit numerical responses are recorded with a leading "0" (*e.g.,* if participant is 5 years old, record "05").

Question by Question Instructions

The interviewer does not affix the Case ID Label until it has been determined that this individual is eligible or the eligibility status is "PENDING." Once eligibility has been determined, the interviewer affixes the Case ID Label in the box shown in the upper right hand corner. A label is affixed on every page.

The interviewer records the clinic ID for his/her individual clinic. This number is assigned by the Regional Network Center and it is recorded on every page. The secondary ID (CAS) is already recorded on this form as it is used only for cases.

1. Interview date

This is the date the interview takes place. Record the date of the interview in the appropriate boxes. For some clinics, the information on the form is abstracted from other sources and transferred onto this form. In this case, the interviewer records the date the information is abstracted and the form is completed.

2. How was this form completed? MARK ALL THAT APPLY.

The interviewer marks all sources from which information is gathered about the participant. If information is obtained by calling a participant before he/she comes into the clinic, mark "Phone interview." If the participant comes into the clinic and is interviewed in person, the interviewer marks "Face-to-face interview." If information is

abstracted from other sources (*e.g.,* other forms, pulling medical records), the interviewer marks "From existing records." The interviewer marks all applicable answers.

3. Have you been diagnosed with Type 1 diabetes?

The participant answers "Yes" if he/she has been diagnosed with Type 1 diabetes, Insulin Dependent diabetes, Youth Onset diabetes, or Juvenile Onset diabetes. If the participant answers "No," stop completing this form; this participant is ineligible.

4. Is your origin of birth, or primary ethnic origin one of the following? READ CHOICES AND RECORD PARTICIPANT'S RESPONSE.

In Asia-Pacific or European Networks read the categories listed in the first section of the question: Cameroon, China, India or Thailand. If the participant answers "None of the above," stop completing this form; this participant is ineligible.

In the North American Network, read the choices listed under the second section of the question: Mexican-American, African-American or both. If the participant answers "None of the above," stop completing this form; this participant is ineligible.

5. Have you or any of your immediate family members previously participated in any of the following genetic studies? READ/SHOW PARTICIPANT CUE CARD.

The interviewer reads or shows the participant the cue card that includes the list of previously conducted genetic studies the T1DGC has genetic data from. The participant responds "Yes" if he/she or member(s) of their immediate family (*i.e.,* the participant, the participant's full biological siblings and/or the participant's biological parents) has participated in any of the genetic studies listed on the card. If the participant answers "Yes," stop completing this form; this individual is ineligible. If the participant does not know this information, the interviewer marks "Don't know" and continues completing the form. This individual's eligibility is "PENDING." If the participant answers "No," the interviewer continues completing the form.

6. At what age were you diagnosed with Type 1 diabetes?

The participant gives the age he/she was diagnosed with Type 1 diabetes. If he/she cannot recall their age, an attempt is made to guess, or tell the interviewer in what year they were diagnosed. The age of diagnosis is calculated from the year of diagnosis. If the age of diagnosis is 35 years or under, stop completing this form; this participant is ineligible. The participant's age is recorded in years. If the participant was less than 1 year old, record "00."

7. Did you use insulin within six months of being diagnosed?

The participant answers "Yes" if insulin was used at any point during the first six months after he/she was diagnosed with Type 1 diabetes. This excludes nasal or inhaled insulin. If the participant answers "Yes," skip to Question 8. If the participant answers "No," the interviewer continues to Question 7a.

7a. Is there any other information to suggest you have Type 1 (insulin dependent) diabetes?

If the participant answers "Yes," the interviewer applies to the Eligibility Committee who reviews the information submitted on possible affected participants (*e.g.,* the participant was diagnosed early in the natural history via autoantibodies and/or OGTT and thus is not on insulin). The interviewer completes the *T1DGC Application to Eligibility Committee* and sends it to the Regional Network Center. The interviewer continues completing the form. This participant's eligibility is "PENDING." If the participant answers "No," stop completing this form; this participant is ineligible.

8. Once you started using insulin, did you ever stop using insulin for a period of six months or more for reasons other than a pancreas transplant?

The participant answers "Yes" if insulin use was started but discontinued for 6 months or longer. More than one interruption is permitted if each is within the allotted time frame. If a participant has had a pancreas transplant and has stopped insulin use for more than 6 months because of the transplant, they are not excluded from participating in the T1DGC. If the participant answers "Yes," stop completing this form;

this participant is ineligible. The participant answers "No" if insulin use was never disrupted after starting on insulin, or if any insulin was stopped for periods within 6months. If the participant has not been diagnosed for six months, the "Not applicable" box is marked. However, this does not make the participant ineligible, continue with the form.

9. What is your date of birth?

Record the date of birth in the appropriate boxes. For some clinics, this information is considered an identifier and thus cannot be collected. In this case, the interviewer marks the "Can not collect" box, but must answer Question 10. If clinics are able to collect a portion of the date of birth, the year is recorded in the appropriate boxes.

10. What is your current age?

The participant responds by giving his/her current age at the time of the interview. If the information is abstracted from other sources and transferred onto this form, the interviewer determines the participant's current age. The participant's age is recorded in years.

11. Do you have a specific genetic disorder or disease that caused your diabetes? This would include maturity onset diabetes of youth (MODY). IF YES OR DON'T KNOW, READ/SHOW PARTICIPANT CUE CARD.

The participant answers "Yes" if he/she has been diagnosed with another genetic disease that is known to be associated with non-classical insulin dependent diabetes. If the participant answers "Yes" or "Don't know" show or read the participant the cue card listing the genetic disorders and diseases that exclude a person from participating in the T1DGC. If the participant answers "Yes," stop completing this form; this participant is ineligible. If the participant answers "No," continue completing the form. If the participant still does not know, mark the "Don't know" box and continue completing the form. This participant's eligibility is "PENDING."

12. Are you willing to participate in this study? READ BRIEF DESCRIPTION OF THE STUDY TO PARTICIPANT FROM CUE CARD.

The participant now has the option to participate in the T1DGC. Participant involvement in the study is discussed. The interviewer reads the cue card containing a brief description of the study. The participant answers "Yes" if he/she is interested in learning more about the study and participating. If the participant answers "No," stop completing this form; this participant is ineligible. If the participant has already given his/her consent to participate in the study prior to completing the eligibility form, mark the "Has signed consent" box and continue with the form. If the participant answers "Don't know," continue completing the form and follow-up at a later date for a definitive answer. This participant's eligibility is "PENDING."

13. In what region do you live, or to what tribe do you belong? IN CHINA, INDIA OR CAMEROON, HAND PARTICIPANT CUE CARD AND RECORD RESPONSE.

In China, India or Cameroon, the participant chooses one region or tribe. The interviewer hands (or reads) the participant the cue card containing a list of regions or tribes to choose from. If a participant chooses more than one region or tribe, the interviewer asks which region or tribe he/she most identifies with and records that choice. Record the appropriate code(s) in the boxes. In North America and Thailand, the region or tribe is not applicable; the interviewer marks "Not Applicable."

Questions 14-19 are directed toward clinic staff and are completed as the activity occurs (*i.e.,* after interviewing, after editing, and after receiving the *T1DGC Application to Eligibility Committee*).

INTERVIEWER COMPLETED

14. Is this person eligible to participate in this study?

The interviewer reviews the questions to ensure this person meets eligibility requirements. The interviewer marks "Yes" if this person meets all eligibility

requirements, and skips to Question 16. The interviewer marks "No" if at one point during the interview he/she came to a "STOP-INELIGIBLE" statement, and skips to Question 16. The interviewer marks "PENDING" if one or more questions were marked as "Don't know," or the interviewer is in the process of applying to the Eligibility Committee. If "PENDING" is marked, the interviewer re-contacts the appropriate individuals within 10 days in order to determine eligibility or waits until a decision is made by the Eligibility Committee.

15. Is an application to the Eligibility Committee required?

The interviewer marks "Yes" if the participant appears to have Type 1 diabetes, but does not meet the T1DGC definition of diabetes. The interviewer completes the *T1DGC Application to Eligibility Committee* and sends it to the Regional Network Center. The interviewer continues completing the form. If the interviewer does not need to apply to the Eligibility Committee, the interviewer marks "No" and continues completing the form.

16. Interviewer ID

The interviewer records his/her five-digit assigned code in the appropriate boxes after completion of the *T1DGC Case Eligibility Form*.

17. ID of person editing

This is not completed until a clinic staff member reviews the form to ensure completion and accuracy. The person editing and reviewing the form records his/her five-digit assigned code in the appropriate boxes.

COMPLETED ONLY IF APPLICATION TO ELIGIBILITY COMMITTEE IS REQUIRED.

18. Did the Eligibility Committee approve inclusion in the study?

The interviewer completes this section **only** if a *T1DGC Application to Eligibility Committee* was sent to and a decision was made by the Eligibility Committee. The interviewer marks "Yes" if the Eligibility Committee decided the participant is eligible to

participate, or marks “No” if the Eligibility Committee decided this participant is ineligible to participate in the T1DGC.

19. Date Eligibility Committee decision received by clinic

The interviewer records the date the application is returned to the clinic with a decision regarding the eligibility of the participant. Once information is received regarding the eligibility status of the participant, the clinic corrects Question 14 regarding eligibility status.

APPENDIX G
CASE ELIGIBILITY FORM (GUARDIAN):
QUESTION BY QUESTION INSTRUCTIONS

These instructions are meant to assist the interviewer and to provide answers to any questions from a participant or clinic staff member.

This form is administered to a guardian (*i.e.,* biological mother, biological father or other legal guardian) of the case. The case is an individual diagnosed with Type 1 diabetes. **This form is used if the case is under the legal age to give consent and it is determined by clinic staff that the case is unable to understand and answer all of the questions.** Only one guardian answers the questions; however, more than one can be present at the interview. The interviewer reads the questions to the guardian and marks or records appropriate answers.

Information in all capital letters is an instruction to the interviewer and is not read to the participant.

If at any point during the screening process, the interviewer marks a shaded box, the prospective individual is deemed ineligible.

For eligible participants, please complete all parts of the form. Note that certain individual items may be marked "Don't know" and with an asterisk. In these cases, continue completing the form and contact the appropriate individuals within 10 days in order to collect information not known at the time of the initial screening. The participant may need to contact his/her physician or other family members in order to obtain information. All "PENDING" responses refer to eligibility criteria and must be resolved before the form is forwarded to the Regional Network Center. Items without a "PENDING" status should be followed-up, but forms should be forwarded to the Regional Network Center when it has become apparent that this information will not be found. There may also be situations in which a participant diagnosed with Type 1

diabetes does not meet the Type 1 Diabetes Genetics Consortium (T1DGC) criteria for Type 1 diabetes. In this case the interviewer completes a *T1DGC Application to Eligibility Committee*.

All dates are written as day first, month second, and year third. The day is recorded numerically. If the day is a single-digit number, a "0" is recorded in the first box. The month is written out in its entirety (*e.g.,* January, February). The year is recorded numerically, with all four digits of the year included (*e.g.,* 1950). All single digit numerical responses are recorded with a leading "0" (*e.g.,* if participant is 5 years old, record "05").

Question by Question Instructions

The interviewer does not affix the Case ID Label until it has been determined that this individual is eligible or the eligibility status is "PENDING." Once eligibility has been determined, the interviewer affixes the Case ID Label in the box shown in the upper right hand corner. A label is affixed on every page.

The interviewer records the clinic ID for his/her individual clinic. This number is assigned by the Regional Network Center and it is recorded on every page. The secondary ID (CAS) is already recorded on this form as it is used only for cases.

1. Interview date

This is the date the interview takes place. Record the date of the interview in the appropriate boxes. For some clinics, the information on the form is abstracted from other sources and transferred onto this form. In this case, the interviewer records the date the information is abstracted and the form is completed.

2. How was this form completed? MARK ALL THAT APPLY.

The interviewer marks all sources from which information is gathered about the participant. If information is obtained by calling a participant before he/she comes into the clinic, mark "Phone interview." If the participant comes into the clinic and is

interviewed in person, the interviewer marks "Face-to-face interview." If information is abstracted from other sources (*e.g.,* other forms, pulling medical records), the interviewer marks "From existing records." The interviewer marks all applicable answers.

3. Who is completing this form? ONLY ONE GUARDIAN IS INTERVIEWED.

The interviewer determines the relationship the guardian has with the case. The interviewer may ask the participant his/her relationship to the child, if it is not already known. The interviewer marks "Biological Father" if the man completing the interview believes himself to be the biological father of the case. The interviewer marks "Biological Mother" if the woman completing the interview gave birth to the case. The interviewer marks "Other Guardian" if the person completing this form is neither biological parent of the case.

4. Has this child been diagnosed with Type 1 diabetes?

The participant answers "Yes" if this child has been diagnosed with Type 1 diabetes, Insulin Dependent diabetes, Youth Onset diabetes, or Juvenile Onset diabetes. If the participant answers "No," stop completing this form; this participant is ineligible.

5. Is this child's origin of birth, or primary ethnic origin one of the following? READ CHOICES AND RECORD PARTICIPANT'S RESPONSE.

In Asia-Pacific or European Networks, read the categories listed in the first section of the question: Cameroon, China, India or Thailand. If the guardian answers "None of the above," stop completing this form; this participant is ineligible.

In the North American Network, read the choices listed under the second section of the question: Mexican-American, African-American or both. If the guardian answers "None of the above," stop completing this form; this participant is ineligible.

6. Has this child or any of his/her immediate family members previously participated in any of the following genetic studies? READ/SHOW PARTICIPANT CUE CARD.

The interviewer reads or shows the guardian the cue card that includes the list of previously conducted genetic studies the T1DGC has genetic data from. The guardian responds "Yes" if this child or member(s) of his/her immediate family (*i.e.,* the case, the case's full biological siblings and/or the case's biological parents) has participated in any of the genetic studies listed on the card. If the guardian answers "Yes," stop completing this form; this individual is ineligible. If the guardian does not know this information, the interviewer marks "Don't know" and continues completing the form. This individual's eligibility is "PENDING." If the guardian answers "No," the interviewer continues completing the form.

7. How old was this child when he/she was diagnosed with Type 1 diabetes?

The guardian gives the age the case was diagnosed with Type 1 diabetes. If he/she cannot recall the child's age, an attempt is made to guess, or tell the interviewer in what year the child was diagnosed. The age of diagnosis is calculated from the year of diagnosis. If the age of diagnosis is 35 years or older, stop completing this form; this participant is ineligible. The child's age is recorded in years. If the child was less than 1 year old, record "00."

8. Did this child use insulin within six months of being diagnosed?

The guardian answers "Yes" if insulin was used at any point during the first six months after the case was diagnosed with Type 1 diabetes. This excludes nasal or inhaled insulin. If the guardian answers "Yes," skip to Question 9. If the guardian answers "No," the interviewer continues to Question 8a.

8a. Is there any other information to suggest that this child has Type 1 (insulin dependent) diabetes?

If the guardian answers "Yes," the interviewer applies to the Eligibility Committee who reviews the information submitted on possible affected participants (*e.g.,* the

participant was diagnosed early in the natural history via autoantibodies and/or OGTT and thus is not on insulin). The interviewer completes the *T1DGC Application to Eligibility Committee* and sends it to the Regional Network Center. The interviewer continues completing the form. This participant's eligibility is "PENDING." If the guardian answers "No," stop completing this form; this participant is ineligible.

9. Once this child started using insulin, did he/she ever stop using insulin for a period of six months or more for reasons other than a pancreas transplant?

The guardian answers "Yes" if the case's insulin use was started but discontinued for six months or longer. More than one interruption is permitted if each is within the allotted time frame. If the case has had a pancreas transplant and has stopped using insulin for more than six months because of the transplant, they are not excluded from participating in the T1DGC. If the guardian answers "Yes," stop completing this form; this participant is ineligible. The guardian answers "No" if insulin use was never disrupted after starting on insulin, or if any insulin was stopped for periods within six months. If the participant has not been diagnosed for six months, the "Not applicable" box is marked. However, this does not make this participant ineligible, continue with the form.

10. What is this child's date of birth?

Record the date of birth in the appropriate boxes. For some clinics, this information is considered an identifier and thus cannot be collected. In this case, the interviewer marks the "Can not collect" box, but must answer Question 11. If clinics are able to collect a portion of the date of birth, the year is recorded in the appropriate boxes.

11. What is this child's current age? CHILDREN LESS THAN 12 MONTHS CAN BE INCLUDED AFTER FIRST BIRTHDAY.

The guardian responds by giving the current age of the child at the time of the interview. If the information is abstracted from other sources and transferred onto this form, the interviewer determines the child's current age. The child's age is recorded in

years. If the child is less than 12 months old, mark the "Less than 12 months" box and continue completing this form. This participant's eligibility is "PENDING." However, the child's family is re-contacted after the child has had his/her first birthday.

12. Does this child have a specific genetic disorder or disease that caused his/her diabetes? This would include maturity onset diabetes of youth (MODY). IF YES OR DON'T KNOW, READ/SHOW PARTICIPANT CUE CARD.

The guardian answers "Yes" if the child has been diagnosed with another genetic disease that is known to be associated with non-classical insulin dependent diabetes. If the guardian answers "Yes" or "Don't know," show or read the participant the cue card listing the genetic disorders and diseases that exclude a person from participating in the T1DGC. If the guardian answers "Yes," stop completing this form; this participant is ineligible. If the guardian answers "No," continue completing the form. If the guardian still does not know, mark the "Don't know" box and continue completing the form. This participant's eligibility is "PENDING."

13. Are you willing to have this child participate in this study? READ BRIEF DESCRIPTION OF THE STUDY TO PARTICIPANT FROM CUE CARD.

The guardian now has the option to allow this child to participate in the T1DGC. Participant involvement in the study is discussed. The interviewer reads the cue card containing a brief description of the study. The guardian answers "Yes" if he/she is interested in learning more about the study and allowing this child to participate. If the guardian answers "No," stop completing this form; this participant is ineligible. If the guardian has already given their consent for this child to participate in the study prior to completing the eligibility form, mark the "Has signed consent" box and continue with the form. If the guardian answers "Don't know," continue completing the form and follow-up at a later date for a definitive answer. This participant's eligibility is "PENDING."

14. In what region does this child live, or to what tribe does this child belong? IN CHINA, INDIA OR CAMEROON, HAND PARTICIPANT CUE CARD AND RECORD RESPONSE.

In China, India or Cameroon, the participant chooses one region or tribe. The interviewer hands (or reads) the participant the cue card containing a list of regions or tribes to choose from. If a participant chooses more than one region or tribe, the interviewer asks which region or tribe he/she most identifies with and records that choice. Record the appropriate code(s) in the boxes. In North America and Thailand, the region or tribe is not applicable; the interviewer marks "Not Applicable."

Questions 15-20 are directed toward clinic staff and are completed as the activity occurs (*i.e.,* after interviewing, after editing, and after receiving the *T1DGC Application to Eligibility Committee*).

INTERVIEWER COMPLETED

15. Is this person eligible to participate in this study?

The interviewer reviews the questions to ensure this child meets eligibility requirements. The interviewer marks "Yes" if this child meets all eligibility requirements, and skips to Question 17. The interviewer marks "No" if at one point during the interview he/she came to a "STOP-INELIGIBLE" statement, and skips to Question 17. The interviewer marks "PENDING" if one or more questions regarding the child were marked as "Don't know," or the interviewer is in the process of applying to the Eligibility Committee. If "PENDING" is marked, the interviewer re-contacts the appropriate individuals within 10 days in order to determine eligibility or waits until a decision is made by the Eligibility Committee.

16. Is an application to the Eligibility Committee required?

The interviewer marks "Yes" if the child appears to have Type 1 diabetes, but does not meet the T1DGC definition of diabetes. The interviewer completes the *T1DGC Application to Eligibility Committee* and sends it to the Regional Network Center. The

interviewer continues completing the form. If the interviewer does not need to apply to the Eligibility Committee, the interviewer marks "No" and continues completing the form.

17. Interviewer ID

The interviewer records his/her five-digit assigned code in the appropriate boxes after completion of the *T1DGC Case Eligibility Form*.

18. ID of person editing

This is not completed until a clinic staff member reviews the form to ensure completion and accuracy. The person editing and reviewing the form records his/her five-digit assigned code in the appropriate boxes.

COMPLETED ONLY IF APPLICATION TO ELIGIBILITY COMMITTEE IS REQUIRED.

19. Did the Eligibility Committee approve inclusion in the study?

The interviewer completes this section **only** if a *T1DGC Application to Eligibility Committee* was sent to and a decision was made by the Eligibility Committee. The interviewer marks "Yes" if the Eligibility Committee decided the child is eligible to participate, or marks "No" if the Eligibility Committee decided this child is ineligible to participate in the T1DGC.

20. Date Eligibility Committee decision received by clinic

The interviewer records the date the application is returned to the clinic with a decision regarding the eligibility of the child. Once information is received regarding the eligibility status of the child, the clinic corrects Question 15 regarding eligibility status.

APPENDIX H
CONTROL ELIGIBILITY FORM (CONTROL):
QUESTION BY QUESTION INSTRUCTIONS

These instructions are meant to assist the interviewer and to provide answers to any questions from a participant or clinic staff member.

This form is administered to the control. The control is an individual who has not been diagnosed with Type 1 diabetes. **This form is used if the control is of legal age to give consent and it is determined by clinic staff that the control is able to understand and answer all of the questions.** Only the control answers questions; however, the legal guardians of the control can be present at the interview. The interviewer reads the questions to the control and marks or records appropriate answers.

Information in all capital letters is an instruction to the interviewer and is not read to the participant.

If at any point during the screening process, the interviewer marks a shaded box, the prospective participant is deemed ineligible.

For eligible participants, please complete all parts of the form. Note that certain individual items may be marked "Don't know" and with an asterisk. In these cases, continue completing the form and contact the appropriate individuals within 10 days in order to collect information not known at the time of the initial screening. The participant may need to contact his/her physician or other family members in order to obtain information. All "PENDING" responses refer to eligibility criteria and must be resolved before the form is forwarded to the Regional Network Center. Items without a "PENDING" status should be followed-up, but forms should be forwarded to the Regional Network Center when it has become apparent that this information will not be found.

All dates are written as day first, month second, and year third. The day is recorded numerically. If the day is a single-digit number, a "0" is recorded in the first box. The month is written out in its entirety (*e.g.,* January, February). The year is recorded numerically, with all four digits of the year included (*e.g.,* 1950). All single digit numerical responses are recorded with a leading "0" (*e.g.,* if participant is 5 years old, record "05").

Question by Question Instructions

The interviewer does not affix the Control ID Label until it has been determined that this individual is eligible or the eligibility status is "PENDING." Once eligibility has been determined, the interviewer affixes the Control ID Label in the box shown in the upper right hand corner. A label is affixed on every page.

The interviewer records the clinic ID for his/her individual clinic. This number is assigned by the Regional Network Center and it is recorded on every page. The secondary ID (CON) is already recorded on this form as it is used only for controls.

1. Interview date

This is the date the interview takes place. Record the date of the interview in the appropriate boxes. For some clinics, the information on the form is abstracted from other sources and transferred onto this form. In this case, the interviewer records the date the information is abstracted and the form is completed.

2. How was this form completed? MARK ALL THAT APPLY.

The interviewer marks all sources from which information is gathered about the participant. If information is obtained by calling a participant before he/she comes into the clinic, mark "Phone interview." If the participant comes into the clinic and is interviewed in person, the interviewer marks "Face-to-face interview." If information is abstracted from other sources (*e.g.,* other forms, pulling medical records), the interviewer marks "From existing records." The interviewer marks all applicable answers.

3. Have you ever been diagnosed with Type 1 diabetes, Type 2 diabetes, maturity onset diabetes of youth, (MODY)?

The participant answers "No" if he/she has not been diagnosed with any form of diabetes. This includes, but is not limited to Type 1 diabetes, Type 2 diabetes, and MODY. If the participant answers "Yes," stop completing this form; this participant is ineligible.

4. Is your origin of birth, or primary ethnic origin one of the following? READ CHOICES AND RECORD PARTICIPANT'S RESPONSE.

In Asia-Pacific or European Networks read the categories listed in the first section of the question: Cameroon, China, India or Thailand. If the participant answers "None of the above," stop completing this form; this participant is ineligible.

In the North American Network, read the choices listed under the second section of the question: Mexican-American, African-American or both. If the participant answers "None of the above," stop completing this form; this participant is ineligible.

5. Have you or any of your immediate family members previously participated in any of the following genetic studies? READ/SHOW PARTICIPANT CUE CARD.

The interviewer reads or shows the participant the cue card that includes the list of previously conducted genetic studies the T1DGC has genetic data from. The participant responds "Yes" if he/she or member(s) of their immediate family (*i.e.,* the participant, the participant's full biological siblings and/or the participant's biological parents) has participated in any of the genetic studies listed on the card. If the participant answers "Yes," stop completing this form; this individual is ineligible. If the participant does not know this information, the interviewer marks "Don't know" and continues completing the form. This individual's eligibility is "PENDING." If the participant answers "No," the interviewer continues completing the form.

6. Has any one of the following biological relatives – father, mother, brother(s), sister(s) or children ever been diagnosed with Type 1 diabetes, Type 2 diabetes, or maturity onset diabetes of youth (MODY)?

The participant answers "No" if no biological relative has been diagnosed with any form of diabetes. This includes, but is not limited to Type 1 diabetes, Type 2 diabetes, and MODY. If the participant answers "Yes," stop completing this form; this participant is ineligible.

7. Do you have any of the following diseases? READ/SHOW PARTICIPANT CUE CARD.

The interviewer hands (or reads) the cue card containing a list of diseases. If the participant answers "Yes," stop completing this form; this participant is ineligible. If the participant does not know this information, the interviewer marks "Don't know" and continues completing the form. This individual's eligibility is "PENDING." If the participant answers "No," the interviewer continues completing the form.

8. Are you willing to participate in this study? READ BRIEF DESCRIPTION OF THE STUDY TO PARTICIPANT FROM CUE CARD.

The participant now has the option to participate in the T1DGC. Participant involvement in the study is discussed. The interviewer reads the cue card containing a brief description of the study. The participant answers "Yes" if he/she is interested in learning more about the study and participating. If the participant answers "No," stop completing this form; this participant is ineligible. If the participant has already given his/her consent to participate in the study prior to completing the eligibility form, mark the "Has signed consent" box and continue with the form. If the participant answers "Don't know," continue completing the form and follow-up at a later date for a definitive answer. This participant's eligibility is "PENDING."

9. What is your date of birth?

Record the date of birth in the appropriate boxes. For some clinics, this information is considered an identifier and thus cannot be collected. In this case, the

interviewer marks the "Can not collect" box, but must answer Question 10. If clinics are able to collect a portion of the date of birth, the year is recorded in the appropriate boxes.

10. What is your current age?

The participant responds by giving his/her current age at the time of the interview. If the information is abstracted from other sources and transferred onto this form, the interviewer determines the participant's current age. The participant's age is recorded in years.

11. Gender

The participant responds by giving his/her gender.

12a. Are you Latino, Hispanic or of Spanish origin?

The participant answers "Yes" if he/she considers himself/herself to be either Latino, Hispanic or of Spanish origin. For some clinics, this question is not asked (*e.g.,* Asia-Pacific). In this case, the interviewer marks "Not applicable" and continues with the form. **"Not applicable" is only marked when this question is not read to the participant.** Regardless of the answer to this question, the participant must answer Question 12b.

12b. Which of the following best describes your race (or ethnic origin)? HAND PARTICIPANT CUE CARD AND RECORD PARTICIPANT'S RESPONSES.

This question can be read differently depending on the clinic; either the word "race" or "ethnic origin" may be used due to cultural sensitivity. The interviewer hands (or reads) the participant the cue card containing a list of races (or ethnic origins) to choose from. The participant chooses up to three responses that best describe his/her race (or ethnic origin). If the participant does not feel that any race (or ethnic origin) describes his/her race (or ethnic origin), the entire list found in **Chapter V,** *Interviewing Instructions,* Appendix K should be shown to the participant and choices should be made from this list. Record the appropriate code(s) in the boxes. At least one set of

boxes must be completed. If a participant chooses more than one category, the interviewer asks which race (or ethnic origin) he/she most identifies with and records that choice in the first set of boxes with the word "Primary" beside it.

13. In what region do you live, or to what tribe do you belong? IN CHINA, INDIA OR CAMEROON, HAND PARTICIPANT CUE CARD AND RECORD RESPONSE.

In China, India or Cameroon, the participant chooses one region or tribe. The interviewer hands (or reads) the participant the cue card containing a list of regions or tribes to choose from. If a participant chooses more than one region or tribe, the interviewer asks which region or tribe he/she most identifies with and records that choice. Record the appropriate code(s) in the boxes. In North America and Thailand, the region or tribe is not applicable; the interviewer marks "Not Applicable."

14. Have you participated in any of the following regional, national or international studies? READ/SHOW PARTICIPANT CUE CARD.

The interviewer hands (or reads) the participant the cue card listing previous and ongoing studies. The participant responds "Yes" if he/she has participated in any of the studies on the cue card. If the participant answers "Yes," the interviewer continues with Question 14a. If the participant answers "No" or "Don't know," skip to Question 15.

14a. In which studies have you participated? RECORD MAXIMUM OF FIVE STUDY CODES.

The participant responds by giving the study names in which he/she has participated. The interviewer records up to five study codes that correspond with the study(ies) in which the control has participated.

Questions 15-17 are directed toward clinic staff and are completed as the activity occurs (*i.e.*, after interviewing and after editing).
INTERVIEWER COMPLETED

15. Is this person eligible to participate in this study?

The interviewer reviews the questions to ensure this person meets eligibility requirements. The interviewer marks "Yes" if this person meets all eligibility requirements and continues completing the form. The interviewer marks "No" if at one point during the interview he/she came to a "STOP-INELIGIBLE" statement and continues completing the form. The interviewer marks "PENDING" if one or more questions were marked as "Don't know." If "PENDING" is marked, the interviewer re-contacts the appropriate individuals within 10 days in order to determine eligibility.

16. Interviewer ID

The interviewer records his/her five-digit assigned code in the appropriate boxes after completion of the *T1DGC Control Eligibility Form*.

17. ID of person editing

This is not completed until a clinic staff member reviews the form to ensure completion and accuracy. The person editing and reviewing the form records his/her five-digit assigned code in the appropriate boxes.

APPENDIX I
CONTROL ELIGIBILITY FORM (GUARDIAN):
QUESTION BY QUESTION INSTRUCTIONS

These instructions are meant to assist the interviewer and to provide answers to any questions from a participant or clinic staff member.

This form is administered to a guardian (*i.e.,* biological mother, biological father or other legal guardian) of the control. The control is an individual who has not been diagnosed with Type 1 diabetes. **This form is used if the control is under the legal age to give consent and it is determined by clinic staff that the control is unable to understand and answer all of the questions.** Only one guardian answers the questions; however, more than one can be present at the interview. The interviewer reads the questions to the guardian and marks or records appropriate answers.

Information in all capital letters is an instruction to the interviewer and is not read to the participant.

If at any point during the screening process, the interviewer marks a shaded box, the prospective individual is deemed ineligible.

For eligible participants, please complete all parts of the form. Note that certain individual items may be marked "Don't know" and with an asterisk. In these cases, continue completing the form and contact the appropriate individuals within 10 days in order to collect information not known at the time of the initial screening. The guardian may need to contact his/her child's physician or other family members in order to obtain information. All "PENDING" responses refer to eligibility criteria and must be resolved before the form is forwarded to the Regional Network Center. Items without a "PENDING" status should be followed-up, but forms should be forwarded to the Regional Network Center when it has become apparent that this information will not be found.

All dates are written as day first, month second, and year third. The day is recorded numerically. If the day is a single-digit number, a "0" is recorded in the first box. The month is written out in its entirety (*e.g.,* January, February). The year is recorded numerically, with all four digits of the year included (*e.g.,* 1950). All single digit numerical responses are recorded with a leading "0" (*e.g.,* if participant is 5 years old, record "05").

Question by Question Instructions

The interviewer does not affix the Control ID Label until it has been determined that this individual is eligible or the eligibility status is "PENDING." Once eligibility has been determined, the interviewer affixes the Control ID Label in the box shown in the upper right hand corner. A label is affixed on every page.

The interviewer records the clinic ID for his/her individual clinic. This number is assigned by the Regional Network Center and it is recorded on every page. The secondary ID (CON) is already recorded on this form as it is used only for controls.

1. Interview date

This is the date the interview takes place. Record the date of the interview in the appropriate boxes. For some clinics, the information on the form is abstracted from other sources and transferred onto this form. In this case, the interviewer records the date the information is abstracted and the form is completed.

2. How was this form completed? MARK ALL THAT APPLY.

The interviewer marks all sources from which information is gathered about the participant. If information is obtained by calling a participant's guardian before he/she comes into the clinic, mark "Phone interview." If the guardian comes into the clinic and is interviewed in person, the interviewer marks "Face-to-face interview." If information is abstracted from other sources (*e.g.,* other forms, pulling medical records), the interviewer marks "From existing records." The interviewer marks all applicable answers.

3. Who is completing this form? ONLY ONE GUARDIAN IS INTERVIEWED.

The interviewer determines the relationship the guardian has with the control. The interviewer may ask the participant his/her relationship to the child, if it is not already known. The interviewer marks "Biological Father" if the man completing the interview believes himself to be the biological father of the control. The interviewer marks "Biological Mother" if the woman completing the interview gave birth to the control. The interviewer marks "Other Guardian" if the person completing this form is neither biological parent of the control.

4. Has this child ever been diagnosed with Type 1 diabetes, Type 2 diabetes, or maturity onset diabetes of youth (MODY)?

The guardian answers "Yes" if this child has been diagnosed with Type 1 diabetes, Type 2 diabetes or MODY. If the guardian answers "Yes," stop this participant is ineligible. If the guardian answers "No," continue completing this form.

5. Is this child's origin of birth, or primary ethnic origin one of the following? READ CHOICES AND RECORD PARTICIPANT'S RESPONSE.

In Asia-Pacific or European Networks read the categories listed in the first section of the question: Cameroon, China, India or Thailand. If the guardian answers "None of the above," stop completing this form; this participant is ineligible.

In the North American Network, read the choices listed under the second section of the question: Mexican-American, African-American or both. If the guardian answers "None of the above," stop completing this form; this participant is ineligible.

6. Has this child or any of his/her immediate family members previously participated in any of the following genetic studies? READ/SHOW PARTICIPANT CUE CARD.

The interviewer reads or shows the guardian the cue card that includes the list of previously conducted genetic studies the T1DGC has genetic data from. The guardian responds "Yes" if this child or member(s) of his/her immediate family (*i.e.*, the control,

the control's full biological siblings and/or the control's biological parents) has participated in any of the genetic studies listed on the card. If the guardian answers "Yes," stop completing this form; this individual is ineligible. If the guardian does not know this information, the interviewer marks "Don't know" and continues completing the form. This individual's eligibility is "PENDING." If the guardian answers "No," the interviewer continues completing the form.

7. Has any one of this child's biological relatives – father, mother, brother(s), sister(s) or children ever been diagnosed with Type 1 diabetes, type 2 diabetes, or MODY?

The guardian answers "Yes," if any of this child's biological relative has been diagnosed with Type 1 diabetes, Insulin Dependent diabetes, Youth Onset diabetes, or Juvenile Onset diabetes. If the guardian answers "Yes," stop, this participant is ineligible. If the guardian answers "No," the interviewer continues completing the form. If the guardian does not know this information, the interviewer marks "Don't know" and continues completing the form. This person's eligibility is "PENDING."

8. Does this child have any of the following diseases? READ/SHOW PARTICIPANT CUE CARD.

The interviewere hands (or reads) the cue card containing a list of diseases. If the guardian answers "Yes," stop completing this form; this participant is ineligible. If the guardian does not know this information, the interviewer marks "Don't know" and continues completing the form. This individual's eligibility is "PENDING." If the guardian answers "No," the interviewer continues completing the form.

9. Are you willing to have this child participate in this study? READ BRIEF DESCRIPTION OF THE STUDY TO PARTICIPANT FROM CUE CARD.

The guardian now has the option to allow this child to participate in the T1DGC. The child's involvement in the study is discussed. The interviewer reads the cue card containing a brief description of the study. The guardian answers "Yes" if he/she is interested in learning more about the study and allowing this child to participate. If the

guardian answers "No," stop completing this form; this participant is ineligible. If the guardian has already given his/her consent for this child to participate in the study prior to completing the eligibility form, mark the "Has signed consent" box and continue with the form. If the guardian answers "Don't know," continue completing the form and follow-up at a later date for a definitive answer. This participant's eligibility is "PENDING."

10. What is this child's date of birth?

Record the date of birth in the appropriate boxes. For some clinics, this information is considered an identifier and thus cannot be collected. In this case, the interviewer marks the "Can not collect" box, but must answer Question 11. If clinics are able to collect a portion of the date of birth, the year is recorded in the appropriate boxes.

11. What is this child's current age? CHILDREN LESS THAN 12 MONTHS CAN BE INCLUDED AFTER FIRST BIRTHDAY.

The guardian responds by giving the current age of the child at the time of the interview. If the information is abstracted from other sources and transferred onto this form, the interviewer determines the child's current age. The child's age is recorded in years. If the child is less than 12 months old, mark the "Less than 12 months" box and continue completing this form. This participant's eligibility is "PENDING." However, the child's family is re-contacted after the child has had his/her first birthday.

12. What is this child's gender?

The participant responds by giving the child's gender.

13. Is this child Latino, Hispanic or of Spanish origin?

The guardian answers "Yes" if he/she considers this child to be either Latino, Hispanic or of Spanish origin. For some clinics, this question is not asked (*e.g.,* Asia-Pacific). In this case, the interviewer marks "Not applicable" and continues with the form. **"Not applicable" is only marked when this question is not read to the**

participant. Regardless of the answer to this question, the guardian must answer Question 13b.

13b. Which of the following best describes this child's race (or ethnic origin)? HAND GUARDIAN CUE CARD AND RECORD RESPONSES.

This question can be read differently depending on the clinic; either the word "race" or "ethnic origin" may be used due to cultural sensitivity. The interviewer hands (or reads) the guardian the cue card containing a list of races (or ethnic origins) to choose from. The guardian chooses up to three responses that best describe this child's race (or ethnic origin). If the guardian does not feel that any race (or ethnic origin) describes this child's race (or ethnic origin), the entire list found in **Chapter V,** *Interviewing Instructions,* Appendix K should be shown to the guardian and choices should be made from this list. Record the appropriate code(s) in the boxes. At least one set of boxes must be completed. If a guardian chooses more than one category, the interviewer asks which race (or ethnic origin) the child most identifies with and records that choice in the first set of boxes with the word "Primary" beside it.

14. In what region does this child live, or to what tribe does this child belong? In what region do you live, or to what tribe do you belong? IN CHINA, INDIA OR CAMEROON, HAND PARTICIPANT CUE CARD AND RECORD RESPONSE.

In China, India or Cameroon, the participant chooses one region or tribe. The interviewer hands (or reads) the participant the cue card containing a list of regions or tribes to choose from. If a participant chooses more than one region or tribe, the interviewer asks which region or tribe he/she most identifies with and records that choice. Record the appropriate code(s) in the boxes. In North America and Thailand, the region or tribe is not applicable; the interviewer marks "Not Applicable."

15. Has this child participated in any of the following regional, national or international studies? READ/SHOW GUARDIAN CUE CARD.

The interviewer hands (or reads) the guardian the cue card listing previous and ongoing studies. The guardian responds "Yes" if this child has participated in any of the

studies on the cue card. If the guardian answers "Yes," the interviewer continues with Question 15a. If the guardian answers "No" or "Don't know," skip to Question 16.

15a. In which studies has this child participated? RECORD MAXIMUM OF FIVE STUDY CODES.

The guardian responds by giving the study names in which this child has participated. The interviewer records up to five study codes that correspond with the study(ies) in which the child has participated.

Questions 16-18 are directed toward clinic staff and are completed as the activity occurs (*i.e.*, after interviewing and after editing).

INTERVIEWER COMPLETED

16. Is this child eligible to participate in this study?

The interviewer reviews the questions to ensure this child meets eligibility requirements. The interviewer marks "Yes" if this child meets all eligibility requirements, and continues completing the form. The interviewer marks "No" if at one point during the interview he/she came to a "STOP-INELIGIBLE" statement, and continues completing the form. The interviewer marks "PENDING" if one or more questions regarding the case were marked as "Don't know." If "PENDING" is marked, the interviewer re-contacts the appropriate individuals within 10 days in order to determine eligibility.

17. Interviewer ID

The interviewer records his/her five-digit assigned code in the appropriate boxes after completion of the *T1DGC Control Eligibility Form*.

18. ID of person editing

This is not completed until a clinic staff member reviews the form to ensure completion and accuracy. The person editing and reviewing the form records his/her five-digit assigned code in the appropriate boxes.

APPENDIX J

APPLICATION TO ELIGIBILITY COMMITTEE: QUESTION BY QUESTION INSTRUCTIONS

These instructions are meant to assist the interviewer and to provide answers to any questions from a participant or clinic staff member.

This form is completed by the interviewer about an affected sibling who does not have Type 1 diabetes as defined by the study protocol: diagnosis before the age of 35 years and insulin use within the first 6 months of diagnosis without stopping for 6 months or more.

Many responses on this form are transferred directly from responses on the *T1DGC Eligibility Form*. The interviewer copies information exactly as it is recorded on the *T1DGC Eligibility Form*.

All dates are written as day first, month second, and year third. The day is recorded numerically. If the day is a single-digit number, a "0" is recorded in the first box. The month is written out in its entirety (*e.g.,* January, February). The year is recorded numerically, with all four digits of the year included (*e.g.,* 1950). All single digit numerical responses are recorded with a leading "0" (*e.g.,* if participant is 5 years old, record "05").

Question by Question Instructions

The interviewer affixes the Family ID Label in the box shown in the upper right hand corner. A label is affixed on every page.

The interviewer records the participant identifier for the proband or affected sibling. For the **proband**, this number is "03." For the **affected sibling**, this number is "04." For the first **additional** affected sibling, this number is "07." For the second

additional affected sibling, this number is "08." For the third **additional** affected sibling, this number is "09."

The interviewer records the clinic ID for his/her individual clinic. This number is assigned by the Regional Network Center and it is recorded on every page.

The interviewer records the secondary ID for the proband or affected sibling. The secondary ID is "AS1" for the proband, "AS2" for the affected sibling, "AS3" for the first additional affected sibling, "AS4" for the second additional affected sibling, and "AS5" for the third additional affected sibling, the secondary ID is "AS5." The secondary ID is recorded on every page.

1. Date completed

This is the date the interviewer completed this form. Record the date in the appropriate boxes.

2. Is this application for the proband or the affected sibling?

The interviewer marks whether the application is for the proband or an affected sibling. The proband is the first child diagnosed with diabetes in a family.

3. At what age was the participant diagnosed with Type 1 diabetes?

The interviewer records the participant's age at diagnosis in the appropriate boxes.

4. Did the participant use insulin within six months of being diagnosed?

The interviewer marks the appropriate box. If the participant did not use insulin within six months of being diagnosed, the interviewer provides additional information; if the participant did use insulin within six months of being diagnosed, the interviewer skips to Question 5.

If no, please provide additional information or explanation:

The interviewer records any additional information or an explanation as to why the participant did not use insulin within six months of being diagnosed. If there is no additional information, the interviewer records "None."

5. Once the participant started using insulin, did he/she ever stop using insulin for a period of six months or more for reasons other than a pancreas transplant?

The interviewer marks the appropriate box. If the participant stopped using insulin for a period of six months or more for reasons other than a pancreas transplant, the interviewer provides additional information; if the participant has not stopped using insulin for six months or more or has not been diagnosed for six months, the interviewer skips to Question 6.

If yes, please provide additional information or explanation:

The interviewer records any additional information or an explanation as to why the participant stopped using insulin for six months or more. If there is no additional information, the interviewer records "None."

6. What is the participant's current age?

The interviewer records the participant's current age in the appropriate boxes.

7. Which of the following best describes the participant's race (or ethnic origin)? RECORD UP TO THREE RACE/ETHNICITY CODES FROM CUE CARD.

The interviewer records up to three responses that best describe the participant's race (or ethnic origin). Record the appropriate code(s) in the boxes. At least one set of boxes must be completed. If the participant fits into more than one category, the interviewer should record the race (or ethnic origin) the participant most identifies with in the first set of boxes with the word "Primary" beside it.

8. How many full brothers/sisters does the participant have that have been diagnosed with Type 1 diabetes? Full brothers and sisters are those that have the same biological mother and same biological father.

The interviewer records the number of biological siblings the participant has who have been diagnosed with Type 1 diabetes. Both living and deceased brothers and sisters are included. Stepsiblings, adopted siblings and half siblings are not included.

8a. How many of them meet the T1DGC definition of Type 1 diabetes? That is, diagnosis before 35 years old, insulin use within 6 months of diagnosis without stopping for 6 months or more.

The interviewer records the number of biological siblings who have been diagnosed with Type 1 diabetes as defined by the T1DGC.

9. Are there any laboratory data that might suggest the participant has Type 1 diabetes? If so, please include below. Include information such as autoantibodies and/or c-peptide.

The interviewer records any laboratory data that helps to confirm a Type 1 diabetes diagnosis. This data can be obtained from various sources including physicians, hospital records, or other study data. Laboratory documentation can be attached to the application, if available. If there is no laboratory data, the interviewer records "None."

10. Do any other family members have Type 1 diabetes or another autoimmune disease (*e.g.,* multiple sclerosis, thyroid disease, rheumatoid arthritis, etc.)? Include parents, grandparents, half-siblings, aunts and uncles.

The interviewer records any family member(s) who have been diagnosed with Type 1 diabetes or another autoimmune disease. Please record both the family member's relationship to the participant (*e.g.,* father, brother*)* and the disease(s) this person has been diagnosed with. If there are no other family members with Type 1 diabetes or other autoimmune diseases, the interviewer records "None."

11. What symptoms occurred around the time of diagnosis that are indicative of Type 1 diabetes (for example, diabetic ketoacidosis or other presenting symptoms)?

The interviewer records symptoms indicative of Type 1 diabetes that the participant displayed at the time of diagnosis. If there were no symptoms indicative of Type 1 diabetes, the interviewer records "None."

12. What is the participant's estimated weight loss at time of diagnosis?

The interviewer records the participant's estimated weight loss at the time of diagnosis in the appropriate boxes. The interviewer marks whether the weight is measured in pounds **or** kilograms.

13. What is the participant's estimated BMI or weight at time of diagnosis?

The interviewer records the participant's body mass index (BMI) **or** the participant's weight in the appropriate boxes. If the participant's weight is recorded, the interviewer marks whether the weight is measured in pounds **or** kilograms.

14. Interviewer ID

The interviewer records his/her five-digit assigned code in the appropriate boxes after the completion of the *T1DGC Application to Eligibility Committee.*

15. ID of person editing this form

This is not completed until a clinic staff member reviews the form to ensure completion and accuracy. The person editing and reviewing the form records his/her five-digit assigned code in the appropriate boxes.

16. Date FAXed to Regional Network Center

The interviewer records the date this form is FAXed to the Regional Network Center in the appropriate boxes.

COMPLETED BY REGIONAL NETWORK CENTER

17. Date FAXed to Coordinating Center

A staff member at the Regional Network Center reviews the form and records the date the form is FAXed to the Coordinating Center in the appropriate boxes.

COMPLETED BY COORDINATING CENTER

18. Date FAXed to Eligibility Committee Members

A staff member at the Coordinating Center reviews the form and records the date the form is FAXed to all members of the Eligibility Committee in the appropriate boxes.

19. Eligibility Committee decision

A staff member at the Coordinating Center marks “Approved” if a majority of Eligibility Committee members agree that this participant is eligible for participation in the T1DGC and skips to Question 21. The staff member at the Coordinating Center marks “Ineligible” if a majority of Eligibility Committee members agree that this participant this participant does not meet the criteria for inclusion in the T1DGC and skips to Question 21. If the Eligibility Committee members are undecided and need more information to make a decision, the staff member at the Coordinating Center marks “Need more information” and continues to Question 20.

20. Additional information requested by Eligibility Committee

A staff member at the Coordinating Center summarizes the additional information requested by the Eligibility Committee prior to a decision being made.

21. Date decision FAXed to Regional Network Center

A staff member at the Coordinating Center records the date the completed form is FAXed to the Regional Network Center in the appropriate boxes.

COMPLETED BY REGIONAL NETWORK CENTER

22. Date decision FAXed to Clinic

A staff member at the Regional Network Center records the date the completed form is FAXed to the clinic in the appropriate boxes.

APPENDIX K
APPLICATION TO ELIGIBILITY COMMITTEE FOR CASES: QUESTION BY QUESTION INSTRUCTIONS

These instructions are meant to assist the interviewer and to provide answers to any questions from a participant or clinic staff member.

This form is completed by the interviewer about a case participant who does not have Type 1 diabetes as defined by the study protocol: diagnosis before the age of 35 years and insulin use within the first six months of diagnosis without stopping for six months or more.

Many responses on this form are transferred directly from responses on the *T1DGC Eligibility Form*. The interviewer copies information exactly as it is recorded on the *T1DGC Eligibility Form*.

All dates are written as day first, month second, and year third. The day is recorded numerically. If the day is a single-digit number, a "0" is recorded in the first box. The month is written out in its entirety (*e.g.,* January, February). The year is recorded numerically, with all four digits of the year included (*e.g.,* 1950). All single digit numerical responses are recorded with a leading "0" (*e.g.,* if participant is 5 years old, record "05").

Question by Question Instructions

The interviewer affixes the Case ID Label in the box shown in the upper right hand corner. A label is affixed on every page.

The interviewer records the clinic ID for his/her individual clinic. This number is assigned by the Regional Network Center and it is recorded on every page.

The secondary identifier for the case (CAS) is included on each page of the form.

1. Date completed

This is the date the interviewer completed this form. Record the date in the appropriate boxes.

2. At what age was the participant diagnosed with Type 1 diabetes?

The interviewer records the participant's age at diagnosis in the appropriate boxes.

3. Did the participant use insulin within six months of being diagnosed?

The interviewer marks the appropriate box. If the participant did not use insulin within six months of being diagnosed, the interviewer provides additional information; if the participant did use insulin within six months of being diagnosed, the interviewer skips to Question 4.

If no, please provide additional information or explanation:

The interviewer records any additional information or an explanation as to why the participant did not use insulin within six months of being diagnosed. If there is no additional information, the interviewer records "None."

4. Once the participant started using insulin, did he/she ever stop using insulin for a period of six months or more for reasons other than a pancreas transplant?

The interviewer marks the appropriate box. If the participant stopped using insulin for a period of six months or more for reasons other than a pancreas transplant, the interviewer provides additional information; if the participant has not stopped using insulin for six months or more or has not been diagnosed for six months, the interviewer skips to Question 5.

If yes, please provide additional information or explanation:

The interviewer records any additional information or an explanation as to why the participant stopped using insulin for six months or more. If there is no additional information, the interviewer records "None."

5. What is the participant's current age?

The interviewer records the participant's current age in the appropriate boxes.

6. Which of the following best describes the participant's race (or ethnic origin)? RECORD UP TO THREE RACE/ETHNICITY CODES FROM CUE CARD.

The interviewer records up to three responses that best describe the participant's race (or ethnic origin). Record the appropriate code(s) in the boxes. At least one set of boxes must be completed. If the participant fits into more than one category, the interviewer should record the race (or ethnic origin) the participant most identifies with in the first set of boxes with the word "Primary" beside it.

7. How many full brothers/sisters does the participant have that have been diagnosed with Type 1 diabetes? Full brothers and sisters are those that have the same biological mother and same biological father.

The interviewer records the number of biological siblings the participant has who have been diagnosed with Type 1 diabetes. Both living and deceased brothers and sisters are included. Stepsiblings, adopted siblings and half siblings are not included.

7a. How many of them meet the T1DGC definition of Type 1 diabetes? That is, diagnosis before 35 years old, insulin use within six months of diagnosis without stopping for six months or more.

The interviewer records the number of biological siblings who have been diagnosed with Type 1 diabetes as defined by the T1DGC.

8. Are there any laboratory data that might suggest the participant has Type 1 diabetes? If so, please include below. Include information such as autoantibodies and/or c-peptide. (Include reference ranges/values.)

The interviewer records any laboratory data that helps to confirm a Type 1 diabetes diagnosis. Data can be obtained from various sources including physicians, hospital records, or other study data. Laboratory documentation can be attached to the application, if available. If at all possible, reference ranges/values used by the laboratory should be included. If there are no laboratory data, the interviewer records "None."

9. Do any other family members have Type 1 diabetes or another autoimmune disease (*e.g.,* multiple sclerosis, thyroid disease, rheumatoid arthritis, etc.)? Include parents, grandparents, half-siblings, aunts and uncles.

The interviewer records any family member(s) who have been diagnosed with Type 1 diabetes or another autoimmune disease. Please record both the family member's relationship to the participant (*e.g.,* father, brother*)* and the disease(s) this person has been diagnosed with. If there are no other family members with Type 1 diabetes or other autoimmune diseases, the interviewer records "None."

10. What symptoms occurred around the time of diagnosis that are indicative of Type 1 diabetes (for example, diabetic ketoacidosis or other presenting symptoms)?

The interviewer records symptoms indicative of Type 1 diabetes that the participant displayed at the time of diagnosis. If there were no symptoms indicative of Type 1 diabetes, the interviewer records "None."

11. What is the participant's estimated weight loss at time of diagnosis?

The interviewer records the participant's estimated weight loss at the time of diagnosis in the appropriate boxes. The interviewer marks whether the weight is measured in pounds **or** kilograms.

12. What is the participant's estimated BMI or weight at time of diagnosis?

The interviewer records the participant's body mass index (BMI) **or** the participant's weight in the appropriate boxes. If the participant's weight is recorded, the interviewer marks whether the weight is measured in pounds **or** kilograms.

13. Interviewer ID

The interviewer records his/her five-digit assigned code in the appropriate boxes after the completion of the *T1DGC Application to Eligibility Committee.*

14. ID of person editing this form

This is not completed until a clinic staff member reviews the form to ensure completion and accuracy. The person editing and reviewing the form records his/her five-digit assigned code in the appropriate boxes.

15. Date FAXed to Regional Network Center

The interviewer records the date this form is FAXed to the Regional Network Center in the appropriate boxes.

COMPLETED BY REGIONAL NETWORK CENTER

16. Date FAXed to Coordinating Center

A staff member at the Regional Network Center reviews the form and records the date the form is FAXed to the Coordinating Center in the appropriate boxes.

COMPLETED BY COORDINATING CENTER

17. Date FAXed to Eligibility Committee Members

A staff member at the Coordinating Center reviews the form and records the date the form is FAXed to all members of the Eligibility Committee in the appropriate boxes.

18. Eligibility Committee decision

A staff member at the Coordinating Center marks "Approved" if a majority of Eligibility Committee members agree that this participant is eligible for participation in the T1DGC and skips to Question 20. The staff member at the Coordinating Center marks "Ineligible" if a majority of Eligibility Committee members agree that this participant this participant does not meet the criteria for inclusion in the T1DGC and skips to Question 20. If the Eligibility Committee members are undecided and need more information to make a decision, the staff member at the Coordinating Center marks "Need more information" and continues to Question 19.

19. Additional information requested by Eligibility Committee

A staff member at the Coordinating Center summarizes the additional information requested by the Eligibility Committee prior to a decision being made.

20. Date decision FAXed to Regional Network Center

A staff member at the Coordinating Center records the date the completed form is FAXed to the Regional Network Center in the appropriate boxes.

COMPLETED BY REGIONAL NETWORK CENTER

21. Date decision FAXed to Clinic

A staff member at the Regional Network Center records the date the completed form is FAXed to the clinic in the appropriate boxes.

APPENDIX L

ELIGIBILITY COMMITTEE ADJUDICATION FORM: QUESTION BY QUESTION INSTRUCTIONS

This form is completed by a member of the Eligibility Committee after review of a *T1DGC Application to Eligibility Committee* for a proband, affected sibling, or case. All dates are written as day first, month second, and year third. The day is recorded numerically. If the day is a single-digit number, a "0" is recorded in the first box. The month is written out in its entirety (*e.g.,* January, February). The year is recorded numerically, with all four digits of the year included (*e.g.,* 1950).

Question by Question Instructions

A staff member at the Coordinating Center records the Participant ID and the participant's Secondary ID in the boxes shown in the upper right hand corner.

COMPLETED BY COORDINATING CENTER

1. Date form received at Coordinating Center

A staff member at the Coordinating Center records the date the *T1DGC Application to Eligibility Committee* is received at the Coordinating Center.

2. Date FAXed to Eligibility Committee members

A staff member at the Coordinating Center records the date the completed *T1DGC Application to Eligibility Committee* and the blank *T1DGC Eligibility Committee Adjudication Form* are FAXed to the members of the Eligibility Committee members.

COMPLETED BY ELIGIBIILITY COMMITTEE MEMBER

COMPLETE THIS FORM AND FAX TO COORDINATING CENTER (ATTENTION: ELIZABETH SIDES) AT 336-716-5425.

3. Date form reviewed

The Eligibility Committee member records the date the *T1DGC Application to Eligibility Committee* is reviewed.

4. Member decision

The Eligibility Committee member marks their decision regarding inclusion of the participant in the T1DGC. The member marks "Approve" if he/she has no other questions and believes this participant has Type 1 diabetes and can be included in the T1DGC. The member marks "Ineligible" if he/she does not think this participant has Type 1 diabetes and should not be included in the T1DGC. If the member marks "Approve" or "Ineligible," the member skips to Question 6. The member marks "Need more information" if he/she is unable to make a decision about the participation of the individual without further information.

5. What other information do you feel is necessary to have prior to making a final decision about the potential participant?

The Eligibility Committee member records any information he/she must have prior to making a decision regarding the individual's eligibility.

6. Reviewer name

The Eligibility Committee member writes his/her name on the line provided.

COMPLETED BY COORDINATING CENTER

7. Date completed form received at Coordinating Center

A staff member at the Coordinating Center records the date the *T1DGC Eligibility Committee Adjudication Form* is received at the Coordinating Center.

APPENDIX M

ASP APPLICATION FOR ADDITIONAL AFFECTED SIBLING: QUESTION BY QUESTION INSTRUCTIONS

These instructions are meant to assist the interviewer and to provide answers to any questions from a participant or clinic staff member.

This form is administered to the proband (the first child diagnosed with diabetes in the family) or the guardian *(i.e.,* biological mother, biological father or other legal guardian) of the affected sibling. Only one person answers the questions, however more than one can be present at the interview. The interviewer reads the questions to the participant and marks or records appropriate answers.

Information in all capital letters is an instruction to the interviewer and is not read to the participant.

If at any point during the screening process, the interviewer marks a shaded box, the prospective affected sibling is deemed ineligible. The family may still be eligible.

For eligible participants, please complete all parts of the form. Note that certain individual items may be marked "Don't know" and with an asterisk. In these cases, continue completing the form and contact the appropriate individuals within 10 days in order to collect information not known at the time of the initial screening. The participant may need to contact his/her physician or other family members in order to obtain information. All "PENDING" responses refer to eligibility criteria and must be resolved before the form is forwarded to the Regional Network Center. Items without a "PENDING" status should be followed-up, but forms should be forwarded to the Regional Network Center when it has become apparent that this information will not be found. The family may still be eligible, and the clinic should continue collecting data and blood samples on eligible members of the family. There may also be situations in which a participant diagnosed with Type 1 diabetes does not meet the Type 1 Diabetes

Genetics Consortium (T1DGC) criteria for Type 1 diabetes. In this case the interviewer completes a *T1DGC Application to Eligibility Committee*.

All dates are written as day first, month second, and year third. The day is recorded numerically. If the day is a single-digit number, a "0" is recorded in the first box. The month is written out in its entirety (*e.g.,* January, February). The year is recorded numerically, with all four digits of the year included (*e.g.,* 1950). All single digit numerical responses are recorded with a leading "0" (*e.g.,* if participant is 5 years old, record "05").

Question by Question Instructions

The interviewer does not affix the Family ID Label until it has been determined that this participant is eligible or his/her eligibility status is "PENDING." Once eligibility has been determined, the interviewer affixes the Family ID Label in the box shown in the upper right hand corner. A label is affixed on every page.

The interviewer records the participant identifier for the additional affected sibling. For the first **additional** affected sibling, this number is "07." For the second **additional** affected sibling, this number is "08." For the third **additional** affected sibling, this number is "09." These boxes are recorded on every page.

The interviewer records the clinic ID for his/her individual clinic. This number is assigned by the Regional Network Center and it is recorded on every page.

The interviewer records the secondary ID for the additional affected sibling. The secondary ID is "AS3" for the first **additional** affected sibling, "AS4" for the second **additional** affected sibling, and "AS5" for the third **additional** affected sibling.

1. Interview date

This is the date the interview takes place. Record the date of the interview in the appropriate boxes. For some clinics, the information on the form is abstracted from

other sources and transferred onto this form. In this case, the interviewer records the date the information is abstracted and the form is completed.

2. How was this form completed? MARK ALL THAT APPLY.

The interviewer marks all sources from which information is gathered about the participant. If information is obtained by calling a participant before he/she comes into the clinic, mark "Phone interview." If the participant comes into the clinic and is interviewed in person, the interviewer marks "Face-to-face interview." If information is abstracted from other sources (*e.g.,* other forms, pulling medical records), the interviewer marks "From existing records." The interviewer marks all applicable answers.

3. Who is completing this form? IF GUARDIAN COMPLETING FORM, READ ITALICIZED TEXT. ONLY ONE GUARDIAN IS INTERVIEWED.

The interviewer determines the relationship the participant has with the affected sibling. The interviewer may ask the participant his/her relationship to the sibling, if it is not already known. The interviewer marks "Proband" if the person completing the interviewer is the sibling of the affected sibling. The interviewer marks "Biological Father" if the man completing the interview believes himself to be the biological father of both the proband and the affected sibling. The interviewer marks "Biological Mother" if the woman completing the interview gave birth to both the proband and the affected sibling. The interviewer marks "Other Guardian" if the person completing this form is neither biological parent of the proband and the affected sibling. The interviewer should be aware of the relationship the participant has to the sibling while administering this questionnaire. If the form is administered to the guardian, the italicized text in parentheses is read. Versions of questions may differ based upon the relationship to the affected sibling.

ONLY ONE INDIVIDUAL OF AN IDENTICAL TWIN PAIR MAY PARTICIPATE AS AN AFFECTED SIBLING.

4. Do you *(Does this child)* have another living full brother or sister who is not an identical twin who has been diagnosed with Type 1 diabetes? Full brothers and sisters are those that have the same biological mother and same biological father.

The participant answer "Yes" if he/she, or the proband, has another full brother or sister with Type 1 diabetes, Insulin Dependent diabetes, Youth Onset diabetes, or Juvenile Onset diabetes. This affected sibling cannot be the proband's, or another affected sibling's, identical twin, however a fraternal twin is eligible to participate. If the participant is unsure if the twins are fraternal or identical, both should participate. If the participant answers "No" or "Don't know," stop completing this form; this participant is ineligible.

5. At what age was this brother/sister *(child)* diagnosed with Type 1 diabetes?

The participant gives the age the affected sibling was diagnosed with Type 1 diabetes. If he/she cannot recall the sibling's age, an attempt is made to guess, or tell the interviewer in what year the sibling was diagnosed. The age of diagnosis is calculated from the year of diagnosis. If the age of diagnosis is 35 years or older, stop completing this form; this participant is ineligible. If the participant has no recollection of the sibling's age at diagnosis or the year of diagnosis, mark the "Don't know" box and continue with the form. This participant's eligibility is "PENDING." The sibling's age is recorded in years. If the child was less than 1 year old, record "00."

6. Did this brother/sister *(child)* use insulin within six months of being diagnosed?

The participant answers "Yes" if insulin was used at any point during the first six months after the affected sibling was diagnosed with Type 1 diabetes. This excludes nasal or inhaled insulin. If the participant answers "Yes," skip to Question 7. If the participant answers "No," the interviewer continues to Question 6a. If the participant does not know this information, mark the "Don't know" box and continue completing the form. This participant's eligibility is "PENDING."

6a. Is there any other information to suggest that this brother/sister *(child)* has Type 1 (insulin dependent) diabetes?

If the participant answers "Yes," the interviewer applies to the Eligibility Committee who reviews the information submitted on possible affected participants (*e.g.,* the participant was diagnosed early in the natural history via autoantibodies and/or OGTT and thus is not on insulin). The interviewer completes the *T1DGC Application to Eligibility Committee* and sends it to the Regional Network Center. The interviewer continues completing the form. This participant's eligibility is "PENDING." If the participant answers "No," stop completing this form; this participant is ineligible.

7. Once this brother/sister *(child)* started using insulin, did he/she ever stop using insulin for a period of six months or more for reasons other than a pancreas transplant?

The participant answers "Yes" if the affected sibling's insulin use was started but discontinued for six months or longer. More than one interruption is permitted as long as each is within the allotted time frame. If the affected sibling has had a pancreas transplant and has stopped using insulin for more than six months because of the transplant, they are not excluded from participating in the T1DGC. If the participant answers "Yes," stop completing this form; this participant is ineligible. The participant answers "No" if insulin use was never disrupted after starting on insulin, or if any insulin was stopped for periods within 6 months. If the participant has not been diagnosed for six months, the "Not applicable" box is marked. However, this does not make this participant ineligible, continue with the form. If the participant answers "Don't know," continue with the form; this participant's eligibility is "PENDING."

8. What is this brother/sister's *(child's)* date of birth?

Record the date of birth in the appropriate boxes. For some clinics, this information is considered an identifier and thus cannot be collected. In this case, the interviewer marks the "Can not collect" box, but must answer Question 9. If clinics are able to collect a portion of the date of birth, the year is recorded in the appropriate

boxes. If the participant doesn't know this information, mark the "Don't know" box and continue with the form.

9. What is this brother/sister's *(child's)* current age? CHILDREN LESS THAN 12 MONTHS CAN BE INCLUDED AFTER FIRST BIRTHDAY.

The participant responds by giving the current age of the affected sibling at the time of the interview. If the information is abstracted from other sources and transferred onto this form, the interviewer determines the affected sibling's current age. The affected sibling's age is recorded in years. If the sibling is less than 12 months old, mark the "Less than 12 months" box and continue completing the form. This participant's eligibility is "PENDING." The participant's family can be re-contacted after the sibling has had his/her first birthday. However, the clinic continues collecting data and laboratory samples on members of the family over 12 months old. The family's status is **not** "PENDING." If the participant does not know the sibling's current age mark the "Don't know" box and continue with the form.

10. Does this brother/sister *(child)* have a specific genetic disorder or disease that caused his/her diabetes? This would include maturity onset diabetes of youth (MODY). IF YES OR DON'T KNOW, READ/SHOW PARTICIPANT CUE CARD.

The participant answers "Yes" if the affected sibling has been diagnosed with another genetic disease that is known to be associated with non-classical insulin dependent diabetes. If the participant answers "Yes" or "Don't know," show or read the participant the cue card listing the genetic disorders and diseases that exclude a person from participating in the T1DGC. If the participant answers "Yes," stop completing this form; this participant is ineligible. If the participant answers "No," continue completing the form. If the participant still does not know, mark the "Don't know" box and continue completing the form. This participant's eligibility is "PENDING."

Questions 11-16 are directed toward clinic staff and are completed as the activity occurs (*i.e.,* after interviewing, after editing, and after receiving the *T1DGC Application to Eligibility Committee*).

INTERVIEWER COMPLETED

11. Is this affected sibling eligible to participate in this study?

The interviewer reviews the questions to ensure this participant meets eligibility requirements. The interviewer marks "Yes" if this participant meets all eligibility requirements, and skips to Question 13. The interviewer marks "No" if at one point during the interview he/she came to a "STOP-INELIGIBLE" statement, and skips to Question 13. The interviewer marks "PENDING" if one or more questions about the affected sibling were marked as "Don't know" or the interviewer is in the process of applying to the Eligibility Committee. If "PENDING" is marked, the interviewer re-contacts the appropriate individuals within 10 days in order to determine eligibility or waits until a decision is made by the Eligibility Committee.

12. Is an application to the Eligibility Committee required?

The interviewer marks "Yes" if the affected sibling appears to have Type 1 diabetes, but does not meet the T1DGC definition of diabetes. The interviewer completes the *T1DGC Application to Eligibility Committee* and sends it to the Regional Network Center. The interviewer continues completing the form. If the interviewer does not need to apply to the Eligibility Committee, the interviewer marks "No" and continues completing the form.

13. Interviewer ID

The interviewer records his/her five-digit assigned code in the appropriate boxes after completion of the *T1DGC ASP Application for Additional Affected Sibling*.

14. ID of person editing this form

This is not completed until a clinic staff member reviews the form to ensure completion and accuracy. The person editing and reviewing the form records his/her five-digit assigned code in the appropriate boxes.

COMPLETED ONLY IF APPLICATION TO ELIGIBILITY COMMITTEE REQUIRED.

15. Did the Eligibility Committee approve inclusion in the study?

The interviewer completes this section **only** if a *T1DGC Application to Eligibility Committee* was sent to and a decision was made by the Eligibility Committee. The interviewer marks "Yes" if the Eligibility Committee decided the participant is eligible to participate, or marks "No" if the Eligibility Committee decided this participant is ineligible to participate in the T1DGC.

16. Date Eligibility Committee decision received by clinic:

The interviewer records the date the application is returned to the clinic with a decision regarding the eligibility of the affected sibling. Once information is received regarding the eligibility status of the affected sibling, the clinic corrects Question 11 regarding eligibility status.

INTERVIEWING INSTRUCTIONS

TABLE OF CONTENTS

I. EXAM FORMS OVERVIEW

This section of the *Type 1 Diabetes Genetics Consortium (T1DGC) Manual of Operations* encompasses the instructions for the administration of all exam forms that are used during the examination. See **Chapter II,** *Guidelines,* for a summary of the exam forms, when they are administered, and to whom.

Before a participant comes into the clinic, prepare and review the forms for the exam. For ASP and trio families, these forms include: the *T1DCG Consent Summary Form* (one for each family); the *Informed Consent* (one for each participating family member); the *T1DGC Exam Form* (one for each participating family member); and the *T1DGC Blood Collection Form* (one or each participating family member).

In the Case/Control Study, the forms include the *Informed Consent* (one for each individual), the *T1DGC Exam Form* (for cases only), and the *T1DGC Blood Collection Form* (one for each individual). There is no *T1DGC Consent Summary Form* for the Case/Control study.

See Appendices A-E for comprehensive instructions (Q x Qs) for the *T1DCG ASP Consent Summary Form* and each *T1DGC ASP Exam Form*. See Appendices F-H for comprehensive instructions (Q x Qs) for the *T1DGC Trio Consent Summary Form* and each *T1DGC Trio Exam Form.* See Appendix I for comprehensive instructions (Q x Qs) for the *T1DGC Case Exam Form.* See **Chapter VI**, *Blood Collection and Processing,* for the instructions to complete the *T1DGC Blood Collection Form*s.

If the *T1DGC Exam Form* is completed over the phone prior to the participant signing the *Informed Consent*, when the participant comes into the clinic for blood collection and to sign the *Informed Consent*, the responses on the *T1DGC Exam Form* should be reviewed with the participant and the date of interview changed to the date the participant was seen in the clinic.

For certain networks, it is necessary for the interviewer to translate the questions on the forms to another language in order for the participant to understand the questions. It is critical that the meaning and intent of questions be maintained. The interviewer must be fluent in both the participant's native tongue and English to ensure that correct responses are elicited and recorded.

II. INTERVIEWING PRINCIPLES AND PROCEDURES

Interviewing, in part, is a science and also an art. There are definite rules that produce valid results and general guidelines to follow, but much depends on the sensitivity of the interviewer. The procedures and techniques that follow will help you to conduct interviews that yield valid data.

A. Developing a Good Interviewing Relationship

Interviewing is a major component of the T1DGC study, and therefore it is crucial that interviewers present questions appropriately and record participant responses precisely and accurately. In order to maintain an objective information-gathering atmosphere, the interviewer must convey that he/she is an understanding person capable of accepting information in a non-judgmental manner and convey an interest in what the participant is saying. The participant must find satisfaction in talking to a receptive person without the fear of appearing inadequate.

It is the interviewer's responsibility to obtain full and accurate information by eliciting cooperation from participants, establishing and maintaining rapport, and encouraging active participation in a strictly neutral way. Interviewers are skilled professionals. Their skills make it possible for participants to give frank, complete, and relevant answers to questions.

In general, the majority of participants are willing to be interviewed. A confident, enthusiastic approach that assumes people are willing to be interviewed is the most effective technique.

To increase the participant's cooperativeness, be prepared and know the material. Participants need to feel that the interviewer is interested in the study and in their responses. Be an active listener and establish comfortable eye contact with the participant. Offer convincing statements about the purpose of the study. Discuss how the participant was selected. Describe the beneficial uses of the research findings to both the participant and to the community.

B. Type of Questions

1. *Pre-coded Questions:* With pre-coded questions, mark an "X" in the correct response box. In addition to marking a box, it is very important that you record the participant's verbatim response on the form whenever there is uncertainty about which code is appropriate.

2. *Multiple Answer Questions:* With multiple answer questions, mark an "X" in all correct response boxes. If the participant is unsure about any or all of the information, only the "Don't know" box should be marked. In some cases a "None of the above" choice can be marked if none of the responses are correct.

3. *Fill-in-the-Box Questions:* With fill-in-the-box questions, the correct numbers should be recorded in the corresponding boxes. If there are two boxes, and the digit is a single-digit number, a leading "0" (zero) is placed in the first box. **Each box must contain a numerical value.**

C. Interviewer Administered Questionnaires

There are several standard procedures for reading questions. Read in a natural conversation rhythm and in a normal tone of voice. Be cautious about reading questions too rapidly. The participant may not feel comfortable asking that questions be repeated and consequently the answer will not reflect his/her true thoughts on the issue. Be aware of the participant's facial expressions (*e.g.,* puzzled, confused). Repeat the question if it is answered inappropriately, but repeat it exactly as written. Show no impatience when asked to repeat a question.

Each question must be asked of each participant in the same way and in the same order to ensure that comparable information is being obtained from all participants in the study.

1. Interview instructions are provided throughout the interview on the forms. These instructions are not to be read to participants but are intended to give the interviewer direction. The interviewer instructions appear in all capital letters.

2. Read only those choices that appear in the question and those you are instructed to read.

3. Ask the questions exactly as worded and in the same order as they appear in the questionnaires. Minor changes in wording can completely change the meaning of a question. Unless each interviewer asks the questions exactly as shown, the answers are not valid. Similarly, follow the sequence of questions. Do not ask questions out of order.

4. Ask every question. It is the interviewer's responsibility to ask every question. Often a previous statement by the participant will partially answer another question, but rarely does it answer that question completely. Do not omit questions and do not assume you know the answer to the question.

5. Follow skip patterns. For several questions, answering a question by responding in one way, makes one or more questions after this question irrelevant. Throughout the forms, the interviewer may be directed to skip to another question. Questions that are skipped should not be answered.

D. How to Get Satisfactory Answers

1. Learn the purpose of each question. In order to interview well, you need to understand the type of information we are trying to capture with each particular question. Unless you understand its purpose, you may not be able to judge when a response is adequate and when you must probe for clarification or for additional information.

2. Do not attempt to interpret or explain the question; maintain neutrality. If a participant does not seem to understand a question, repeat the question slowly and clearly. Give the participant time to think about the question (while simultaneously being aware of time allowed for administering the form). Unless there are other instructions about handling specific questions, the acceptable reply for a participant who wants to know what a question means is "whatever it means to you". Do not attempt to explain the purpose of a question.

3. Do not define terms used in questions. Some participants may ask what is meant by a word used in a question. Leave the matter of definition to the participant, suggesting "whatever you think _____ means" or "however you use the term _____".

4. Do not leave a question until you have an adequate answer or have determined that a participant cannot give a clear answer.

E. How to Record the Interviews

1. In order to best record participants' responses, the following suggestions are recommended:
   a. Be prepared to write.
   b. Periodically establish eye contact with the participant while writing.
   c. If you question whether you marked the correct response, be sure to record the participant's verbatim response on the form.
   d. If you make a recording mistake, cross out the error with two horizontal lines. Then circle, initial, and date the correct answer. **Never use white out to erase a mistake.**

2. The form sets are FAXed or photocopies are mailed to the Regional Network Center for data entry. Therefore, the following recording techniques are mandatory to ensure clarity and quality of the answers on the forms:
   a. Mark a response box with an "X," not a check. Otherwise, the data editor will have to re-mark the answers before sending the form set.

b. A black, medium-tip ballpoint pen must be used to record answers. Pencils are never used to complete data forms.

c. If a wrong answer is inadvertently marked, draw two horizontal lines through the wrong answer. Mark an "X" in the correct response box, circle the correct response box, and write your initials and the date next to the correct response. **Never use white out on any form. All corrections must be documented as described above.**

d. If no answer is given and there is not an appropriate response box, mark the "Not applicable" or "Question not asked" box.

e. Numerals must be printed clearly and legibly. It is requested that the following numerals be recorded in this manner:
Zero has a line drawn through it (Ø);
One is written as a single vertical line (|); and
Seven has a line drawn through the stem (7̸).

III. USING THE CUE CARDS

There are a number of cue cards to assist you and the participant in completing the exam forms. Some of these cue cards contain information that are read to the participant before the participant answers the questions. Other cue cards are handed to the participant so that they may select any correct responses. If a participant cannot read English, the interviewer may need to read all cue cards to the participants.

The cue cards that are read to the participant do not have to be read exactly as written. These cue cards are meant to help you when there is doubt about what to say. Although the cue card does not have to be read exactly as written, the information on the cue card must be conveyed to the participant to capture the correct response(s). The cue cards that are handed to the participant usually contain a list of choices from which a participant may select. Table 1 provides a summary of the cue cards and when and how they are used. Cue cards are network-specific, listing only the relevant responses. The cue cards provided in Appendix J list all applicable responses and

should be referenced if the interviewer believes the participant will benefit from seeing the complete list.

The *Classification of Cultural and Ethnic Groups* (Appendix K) will be used to develop the network-specific ethnicity cue card (Cue Card 4) in the North American and United Kingdom Networks; the entire list may be referenced if a participant does not identify with categories on the network-specific cue card. In the Asia-Pacific and European Networks, the entire list will be used rather than a cue card.

Categories listed as "no further designation" mean that a participant does not identify with one of the smaller, more definitive categories (*e.g.*, a participant is British, but not English, Scottish or Welsh). For North American trio family participants it is important to use a designation other than "810, North American, no other designation" because this does not provide sufficient information regarding race or ethnic origin. For further information regarding this, refer to **Chapter III,** *Recruitment* and **Chapter IV**, *Eligibility*.

Categories listed as "not elsewhere classified" mean that a participant identifies with the primary classification, but is part of a smaller group of people within that category (*e.g.*, Inuit).

Cue Card 6 contains a list of regional, national, and international studies that are funded by either the National Institutes of Health (NIH) or by the Juvenile Diabetes Research Foundation (JDRF). Participation in any of these studies is not an exclusion criterion; however, the T1DGC is interested in compiling information regarding overlap of participants between the T1DGC and these studies. If a participant is uncertain about participation in one of these studies, the descriptions provided below may be used.

DPT-1 (Diabetes Prevention Trial – Type 1): An international multi-centered trial looking at whether antigen treatment (either injected or oral insulin) could delay or prevent the onset of Type1 diabetes in those at risk for Type 1 diabetes.

TrialNet (Type 1 Diabetes TrialNet): Based upon the clinical trial network created for DPT-1. TrialNet conducts large scale trials aimed at preventing Type 1 diabetes and preserving beta cell function in patients with recent onset Type 1 diabetes.

TEDDY (Consortium for Identification of the Environmental Determinants of Diabetes in the Young): An international consortium to identify infectious agents, dietary factors, or other environmental factors which may trigger Type 1 diabetes in genetically susceptible individuals from birth.

SEARCH (SEARCH for Diabetes in Youth): An epidemiological study focusing on children and youth in the United States who have diabetes. The study goals are to identify the number of children and youth under age 20 who have diabetes and learn how Type 1 and Type 2 diabetes differs. Additionally, researchers will learn about complications, the different types of medical care received, and how diabetes affects the lives of children and youth who have diabetes.

GoKinD (Genetics of Kidneys in Diabetes): Investigating the role genes play in causing nephropathy in people with Type 1 diabetes. The fundamental aim of GoKinD is to facilitate investigator-driven research into the genetic basis of diabetic nephropathy by collecting the necessary DNA samples to determine if there are genetic differences between people who do and do not develop diabetic kidney disease. GoKinD is a multi-clinic study across the United States and Canada.

TRIGR (Trial to Reduce IDDM in the Genetically at Risk): An international trial to determine whether delayed exposure to intact food proteins will reduce the chances of developing Type 1 diabetes in babies genetically at risk for the disease.

EDIC (Epidemiology of Diabetes Interventions and Complications): A multi-center, longitudinal, observational study designed as follow-up to the Diabetes Control and Complications Trial (DCCT). Data collection focuses on nephropathy and macro vascular complications.

FIND (The Family Investigation of Nephropathy and Diabetes): A multi-center consortium established to identify the genes responsible for diabetic nephropathy. Participants have cell lines created, and a repository containing stored urine and serum samples has been developed.

ENDIT (European Nicotinamide Diabetes Intervention Trial): Randomized controlled trial assessing the effect of nicotinamide treatment on the development of Type 1 diabetes in non-diabetic autoantibody-positive (ICA) first-degree relatives of patients with Type 1 diabetes.

PANDA (Prospective Assessment in Newborns for Diabetes Autoimmunity): Study attempting to define the interactions of genes and environmental factors that initiate or protect children from Type 1 diabetes. Newborns at high genetic risk are being followed prospectively to identify dietary factors, infectious agents or other environmental factors that may trigger autoimmunity.

Australian Type 1 Diabetes Repository: Aims to identify genes and immune markers that predispose to Type 1 diabetes. A blood sample is collected from family members of a person with Type 1 diabetes (including the person with Type 1 diabetes). The repository stores samples of cells or DNA and keeps information about the genetic and other relevant tests in a data base for ongoing and future diabetes research.

EURODIAB TIGER: Prospective, international register which included children with onset of diabetes before age 15, in 36 different centers throughout Europe. This study has provided interesting epidemiological information about geographical and seasonal variations in incidence of the disease.

BOX (Bart's Oxford Family Study of Childhood Diabetes): A longitudinal study aiming to enroll the families of all people living in the Oxford region who develop diabetes before the age of 21 in order to investigate the genetic and environmental factors contributing to the development of diabetes.

Cue Cards 7 and 8 (Pedigree) are not referred to in the exam forms as are the others. These may be useful in identifying family members, but their use is optional.

Cue Card 9 is not referred to on the *North American Trio Pre-Eligibility Form* or the Case/Control eligibility forms but is provided to clinic staff in order to quickly allow clinic staff to review the definition of ethnicity/race for North American trios, cases and controls.

Cue Card 10 will only be used in China, India and Cameroon and provides the region and tribe categories for the Case/Control Study.

Table 1. Summary of Cue Cards and Intended Use

Cue Card	Cue Card Title	When Used	Interviewer or Self-Read
1	Genetic Studies	Eligibility Form	Self-Read
2	Exclusion Disorders	Eligibility Form	Self-Read
3	Description of Study	Eligibility Form	Interviewer Read
4	Race/Ethnic Origin	Exam Form	Self-Read
5	Diseases or Disorders	Exam Form	Self-Read
6	Previous Studies	Exam Form	Self-Read
7-8	Pedigree	Exam Forms	Interviewer uses to identify family members
9	Definitions for North American Network Only	NA Trio Pre-Eligibility and Case/Control Eligibility Forms	Interviewer uses to clarify definition of ethnicity/race
10	Region/Tribe	Case/ Control Eligibility Forms	Self-Read

IV. FOLLOWING TRAINING

Familiarize yourself with the questionnaires. Read the instructions carefully. Administer questionnaires to yourself just as you would a participant and probe yourself if an answer to a question is uncodable or otherwise inadequate. Complete the interview with a co-worker or family member. Re-read the instructions watching for any errors you make so that you do not repeat them on subsequent interviews. Study the comprehensive instructions (Q x Qs) thoroughly so that you understand the purpose of the questions. You may wish to re-read this manual following the conduct of interviews. It may provide a different perspective and reinforce what you have experienced. Complete the pilot study and carefully note the specific feedback from the Regional Network Center.

V. CONFIDENTIALITY BETWEEN PARTICIPANT AND INTERVIEWER

Participants may be hesitant to participate or disclose personal information if they are unsure where this information is going or what is done with the information they disclose. In order to help participants feel at ease, confidentiality practices must be explained fully.

A. How to Explain the Flow of Information

1. Be familiar with where participant information and laboratory samples are sent.

2. The identifier that allows the clinics, the Regional Network Center, the Coordinating Center and the laboratories to identify a participant is an ID that contains a network identifier, family identifier and personal identifier. The only individuals who know the identity of participants are the clinic staff.

3. Information is not disclosed to other family members or any other participants in the study.

4. Information is seen only by the Clinic Coordinator and other clinic staff.

5. Information received from questionnaires is sent to the Regional Network Center, using only the participant's ID number, where a data entry coordinator views the answers while entering them into a computer.

6. These data are transmitted to the Coordinating Center where it is analyzed. There also are data edits for incomplete or incorrect information that are corrected by the Regional Network Center and the clinics.

7. Blood samples are sent to regional laboratories for storage and analysis. A cell line sample, DNA aliquots, and storage samples are sent to a Central NIDDK Repository for storage. DNA aliquots are sent to genotyping facilities around the world for study-directed genotyping projects.

8. Members of the Type 1 Diabetes Genetics Consortium and the scientific community at large can request cell lines and blood samples. These scientists are from all over the world.

B. Participant Confidentiality

All information regarding a participant is confidential. Participant files and study documents are kept secure using the same protocol as is used by individual clinics for patient charts. Information sent to the Regional Network Center, the Coordinating Center, and the laboratories has no personal identifiers.

VI. ANSWERING DIFFICULT QUESTIONS

Being familiar with the information is not enough when participants ask you difficult questions that you may or may not be able to answer. The following contains appropriate answers to difficult questions that participants may ask. However, if you are unsure of how to respond to a participant's question, be familiar with other resources you can access or where to direct the participant (*e.g.,* Principal Investigator, physicians, etc.).

A. How was I chosen for this study? How did you get my name?

The answer to this question varies by network and/or clinic and the mode of recruitment. Some possible answers include:

We received your name from the national registry.

Another study put us in contact with you.

Your child (or brother/sister) participated in another study with us, and now we would like to get their biological family's information.

B. Will I be informed of the paternity for myself (or my sibling or my children)?

Although the Coordinating Center in Winston-Salem, North Carolina, United States of America, will know the paternity of you, your siblings, and your children, this information is not transmitted to the Regional Network Center or the clinics. I will not know this information nor can I obtain this information. Further, information at the Coordinating Center is stored only by participant ID; they will not know your name.

C. Why I am ineligible to participate in this study?

You do not meet the study criteria for a person with Type 1 diabetes. I am not disagreeing with your doctor's opinion, but you do not meet the criteria for this study. If you have any questions about your diabetes, I will try to help or you can talk to your physician.

D. Why isn't my other sibling able to participate as well?

This particular study is only interested in the children that have Type 1 diabetes, and only up to two children who do not have diabetes in a family are able to participate. Since this is a genetic study, we are able to obtain more information from those siblings that have Type 1 diabetes than those who do not.

E. Who will receive my genetic information?

Clinics should have on hand a list of the Regional Network Center, regional laboratories, and the Coordinating Center so that it is readily available if a participant

asks for this information. If the participant wants a verbal answer only, the following will probably satisfy their curiosity.

Your blood samples will go to two different laboratories, one for analysis and one for creation of a cell line. The results from the laboratory will be sent to the Coordinating Center in Winston-Salem, North Carolina, United States of America for analyses. The group of scientists that are participating in this study can apply to the Coordinating Center to get your information, although this does not always mean they will receive it. These scientists are kept from knowing your identity.

F. Why should I participate in this study?

You will be part of an important research program to help understand the causes of Type 1 diabetes. This project is different from previous studies of genes related to Type 1 diabetes because it is much larger and because we can now apply new tools to genetic analyses.

G. What happens if I decide not to participate or to withdraw?

Nothing will change. We will still continue to treat you to the best of our ability. Participation is strictly voluntary.

H. Can my cell line be used to clone me?

Copies of your blood cells will be made to make a marker in order to identify potential genes that may lead to Type 1 diabetes. However, no one will use your DNA to make another person.

APPENDIX A
ASP CONSENT SUMMARY FORM:
QUESTION BY QUESTION INSTRUCTIONS

These instructions are meant to assist the interviewer and to provide answers to any questions from a participant or clinic staff member.

This form is completed as members of the family consent, assent, sign authorization, and/or refuse to be included in this study. In order for a family to be included, two affected siblings must consent to participate or parents consent to his/her participation in this study. As family members sign the *Informed Consent*, clinic staff assigns individual Participant ID Labels and records the appropriate information.

A child or a guardian can sign the *Informed Consent*. If the child is not old enough to consent for himself/herself, at least one guardian must sign the *Informed Consent*. Consult your local IRB or Ethics Committee for specific requirements. Assent is an agreement with a child that is not old enough to sign a consent form, stating that he/she is willing to participate in the study and understands what the study entails. This can be verbal or written. Certain IRBs or Ethics Committees may require both guardians to sign a consent form and the child to consent or assent. Written authorization is required in the United States **only**, and may be embedded within the *Informed consent*. However, any North American clinic and those clinics within Puerto Rico must have the "Consent and written authorization" or "Consent, assent and written authorization" box marked in order for a participant to enroll in the study.

If a non-essential family member (*i.e.,* either biological parent or either unaffected sibling) refuses or is not available, the question should not be completed.

All dates are written as day first, month second, and year third. The day is recorded numerically. If the day is a single-digit number, a "0" is recorded in the first

box. The month is written out in its entirety (*e.g.,* January, February). The year is recorded numerically, with all four digits of the year included (*e.g.,* 1950).

Question by Question Instructions

The interviewer affixes the Family ID Label in the box shown in the upper right hand corner. A label is affixed on every page.

The interviewer records the clinic ID for his/her individual clinic. This number is assigned by the Regional Network Center and it is recorded on every page.

1. Proband (AS1)

This person **must** consent in order for the family to be included. Once he/she consents, provides written authorization and/or assents, mark the consent status box, record the date the *Informed Consent* is signed and affix the Proband ID Label in the box.

The interviewer marks "Consent" if the proband or his/her guardian(s) signs the *Informed Consent*. The interviewer marks "Refused" if the proband does not want to participate in this study. This form is not completed further if "Refused" is marked, unless there is another affected child in the family. For some clinics, the guardian(s) must sign the *Informed Consent*, and the proband must either sign the *Informed Consent* or make a verbal agreement (*i.e.,* assent) stating he/she understands what the study entails. The interviewer marks "Consent and assent" in cases such as these. For clinics within the United States, a *Written Authorization* must also be completed, and the interviewer marks "Consent and written authorization." The interviewer marks "Consent, assent and written authorization" for clinics within the United States where written authorization is required, the *Informed Consent* is signed and assent is obtained. The interviewer marks "Not available" if the proband is unable to be reached. This form is not completed further if "Not available" is marked, unless there is another affected child in the family.

Record the date the *Informed Consent* is signed in the appropriate boxes. Two date fields for "Date informed consent signed" are provided for cases in which both guardians must sign the *Informed Consent*, or where a guardian must sign the *Informed Consent* and the proband must assent to participation. Only one date is required.

2. Affected Sibling (AS2)

This person **must** consent in order for the family to be included. Once he/she consents, provides written authorization and/or assents, mark the consent status box, record the date the *Informed Consent* is signed and affix the Affected Sibling ID Label in the box.

The interviewer marks "Consent" if the affected sibling or his/her guardian(s) signs the *Informed Consent*. The interviewer marks "Refused" if the affected sibling does not want to participate in this study. This form is not completed further if "Refused" is marked, unless there is another affected child in the family. For some clinics, the guardian(s) must sign the *Informed Consent*, and the affected sibling must either sign the *Informed Consent* or make a verbal agreement (*i.e.,* assent) stating he/she understands what the study entails. The interviewer marks "Consent and assent" in cases such as these. For clinics within the United States, a *Written Authorization* must also be completed, and the interviewer marks "Consent and written authorization." The interviewer marks "Consent, assent and written authorization" for clinics within the United States where written authorization is required, the *Informed Consent* is signed and assent is obtained. The interviewer marks "Not available" if the affected sibling is unable to be reached. This form is not completed further if "Not available" is marked, unless there is another affected child in the family.

Record the date the *Informed Consent* is signed in the appropriate boxes. Two date fields for "Date informed consent signed" are provided for cases in which both guardians must sign the *Informed Consent*, or where a guardian must sign the *Informed Consent* and the affected sibling must assent to participation. Only one date is required.

3. Father (FA)

This person does not have to consent in order for the family to be included. If the father consents, provides written authorization and/or assent, mark the consent status box, record the date the *Informed Consent* is signed and affix the Father ID Label in the box.

The interviewer marks "Consent" if the father signs the *Informed Consent*. The interviewer marks "Refused" if the father does not want to participate in this study. If the father is not able to sign the *Informed Consent* himself, the child must sign the *Informed Consent* and the father must either sign the *Informed Consent* or make a verbal agreement (*i.e.,* assent) stating he understands what the study entails. The interviewer marks "Consent and assent" in cases such as these. For clinics within the United States, a *Written Authorization* must also be completed, and the interviewer marks "Consent and written authorization." The interviewer marks "Consent, assent and written authorization" for clinics within the United States where written authorization is required, the *Informed Consent* is signed and assent is obtained. The interviewer marks "Not available" if the father is unable to be reached. If the father refuses or is not available, this question should not be completed.

Record the date the *Informed Consent* is signed in the appropriate boxes. Two date fields for "Date informed consent signed" are provided for cases in which both the father and a child must sign the *Informed Consent*. Only one date is required.

4. Mother (MO)

This person does not have to consent in order for the family to be included. If the mother consents, provides written authorization and/or assent, mark the consent status box, record the date the *Informed Consent* is signed and affix the Mother ID Label in the box.

The interviewer marks "Consent" if the mother signs the *Informed Consent*. The interviewer marks "Refused" if the mother does not want to participate in this study. If

the mother is not able to sign the *Informed Consent* herself, the child must sign the *Informed Consent* and the mother must either sign the *Informed Consent* or make a verbal agreement (*i.e.,* assent) stating she understands what the study entails. The interviewer marks "Consent and assent" in cases such as these. For clinics within the United States, a *Written Authorization* must also be completed, and the interviewer marks "Consent and written authorization." The interviewer marks "Consent, assent and written authorization" for clinics within the United States where written authorization is required, the *Informed Consent* is signed and assent is obtained. The interviewer marks "Not available" if the mother is unable to be reached. If the mother refuses or is not available, this question should not be completed.

Record the date the *Informed Consent* is signed in the appropriate boxes. Two date fields for "Date informed consent signed" are provided for cases in which both the mother and a child must sign the *Informed Consent*. Only one date is required.

5-6. Unaffected Sibling (UN1 and UN2)

This person does not have to consent in order for the family to be included. If the unaffected sibling consents, provides written authorization and/or assent, mark the consent status box, record the date the *Informed Consent* is signed and affix the Unaffected Sibling ID Label in the box.

The interviewer marks "Consent" if the unaffected sibling or his/her guardian(s) signs the *Informed Consent*. The interviewer marks "Refused" if the unaffected sibling does not want to participate in this study. For some clinics, the guardian(s) must sign the *Informed Consent*, and the unaffected sibling must either sign the *Informed Consent* or make a verbal agreement (*i.e.,* assent) stating he/she understands what the study entails. The interviewer marks "Consent and assent" in cases such as these. For clinics within the United States, a *Written Authorization* must also be completed, and the interviewer marks "Consent and written authorization." The interviewer marks "Consent, assent and written authorization" for clinics within the United States where written authorization is required, the *Informed Consent* is signed and assent is obtained. The

interviewer marks “Not available” if the unaffected sibling is unable to be reached. If the unaffected sibling refuses or is not available, this question should not be completed.

Record the date the consent is signed in the appropriate boxes. Two date fields for “Date informed consent signed” are provided for cases in which both guardians must sign the *Informed Consent*, or where a guardian must sign the *Informed Consent* and the unaffected sibling must assent to participation. Only one date is required.

Questions 7-9 are used for recording information on additional siblings if the initial contacts refused, were unavailable or if additional affected siblings are participating in the study. In addition to marking consent status, recording the date the *Informed Consent* is signed and affixing the label, the interviewer marks whether this is an affected sibling or an unaffected sibling.

7-9. Other Sibling(s)

The interviewer records whether the participant is an affected or unaffected sibling. If this participant is an affected sibling, he/she must meet T1DGC criteria for Type 1 diabetes as determined by the *T1DGC ASP Eligibility Form* or the *T1DGC ASP Application for Additional Sibling* (see **Chapter IV,** *Eligibility*). If the participant does not have diabetes, the interviewer marks unaffected sibling.

If the sibling consents, provides written authorization and/or assent, mark the consent status box, record the date the *Informed Consent* is signed and affix the Additional Sibling ID Label in the box.

The interviewer marks “Consent” if the sibling or his/her guardian(s) signs the *Informed Consent*. The interviewer marks “Refused” if the sibling does not want to participate in this study. For some clinics, the guardian(s) must sign the *Informed Consent*, and the sibling must either sign the *Informed Consent* or make a verbal agreement (*i.e.,* assent) stating he/she understands what the study entails. The interviewer marks “Consent and assent” in cases such as these. For clinics within the

United States, a *Written Authorization* must also be completed, and the interviewer marks “Consent and written authorization.” The interviewer marks “Consent, assent and written authorization” for clinics within the United States where written authorization is required, the *Informed Consent* is signed and assent is obtained. The interviewer marks “Not available” if the sibling is unable to be reached. If this is an extra additional affected sibling, and the affected sibling refuses, or is not available, this question should not be completed.

Record the date the *Informed Consent* is signed in the appropriate boxes. Two date fields for “Date informed consent signed” are provided for cases in which both guardians must sign the *Informed Consent*, or where a guardian must sign the *Informed Consent* and the sibling must assent to participation. Only one date is required.

Questions 10-12 are directed toward clinic staff and are completed as the activity occurs (*i.e.,* after interviewing, after editing, and after no further family members are expected to come into the clinic).

10. Interviewer ID

The interviewer records his/her five-digit assigned code in the appropriate boxes after completion of the *T1DGC ASP Consent Summary Form*.

11. ID of person editing

This is not completed until a clinic staff member reviews the form to ensure completion and accuracy. The person editing and reviewing the form records his/her five-digit assigned code in the appropriate boxes.

12. Close-out Date

This portion is recorded when the clinic staff has obtained informed consent from one or more members of the family. This date is updated as new members of the family sign the informed consent. The date should always match the date the last family member consented. Record the close-out date in the appropriate boxes.

APPENDIX B
ASP EXAM FORM (PROBAND):
QUESTION BY QUESTION INSTRUCTIONS

These instructions are meant to assist the interviewer and to provide answers to any questions from a participant or clinic staff member.

This form is administered to the proband or to the proband's guardian (*i.e.,* the biological mother, the biological father, or other legal guardian). The proband is the first child diagnosed with Type 1 diabetes in the family. Only one person is interviewed, although more than one can be present. The interviewer reads the questions to the participant and marks or records appropriate answers. For some questions the interviewer reads all the choices listed to the participant and marks affirmative responses.

Information in all capital letters is an instruction to the interviewer and is not read to the participant.

Please complete all parts of the form. Note that certain individual items may be marked "Don't know" and with an asterisk. In these cases, continue completing the form and contact the appropriate individuals within 10 days in order to collect information not known at the time of the initial exam. The participant may need to contact his/her physician or other family members in order to obtain information. Items should be followed-up, but forms should be forwarded to the Regional Network Center when it has become apparent that this information will not be found.

All dates are written as day first, month second, and year third. The day is recorded numerically. If the day is a single-digit number, a "0" is recorded in the first box. The month is written out in its entirety (*e.g.,* January, February). The year is recorded numerically, with all four digits of the year included (*e.g.,* 1950). Any single

digit numerical response is recorded with a leading "0" (*e.g.,* if participant is 5 years old, record "05").

Question by Question Instructions

The interviewer affixes the proband's Participant ID Label in the box shown in the upper right hand corner. A label is affixed on every page.

The interviewer records the clinic ID for his/her individual clinic. This number is assigned by the Regional Network Center and it is recorded on every page.

The interviewer records the secondary ID for the proband. The secondary ID is "AS1" and it is recorded on every page.

1. Interview Date

This is the date the interview takes place. Record the date of the interview in the appropriate boxes. For some clinics, the information on the form is abstracted from other sources and transferred onto this form. In this case, the interviewer records the date the information is abstracted and the form is completed. **This form should never be completed until the participant has signed the *Informed Consent*.**

2. How was this form completed? MARK ALL THAT APPLY.

The interviewer marks all sources from which information is gathered about the participant. If information is obtained by calling a participant before he/she comes into the clinic, mark "Phone interview." If the participant comes into the clinic and is interviewed in person, the interviewer marks "Face-to-face interview." If information is abstracted from other sources (*e.g.,* other forms, pulling medical records), the interviewer marks "From existing records." The interviewer marks all applicable answers.

3. Who is completing this form? PROBAND IS THE FIRST CHILD DIAGNOSED WITH TYPE 1 DIABETES. IF GUARDIAN COMPLETING FORM, READ ITALICIZED TEXT. ONLY ONE GUARDIAN IS INTERVIEWED.

The interviewer marks "Proband" if the participant is answering questions about himself/herself. If a guardian is answering the questions, the interviewer determines the relationship the guardian has with the proband. The interviewer may ask the participant his/her relationship to the child, if it is not already known. The interviewer marks "Biological Father" if the man completing the interview believes himself to be the biological father of the proband. The interviewer marks "Biological Mother" if the woman completing the interview gave birth to the proband. The interviewer marks "Other Guardian" if the person completing this form is neither biological parent of the proband. Only one guardian answers the questions, however more than one guardian can be present at the interview. The interviewer should be aware of the relationship the guardian has to the child while administering this questionnaire. If the form is administered to the guardian, the italicized text in parentheses is read. Versions of questions may differ based upon the relationship to the proband.

4. *(Your child's)* Gender

The participant responds by giving his/her, or the child's, gender.

5. What is your *(child's)* date of birth?

Record the date of birth in the appropriate boxes. For some clinics, this information is considered an identifier and thus cannot be collected. In this case, the interviewer marks the "Can not collect" box, but must answer Question 6. If clinics are able to collect a portion of the date of birth, the year is recorded in the appropriate boxes.

6. What is your *(child's)* current age?

The participant responds by giving his/her current age, or that of the child, at the time of the interview. If the information is abstracted from other sources and transferred

onto this form, the interviewer determines the proband's current age. The proband's age is recorded in years.

7a. Are you *(Is your child)* Latino, Hispanic or of Spanish origin?

The participant answers "Yes" if he/she considers himself/herself, or the child, to be either Latino, Hispanic or of Spanish origin. For some clinics, this question is not asked (*e.g.,* Asia-Pacific). In this case, the interviewer marks "Not applicable" and continues with the form. **"Not applicable" is only marked when this question is not read to the participant.** Regardless of the answer to this question, the participant must answer Question 7b.

7b. Which of the following best describes your *(child's)* race (or ethnic origin)? HAND PARTICIPANT CUE CARD AND RECORD PARTICIPANT'S RESPONSES.

This question can be read differently depending on the clinic; either the word "race" or "ethnic origin" may be used due to cultural sensitivity. The interviewer hands (or reads) the participant the cue card containing a list of races (or ethnic origins) to choose from. The participant chooses up to three responses that best describe his/her, or the child's, race (or ethnic origin). If the participant does not feel that any race (or ethnic origin) describes his/her, or the child's race (or ethnic origin), the entire list found in Appendix K should be shown to the participant and choices should be made from this list. Record the appropriate code(s) in the boxes. At least one set of boxes must be completed. If a participant chooses more than one category, the interviewer asks which race (or ethnic origin) he/she, or the child, most identifies with and records that choice in the first set of boxes with the word "Primary" beside it.

8. Do you *(Does your child)* have any of the following diseases? HAND PARTICIPANT CUE CARD AND MARK ALL REPORTED RESPONSES.

The interviewer hands (or reads) the participant the cue card containing a list of diseases. The participant informs the interviewer whether he/she, or the child, has any of the diseases listed on the card. If the participant reports that the proband has any of the diseases, mark the appropriate box. Leave boxes blank for negative answers. If

the participant does not have any of the medical conditions listed, mark the "None of the above" box. If the participant answers "Don't know," the interviewer continues with the form. If the participant has one or more of the diseases, but does not know about another disease, mark the box beside the known disease(s). Do not mark "Don't know."

9. At the time you were *(your child was)* diagnosed with diabetes, would you consider your *(their)* body size as thin, medium or heavy?

The participant recalls the size of his/her, or the child's, body at the time of diagnosis. This is a subjective measure and is up to the participant's perception of thin, medium and heavy. If the participant cannot recollect the proband's body size, mark the "Don't know" box, continue with the form.

Family History.

In this section we wish to obtain information about living and deceased members of your *(child's)* family. We are only interested in your *(child's)* biological relatives.

QUESTION 10 REFERS TO THE PROBAND'S CHILDREN.

10. Do you *(Does your child)* have any children? Exclude any adopted children or stepchildren.

The participant responds "Yes" if he/she, or the child, has any biological children and continues to Question 10a. Both living and deceased children are included. Stepchildren and adopted children are not included. The participant responds "No" if he/she, or the child, does not have any children, but the proband is old enough to have children. The interviewer skips to Question 11. The interviewer marks "Question not asked" if the proband is not old enough to have children and the interviewer does not ask the question and skips to Question 11. If the participant does not know this information, but the proband is old enough to have children, mark the "Don't know" box and skip to Question 11.

10a. How many children do you *(does your child)* have?

The participant responds by giving the number of biological children he/she, or the child, has.

10b. How many of them have Type 1 diabetes? That is, diagnosis before 35 years old, insulin use within 6 months of diagnosis without stopping for 6 months or more.

The participant responds by giving the number of biological children he/she or the child has who have been diagnosed with Type 1 diabetes, as defined by the T1DGC.

10c. How many of them have another type of diabetes?

The participant responds by giving the number of biological children he/she, or the child, has who have been diagnosed with a type of diabetes other than Type 1 diabetes, or Type 1 diabetes that does not meet the T1DGC definition.

10d. How many of them are not affected or you don't know if they are affected with any type of diabetes?

The participant responds by giving the number of biological children he/she, or the child, has without any form of diabetes, or is unsure of the children's diabetes status. The interviewer performs a quick check to be certain the answers to Questions 10b, 10c, and 10d add up to the answer given in Question 10a.

11. Is your *(child's)* biological mother participating in this study?

The participant answers "Yes" if the biological mother of the proband has been contacted and is interested in participating in this study. If the child's mother is participating, she will answer these questions on the *T1DGC ASP Exam Form (Parent Data from Source.* The interviewer skips to Question 12. If the participant answers "No" or "Don't know," continue to Question 11a.

QUESTIONS 11a-11c REFER TO THE PROBAND'S MATERNAL RELATIVES.

11a. Which of the following biological relatives have been diagnosed with Type 1 diabetes? That is, diagnosis before 35 years old, insulin use within 6 months of diagnosis without stopping for 6 months or more.

The interviewer can expect a "Yes" or "No" answer to each choice. The participant only answers "Yes" if the family member has been diagnosed with Type 1 diabetes, as defined by the T1DGC. If the participant answers "Don't know" to any of the questions, continue with the form.

11b. Which of the following biological relatives have been diagnosed with another type of diabetes?

The interviewer can expect a "Yes" or "No" answer to each choice. If the participant answers "Don't know" to any of the questions, continue with the form.

11c. Do you *(Does your child)* have any full aunts and uncles on your *(child's)* mother's side?

The participant responds "Yes" if he/she, or the child, has any biological full aunts and uncles on their mother's side. These are the biological mother's full siblings. Both living and deceased aunts and uncles are included. Step-aunts, step-uncles, adopted aunts, adopted uncles, aunts-in-law and uncles-in-law are not included. If the participant answers "No" or "Don't know," the interviewer skips to Question 12. If the participant answers "Don't know," continue with the form. If the participant answers, "Yes," continue to Question 11c1.

11c1. How many full aunts and uncles on your *(child's)* mother's side do you *(does your child)* have?

The participant responds by giving the number of biological aunts and uncles he/she, or the child, has on their mother's side.

11c2. How many of them have Type 1 diabetes? That is, diagnosis before 35 years old, insulin use within 6 months of diagnosis without stopping for 6 months or more.

The participant responds by giving the number of biological aunts and uncles he/she, or the child, has on their mother's side who have been diagnosed with Type 1 diabetes, as defined by the T1DGC.

11c3. How many of them have another type of diabetes?

The participant responds by giving the number of biological aunts and uncles he/she, or the child, has on their mother's side who have been diagnosed with a type of diabetes other than Type 1 diabetes, or Type 1 diabetes that does not meet the T1DGC definition.

11c4. How many of them are not affected or you don't know if they are affected with any type of diabetes?

The participant responds by giving the number of biological aunts and uncles he/she, or the child, has on their mother's side without any form of diabetes, or is unsure of their diabetes status. The interviewer performs a quick check to be certain the answers to Questions 11c2, 11c3, and 11c4 add up to the answer given in Question 11c1.

12. Is your *(child's)* biological father participating in this study?

The participant answers "Yes" if the biological father of the proband has been contacted and is interested in participating in this study. If the child's father is participating, he will answer these questions on the *T1DGC ASP Exam Form (Parent Data from Source);* the interviewer skips to Question 13. If the participant answers "No" or "Don't know," continue to Question 12a.

QUESTIONS 12a-12c REFER TO THE PROBAND'S PATERNAL RELATIVES.

12a. Which of the following biological relatives have been diagnosed with Type 1 diabetes? That is, diagnosis before 35 years old, insulin use within 6 months of diagnosis without stopping for 6 months or more.

The interviewer can expect a "Yes" or "No" answer to each choice. The participant only answers "Yes" if the family member has been diagnosed with Type 1 diabetes, as defined by the T1DGC. If the participant answers "Don't know" to any of the questions, continue with the form.

12b. Which of the following biological relatives have been diagnosed with another type of diabetes?

The interviewer can expect a "Yes" or "No" answer to each choice. If the participant answers "Don't know" to any of the questions, continue with the form.

12c. Do you *(Does your child)* have any full aunts and uncles on your *(child's)* father's side?

The participant responds "Yes" if he/she, or the child, has any biological full aunts and uncles on their father's side. These are the biological father's full siblings. Both living and deceased aunts and uncles are included. Step-aunts, step-uncles, adopted aunts, adopted uncles, aunts-in-law and uncles-in-law are not included. If the participant answers "No" or "Don't know," the interviewer skips to Question 13. If the participant answers "Don't know," continue with the form. If the participant answers, "Yes," continue to Question 12c1.

12c1. How many full aunts and uncles on your *(child's)* father's side do you *(does your child)* have?

The participant responds by giving the number of biological aunts and uncles he/she or the child has, on their father's side.

12c2. How many of them have Type 1 diabetes? That is, diagnosis before 35 years old, insulin use within 6 months of diagnosis without stopping for 6 months or more.

The participant responds by giving the number of biological aunts and uncles he/she or the child has, on their father's side who have been diagnosed with Type 1 diabetes, as defined by the T1DGC.

12c3. How many of them have another type of diabetes?

The participant responds by giving the number of biological aunts and uncles he/she, or the child, has on their father's side who have been diagnosed with a type of diabetes other than Type 1 diabetes, or Type 1 diabetes that does not meet the T1DGC definition.

12c4. How many of them are not affected or you don't know if they are affected with any type of diabetes?

The participant responds by giving the number of biological aunts and uncles he/she, or the child, has on their father's side without any form of diabetes, or is unsure of their diabetes status. The interviewer performs a quick check to be certain the answers to Questions 12c2, 12c3, and 12c4 add up to the answer given in Question 12c1.

13. How many full brothers and sisters do you *(does your child)* have? Full brothers and sisters are those that have the same biological mother and same biological father.

The participant responds by giving the number of biological brothers and sisters he/she, or the child, has. Both living and deceased brothers and sisters are included in this count. Step-siblings, adopted siblings and half siblings are not included. Any siblings participating in this study are included in this count. This number should always be equal to or exceed the number of siblings participating in the T1DGC.

13a. How many of them have Type 1 diabetes? That is, diagnosis before 35 years old, insulin use within 6 months of diagnosis without stopping for 6 months or more.

The participant responds by giving the number of biological brothers and sisters he/she, or the child, has who have been diagnosed with Type 1 diabetes, as defined by the T1DGC. This number should always be equal to or exceed the number of affected siblings participating in the T1DGC.

13b. How many of them have another type of diabetes?

The participant responds by giving the number of biological brothers and sisters he/she, or the child, has who have been diagnosed with a type of diabetes other than Type 1 diabetes, or Type 1 diabetes that does not meet the T1DGC definition.

13c. How many of them are not affected or you don't know if they are affected with any type of diabetes?

The participant responds by giving the number of biological brothers and sisters he/she, or the child, has without any form of diabetes, or is unsure of their diabetes status. This number should always be equal to or exceed the number of unaffected siblings participating in the T1DGC. The interviewer performs a quick check to be certain the answers to Questions 13a, 13b, and 13c add up to the answer given in Question 13.

14. Do you *(Does your child)* have any half siblings with the common parent being your *(child's)* mother?

The participant responds "Yes" if he/she, or the child, has any half brothers and sisters on their mother's side; the interviewer continues to Question 14a. Both living and deceased half brothers and sisters are included. Step-siblings and adopted siblings are not included. If the participant answers "No" or "Don't know," skip to Question 15.

14a. How many half brothers and sisters do you *(does your child)* have with common parent being your *(child's)* mother?

The participant responds by giving the number of half brothers and sisters he/she, or the child, has on their mother's side.

14b. How many of them have Type 1 diabetes? That is, diagnosis before 35 years old, insulin use within 6 months of diagnosis without stopping for 6 months or more.

The participant responds by giving the number of half brothers and sisters he/she, or the child, has on their mother's side who have been diagnosed with Type 1 diabetes, as defined by the T1DGC.

14c. How many of them have another type of diabetes?

The participant responds by giving the number of half brothers and sisters he/she, or the child, has on their mother's side who have been diagnosed with a type of diabetes other than Type 1 diabetes, or Type 1 diabetes that does not meet the T1DGC definition.

14d. How many of them are not affected or you don't know if they are affected with any type of diabetes?

The participant responds by giving the number of half brothers and sisters he/she, or the child, has on their mother's side without any form of diabetes, or is unsure of their diabetes status. The interviewer performs a quick check to be certain the answers to Questions 14b, 14c, and 14d add up to the answer given in Question 14a.

15. Do you *(Does your child)* have any half siblings with the common parent being your *(child's)* father?

The participant responds "Yes" if he/she, or the child, has any half brothers and sisters on their father's side; the interviewer continues to Question 15a. Both living and

deceased half brothers and sisters are included. Step-siblings and adopted siblings are not included. If the participant answers "No" or "Don't know," skip to Question 16.

15a. How many half brothers and sisters do you *(does your child)* have with common parent being your *(child's)* father?

The participant responds by giving the number of half brothers and sisters he/she, or the child, has on their father's side

15b. How many of them have Type 1 diabetes? That is, diagnosis before 35 years old, insulin use within 6 months of diagnosis without stopping for 6 months or more.

The participant responds by giving the number of half brothers and sisters he/she, or the child, has on their father's side who have been diagnosed with Type 1 diabetes, as defined by the T1DGC.

15c. How many of them have another type of diabetes?

The participant responds by giving the number of half brothers and sisters he/she, or the child, has on their father's side who have been diagnosed with a type of diabetes other than Type 1 diabetes, or Type 1 diabetes that does not meet the T1DGC definition.

15d. How many of them are not affected or you don't know if they are affected with any type of diabetes?

The participant responds by giving the number of half brothers and sisters he/she, or the child, has on their father's side without any form of diabetes, or is unsure of their diabetes status. The interviewer performs a quick check to be certain the answers to Questions 15b, 15c, and 15d add up to the answer given in Question 15a.

16. Have you *(Has your child)* participated in any of the following regional, national or international studies? READ/SHOW PARTICIPANT CUE CARD.

The interviewer hands (or reads) the participant the cue card listing previous and ongoing studies. The participant responds "Yes" if he/she, or the child, has participated in any of the studies on the cue card. If the participant answers "Yes," the interviewer continues with Question 16a. If the participant answers "No" or "Don't know," skip to Question 17.

16a. In which studies have you *(has your child)* participated? RECORD MAXIMUM OF FIVE STUDY CODES.

The participant responds by giving the study names in which he/she, or the child, has participated. The interviewer records up to five study codes that correspond with the study(ies) the proband has participated in.

Questions 17-18 are directed toward clinic staff and are completed as the activity occurs (*i.e.,* after interviewing and after editing).

17. Interviewer ID

The interviewer records his/her five-digit assigned code in the appropriate boxes after completion of the *T1DGC ASP Exam Form*.

18. ID of person editing

This is not completed until a clinic staff member reviews the form to ensure completion and accuracy. The person editing and reviewing the form records his/her five-digit assigned code in the appropriate boxes.

APPENDIX C
ASP EXAM FORM (AFFECTED SIBLING):
QUESTION BY QUESTION INSTRUCTIONS

These instructions are meant to assist the interviewer and to provide answers to any questions from a participant or clinic staff member.

This form is administered to the affected sibling or to the affected sibling's guardian (*i.e.,* the biological mother, the biological father, or other legal guardian). The affected sibling is the second child diagnosed with Type 1 diabetes in the family. This form is also completed for any additional affected siblings approved to participate. Only one person is interviewed, although more than one can be present. The interviewer reads the questions to the participant and marks or records the appropriate answers. For some questions the interviewer reads all the choices listed to the participant and marks affirmative responses.

Information in all capital letters is an instruction to the interviewer and is not read to the participant.

Please complete all parts of the form. Note that certain individual items may be marked "Don't know" and with an asterisk. In these cases, continue completing the form and contact the appropriate individuals within 10 days in order to collect information not known at the time of the initial exam. The participant may need to contact his/her physician or other family members in order to obtain information. Items should be followed-up, but forms should be forwarded to the Regional Network Center when it has become apparent that this information will not be found.

All dates are written as day first, month second, and year third. The day is recorded numerically. If the day is a single-digit number, a "0" is recorded in the first box. The month is written out in its entirety (*e.g.,* January, February). The year is recorded numerically, with all four digits of the year included (*e.g.,* 1950). Any single

digit numerical response is recorded with a leading "0" (*e.g.,* if participant is 5 years old, record "05").

Question by Question Instructions

The interviewer affixes the affected sibling's Participant ID Label in the box shown in the upper right hand corner. A label is affixed on every page.

The interviewer records the clinic ID for his/her individual clinic. This number is assigned by the Regional Network Center and it is recorded on every page.

The interviewer records the secondary ID for the affected sibling. The secondary ID is "AS2" and it is recorded on every page. Any additional siblings have a secondary ID of "AS3," "AS4," or "AS5."

1. Interview Date

This is the date the interview takes place. Record the date of the interview in the appropriate boxes. For some clinics, the information on the form is abstracted from other sources and transferred onto this form. In this case, the interviewer records the date the information is abstracted and the form is completed. **This form should never be completed until the participant has signed the *Informed Consent*.**

2. How was this form completed? MARK ALL THAT APPLY.

The interviewer marks all sources from which information is gathered about the participant. If information is obtained by calling a participant before he/she comes into the clinic, mark "Phone interview." If the participant comes into the clinic and is interviewed in person, the interviewer marks "Face-to-face interview." If information is abstracted from other sources (*e.g.,* other forms, pulling medical records), the interviewer marks "From existing records." The interviewer marks all applicable answers.

3. Who is completing this form? AFFECTED SIBLING IS THE SECOND CHILD DIAGNOSED WITH TYPE 1 DIABETES. IF GUARDIAN COMPLETING FORM, READ ITALICIZED TEXT. ONLY ONE GUARDIAN IS INTERVIEWED.

The interviewer marks "Affected Sibling" if the participant is answering questions about himself/herself. If a guardian is answering the questions, the interviewer determines the relationship the guardian has with the affected sibling. The interviewer may ask the participant his/her relationship to the child, if it is not already known. The interviewer marks "Biological Father" if the man completing the interview believes himself to be the biological father of the affected sibling. The interviewer marks "Biological Mother" if the woman completing the interview gave birth to the affected sibling. The interviewer marks "Other Guardian" if the person completing this form is neither biological parent of the affected sibling. Only one guardian answers the questions, however more than one guardian can be present at the interview. The interviewer should be aware of the relationship the guardian has to the child while administering this questionnaire. If the form is administered to the guardian, the italicized text in parentheses is read. Versions of questions may differ based upon the relationship to the affected sibling.

4. *(Your child's)* Gender

The participant responds by giving his/her, or the child's, gender.

5. What is your *(child's)* date of birth?

Record the date of birth in the appropriate boxes. For some clinics, this information is considered an identifier and thus cannot be collected. In this case, the interviewer marks the "Can not collect" box, but must answer Question 6. If clinics are able to collect a portion of the date of birth, the year is recorded in the appropriate boxes.

6. What is your *(child's)* current age?

The participant responds by giving his/her current age, or that of the child, at the time of the interview. If the information is abstracted from other sources and transferred

onto this form, the interviewer determines the affected sibling's current age. The affected sibling's age is recorded in years.

7a. Are you *(Is your child)* Latino, Hispanic or of Spanish origin?

The participant answers "Yes" if he/she considers himself/herself or the child, to be either Latino, Hispanic or of Spanish origin. For some clinics, this question is not asked (*e.g.,* Asia-Pacific). In this case, the interviewer marks "Not applicable" and continues with the form. **"Not applicable" is only marked when this question is not read to the participant.** Regardless of the answer to this question, the participant must answer Question 7b.

7b. Which of the following best describes your *(child's)* race (or ethnic origin)? HAND PARTICIPANT CUE CARD AND RECORD PARTICIPANT'S RESPONSES.

This question can be read differently depending on the clinic; either the word "race" or "ethnic origin" may be used due to cultural sensitivity. The interviewer hands (or reads) the participant the cue card containing a list of races (or ethnic origins) to choose from. The participant chooses up to three responses that best describe his/her, or their child's, race (or ethnic origin). If the participant does not feel that any race (or ethnic origin) describes his/her, or the child's race (or ethnic origin), the entire list found in Appendix K should be shown to the participant and choices should be made from this list. Record the appropriate code(s) in the boxes. At least one set of boxes must be completed. If a participant chooses more than one category, the interviewer asks which race (or ethnic origin) he/she, or the child, most identifies with and records that choice in the first set of boxes with the word "Primary" beside it.

8. Do you (Does your child) have any of the following diseases? HAND PARTICIPANT CUE CARD AND MARK ALL REPORTED RESPONSES.

The interviewer hands (or reads) the participant the cue card containing a list of diseases. The participant informs the interviewer whether he/she, or the child, has any of the diseases listed on the card. If the participant reports that the affected sibling has any of the diseases, mark the appropriate box. Leave boxes blank for negative

answers. If the participant does not have any of the medical conditions listed, mark the "None of the above" box. If the participant answers "Don't know," the interviewer continues with the form. If a participant has one or more of the diseases, but does not know about another disease, mark the box beside the known disease(s). Do not mark the "Don't know" box.

9. At the time you were *(your child was)* diagnosed with diabetes, would you consider your *(their)* body size as thin, medium or heavy?

The participant recalls the size of his/her, or the child's, body at the time of diagnosis. This is a subjective measure and it is up to the participant's perception of thin, medium and heavy. If the participant cannot recollect the affected sibling's body size, mark the "Don't know" box, continue with the form.

Family History.

In this section we wish to obtain information about all of your *(child's)* biological children.

QUESTION 10 REFERS TO THE AFFECTED SIBLING'S CHILDREN.

10. Do you *(Does your child)* have any children? Exclude any adopted children or stepchildren.

The participant responds "Yes" if he/she, or the child, has any biological children and continues to Question 10a. Both living and deceased children are included. Stepchildren and adopted children are not included. The participant responds "No" if he/she, or the child, does not have any children, but the affected sibling is old enough to have children. The interviewer skips to Question 11. The interviewer marks "Question not asked" if the affected sibling is not old enough to have children and the interviewer does not ask the question, and skips to Question 11. If the participant does not know this information, but the affected sibling is old enough to have children, mark the "Don't know" box and skip to Question 11.

10a. How many children do you *(does your child)* have?

The participant responds by giving the number of biological children he/she, or the child, has.

10b. How many of them have Type 1 diabetes? That is, diagnosis before 35 years old, insulin use within 6 months of diagnosis without stopping for 6 months or more.

The participant responds by giving the number of biological children he/she or the child has who have been diagnosed with Type 1 diabetes, as defined by the T1DGC.

10c. How many of them have another type of diabetes?

The participant responds by giving the number of biological children he/she, or the child, has who have been diagnosed with a type of diabetes other than Type 1 diabetes, or Type 1 diabetes that does not meet the T1DGC definition.

10d. How many of them are not affected or you don't know if they are affected with any type of diabetes?

The participant responds by giving the number of biological children he/she, or the child, has without any form of diabetes, or is unsure of the children's diabetes status. The interviewer performs a quick check to be certain the answers to Questions 10b, 10c, and 10d add up to the answer given in Question 10a.

11. Have you *(Has your child)* participated in any of the following regional, national or international studies? READ/SHOW PARTICIPANT CUE CARD.

The interviewer hands (or reads) the participant the cue card listing previous and ongoing studies. The participant responds "Yes" if he/she or the child has participated in any of the studies on the cue card. If the participant answers "Yes," the interviewer continues with Question 11a. If the participant answers "No" or "Don't know," skip to Question 12.

11a. In which studies have you *(has your child)* participated? RECORD MAXIMUM OF FIVE STUDY CODES.

The participant responds by giving the study names in which he/she, or the child, has participated. The interviewer records up to five study codes that correspond with the study(ies) the affected sibling has participated in.

Questions 12-13 are directed toward clinic staff and are completed as the activity occurs (*i.e.,* after interviewing and after editing).

12. Interviewer ID

The interviewer records his/her five-digit assigned code in the appropriate boxes after completion of the *T1DGC ASP Exam Form*.

13. ID of person editing

This is not completed until a clinic staff member reviews the form to ensure completion and accuracy. The person editing and reviewing the form records his/her five-digit assigned code in the appropriate boxes.

APPENDIX D
ASP EXAM FORM (PARENT):
QUESTION BY QUESTION INSTRUCTIONS

These instructions are meant to assist the interviewer and to provide answers to any questions from a participant or clinic staff member.

This form is administered to each biological parent of the proband and affected sibling. The interviewer reads the questions to the participant and marks or records appropriate answers. For some questions the interviewer reads all the choices listed to the participant and marks affirmative responses.

Information in all capital letters is an instruction to the interviewer and is not read to the participant.

Please complete all parts of the form. Note that certain individual items may be marked "Don't know" and with an asterisk. In these cases, continue completing the form and contact the appropriate individuals within 10 days in order to collect information not known at the time of the initial exam. The participant may need to contact his/her physician or other family members in order to obtain information. Items should be followed-up, but forms should be forwarded to the Regional Network Center when it has become apparent that this information will not be found.

All dates are written as day first, month second, and year third. The day is recorded numerically. If the day is a single-digit number, a "0" is recorded in the first box. The month is written out in its entirety (*e.g.,* January, February). The year is recorded numerically, with all four digits of the year included (*e.g.,* 1950). Any single digit numerical response is recorded with a leading "0" (*e.g.,* if participant is 5 years old, record "05").

Question by Question Instructions

The interviewer affixes the mother or father's Participant ID Label in the box shown in the upper right hand corner. A label is affixed on every page.

The interviewer records the clinic ID for his/her individual clinic. This number is assigned by the Regional Network Center and it is recorded on every page.

The interviewer records the secondary ID for the mother or father. The secondary ID is "MO" for the mother and "FA" for the father. The secondary ID is recorded on every page.

1. Interview date

This is the date the interview takes place. Record the date of the interview in the appropriate boxes. For some clinics, the information on the form is abstracted from other sources and transferred onto this form. In this case, the interviewer records the date the information is abstracted and the form is completed. **This form should never be completed until the participant has signed the *Informed Consent*.**

2. How was this form completed? MARK ALL THAT APPLY.

The interviewer marks all sources from which information is gathered about the participant. If information is obtained by calling a participant before he/she comes into the clinic, mark "Phone interview." If the participant comes into the clinic and is interviewed in person, the interviewer marks "Face-to-face interview." If information is abstracted from other sources (*e.g.,* other forms, pulling medical records), the interviewer marks "From existing records." The interviewer marks all applicable answers.

3. Gender

The participant responds by giving his/her gender.

4. What is your date of birth?

Record the date of birth in the appropriate boxes. For some clinics, this information is considered an identifier and thus cannot be collected. In this case, the interviewer marks the "Can not collect" box, but must answer Question 5. If clinics are able to collect a portion of the date of birth, the year is recorded in the appropriate boxes.

5. What is your current age?

The participant responds by giving his/her current age at the time of the interview. If the information is abstracted from other sources and transferred onto this form, the interviewer determines the participant's current age. The participant's age is recorded in years.

6a. Are you Latino, Hispanic or of Spanish origin?

The participant answers "Yes" if he/she considers himself/herself to be either Latino, Hispanic or of Spanish origin. For some clinics, this question is not asked (*e.g.,* Asia-Pacific). In this case, the interviewer marks "Not applicable" and continues with the form. **"Not applicable" is only marked when this question is not read to the participant.** Regardless of the answer to this question, the participant must answer Question 6b.

6b. Which of the following best describes your race (or ethnic origin)? HAND PARTICIPANT CUE CARD AND RECORD PARTICIPANT'S RESPONSES.

This question can be read differently depending on the clinic; either the word "race" or "ethnic origin" may be used due to cultural sensitivity. The interviewer hands (or reads) the participant the cue card containing a list of races (or ethnic origins) to choose from. The participant chooses up to three responses that best describe his/her race (or ethnic origin). If the participant does not feel that any race (or ethnic origin) describes his/her race (or ethnic origin), the entire list found in Appendix K should be shown to the participant and choices should be made from this list. Record the appropriate code(s) in the boxes. At least one set of boxes must be completed. If a

participant chooses more than one category, the interviewer asks which race (or ethnic origin) he/she most identifies with and records that choice in the first set of boxes with the word “Primary” beside it.

7. Have you been diagnosed with diabetes?

The participant answers “Yes” if they have been diagnosed with any form of diabetes. This includes, but is not limited to Type 1 diabetes, Type 2 diabetes and MODY. If the participant answers “No” or “Don’t know,” the interviewer skips to Question 12. If the participant answers “Don’t know,” continue with the form. If the participant answers “Yes,” continue with Question 8.

8. What type of diabetes do you have?

The interviewer reads the entire list to the participant and marks all applicable answers. If the participant answers “Don’t know,” continue with the form.

9. At what age or on what date were you diagnosed with diabetes?

The participant gives the age he/she was when diagnosed with diabetes. If he/she cannot recall their age, an attempt is made to guess, or tell the interviewer the date of diagnosis. If only the year is known, that is acceptable. The participant’s age is recorded in years. If the participant was less than 1 year old, record “00.” If the participant has no recollection of his/her age at diagnosis or year of diagnosis, mark the “Don’t know” box and continue with the form.

10. Did you use insulin within six months of being diagnosed?

The participant answers “Yes” if insulin was used at any point during the first six months after he/she was diagnosed with diabetes. This excludes nasal or inhaled insulin. If the participant answers “Yes,” continue to Question 11. If the participant answers “No,” skip to Question 12.

11. Once you started using insulin, did you ever stop using insulin for a period of six months or more for reasons other than a pancreas transplant?

The participant answers "Yes" if insulin use was started but discontinued for 6 months or longer. More than one interruption is permitted if each is within the allotted time frame. If a participant has had a pancreas transplant and has stopped insulin use for more than 6 months because of the transplant, the participant answers "No." The participant answers "No" if insulin use was never disrupted after starting on insulin, or if any insulin was stopped for periods within 6 months.

12. Do you have any of the following diseases? HAND PARTICIPANT CUE CARD AND MARK ALL REPORTED RESPONSES.

The interviewer hands (or reads) the participant the cue card containing a list of diseases. The participant informs the interviewer whether he/she has any of the diseases listed on the card. If the participant reports having any of the diseases, mark the appropriate box. Leave boxes blank for negative answers. If the participant does not have any of the medical conditions listed, mark the "None of the above" box. If the participant answers "Don't know," the interviewer continues with the form. If a participant has one or more of the diseases, but does not know about another disease, mark the box beside the known disease(s). Do not mark the "Don't know" box.

Family History.

In this section we wish to obtain information about living and deceased members of your family. We are only interested in your biological relatives.

13. Have any of the following biological relatives – mother, father, sister(s) or brother(s) – ever been diagnosed with diabetes?

The participant responds "Yes" if any member of his/her immediate family (*i.e.,* biological parents and/or full biological siblings) has been diagnosed with diabetes and continues to Question 14. If the participant responds "No" or "Don't know," skip to Question 17.

14. Does/did your biological mother have diabetes?

The participant responds "Yes" if his/her mother has been diagnosed with any form of diabetes. This includes, but is not limited to Type 1 diabetes, Type 2 diabetes and MODY. If the participant answers "No" or "Don't know," the interviewer skips to Question 15. If the participant answers "Yes," continue with Question 14a.

14a. What type of diabetes does/did she have?

The interviewer reads the entire list to the participant and marks all applicable answers. If the participant answers "Don't know," continue with the form.

15. Does/did your biological father have diabetes?

The participant responds "Yes" if his/her father has been diagnosed with any form of diabetes. This includes, but is not limited to Type 1 diabetes, Type 2 diabetes and MODY. If the participant answers "No" or "Don't know," the interviewer skips to Question 16. If the participant answers "Yes," continue with Question 15a.

15a. What type of diabetes does/did he have?

The interviewer reads the entire list to the participant and marks all applicable answers. If the participant answers "Don't know," continue with the form.

16. Do you have any full brothers/sisters? Full brothers and sisters are those that have the same biological mother and same biological father.

The participant responds "Yes" if he/she has any biological brothers and sisters and continues to Question 16a. Both living and deceased brothers and sisters are included. Step-siblings, adopted siblings and half siblings are not included. If the participant answers "No" or "Don't know," skip to Question 17.

16a. How many full brothers/sisters do you have?

The participant responds by giving the number of biological brothers and sisters he/she has.

16b. How many of them have Type 1 diabetes? That is, diagnosis before 35 years old, insulin use within 6 months of diagnosis without stopping for 6 months or more.

The participant responds by giving the number of biological brothers and sisters he/she has who have been diagnosed with Type 1 diabetes, as defined by the T1DGC.

16c. How many of them have another type of diabetes?

The participant responds by giving the number of their biological brothers and sisters diagnosed with a type of diabetes other than Type 1 diabetes, or Type 1 diabetes that does not meet the T1DGC definition.

16d. How many of them are not affected or you don't know if they are affected?

The participant responds by giving the number of biological brothers and sisters he/she has without any form of diabetes, or is unsure of their diabetes status. The interviewer performs a quick check to be certain the answers to Questions 16b, 16c, and 16d add up to the answer given in Question 16a.

17. Have you participated in any of the following regional, national or international studies? READ/SHOW PARTICIPANT CUE CARD.

The interviewer hands (or reads) the participant the cue card listing previous and ongoing studies. The participant responds "Yes" if he/she has participated in any of the studies on the cue card. If the participant answers "Yes," the interviewer continues with Question 17a. If the participant answers "No" or "Don't know," skip to Question 18.

17a. In which studies have you participated? RECORD MAXIMUM OF FIVE STUDY CODES.

The participant responds by giving the study names in which he/she has participated. The interviewer records up to five study codes that correspond with the study(ies) he/she has participated in.

Questions 18-19 are directed toward clinic staff and are completed as the activity occurs *(i*.e., after interviewing and after editing).

18. Interviewer ID

The interviewer records his/her five-digit assigned code in the appropriate boxes after completion of the *T1DGC ASP Exam Form*. .

19. ID of person editing

This is not completed until a clinic staff member reviews the form to ensure completion and accuracy. The person editing and reviewing the form records his/her five-digit assigned code in the appropriate boxes.

APPENDIX E
ASP EXAM FORM (UNAFFECTED SIBING): QUESTION BY QUESTION INSTRUCTIONS

These instructions are meant to assist the interviewer and to provide answers to any questions from a participant or clinic staff member.

This form is administered to the unaffected sibling or to the unaffected sibling's guardian (*i.e.,* the biological mother, the biological father, or other legal guardian). The unaffected sibling is a child not diagnosed with any form of diabetes. Only one person is interviewed, although more than one can be present. The interviewer reads the questions to the participant and marks or records appropriate answers. For some questions the interviewer reads the choices listed to the participant and marks affirmative responses.

Information in all capital letters is an instruction to the interviewer and is not read to the participant.

Please complete all parts of the form. Note that certain individual items may be marked "Don't know" and with an asterisk. In these cases, continue completing the form and contact the appropriate individuals within 10 days in order to collect information not known at the time of the initial exam. The participant may need to contact his/her physician or other family members in order to obtain information. Items should be followed-up, but forms should be forwarded to the Regional Network Center when it has become apparent that this information will not be found.

All dates are written as day first, month second, and year third. The day is recorded numerically. If the day is a single-digit number, a "0" is recorded in the first box. The month is written out in its entirety (*e.g.,* January, February). The year is recorded numerically, with all four digits of the year included (*e.g.,* 1950). Any single

digit numerical response is recorded with a leading "0" (*e.g.,* if participant is 5 years old, record "05").

Question by Question Instructions

The interviewer affixes the unaffected sibling's Participant ID Label in the box shown in the upper right hand corner. A label is affixed on every page.

The interviewer records the clinic ID for their individual clinic. This number is assigned by the Regional Network Center and it is recorded on every page.

The interviewer records the secondary ID for the unaffected sibling. The secondary ID is "UN1" or "UN2" and it is recorded on every page.

1. Interview Date

This is the date the interview takes place. Record the date of the interview in the appropriate boxes. For some clinics, the information on the form is abstracted from other sources and transferred onto this form. In this case, the interviewer records the date the information is abstracted and the form is completed. **This form should never be completed until the participant has signed the *Informed Consent*.**

2. How was this form completed? MARK ALL THAT APPLY.

The interviewer marks all sources from which information is gathered about the participant. If information is obtained by calling a participant before he/she comes into the clinic, mark "Phone interview." If the participant comes into the clinic and is interviewed in person, the interviewer marks "Face-to-face interview." If information is abstracted from other sources (*e.g.,* other forms, pulling medical records), the interviewer marks "From existing records." The interviewer marks all applicable answers.

3. Who is completing this form? UNAFFECTED SIBLING IS A CHILD WHO HAS NOT BEEN DIAGNOSED WITH DIABETES. IF GUARDIAN COMPLETING FORM, READ ITALICIZED TEXT. ONLY ONE GUARDIAN IS INTERVIEWED.

The interviewer marks "Unaffected Sibling" if the participant is answering questions about himself/herself. If a guardian is answering the questions, the interviewer determines the relationship the guardian has with the unaffected sibling. The interviewer may ask the participant his/her relationship to the child, if it is not already known. The interviewer marks "Biological Father" if the man completing the interview believes himself to be the biological father of the unaffected sibling. The interviewer marks "Biological Mother" if the woman completing the interview gave birth to the unaffected sibling. The interviewer marks "Other Guardian" if the person completing this form is neither biological parent of the unaffected sibling. Only one guardian answers the questions, however more than one guardian can be present at the interview. The interviewer should be aware of the relationship the guardian has to the child while administering this questionnaire. If the form is administered to the guardian, the italicized text in parentheses is read. Versions of questions may differ based upon the relationship to the unaffected sibling.

4. *(Your child's)* Gender

The participant responds by giving his/her, or the child's, gender.

5. What is your *(child's)* date of birth?

Record the date of birth in the appropriate boxes. For some clinics, this information is considered an identifier and thus cannot be collected. In this case, the interviewer marks the "Can not collect" box, but must answer Question 6. If clinics are able to collect a portion of the date of birth, the year is recorded in the appropriate boxes.

6. What is your *(child's)* current age?

The participant responds by giving his/her current age, or that of the child, at the time of the interview. If the information is abstracted from other sources and transferred

onto this form, the interviewer determines the unaffected sibling's current age. The unaffected sibling's age is recorded in years.

7a. Are you *(Is your child)* Latino, Hispanic or of Spanish origin?

The participant answers "Yes" if he/she considers himself/herself or the child, to be either Latino, Hispanic or of Spanish origin. For some clinics, this question is not asked (*e.g.,* Asia-Pacific). In this case, the interviewer marks "Not applicable" and continues with the form. **"Not applicable" is only marked when this question is not read to the participant.** Regardless of the answer to this question, the participant must answer Question 7b.

7b. Which of the following best describes your *(child's)* race (or ethnic origin)? HAND PARTICIPANT CUE CARD AND RECORD PARTICIPANT'S RESPONSES.

This question can be read differently depending on the clinic; either the word "race" or "ethnic origin" may be used due to cultural sensitivity. The interviewer hands (or reads) the participant the cue card containing a list of races (or ethnic origins) to choose from. The participant chooses up to three responses that best describe his/her, or the child's, race (or ethnic origin). If the participant does not feel that any race (or ethnic origin) describes his/her, or the child's race (or ethnic origin), the entire list found in Appendix K should be shown to the participant and choices should be made from this list. Record the appropriate code(s) in the boxes. At least one set of boxes must be completed. If a participant chooses more than one category, the interviewer asks which race (or ethnic origin) he/she, or the child, most identifies with and records that choice in the first set of boxes with the word "Primary" beside it.

8. Have you (Has your child) ever been diagnosed with diabetes?

The participant answers "Yes" if he/she, or the child, has been diagnosed with any form of diabetes. This includes, but is not limited to Type 1 diabetes, Type 2 diabetes, and MODY. If the participant answers "Yes" or "Don't know," stop completing this form; this participant is ineligible. If the participant answers "No," continue to Question 9.

9. Do you (Does your child) have any of the following diseases? HAND PARTICIPANT CUE CARD AND MARK ALL REPORTED RESPONSES.

The interviewer hands (or reads) the participant the cue card containing a list of diseases. The participant informs the interviewer whether he/she, or the child, has any of the diseases listed on the card. If the participant reports that the unaffected sibling has any of the diseases, mark the appropriate box. Leave boxes blank for negative answers. If the participant does not have any of the medical conditions listed, mark the "None of the above" box. If the participant answers "Don't know," the interviewer continues with the form. If a participant has one or more of the diseases, but does not know about another disease, mark the box beside the known disease(s). Do not mark "Don't know."

Family History.

In this section we wish to obtain information about all of your *(child's)* biological children.

QUESTION 10 REFERS TO THE UNAFFECTED SIBLING'S CHILDREN.

10. Do you *(Does your child)* have any children? Exclude any adopted children or stepchildren.

The participant responds "Yes" if he/she, or the child, has any biological children and continues to Question 10a. Both living and deceased children are included. Stepchildren and adopted children are not included. The participant responds "No" if he/she, or the child, does not have any children, but the unaffected sibling is old enough to have children. The interviewer skips to Question 11. The interviewer marks "Question not asked" if the unaffected sibling is not old enough to have children and the interviewer does not ask the question and skips to Question 11. If the participant does not know this information, but the unaffected sibling is old enough to have children, mark the "Don't know" box and skip to Question 11.

10a. How many children do you *(does your child)* have?

The participant responds by giving the number of biological children he/she, or the child, has.

10b. How many of them have Type 1 diabetes? That is, diagnosis before 35 years old, insulin use within 6 months of diagnosis without stopping for 6 months or more.

The participant responds by giving the number of biological children he/she, or the child, has who have been diagnosed with Type 1 diabetes, as defined by the T1DGC.

10c. How many of them have another type of diabetes?

The participant responds by giving the number of biological children he/she, or the child, has who have been diagnosed with a type of diabetes other than Type 1 diabetes, or Type 1 diabetes that does not meet the T1DGC definition.

10d. How many of them are not affected or you don't know if they are affected with any type of diabetes?

The participant responds by giving the number of biological children he/she, or the child, has without any form of diabetes, or is unsure of the children's diabetes status. The interviewer performs a quick check to be certain the answers to Questions 10b, 10c, and 10d add up to the answer given in Question 10a.

11. Have you *(Has your child)* participated in any of the following regional, national or international studies? READ/SHOW PARTICIPANT CUE CARD.

The interviewer hands (or reads) the participant the cue card listing previous and ongoing studies. The participant responds "Yes" if he/she, or the child, has participated in any of the studies on the cue card. If the participant answers "Yes," the interviewer continues with Question 11a. If the participant answers "No" or "Don't know," skip to Question 12.

11a. In which studies have you *(has your child)* participated? RECORD MAXIMUM OF FIVE STUDY CODES.

The participant responds by giving the study names in which he/she, or the child, has participated. The interviewer records up to five study codes that correspond with the study(ies) the unaffected sibling has participated in.

Questions 12-13 are directed toward clinic staff and are completed as the activity occurs (*i.e.,* after interviewing and after editing).

12. Interviewer ID

The interviewer records his/her five-digit assigned code in the appropriate boxes after completion of the *T1DGC ASP Exam Form*.

13. ID of person editing

This is not completed until a clinic staff member reviews the form to ensure completion and accuracy. The person editing and reviewing the form records his/her five-digit assigned code in the appropriate boxes.

APPENDIX F
TRIO CONSENT SUMMARY FORM:
QUESTION BY QUESTION INSTRUCTIONS

These instructions are meant to assist the interviewer and to provide answers to any questions from a participant or clinic staff member.

This form is completed as members of the family consent, assent, sign authorization, and/or refuse to be included in this study. In order for a family to be included, the proband and his/her biological parents must consent to participate. As family members sign the *Informed Consent*, clinic staff assigns individual Participant ID Labels and records the appropriate information.

A child or a guardian can sign the *Informed Consent*. If the child is not old enough to consent for himself/herself, at least one guardian must sign the *Informed Consent*. Consult your local IRB or Ethics Committee for specific requirements. Assent is an agreement with a child that is not old enough to sign a consent form, stating that he/she is willing to participate in the study and understands what the study entails. This can be verbal or written. Certain IRBs or Ethics Committees may require both guardians to sign a consent form and the child to consent or assent. Written authorization is required in the United States **only**, and may be embedded within the consent form. However, any North American clinic and those clinics within Puerto Rico must have the "Consent and written authorization" or "Consent, assent and written authorization" box marked in order for a participant to enroll in the study.

All dates are written as day first, month second, and year third. The day is recorded numerically. If the day is a single-digit number, a "0" is recorded in the first box. The month is written out in its entirety (*e.g.,* January, February). The year is recorded numerically, with all four digits of the year included (*e.g.,* 1950).

Question by Question Instructions

The interviewer affixes the Family ID Label in the box shown in the upper right hand corner. A label is affixed on every page.

The interviewer records the clinic ID for his/her individual clinic. This number is assigned by the Regional Network Center and it is recorded on every page.

1. Proband (AS1)

This person **must** consent in order for the family to be included. Once he/she consents, provides written authorization and/or assents, mark the consent status box, record the date the *Informed Consent* is signed and affix the Proband ID Label in the box.

The interviewer marks "Consent" if the proband or his/her guardian(s) signs the *Informed Consent*. The interviewer marks "Refused" if the proband does not want to participate in this study. This form is not completed further if "Refused" is marked, unless there is another affected child in the family. For some clinics, the guardian(s) must sign the *Informed Consent*, and the proband must either sign the *Informed Consent* or make a verbal agreement (*i.e.,* assent) stating he/she understands what the study entails. The interviewer marks "Consent and assent" in cases such as these. For clinics within the United States, a *Written Authorization* must also be completed, and the interviewer marks "Consent and written authorization." The interviewer marks "Consent, assent and written authorization" for clinics within the United States where written authorization is required, the *Informed Consent* is signed and assent is obtained. The interviewer marks "Not available" if the proband is unable to be reached. This form is not completed further if "Not available" is marked.

Record the date the *Informed Consent* is signed in the appropriate boxes. Two date fields for "Date informed consent signed" are provided for cases in which both guardians must sign the *Informed Consent*, or where a guardian must sign the *Informed Consent* and the proband must assent to participation. Only one date is required.

2. Father (FA)

This person **must** consent in order for the family to be included. Once he consents, provides written authorization and/or assents, mark the consent status box, record the date the *Informed Consent* is signed and affix the Father ID Label in the box.

The interviewer marks "Consent" if the father signs the *Informed Consent*. The interviewer marks "Refused" if the father does not want to participate in this study. This form is not completed further if "Refused" is marked. If the father is not able to sign the *Informed Consent* himself, the child must sign the *Informed Consent* and the father must either sign the *Informed Consent* or make a verbal agreement (*i.e.,* assent) stating he understands what the study entails. The interviewer marks "Consent and assent" in cases such as these. For clinics within the United States, a *Written Authorization* must also be completed, and the interviewer marks "Consent and written authorization." The interviewer marks "Consent, assent and written authorization" for clinics within the United States where written authorization is required, the *Informed Consent* is signed and assent is obtained. The interviewer marks "Not available" if the father is unable to be reached. This form is not completed further if "Not available" is marked.

Record the date the *Informed Consent* is signed in the appropriate boxes. Two date fields for "Date informed consent signed" are provided for cases in which both the father and a child must sign the *Informed Consent*. Only one date is required.

3. Mother (MO)

This person **must** consent in order for the family to be included. Once he consents, provides written authorization and/or assents, mark the consent status box, record the date the *Informed Consent* is signed and affix the Mother ID Label in the box.

The interviewer marks "Consent" if the mother signs the *Informed Consent*. The interviewer marks "Refused" if the mother does not want to participate in this study. This form is not completed further if "Refused" is marked. If the mother is not able to sign the *Informed Consent* herself, the child must sign a consent form and the mother

must either sign the *Informed Consent* or make a verbal agreement (*i.e.,* assent) stating she understands what the study entails. The interviewer marks "Consent and assent" in cases such as these. For clinics within the United States, a *Written Authorization* must also be completed, and the interviewer marks "Consent and written authorization." The interviewer marks "Consent, assent and written authorization" for clinics within the United States where written authorization is required, the *Informed Consent* is signed and assent is obtained. The interviewer marks "Not available" if the mother is unable to be reached. This form is not completed further if "Not available" is marked.

Record the date the *Informed Consent* is signed in the appropriate boxes. Two date fields for "Date informed consent signed" are provided for cases in which both the mother and a child must sign the *Informed Consent*. Only one date is required.

Questions 4-6 are directed toward clinic staff and are completed as the activity occurs (*i.e.,* after interviewing, after editing, and after no further family members are expected to come into the clinic).

4. Interviewer ID

The interviewer records his/her five-digit assigned code in the appropriate boxes after completion of the *T1DGC Trio Consent Summary Form*.

5. ID of person editing

This is not completed until a clinic staff member reviews the form to ensure completion and accuracy. The person editing and reviewing the form records his/her five-digit assigned code in the appropriate boxes.

6. Close-out Date

This portion is recorded when the clinic staff has obtained informed consent from one or more members of the family. This date is updated as new members of the family sign the informed consent. The date should always match the date the last family member consented. Record the close-out date in the appropriate boxes.

APPENDIX G
TRIO EXAM FORM (PROBAND):
QUESTION BY QUESTION INSTRUCTIONS

These instructions are meant to assist the interviewer and to provide answers to any questions from a participant or clinic staff member.

This form is administered to the proband or to the proband's guardian (*i.e.,* the biological mother, the biological father, or other legal guardian). The proband is a child diagnosed with Type 1 diabetes in the family. Only one person is interviewed, although more than one can be present. The interviewer reads the questions to the participant and marks or records appropriate answers. For some questions the interviewer reads all the choices listed to the participant and marks affirmative responses.

Information in all capital letters is an instruction to the interviewer and is not read to the participant.

Please complete all parts of the form. Note that certain individual items may be marked "Don't know" and with an asterisk. In these cases, continue completing the form and contact the appropriate individuals within 10 days in order to collect information not known at the time of the initial exam. The participant may need to contact his/her physician or other family members in order to obtain information. Items should be followed-up, but forms should be forwarded to the Regional Network Center when it has become apparent that this information will not be found.

All dates are written as day first, month second, and year third. The day is recorded numerically. If the day is a single-digit number, a "0" is recorded in the first box. The month is written out in its entirety (*e.g.,* January, February). The year is recorded numerically, with all four digits of the year included (*e.g.,* 1950). Any single digit numerical response is recorded with a leading "0" (*e.g.,* if participant is 5 years old, record "05").

Question by Question Instructions

The interviewer affixes the proband's Participant ID Label in the box shown in the upper right hand corner. A label is affixed on every page.

The interviewer records the clinic ID for his/her individual clinic. This number is assigned by the Regional Network Center and it is recorded on every page.

The interviewer records the secondary ID for the proband. The secondary ID is "AS1" and it is recorded on every page.

1. Interview Date

This is the date the interview takes place. Record the date of the interview in the appropriate boxes. For some clinics, the information on the form is abstracted from other sources and transferred onto this form. In this case, the interviewer records the date the information is abstracted and the form is completed. **This form should never be completed until the participant has signed the *Informed Consent*.**

2. How was this form completed? MARK ALL THAT APPLY.

The interviewer marks all sources from which information is gathered about the participant. If information is obtained by calling a participant before he/she comes into the clinic, mark "Phone interview." If the participant comes into the clinic and is interviewed in person, the interviewer marks "Face-to-face interview." If information is abstracted from other sources (*e.g.,* other forms, pulling medical records), the interviewer marks "From existing records." The interviewer marks all applicable answers.

3. Who is completing this form? IF GUARDIAN COMPLETING FORM, READ ITALICIZED TEXT. ONLY ONE GUARDIAN IS INTERVIEWED.

The interviewer marks "Proband" if the participant is answering questions about himself/herself. If a guardian is answering the questions, the interviewer determines the relationship the guardian has with the proband. The interviewer may ask the participant

his/her relationship to the child, if it is not already known. The interviewer marks "Biological Father" if the man completing the interview believes himself to be the biological father of the proband. The interviewer marks "Biological Mother" if the woman completing the interview gave birth to the proband. The interviewer marks "Other Guardian" if the person completing this form is neither biological parent of the proband. Only one guardian answers the questions, however more than one guardian can be present at the interview. The interviewer should be aware of the relationship the guardian has to the child while administering this questionnaire. If the form is administered to the guardian, the italicized text in parentheses is read. Versions of questions may differ based upon the relationship to the proband.

4. *(Your child's)* Gender

The participant responds by giving his/her, or the child's, gender.

5. What is your *(child's)* date of birth?

Record the date of birth in the appropriate boxes. For some clinics, this information is considered an identifier and thus cannot be collected. In this case, the interviewer marks the "Can not collect" box, but must answer Question 6. If clinics are able to collect a portion of the date of birth, the year is recorded in the appropriate boxes.

6. What is your *(child's)* current age?

The participant responds by giving his/her current age, or that of the child, at the time of the interview. If the information is abstracted from other sources and transferred onto this form, the interviewer determines the proband's current age. The proband's age is recorded in years.

7a. Are you *(Is your child)* Latino, Hispanic or of Spanish origin?

The participant answers "Yes" if he/she considers himself/herself, or the child, to be either Latino, Hispanic or of Spanish origin. For some clinics, this question is not asked (*e.g.,* Asia-Pacific). In this case, the interviewer marks "Not applicable" and

continues with the form. **"Not applicable" is only marked when this question is not read to the participant.** Regardless of the answer to this question, the participant must answer Question 7b.

7b. Which of the following best describes your *(child's)* race (or ethnic origin)? HAND PARTICIPANT CUE CARD AND RECORD PARTICIPANT'S RESPONSES.

This question can be read differently depending on the clinic; either the word "race" or "ethnic origin" may be used due to cultural sensitivity. The interviewer hands (or reads) the participant the cue card containing a list of races (or ethnic origins) to choose from. The participant chooses up to three responses that best describe his/her, or the child's, race (or ethnic origin). If the participant does not feel that any race (or ethnic origin) describes his/her, or the child's race (or ethnic origin), the entire list found in Appendix K should be shown to the participant and choices should be made from this list. Record the appropriate code(s) in the boxes. At least one set of boxes must be completed. If a participant chooses more than one category, the interviewer asks which race (or ethnic origin) he/she, or the child, most identifies with and records that choice in the first set of boxes with the word "Primary" beside it.

8. Do you *(Does your child)* have any of the following diseases? HAND PARTICIPANT CUE CARD AND MARK ALL REPORTED RESPONSES.

The interviewer hands (or reads) the participant the cue card containing a list of diseases. The participant informs the interviewer whether he/she, or the child, has any of the diseases listed on the card. If the participant reports that the proband has any of the diseases, mark the appropriate box. Leave boxes blank for negative answers. If the participant does not have any of the medical conditions listed, mark the "None of the above" box. If the participant answers "Don't know," the interviewer continues with the form. If a participant has one or more of the diseases, but does not know about another disease, mark the box beside the known disease(s). Do not mark "Don't know."

9. At the time you were *(your child was)* diagnosed with diabetes, would you consider your *(their)* body size as thin, medium or heavy?

The participant recalls the size of his/her, or the child's, body at the time of diagnosis. This is a subjective measure and is up to the participant's perception of thin, medium and heavy. If the participant cannot recollect the proband's body size, mark the "Don't know" box, continue with the form.

Family History.

In this section we wish to obtain information about living and deceased members of your *(child's)* family. We are only interested in your *(child's)* biological relatives.

QUESTION 10 REFERS TO THE PROBAND'S CHILDREN.

10. Do you *(Does your child)* have any children? Exclude any adopted children or stepchildren.

The participant responds "Yes" if he/she, or the child, has any biological children and continues to Question 10a. Both living and deceased children are included. Stepchildren and adopted children are not included. The participant responds "No" if he/she, or the child, does not have any children, but the proband is old enough to have children. The interviewer skips to Question 11. The interviewer marks "Question not asked" if the proband is not old enough to have children and the interviewer does not ask the question and skips to Question 11. If the participant does not know this information, but the proband is old enough to have children, mark the "Don't know" box and skip to Question 11.

10a. How many children do you *(does your child)* have?

The participant responds by giving the number of biological children he/she, or the child, has.

10b. How many of them have Type 1 diabetes? That is, diagnosis before 35 years old, insulin use within 6 months of diagnosis without stopping for 6 months or more.

The participant responds by giving the number of biological children he/she, or the child, has who have been diagnosed with Type 1 diabetes, as defined by the T1DGC.

10c. How many of them have another type of diabetes?

The participant responds by giving the number of biological children he/she, or the child, has who have been diagnosed with a type of diabetes other than Type 1 diabetes, or Type 1 diabetes that does not meet the T1DGC definition.

10d. How many of them are not affected or you don't know if they are affected with any type of diabetes?

The participant responds by giving the number of biological children he/she, or the child, has without any form of diabetes, or is unsure of the children's diabetes status. The interviewer performs a quick check to be certain the answers to Questions 10b, 10c, and 10d add up to the answer given in Question 10a.

11. Do you have any full brothers/sisters? Full brothers and sisters are those that have the same biological mother and same biological father.

The participant responds "Yes" if he/she, or the child, has any full brothers and sisters and continues to Question 11a. Both living and deceased full brothers and sisters are included. Step-siblings, adopted siblings, and half-siblings are not included. If the participant answers "No" or "Don't know," skip to the Question 12.

11a. How many full brothers and sisters do you (does your child) have?

The participant responds by giving the number of biological brothers and sisters he/she, or the child, has.

11b. How many of them have Type 1 diabetes? That is, diagnosis before 35 years old, insulin use within 6 months of diagnosis without stopping for 6 months or more.

The participant responds by giving the number of biological brothers and sisters he/she, or the child, has who have been diagnosed with Type 1 diabetes, as defined by the T1DGC.

11c. How many of them have another type of diabetes?

The participant responds by giving the number of biological brothers and sisters he/she, or the child, has who have been diagnosed with a type of diabetes other than Type 1 diabetes, or Type 1 diabetes that does not meet the T1DGC definition.

11d. How many of them are not affected or you don't know if they are affected with any type of diabetes?

The participant responds by giving the number of biological brothers and sisters he/she, or the child, has without any form of diabetes, or is unsure of their diabetes status. The interviewer performs a quick check to be certain the answers to Questions 11b, 11c, and 11d add up to the answer given in Question 11a.

12. Do you (Does your child) have any half siblings with the common parent being your (child's) mother?

The participant responds "Yes" if he/she, or the child, has any half brothers and sisters on their mother's side; the interviewer continues to Question 12a. Both living and deceased half brothers and sisters are included. Step-siblings and adopted siblings are not included. If the participant answers "No" or "Don't know," skip to Question 13.

12a. How many half brothers and sisters do you *(does your child)* have with common parent being your *(child's)* mother?

The participant responds by giving the number of half brothers and sisters he/she, or the child, has on their mother's side.

12b. How many of them have Type 1 diabetes? That is, diagnosis before 35 years old, insulin use within 6 months of diagnosis without stopping for 6 months or more.

The participant responds by giving the number of half brothers and sisters he/she, or the child, has on their mother's side who have been diagnosed with Type 1 diabetes, as defined by the T1DGC.

12c. How many of them have another type of diabetes?

The participant responds by giving the number of half brothers and sisters he/she, or the child, has on their mother's side who have been diagnosed with a type of diabetes other than Type 1 diabetes, or Type 1 diabetes that does not meet the T1DGC definition.

12d. How many of them are not affected or you don't know if they are affected with any type of diabetes?

The participant responds by giving the number of half brothers and sisters he/she, or the child, has on their mother's side without any form of diabetes, or is unsure of their diabetes status. The interviewer performs a quick check to be certain the answers to Questions 12b, 12c, and 12d add up to the answer given in Question 12a.

13. Do you *(Does your child)* have any half siblings with the common parent being your *(child's)* father?

The participant responds "Yes" if he/she, or the child, has any half brothers and sisters on their father's side; the interviewer continues to Question 13a. Both living and deceased half brothers and sisters are included. Step-siblings and adopted siblings are not included. If the participant answers "No" or "Don't know," skip to Question 14.

13a. How many half brothers and sisters do you *(does your child)* have with common parent being your *(child's)* father?

The participant responds by giving the number of half brothers and sisters he/she, or the child, has on their father's side.

13b. How many of them have Type 1 diabetes? That is, diagnosis before 35 years old, insulin use within 6 months of diagnosis without stopping for 6 months or more.

The participant responds by giving the number of half brothers and sisters he/she, or the child, has on their father's side who have been diagnosed with Type 1 diabetes, as defined by the T1DGC.

13c. How many of them have another type of diabetes?

The participant responds by giving the number of half brothers and sisters he/she, or the child, has on their father's side who have been diagnosed with a type of diabetes other than Type 1 diabetes, or Type 1 diabetes that does not meet the T1DGC definition.

13d. How many of them are not affected or you don't know if they are affected with any type of diabetes?

The participant responds by giving the number of half brothers and sisters he/she, or the child, has on their father's side without any form of diabetes, or is unsure of their diabetes status. The interviewer performs a quick check to be certain the answers to Questions 13b, 13c, and 13d add up to the answer given in Question 13a.

14. Have you *(Has your child)* participated in any of the following regional, national or international studies? READ/SHOW PARTICIPANT CUE CARD.

The interviewer hands (or reads) the participant the cue card listing previous and ongoing studies. The participant responds "Yes" if he/she, or the child, has participated in any of the studies on the cue card. If the participant answers "Yes," the interviewer

continues with Question 14a. If the participant answers “No” or “Don’t know,” skip to Question 15.

14a. In which studies have you *(has your child)* participated? RECORD MAXIMUM OF FIVE STUDY CODES.

The participant responds by giving the study names in which he/she, or the child, has participated. The interviewer records up to five study codes that correspond with the study(ies) the proband has participated in.

Questions 15-16 are directed toward clinic staff and are completed as the activity occurs (*i.e.,* after interviewing and after editing).

15. Interviewer ID

The interviewer records his/her five-digit assigned code in the appropriate boxes after completion of the *T1DGC Trio Exam Form*.

16. ID of person editing

This is not completed until a clinic staff member reviews the form to ensure completion and accuracy. The person editing and reviewing the form records his/her five-digit assigned code in the appropriate boxes.

APPENDIX H
TRIO EXAM FORM (PARENT):
QUESTION BY QUESTION INSTRUCTIONS

These instructions are meant to assist the interviewer and to provide answers to any questions from a participant or clinic staff member.

This form is administered to each biological parent of the proband. The interviewer reads the questions to the participant and marks or records appropriate answers. For some questions the interviewer reads all the choices listed to the participant and marks affirmative responses.

Information in all capital letters is an instruction to the interviewer and is not read to the participant.

Please complete all parts of the form. Note that certain individual items may be marked "Don't know" and with an asterisk. In these cases, continue completing the form and contact the appropriate individuals within 10 days in order to collect information not known at the time of the initial exam. The participant may need to contact his/her physician or other family members in order to obtain information. Items should be followed-up, but forms should be forwarded to the Regional Network Center when it has become apparent that this information will not be found.

All dates are written as day first, month second, and year third. The day is recorded numerically. If the day is a single-digit number, a "0" is recorded in the first box. The month is written out in its entirety (*e.g.,* January, February). The year is recorded numerically, with all four digits of the year included (*e.g.,* 1950). Any single digit numerical response is recorded with a leading "0" (*e.g.,* if participant is 5 years old, record "05").

Question by Question Instructions

The interviewer affixes the mother or father's Participant ID Label in the box shown in the upper right hand corner. A label is affixed on every page.

The interviewer records the clinic ID for his/her individual clinic. This number is assigned by the Regional Network Center and it is recorded on every page.

The interviewer records the secondary ID for the mother or father. The secondary ID is "MO" for the mother and "FA" for the father. The secondary ID is recorded on every page.

1. Interview date

This is the date the interview takes place. Record the date of the interview in the appropriate boxes. For some clinics, the information on the form is abstracted from other sources and transferred onto this form. In this case, the interviewer records the date the information is abstracted and the form is completed. **This form should never be completed until the participants has signed the *Informed Consent*.**

2. How was this form completed? MARK ALL THAT APPLY.

The interviewer marks all sources from which information is gathered about the participant. If information is obtained by calling a participant before he/she comes into the clinic, mark "Phone interview." If the participant comes into the clinic and is interviewed in person, the interviewer marks "Face-to-face interview." If information is abstracted from other sources (*e.g.,* other forms, pulling medical records), the interviewer marks "From existing records." The interviewer marks all applicable answers.

3. Gender

The participant responds by giving his/her gender.

4. What is your date of birth?

Record the date of birth in the appropriate boxes. For some clinics, this information is considered an identifier and thus cannot be collected. In this case, the interviewer marks the "Can not collect" box, but must answer Question 5. If clinics are able to collect a portion of the date of birth, the year is recorded in the appropriate boxes.

5. What is your current age?

The participant responds by giving his/her current age at the time of the interview. If the information is abstracted from other sources and transferred onto this form, the interviewer determines the participant's current age. The participant's age is recorded in years.

6a. Are you Latino, Hispanic or of Spanish origin?

The participant answers "Yes" if he/she considers himself/herself to be either Latino, Hispanic or of Spanish origin. For some clinics, this question is not asked (*e.g.,* Asia-Pacific). In this case, the interviewer marks "Not applicable" and continues with the form. **"Not applicable" is only marked when this question is not read to the participant.** Regardless of the answer to this question, the participant must answer Question 6b.

6b. Which of the following best describes your race (or ethnic origin)? HAND PARTICIPANT CUE CARD AND RECORD PARTICIPANT'S RESPONSES.

This question can be read differently depending on the clinic; either the word "race" or "ethnic origin" may be used due to cultural sensitivity. The interviewer hands (or reads) the participant the cue card containing a list of races (or ethnic origins) to choose from. The participant chooses up to three responses that best describe his/her race (or ethnic origin). If the participant does not feel that any race (or ethnic origin) describes his/her race (or ethnic origin), the entire list found in Appendix K should be shown to the participant and choices should be made from this list. Record the appropriate code(s) in the boxes. At least one set of boxes must be completed. If a

participant chooses more than one category, the interviewer asks which race (or ethnic origin) he/she most identifies with and records that choice in the first set of boxes with the word “Primary” beside it.

7. Have you been diagnosed with diabetes?

The participant answers “Yes” if they have been diagnosed with any form of diabetes. This includes, but is not limited to Type 1 diabetes, Type 2 diabetes and MODY. If the participant answers “No” or “Don’t know,” the interviewer skips to Question 12. If the participant answers “Don’t know,” continue with the form. If the participant answers “Yes,” continue with Question 8.

8. What type of diabetes do you have?

The interviewer reads the entire list to the participant and marks all applicable answers. If the participant answers “Don’t know,” continue with the form.

9. At what age or on what date were you diagnosed with diabetes?

The participant gives the age he/she was when diagnosed with diabetes. If he/she cannot recall their age, an attempt is made to guess, or tell the interviewer the date of diagnosis. If only the year is known, that is acceptable. The participant’s age is recorded in years. If the participant was less than 1 year old, record “00.” If the participant has no recollection of his/her age at diagnosis or year of diagnosis, mark the “Don’t know” box and continue with the form.

10. Did you use insulin within six months of being diagnosed?

The participant answers “Yes” if insulin was used at any point during the first six months after he/she was diagnosed with diabetes. This excludes nasal or inhaled insulin. If the participant answers “Yes,” continue to Question 11. If the participant answers “No,” skip to Question 12.

11. Once you started using insulin, did you ever stop using insulin for a period of six months or more for reasons other than a pancreas transplant?

The participant answers "Yes" if insulin use was started but discontinued for 6 months or longer. More than one interruption is permitted if each is within the allotted time frame. If a participant has had a pancreas transplant and has stopped insulin use for more than 6 months because of the transplant, the participant answers "No." The participant answers "No" if insulin use was never disrupted after starting on insulin, or if any insulin was stopped for periods within 6 months.

12. Do you have any of the following diseases? HAND PARTICIPANT CUE CARD AND MARK ALL REPORTED RESPONSES.

The interviewer hands (or reads) the participant the cue card containing a list of diseases. The participant informs the interviewer whether he/she has any of the diseases listed on the card. If the participant reports having any of the diseases, mark the appropriate box. Leave boxes blank for negative answers. If the participant does not have any of the medical conditions listed, mark the "None of the above" box. If the participant answers "Don't know," the interviewer continues with the form. If a participant has one or more of the diseases, but does not know about another disease, mark the box beside the known disease(s). Do not mark "Don't know."

Family History.

In this section we wish to obtain information about living and deceased members of your family. We are only interested in your biological relatives.

13. Have any of the following biological relatives – mother, father, sister(s) or brother(s) – ever been diagnosed with diabetes?

The participant responds "Yes" if any member of his/her immediate family (*i.e.,* biological parents and/or full biological siblings) has been diagnosed with diabetes and continues to Question 14. If the participant responds "No" or "Don't know," skip to Question 17.

14. Does/did your biological mother have diabetes?

The participant responds "Yes" if his/her mother has been diagnosed with any form of diabetes. This includes, but is not limited to Type 1 diabetes, Type 2 diabetes and MODY. If the participant answers "No" or "Don't know," the interviewer skips to Question 15. If the participant answers "Yes," continue with Question 14a.

14a. What type of diabetes does/did she have?

The interviewer reads the entire list to the participant and marks all applicable answers. If the participant answers "Don't know," continue with the form.

15. Does/did your biological father have diabetes?

The participant responds "Yes" if his/her father has been diagnosed with any form of diabetes. This includes, but is not limited to Type 1 diabetes, Type 2 diabetes and MODY. If the participant answers "No" or "Don't know," the interviewer skips to Question 16. If the participant answers "Yes," continue with Question 15a.

15a. What type of diabetes does/did he have?

The interviewer reads the entire list to the participant and marks all applicable answers. If the participant answers "Don't know," continue with the form.

16. Do you have any full brothers/sisters? Full brothers and sisters are those that have the same biological mother and same biological father.

The participant responds "Yes" if he/she has any biological brothers and sisters and continues to Question 16a. Both living and deceased brothers and sisters are included. Step-siblings, adopted siblings and half siblings are not included. If the participant answers "No" or "Don't know," skip to Question 17.

16a. How many full brothers/sisters do you have?

The participant responds by giving the number of biological brothers and sisters he/she has.

16b. How many of them have Type 1 diabetes? That is, diagnosis before 35 years old, insulin use within 6 months of diagnosis without stopping for 6 months or more.

The participant responds by giving the number of biological brothers and sisters he/she has who have been diagnosed with Type 1 diabetes, as defined by the T1DGC.

16c. How many of them have another type of diabetes?

The participant responds by giving the number of their biological brothers and sisters diagnosed with a type of diabetes other than Type 1 diabetes, or Type 1 diabetes that does not meet the T1DGC definition.

16d. How many of them are not affected or you don't know if they are affected?

The participant responds by giving the number of biological brothers and sisters he/she has without any form of diabetes, or is unsure of their diabetes status. The interviewer performs a quick check to be certain the answers to Questions 16b, 16c, and 16d add up to the answer given in Question 16a.

17. Have you participated in any of the following regional, national or international studies? READ/SHOW PARTICIPANT CUE CARD.

The interviewer hands (or reads) the participant the cue card listing previous and ongoing studies. The participant responds "Yes" if he/she has participated in any of the studies on the cue card. If the participant answers "Yes," the interviewer continues with Question 17a. If the participant answers "No" or "Don't know," skip to Question 18.

17a. In which studies have you participated? RECORD MAXIMUM OF FIVE STUDY CODES.

The participant responds by giving the study names in which he/she has participated. The interviewer records up to five study codes that correspond with the study(ies) he/she has participated in.

Questions 18-19 are directed toward clinic staff and are completed as the activity occurs *(i*.e., after interviewing and after editing).

18. Interviewer ID

The interviewer records his/her five-digit assigned code in the appropriate boxes after completion of the *T1DGC Trio Exam Form*.

19. ID of person editing

This is not completed until a clinic staff member reviews the form to ensure completion and accuracy. The person editing and reviewing the form records his/her five-digit assigned code in the appropriate boxes.

APPENDIX I
CASE EXAM FORM
(CASE DATA FROM PARTICIPANT OR GUARDIAN)
QUESTION BY QUESTION INSTRUCTIONS

These instructions are meant to assist the interviewer and to provide answers to any questions from a participant or clinic staff member.

This form is administered to the case or to the case's guardian (*i.e.,* the biological mother, the biological father, or other legal guardian). Only one person is interviewed, although more than one can be present. The interviewer reads the questions to the participant and marks or records appropriate answers. For some questions the interviewer reads all the choices listed to the participant and marks affirmative responses.

Information in all capital letters is an instruction to the interviewer and is not read to the participant.

Please complete all parts of the form. Note that certain individual items may be marked "Don't know" and with an asterisk. In these cases, continue completing the form and contact the appropriate individuals within 10 days in order to collect information not known at the time of the initial exam. The participant may need to contact his/her physician or other family members in order to obtain information. Items should be followed-up, but forms should be forwarded to the Regional Network Center when it has become apparent that this information will not be found.

All dates are written as day first, month second, and year third. The day is recorded numerically. If the day is a single-digit number, a "0" is recorded in the first box. The month is written out in its entirety (*e.g.,* January, February). The year is recorded numerically, with all four digits of the year included (*e.g.,* 1950). Any single

digit numerical response is recorded with a leading "0" (*e.g.,* if participant is 5 years old, record "05").

Question by Question Instructions

The interviewer affixes the case's Participant ID Label in the box shown in the upper right hand corner. A label is affixed on every page.

The interviewer records the clinic ID for his/her individual clinic. This number is assigned by the Regional Network Center and it is recorded on every page.

The secondary ID for the case, "CAS", has already been recorded on each page of the Exam Form.

1. Interview Date

This is the date the interview takes place. Record the date of the interview in the appropriate boxes. For some clinics, the information on the form is abstracted from other sources and transferred onto this form. In this case, the interviewer records the date the information is abstracted and the form is completed. **This form should never be completed until the participant has signed the *Informed Consent*.**

2. How was this form completed? MARK ALL THAT APPLY.

The interviewer marks all sources from which information is gathered about the participant. If information is obtained by calling a participant before he/she comes into the clinic, mark "Phone interview." If the participant comes into the clinic and is interviewed in person, the interviewer marks "Face-to-face interview." If information is abstracted from other sources (*e.g.,* other forms, pulling medical records), the interviewer marks "From existing records." The interviewer marks all applicable answers.

3. Who is completing this form? CASE IS THE PERSON/CHILD DIAGNOSED WITH TYPE 1 DIABETES. IF GUARDIAN COMPLETING FORM, READ ITALICIZED TEXT. ONLY ONE GUARDIAN IS INTERVIEWED.

The interviewer marks "Case" if the participant is answering questions about himself/herself. If a guardian is answering the questions, the interviewer determines the relationship the guardian has with the case. The interviewer may ask the guardian his/her relationship to the child, if it is not already known. The interviewer marks "Biological Father" if the man completing the interview believes himself to be the biological father of the case. The interviewer marks "Biological Mother" if the woman completing the interview gave birth to the case. The interviewer marks "Other Guardian" if the guardian completing this form is neither biological parent of the case. Only one guardian answers the questions, however more than one guardian can be present at the interview. The interviewer should be aware of the relationship the guardian has to the child while administering this questionnaire. If the form is administered to the guardian, the italicized text in parentheses is read. Versions of questions may differ based upon the relationship to the case.

4. What is your *(child's)* gender?

The participant responds by giving his/her, or the child's, gender.

5. What is your *(child's)* date of birth?

Record the date of birth in the appropriate boxes. For some clinics, this information is considered an identifier and thus cannot be collected. In this case, the interviewer marks the "Can not collect" box, but must answer Question 6. If clinics are able to collect a portion of the date of birth, the year is recorded in the appropriate boxes.

6. What is your *(child's)* current age?

The participant responds by giving his/her current age, or that of the child, at the time of the interview. If the information is abstracted from other sources and transferred

onto this form, the interviewer determines the case's current age. The case's age is recorded in years.

7a. Are you *(Is your child)* Latino, Hispanic or of Spanish origin?

The participant answers "Yes" if he/she considers himself/herself, or the child, to be either Latino, Hispanic or of Spanish origin. For some clinics, this question is not asked (*e.g.,* Asia-Pacific). In this case, the interviewer marks "Not applicable" and continues with the form. **"Not applicable" is only marked when this question is not read to the participant.** Regardless of the answer to this question, the participant must answer Question 7b.

7b. Which of the following best describes your *(child's)* race (or ethnic origin)? HAND PARTICIPANT CUE CARD AND RECORD RESPONSES.

This question can be read differently depending on the clinic; either the word "race" or "ethnic origin" may be used due to cultural sensitivity. The interviewer hands (or reads) the participant the cue card containing a list of races (or ethnic origins) to choose from. The participant chooses up to three responses that best describe his/her, or the child's, race (or ethnic origin). If the participant does not feel that any race (or ethnic origin) describes his/her, or the child's race (or ethnic origin), the entire list found in Appendix K should be shown to the participant and choices should be made from this list. Record the appropriate code(s) in the boxes. At least one set of boxes must be completed. If a participant chooses more than one category, the interviewer asks which race (or ethnic origin) he/she, or the child, most identifies with and records that choice in the first set of boxes with the word "Primary" beside it.

8. Do you *(Does your child)* have any of the following diseases? HAND PARTICIPANT CUE CARD AND MARK ALL REPORTED RESPONSES.

The interviewer hands (or reads) the participant the cue card containing a list of diseases. The participant informs the interviewer whether he/she, or the child, has any of the diseases listed on the card. If the case reports that he/she or the child has any of the diseases, mark the appropriate box. Leave boxes blank for negative answers. If

the case does not have any of the medical conditions listed, mark the "None of the above" box. If the participant answers "Don't know," the interviewer continues with the form. If the case has one or more of the diseases, but does not know about another disease, mark the box beside the known disease(s). Do not mark "Don't know."

9. At the time you were *(your child was)* diagnosed with diabetes, would you consider your *(his/her)* body size as thin, medium or heavy?

The participant recalls the size of his/her body, or the child's body at the time of diagnosis. This is a subjective measure and is up to the participant's perception of thin, medium and heavy. If the participant cannot recollect the body size, mark the "Don't know" box, continue with the form.

Family History.

In this section we wish to obtain information about living and deceased members of your *(child's)* family. We are only interested in your *(child's)* biological relatives.

QUESTION 10 REFERS TO THE CASE'S CHILDREN.

10. Do you *(Does your child)* have any children? Exclude any adopted children or stepchildren.

The participant responds "Yes" if he/she, or the child has any biological children and continues to Question 10a. Both living and deceased children are included. Stepchildren and adopted children are not included. The participant responds "No" if he/she, or the child, does not have any children, but the case is old enough to have children. The interviewer skips to Question 11. The interviewer marks "Question not asked" if the case is not old enough to have children and the interviewer does not ask the question and skips to Question 11. If the participant does not know this information, but the case is old enough to have children, mark the "Don't know" box and skip to Question 11.

10a. How many children do you *(does your child)* have?

The participant responds by giving the number of biological children he/she, or the child, has.

10b. How many of them have Type 1 diabetes? That is, diagnosis before 35 years old, insulin use within 6 months of diagnosis without stopping for 6 months or more.

The participant responds by giving the number of biological children he/she, or the child, has who have been diagnosed with Type 1 diabetes, as defined by the T1DGC.

10c. How many of them have another type of diabetes?

The participant responds by giving the number of biological children he/she, or the child, has who have been diagnosed with a type of diabetes other than Type 1 diabetes, or Type 1 diabetes that does not meet the T1DGC definition.

10d. How many of them are not affected or you don't know if they are affected with any type of diabetes?

The participant responds by giving the number of biological children he/she, or the child, has without any form of diabetes, or is unsure of the children's diabetes status. The interviewer performs a quick check to be certain the answers to Questions 10b, 10c, and 10d add up to the answer given in Question 10a.

QUESTIONS 11a – 11c REFER TO THE CASE'S MATERNAL RELATIVES

11a. Which of the following biological relatives have been diagnosed with Type 1 diabetes? That is, diagnosis before 35 years old, insulin use within 6 months of diagnosis without stopping for 6 months or more.

The interviewer can expect a "Yes" or "No" answer to each choice. The participant only answers "Yes" if the family member has been diagnosed with Type 1

diabetes, as defined by the T1DGC. If the participant answers "Don't know" to any of the questions, continue with the form.

11b. Which of the following biological relatives have been diagnosed with another type of diabetes?

The interviewer can expect a "Yes" or "No" answer to each choice. If the participant answers "Don't know" to any of the questions, continue with the form.

11c. Do you *(Does your child)* have any full aunts and uncles on your *(child's)* mother's side?

The participant responds "Yes" if he/she, or the child, has any biological full aunts and uncles on their mother's side. These are the biological mother's full siblings. Both living and deceased aunts and uncles are included. Step-aunts, step-uncles, adopted aunts, adopted uncles, aunts-in-law and uncles-in-law are not included. If the participant answers "No" or "Don't know," the interviewer skips to Question 12. If the participant answers "Don't know," continue with the form. If the participant answers, "Yes," continue to Question 11c1.

11c1. How many full aunts and uncles on your *(child's)* mother's side do you *(does your child)* have?

The participant responds by giving the number of biological aunts and uncles he/she, or the child, has on their mother's side.

11c2. How many of them have Type 1 diabetes? That is, diagnosis before 35 years old, insulin use within 6 months of diagnosis without stopping for 6 months or more.

The participant responds by giving the number of biological aunts and uncles he/she, or the child, has on their mother's side who have been diagnosed with Type 1 diabetes, as defined by the T1DGC.

11c3. How many of them have another type of diabetes?

The participant responds by giving the number of biological aunts and uncles he/she, or the child, has on their mother's side who have been diagnosed with a type of diabetes other than Type 1 diabetes, or Type 1 diabetes that does not meet the T1DGC definition.

11c4. How many of them are not affected or you don't know if they are affected with any type of diabetes?

The participant responds by giving the number of biological aunts and uncles he/she, or the child, has on their mother's side without any form of diabetes, or is unsure of their diabetes status. The interviewer performs a quick check to be certain the answers to Questions 11c2, 11c3, and 11c4 add up to the answer given in Question 11c1.

QUESTIONS 12a – 12c REFER TO CASE'S PATERNAL RELATIVES

12a. Which of the following biological relatives have been diagnosed with Type 1 diabetes? That is, diagnosis before 35 years old, insulin use within 6 months of diagnosis without stopping for 6 months or more.

The interviewer can expect a "Yes" or "No" answer to each choice. The participant only answers "Yes" if the family member has been diagnosed with Type 1 diabetes, as defined by the T1DGC. If the participant or guardian answers "Don't know" to any of the questions, continue with the form.

12b. Which of the following biological relatives have been diagnosed with another type of diabetes?

The interviewer can expect a "Yes" or "No" answer to each choice. If the participant answers "Don't know" to any of the questions, continue with the form.

12c. Do you *(Does your child)* have any full aunts and uncles on your *(child's)* father's side?

The participant responds "Yes" if he/she, or the child, has any biological full aunts and uncles on their father's side. These are the biological father's full siblings. Both living and deceased aunts and uncles are included. Step-aunts, step-uncles, adopted aunts, adopted uncles, aunts-in-law and uncles-in-law are not included. If the participant answers "No" or "Don't know," the interviewer skips to Question 13. If the participant answers "Don't know," continue with the form. If the participant answers, "Yes," continue to Question 12c1.

12c1. How many full aunts and uncles on your *(child's)* father's side do you *(does your child)* have?

The participant responds by giving the number of biological aunts and uncles he/she, or the child, has on their father's side.

12c2. How many of them have Type 1 diabetes? That is, diagnosis before 35 years old, insulin use within 6 months of diagnosis without stopping for 6 months or more.

The participant responds by giving the number of biological aunts and uncles he/she, or the child, has on their father's side who have been diagnosed with Type 1 diabetes, as defined by the T1DGC.

12c3. How many of them have another type of diabetes?

The participant responds by giving the number of biological aunts and uncles he/she, or the child, has on their father's side who have been diagnosed with a type of diabetes other than Type 1 diabetes, or Type 1 diabetes that does not meet the T1DGC definition.

12c4. How many of them are not affected or you don't know if they are affected with any type of diabetes?

The participant responds by giving the number of biological aunts and uncles he/she, or the child, has on their father's side without any form of diabetes, or is unsure of their diabetes status. The interviewer performs a quick check to be certain the answers to Questions 12c2, 12c3, and 12c4 add up to the answer given in Question 12c1.

13. Do you (*Does your child)* have any full brothers and sisters? Full brothers and sisters are those that have the same biological mother and the same biological father.

The participant responds "Yes" if he/she, or the child, has any full brothers or sisters. Both living and deceased brothers and sisters are included. Step-siblings, adopted siblings and half-siblings are not included. If the participant answers "No" or "Don't know," the interviewer skips to Question 14. If the participant answers "Don't know," continue with the form. If the participant answers "Yes," continue to Question 13a.

13a. How many?

The participant responds by giving the number of biological brothers and sisters he/she, or the child, has. Both living and deceased brothers and sisters are included in this count. Step-siblings, adopted siblings and half siblings are not included.

13b. How many of them have Type 1 diabetes? That is, diagnosis before 35 years old, insulin use within 6 months of diagnosis without stopping for 6 months or more.

The participant responds by giving the number of biological brothers and sisters he/she, or the child, has who have been diagnosed with Type 1 diabetes, as defined by the T1DGC.

13c. How many of them have another type of diabetes?

The participant responds by giving the number of biological brothers and sisters he/she, or the child, has who have been diagnosed with a type of diabetes other than Type 1 diabetes, or Type 1 diabetes that does not meet the T1DGC definition.

13d. How many of them are not affected or you don't know if they are affected with any type of diabetes?

The participant responds by giving the number of biological brothers and sisters he/she, or the child, has without any form of diabetes, or is unsure of their diabetes status. The interviewer performs a quick check to be certain the answers to Questions 13a, 13b, and 13c add up to the answer given in Question 13.

14. Do you *(Does your child)* have any half siblings with the common parent being your *(child's)* mother?

The participant responds "Yes" if he/she, or the child, has any half brothers and sisters on their mother's side; the interviewer continues to Question 14a. Both living and deceased half brothers and sisters are included. Step-siblings and adopted siblings are not included. If the participant answers "No" or "Don't know," skip to Question 15.

14a. How many half brothers and sisters do you *(does your child)* have with common parent being your *(child's)* mother?

The participant responds by giving the number of half brothers and sisters he/she, or the child, has on their mother's side.

14b. How many of them have Type 1 diabetes? That is, diagnosis before 35 years old, insulin use within 6 months of diagnosis without stopping for 6 months or more.

The participant responds by giving the number of half brothers and sisters he/she, or the child, has on their mother's side who have been diagnosed with Type 1 diabetes, as defined by the T1DGC.

14c. How many of them have another type of diabetes?

The participant responds by giving the number of half brothers and sisters he/she, or the child, has on their mother's side who have been diagnosed with a type of diabetes other than Type 1 diabetes, or Type 1 diabetes that does not meet the T1DGC definition.

14d. How many of them are not affected or you don't know if they are affected with any type of diabetes?

The participant responds by giving the number of half brothers and sisters he/she, or the child, has on their mother's side without any form of diabetes, or is unsure of their diabetes status. The interviewer performs a quick check to be certain the answers to Questions 14b, 14c, and 14d add up to the answer given in Question 14a.

15. Do you *(Does your child)* have any half siblings with the common parent being your *(child's)* father?

The participant responds "Yes" if he/she, or the child, has any half brothers and sisters on their father's side; the interviewer continues to Question 15a. Both living and deceased half brothers and sisters are included. Step-siblings and adopted siblings are not included. If the participant answers "No" or "Don't know," skip to Question 16.

15a. How many half brothers and sisters do you *(does your child)* have with common parent being your *(child's)* father?

The participant responds by giving the number of half brothers and sisters he/she, or the child, has on their father's side

15b. How many of them have Type 1 diabetes? That is, diagnosis before 35 years old, insulin use within 6 months of diagnosis without stopping for 6 months or more.

The participant responds by giving the number of half brothers and sisters he/she, or the child, has on their father's side who have been diagnosed with Type 1 diabetes, as defined by the T1DGC.

15c. How many of them have another type of diabetes?

The participant responds by giving the number of half brothers and sisters he/she, or the child, has on their father's side who have been diagnosed with a type of diabetes other than Type 1 diabetes, or Type 1 diabetes that does not meet the T1DGC definition.

15d. How many of them are not affected or you don't know if they are affected with any type of diabetes?

The participant responds by giving the number of half brothers and sisters he/she, or the child, has on their father's side without any form of diabetes, or is unsure of their diabetes status. The interviewer performs a quick check to be certain the answers to Questions 15b, 15c, and 15d add up to the answer given in Question 15a.

16. Have you *(Has your child)* participated in any of the following regional, national or international studies? READ/SHOW PARTICIPANT CUE CARD.

The interviewer hands (or reads) the participant the cue card listing previous and ongoing studies. The participant responds "Yes" if he/she, or the child, has participated in any of the studies on the cue card. If the participant answers "Yes," the interviewer continues with Question 16a. If the participant answers "No" or "Don't know," skip to Question 17.

16a. In which studies have you *(has your child)* participated? RECORD MAXIMUM OF FIVE STUDY CODES.

The participant responds by giving the study names in which he/she, or the child, has participated. The interviewer records up to five study codes that correspond with the study(ies) in which the case has participated.

Questions 17-18 are directed toward clinic staff and are completed as the activity occurs (*i.e.*, after interviewing and after editing).

17. Interviewer ID

The interviewer records his/her five-digit assigned code in the appropriate boxes after completion of the *T1DGC Case Exam Form*.

18. ID of person editing

This is not completed until a clinic staff member reviews the form to ensure completion and accuracy. The person editing and reviewing the form records his/her five-digit assigned code in the appropriate boxes.

APPENDIX J

CUE CARDS

PLEASE TELL THE INTERVIEWER IF YOU OR ANY MEMBERS OF YOUR IMMEDIATE FAMILY HAVE PARTICIPATED IN ANY OF THE FOLLOWING GENETIC STUDIES.

T1DGC (Type 1 Diabetes Genetics Consortium)

HBDI (Human Biological Data Interchange)

BDA-Warren I (British Diabetes Association-Warren I)

SCAND (Scandinavia genome scan)

T1DGC Eligibility Form

PLEASE TELL THE INTERVIEWER IF YOU (OR YOUR CHILD) HAVE HAD ANY OF THE FOLLOWING GENETIC DISEASES OR DISORDERS DIAGNOSED.

Mitochondrial DNA 3243 mutation

Maturity onset diabetes of youth (MODY)

Type A insulin resistance

Leprechaunism

Rabson-Mendelhall syndrome

Lipoathrophic diabetes

Wolfram's Syndrome

T1/DGC Eligibility Form

READ THE BRIEF DESCRIPTION OF THE STUDY TO THE PARTICIPANT.

You are invited to participate in the Type 1 Diabetes Genetics Consortium. This is an international effort to identify genes that affect the risk of Type 1 (or juvenile) diabetes. Finding genes that contribute to Type 1 diabetes may help us better understand the causes of this disease and help develop strategies in disease prevention and treatment. We are looking for families in which at least two siblings have Type 1 diabetes. In these families, we would like the participation of the people with diabetes, other siblings without diabetes, and their biological parents. If you agree to be part of this study, eligible family members will be asked to come in for one visit to give some blood and complete a questionnaire about your health and your family. We will take about 3 tablespoons of blood from your arm, and process this sample so that DNA can be taken out, stored, and used for research. To allow more researchers to work with your blood, and so only one blood collection will be needed, we are requesting permission to produce and store a living cell line, which means we will keep some of your white blood cells alive for future research. By participating in this study, you will be part of an important research program to help understand the causes of Type 1 diabetes.

T1DGC Eligibility Form

PLEASE CHOOSE UP TO THREE RACES (OR ETHNIC ORIGINS) THAT BEST DESCRIBE YOU (*OR YOUR CHILD*). IF YOU SELECT MORE THAN ONE, PLEASE LET THE INTERVIEWER KNOW WITH WHICH RACE (OR ETHNIC ORIGIN) YOU MOST IDENTIFY WITH.

NETWORK SPECIFIC RACE/ETHNIC ORIGIN CODES FROM APPENDIX K

T1DGC Exam Form/T1DGC Control Eligibility Form

PLEASE READ THE ENTIRE LIST BELOW AND REPORT TO THE INTERVIEWER ANY AND ALL DISEASES THAT YOU (OR YOUR CHILD) HAVE HAD DIAGNOSED.

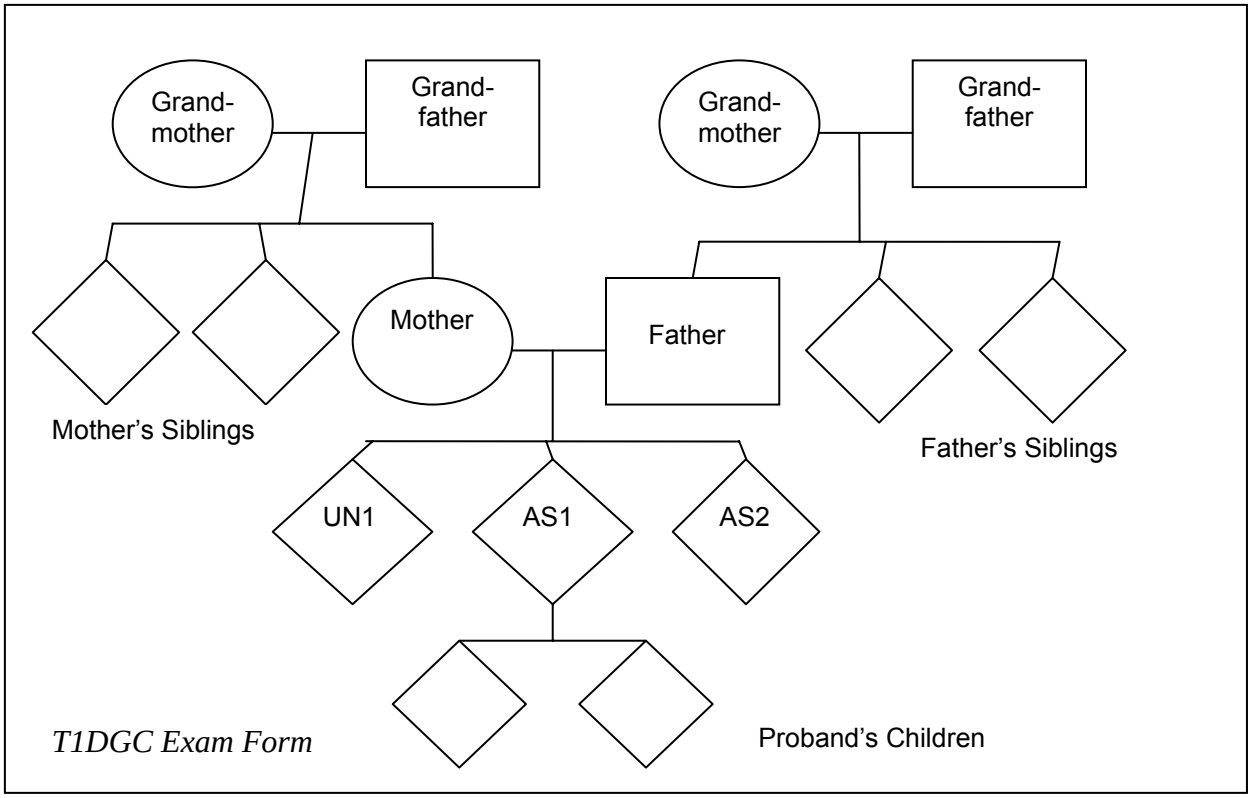
Multiple sclerosis
Celiac disease
Thyroid disease
Myasthenia gravis
Pernicious anemia
Lupus or SLE
Rheumatoid arthritis
Inflammatory Bowel Disease
Vitiligo
Addisons Disease
Psoriasis

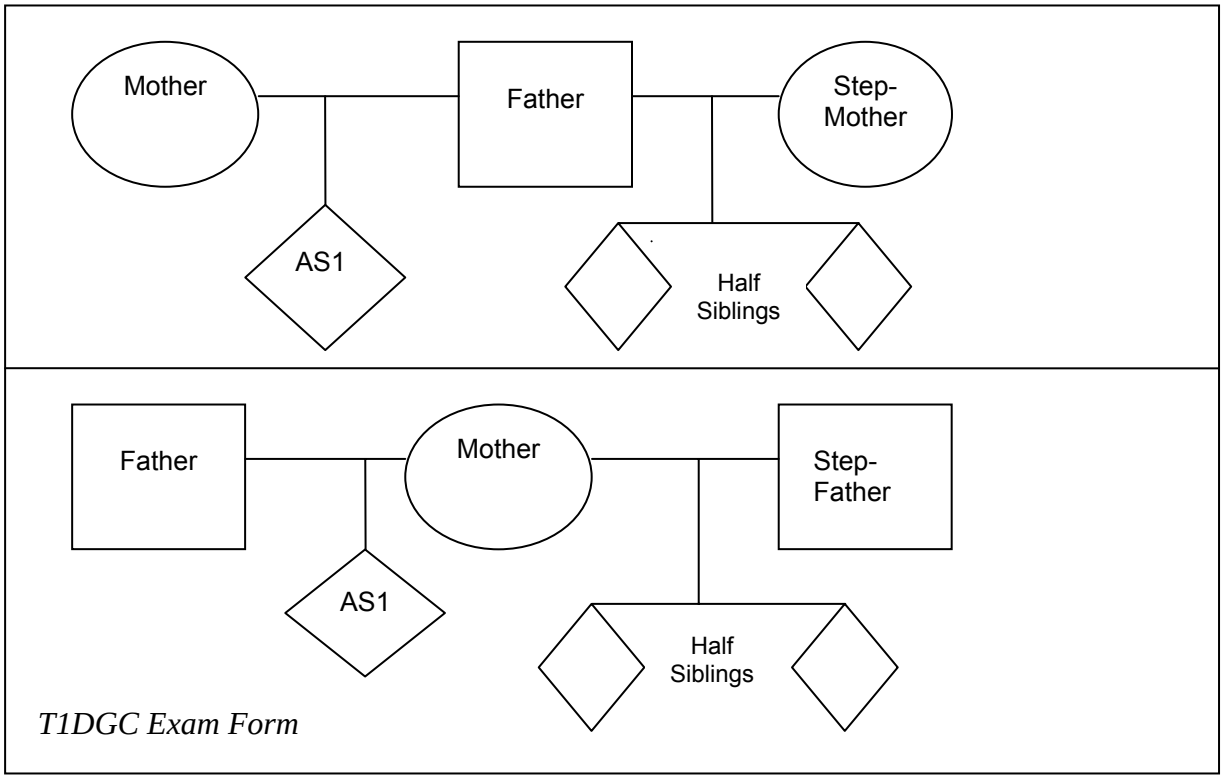
T1DGC Exam Form/T1DGC Control Eligibility Form

PLEASE LET THE INTERVIEWER KNOW IF YOU (OR YOUR CHILD) HAVE PARTICIPATED IN ANY OF THE FOLLOWING REGIONAL, NATIONAL, OR INTERNATIONAL STUDIES. PLEASE IDENTIFY ALL STUDIES IN WHICH YOU (OR YOUR CHILD) HAVE PARTICIPATED.

001 DPT-1
002 TrialNet
003 TEDDY
004 SEARCH
005 GoKinD
006 TRIGR
007 EDIC
008 FIND
009 ENDIT
010 PANDA
011 Australian Type 1 Diabetes Repository
012 EURODIAB TIGER
013 BOX (Bart's Oxford)

T1DGC Exam Form/T1DGC Control Eligibility Form


Grand-
mother
Grand-
father
Grand-
mother
Grand-
father
Mother
Father
Mother's Siblings
Father's Siblings
UN1
AS1
AS2
T1DGC Exam Form
Proband's Children


Mother
Father
Step-
Mother
AS1
Half
Siblings
Father
Mother
Step-
Father
AS1
Half
Siblings
T1DGC Exam Form

DEFINITION OF MEXICAN AMERICAN AND AFRICAN AMERICAN FOR TRIO AND CASE/CONTROL STUDY (**NORTH AMERICAN NETWORK ONLY**)

MEXICAN AMERICAN (CANADIAN):

Any individual of **Mexican** descent living in North America (US or Canada). The proband, case or control does not need to be born in North America. While the primary goal of this collection is to ascertain Mexican American individuals, individuals can be recruited and examined if born in Central America: Belize, Costa Rica, El Salvador, Guatemala, Honduras, Nicaragua, or Panama.

AFRICAN AMERICAN (CANADIAN):

Any individual of **non-Caucasian of African** descent living in North America (US or Canada). This includes (but is not limited to) descent from Egypt and Somalia. The proband, case or control does not need to be born in North America. No Caucasians of African descent qualify (e.g., white South African) can be included as trio families or as cases or controls due to the sufficient number of Caucasian participants from previous collections.

T1DGC North American Trio Pre-Eligibility Form, Case and Control Eligibility Form (North American Network only)

PLEASE CHOOSE THE REGION IN WHICH YOU (*YOUR CHILD)* LIVE OR THE TRIBE TO WHICH YOU (*YOUR CHILD)* BELONG.

ASIA/PACIFIC:

CHINA:

INDIA:

101 Odiya
102 Hindu
103 Muslim
104 Indian

EUROPEAN:

CAMEROON:

205 Western Highlanders (Semi-Bantu or grassfielders)
206 Coastal tropical forest peoples
207 Southern tropical forest people
208 Kirdis and Fulanis

T1DGC Exam Form/T1DGC Case and Control Eligibility Form (Asia/Pacific and European Network only)

APPENDIX K
CLASSIFICATION OF CULTURAL AND ETHNIC GROUPS

Oceanian

100 Oceanian, no further designation

Australian Peoples

110 Australian Peoples, no further designation

111 Australian

112 Australian Aboriginal

113 Australian South Sea Islander

114 Torres Strait Islander

New Zealand Peoples

120 New Zealand Peoples, no further designation

121 Maori

122 New Zealander

Melanesian and Papuan

130 Melanesian and Papuan, no further designation

131 New Caledonian

132 Ni-Vanuatu

133 Papua New Guinean

134 Solomon Islander

139 Melanesian and Papuan, not elsewhere classified (includes Bisorio, Bougainvillian, Huli)

Micronesian

140 Micronesian, no further designation

141 I-Kiribati

142 Nauruan

149 Micronesian, not elsewhere classified (includes Marianas Islander, Marshallese, Palauan)

Polynesian

150 Polynesian, no further designation

151 Cook Islander

152 Fijian

153 Niuean

154 Samoan

155 Tongan

159 Polynesian, not elsewhere classified (includes Hawaiian, Pitcairn Islander, Tahitian)

North-West European

200 North-West European, no further designation

British

210 British, no further designation

211 English

212 Scottish

213 Welsh

219 British, not elsewhere classified (includes Channel Islander, Guernsey Islander, Manx)

Irish

221 Irish

Western European

230 Western European, no further designation

231 Austrian

232 Breton

233 Dutch

234 Flemish

235 French

236 German

237 Swiss

238 Walloon

239 Western European, not elsewhere classified (includes Alsatian, Frisian, Luxembourgish)

Northern European

240 Northern European, no further designation

241 Danish

242 Finnish

243 Icelandic

244 Norwegian

245 Swedish

249 Northern European, not elsewhere classified (includes Faeroese, Greenlandic, Saami)

Southern and Eastern European

300 Southern and Eastern European, no further designation

Southern European

310 Southern European, no further designation

311 Basque

312 Catalan

313 Italian

314 Maltese

315 Portuguese

316 Spanish

319 Southern European, not elsewhere classified (includes Andorran, Galician, Ladin)

South Eastern European

320 South Eastern European, no further designation
321 Albanian
322 Bosnian
323 Bulgarian
324 Croatian
325 Greek
326 Macedonian
327 Moldovan
328 Montenegrin
341 Romanian
342 Roma/Gypsy
343 Serbian
344 Slovene
329 South Eastern European, not elsewhere classified (includes Aromani, Karakachani, Vlach)

Eastern European

330 Eastern European, no further designation
331 Belarusan
332 Czech
333 Estonian
334 Hungarian
335 Latvian
336 Lithuanian
337 Polish
338 Russian
351 Slovak
352 Ukrainian
339 Eastern European, not elsewhere classified (includes Adygei, Khanty, Sorb/Wend)

North African and Middle Eastern

400 North African and Middle Eastern, no further designation

Arab

410 Arab, no further designation
411 Algerian
412 Egyptian
413 Iraqi
414 Jordanian
415 Kuwaiti
416 Lebanese
417 Libyan
418 Moroccan
431 Palestinian
432 Saudi Arabian
433 Syrian
434 Tunisian
419 Arab, not elsewhere classified (includes Baggara, Bedouin, Yemeni)

Jewish

421 Jewish

Other North African and Middle Eastern

490 Other North African and Middle Eastern, no further designation
491 Assyrian/Chaldean
492 Berber
493 Coptic
494 Iranian
495 Kurdish
496 Sudanese

497 Turkish

499 Other North African and Middle Eastern, not elsewhere classified (includes Azande, Beja, Nubian)

South-East Asian

500 South-East Asian, no further designation

Mainland South-East Asian

510 Mainland South-East Asian, no further designation

511 Anglo-Burmese

512 Burmese

513 Hmong

514 Khmer

515 Lao

516 Thai

517 Vietnamese

519 Mainland South-East Asian, not elsewhere classified (includes Arakanese, Karen, Mon)

Maritime South-East Asian

520 Maritime South-East Asian, no further designation

521 Filipino

522 Indonesian

523 Javanese

524 Madurese

525 Malay

526 Sundanese

527 Timorese

529 Maritime South-East Asian, not elsewhere classified (includes Balinese, Irian Jayan, Sumatran)

North-East Asian

600 North-East Asian, no further designation

Chinese Asian

610 Chinese Asian, no further designation

611 Chinese

612 Taiwanese

619 Chinese Asian, not elsewhere classified (includes Hui, Manchu, Yi)

Other North-East Asian

690 Other North-East Asian, no further designation

691 Japanese

692 Korean

693 Mongolian

694 Tibetan

699 Other North-East Asian, not elsewhere classified (includes Ainu, Menba, Xiareba)

Southern and Central Asian

700 Southern and Central Asian, no further designation

Southern Asian

710 Southern Asian, no further designation

711 Anglo-Indian

712 Bengali

713 Burgher

714 Gujarati

715 Gurkha

716 Indian

717 Malayali

718 Marathi

731 Nepalese

732 Pakistani

733 Punjabi

734 Sikh

735 Sinhalese

736 Tamil

719 Southern Asian, not elsewhere classified (includes Bhote, Kashmiri, Sherpa)

Central Asian

720 Central Asian, no further designation

721 Afghan

722 Armenian

723 Georgian

724 Kazakh

725 Pathan

726 Uzbek

729 Central Asian, not elsewhere classified (includes Azerbaijani, Chechen, Tatar)

People of the Americas

800 People of the Americas, no further designation

North American

810 North American, no further designation

811 African American

812 American Caucasian

813 Canadian

814 French Canadian

815 Native North American Indian

816 Mexican American

819 North American, not elsewhere classified (includes Bermudan, Inuit, Metis)

South American

820 South American, no further designation
821 Argentinian
822 Bolivian
823 Brazilian
824 Chilean
825 Colombian
826 Ecuadorian
827 Guyanese
828 Peruvian
851 Uruguayan
852 Venezuelan
829 South American, not elsewhere classified (includes Arawak, Carib, Surinamese)

Central American

830 Central American, no further designation
831 Mexican
832 Nicaraguan
833 Salvadoran
839 Central American, not elsewhere classified (includes Belizean, Costa Rican, Mayan)

Caribbean Islander

840 Caribbean, no further designation
841 Cuban
842 Jamaican
843 Trinidadian (Tobagonian)
849 Caribbean Islander, not elsewhere classified (includes Bahamian, Haitian, Puerto Rican)

Sub-Saharan African

900 Sub-Saharan African, no further designation

Central and West African

910 Central and West African, no further designation
911 Akan
912 Fulani
913 Ghanaian
914 Nigerian
915 Yoruba
919 Central and West African, not elsewhere classified (includes Fang, Kongo, Liberian)

Southern and East African

920 Southern and East African, no further designation
921 Afrikaner
922 Angolan
923 Eritrean
924 Ethiopian
925 Kenyan
926 Malawian
927 Mauritian
928 Mozambican
931 Namibian
932 Oromo
933 Seychellois
934 Somali
935 South African
936 Tanzanian
937 Ugandan
938 Zambian

941 Zimbabwean

929 Southern and East African, not elsewhere classified (includes Afar, Tutsi, Zulu)

Other

998 Refused to Answer

999 Don’t Know

BLOOD COLLECTION AND PROCESSING
TABLE OF CONTENTS

I. PURPOSE

The phlebotomy station is designed to obtain blood samples to: (1) establish cell lines as a source of DNA for genotyping; (2) test for autoantibodies in affected siblings; and (3) establish a plasma and serum storage repository for future assays. It is potentially a difficult station because of the anxiety caused by blood collection and the potential for injury. However, if carefully and professionally done, it provides a positive, safe experience for the participant. Blood collection will take approximately 10 to 15 minutes of the participant's time. This protocol is designed as a guide for the nurses and technicians at the clinics.

II. LABORATORY QUALITY CONTROL

A split sample (or duplicate sample) program is used to determine how well the network laboratories can reproduce autoantibody measurements and DNA yields from the EDTA cell pack. In addition, a repository of quality control samples is created for future assays of interest to the T1DGC investigators.

The purpose of the split sample program is to produce data to: (1) identify problems as they occur, and to communicate this information to the clinic and laboratory for corrective action; and (2) document the performance of the entire process (*i.e.*, sample collection, preparation, processing, shipping and analytical performance).

The quality control procedures consist of providing the laboratories with duplicate samples, one sample labeled with the participant ID and the other with a fictitious (quality control or QC) ID. Each of the clinics collects a QC tube on an approximate 5% sample of the participants for serum samples and 5% for plasma samples. All QC participants must be at least 16 years old (or large for age) due to the additional volume of blood to be collected. (See **Chapter VIII**, *Quality Control*, for specific guidelines and rationale.)

The Clinic Coordinator identifies the QC participants and provides this information to the nurse or technician at the beginning of each clinic week. A *T1DGC Participant and QC Selection Log* has been developed to assist in the selection and tracking of QC participants.

In the event that the additional sample cannot be collected on the identified participant, the nurse or technician collects the QC sample on the **next appropriate participant**. The participant need not be told that he/she is having extra blood collected for QC. The consent form covers the maximum amount of blood to be collected.

III. DESCRIPTION

A. Tests

The following tests are planned for the proband, the affected siblings, and cases: serum IA-2 and GAD65 autoantibodies. The measurement methods for each test are provided in the *Type 1 Diabetes Genetics Consortium (T1DGC) Laboratory Operations Manual*: *Autoantibody and Storage Laboratory* and the rationale for assessment is provided in the *T1DGC Protocol*.

B. Recommendations

The following procedures are designed to standardize sample collection.

1. Blood is collected with the participant in a seated position. The reclining position can be used if desired or if participant has a history of fainting during blood collection.

2. Participants are instructed to drink plenty of water during the 24 hours prior to the clinic exam. Blood collection is easier if participants are well hydrated.

3. No restrictions are required for fasting, vigorous activity, or smoking the day of the exam.

4. Blood collection occurs after the questionnaires for eligible participants have been completed.

5. Participants are encouraged to engage in brisk exercise (*e.g.*, walk up and down a flight of stairs or permit children to run outside) prior to blood collection to increase the number of circulating lymphocytes.

C. General Preparation

The blood collection should take place in an isolated room or one enclosed by dividers. Temperature should be 65-75^{o}F (18-24^{o}C). There should be no direct sunlight on samples.

The room should be equipped with all the necessary supplies. A table or counter should be prepared with the materials and vials needed for blood processing and aliquoting. The centrifuge, refrigerator and freezer should be nearby.

Clinic staff records the temperature of the freezer(s) containing T1DGC samples on the *T1DGC Daily Freezer Temperature Log* each day the clinic is in operation. Any values that are outside the specified range are circled. The expected temperatures are -75^{o} to -65^{o}C, but -20 ^{o}C is acceptable for short-term storage (*i.e.*, one to two months). The *T1DGC Daily Freezer Temperature Log* is sent to the Regional Network Center at the end of each month or as requested.

This station is staffed with a nurse or technician with documented class time and experience in phlebotomy. The technician should be properly attired; gloves must be used at all times while processing blood samples. Certification in T1DGC procedures occurs during or following a training session and prior to data collection. Recertification will occur annually or as requested by the Regional Network Center.

D. Blood Volume

All participants under the age of 16 years have 19.9 ml (20.9 ml in the United Kingdom) of blood collected; this is less than 1.5 tablespoons. All participants aged 16 or older will have 27.4 ml (29.4 ml in the United Kingdom) of blood collected; this is less than 2 tablespoons. The tubes to be used are listed as follows, in priority order:

- one 7.5-ml green top (sodium heparin) tube OR one 8.5-ml yellow top (CPDA) tube;
- one 7.5-ml red top (serum) tube;
- one 4.9-ml purple top (EDTA plasma) tube; and
- one additional 7.5-ml green top (sodium heparin) tube OR one 8.5-ml yellow top (CPDA) tube **in participants 16 years or older**.

Due to the volume of blood to be collected, QC participants should be at least 16 years old (or large for age). Blood collection is split across two individuals to minimize the burden for any one participant. The QC participants are referred to as QC-Red and QC-Purple. A QC-Red participant **must** be a proband, an affected sibling, or a case; a QC-Purple participant can be any participant in the ASP or trio family or a control participant. The QC participants selected have only one additional volume of blood collected, as indicated below, using the following tubes:

QC-Red: one additional 7.5-ml red top (serum) tube for autoantibodies and serum storage; **OR**

QC-Purple: one additional 4.9-ml purple top (EDTA) tube for plasma storage and DNA extraction from the cell pack.

Thus, a QC-Red participant has 5 tubes collected, totaling 34.9 ml (36.9 ml in United Kingdom) or approximately 2.5 tablespoons of blood. A QC-Purple participant has 5 tubes of blood collected, totaling 32.3 ml (34.3 ml in United Kingdom).

IV. BLOOD COLLECTION PROCEDURES

The following steps outline the basic procedures for blood collection in the T1DGC study.

1. Confirm that you have the correct ID labels for each participant. Locate the *T1DGC Blood Collection Form: Original Collection* for each participant in the family and

check that it has a bar-coded Participant ID label on each page of the form. There is a separate *T1DGC Blood Collection Form: Original Collection* for the Case/Control study. Confirm that the aliquot ID labels for samples match the participant ID on the exam form. Record the nurse/technician ID on page 5 of the form.

2. Before collecting blood, ask the participant whether he/she has any bleeding disorders. If the participant reports a history of bleeding disorders, the participant should be sampled under the supervision of a physician.

3. Explain the procedure. An example might be: "I am going to take some blood from the vein in your arm. The purpose of this is to check levels of autoantibodies (affected participants only) and provide samples for DNA analysis. I will be taking three tubes -- about one and a half tablespoons of blood. Are there any questions?" (**NOTE:** The number of tubes and the total amount of blood collected varies depending on whether the participant is older than 16 years and is selected for QC. This script should be adjusted accordingly.)

4. If the participant asks if he/she will receive results, direct the participant to ask the Clinic Coordinator. This will vary between networks.

5. Identify the best available vein. Palpate and trace the path of veins several times with the index finger. If veins are not readily apparent, have participant close his/her fist or lower the extremity over the arm of the chair to allow the veins to fill to capacity.

6. Use a tourniquet to increase venous filling, leaving it on for the shortest time possible.

7. Cleanse the venipuncture site. Allow the area to dry to prevent possible hemolysis of the sample and a burning sensation to the patient when the venipuncture is performed.

8. Use of Sarstedt tubes:
   a. The tube can be used as a vacutainer (by pulling the plunger at the base of the tube down and snapping it off) or as a syringe (by using the plunger to draw blood into the tube).
   b. Insert the **first blood collection tube (7.5-ml green top or 8.5-ml yellow top)** into the holder.
   c. If a tube has been previously or unsuccessfully used, it should be discarded in a proper container, not re-used.
   d. Inspect the tip of the needle visually to determine that it is free of hooks at the end of the point, and that its opening is clear of any small particles that would obstruct the flow of blood. The needle must be sterile. Do not use a needle from a package that is broken or contaminated in any way.

9. Perform the venipuncture, entering the vein in a smooth continuous motion.
   a. Remove the tourniquet as soon as possible. Once the collection has started, do not change the position of the tube until it is withdrawn from the needle. During the procedure, try not to allow the contents of the tube to contact the cap.
   b. Fill the tube as completely as possible. Partially filled tubes should be avoided. **However, if this occurs, do not discard the partially filled tubes.**
   c. When the blood flow ceases or the tube is filled, remove the tube from the holder.
   d. Immediately and thoroughly mix the contents of **ALL** tubes by gently inverting eight (8) times.
   e. To prevent hemolysis, avoid jarring or shaking the tube. Put the tube into a rack or jacket pocket; do not lay on table. NOTE: Hemolysis is the alteration, dissolution or destruction of red blood cells in such a manner that hemoglobin is liberated into the medium in which the cells are suspended. Hemolysis can distort the results of some assays and can compromise the quality and use of storage samples.

f. To obtain additional samples from all participants, insert the **next tubes (the 7.5-ml red top tube followed by the 4.9-ml purple top tube)** into holder and repeat procedure.

g. For adults (those at least 16 years old) only, insert **a second 7.5-ml green top tube or 8.5-ml yellow top tube into holder and repeat procedure**.

h. For QC-Red participants, insert **a second 7.5-ml red top tube into holder and repeat procedure**. For QC-Purple participants, insert **a second 4.9-ml purple top tube into holder and repeat procedure**.

i. Record the time that blood was collected on the *T1DGC Blood Collection Form*.

10. Remove the needle quickly and immediately after filling all tubes. Have participant hold sterile pad firmly for one to two minutes to prevent a hematoma. Discard needle into biohazard box (*i.e.*, sharps container).

11. If no staff member is able to obtain a blood sample, the *Blood Collection Form* should be completed as follows:
    a. record the date blood collection was attempted for exam date on page 1 and the nurse/technician ID on page 5; and
    b. mark “no” for question 2 (“Was any blood collected?”) and record “Staff unable to obtain sample” for the reason.

12. If the participant refuses to have any blood collected, the *Blood Collection Form* should be completed as follows:
    a. record the date blood collection was attempted on page 1 and the nurse/technician ID on page 5; and
    b. mark "no" for question 2 ("Was any blood collected?") and record "Refused" for the reason.

Clinics will not be reimbursed for participants who refuse to have blood collected since the study aims cannot be achieved without a blood sample from which DNA can be extracted. If the proband or affected sibling in an ASP family refuses to have blood collected, the family is ineligible and blood samples should not be obtained from other family members. For this reason, blood collection for the proband and/or affected sibling should precede collection for parents and unaffected siblings whenever possible. In trio families, the family is ineligible if any family member refuses to have blood collected. The Case/Control study is based on individual participants, so if a case or control refuses, he/she is ineligible.

V. BLOOD PROCESSING

A. Description

The proper processing of the collected samples is critical because deviation from the protocol can significantly affect the future use of the samples. It is particularly important that time deadlines in handling are observed and that samples are not left open to the atmosphere longer than necessary.

A total of ninety (90) minutes is permitted between blood collection and final placement of serum and plasma samples in the freezer. Note that this does not apply to the green top or yellow top tubes or to the EDTA cell pack, which are maintained at room temperature and shipped daily to the DNA Repository.

B. Procedure

1. Immediately after collecting the sample, affix one of the large labels with the participant's ID to each of the tubes to identify the samples belonging to each participant. The large labels as well as the smaller aliquot labels are color-coded for each family member as follows: father – blue; mother – pink; proband – purple; affected sibling(s) – green; unaffected sibling(s) – yellow; case – orange; and control – gray.

2. Place the green top or yellow top tube(s) in a test tube rack. Maintain at room

temperature until there is time to prepare the green-top tubes for daily shipping. **DO NOT PROCESS IN CENTRIFUGE AND DO NOT REFRIGERATE AT ANY TIME.** If participant has not consented to creation of a cell line, affix the pre-printed label that indicates “DNA Only – No Cell Line” to the participant’s green top or yellow top tube(s).

3. Place the red top tube in a test tube rack. Allow the sample to clot by standing for at least 30 minutes but not more than 60 minutes at room temperature (65-75^{o}F; 18-24^{o} C).

4. Immediately place the purple top tube into a container of water and ice. Cool the samples on water and ice for 30 minutes but not more than 60 minutes.

5. Do not let **any** of the samples stand in direct sunlight or at extreme temperatures.

6. Centrifuge the red top and purple top tubes, following manufacturer instructions.

7. Record the nurse/technician ID for the person processing the samples on page 5 of the *Blood Collection Form*

VI. ALIQUOTING

A. Preparation

The red top tube and the purple top tube collected for each participant will be aliquoted into a total of 9 cryovials. Refer to "Labeling Aliquot Vials" (section B), “Aliquoting Samples" (section C) and "Blood Collection Flow Charts" (Appendix C) for assistance in this process.

The green top (sodium heparin) or yellow top (CPDA) tubes are **not** processed at the clinics; the green top or yellow top tubes are shipped **daily** to the DNA Repository for processing. Store the green top or yellow top tubes in a rack at room temperature until shipped. **DO NOT REFRIGERATE, CENTRIFUGE OR ALIQUOT.**

The nurse or technician prepares the work area by laying out the plastic transfer pipettes and aliquoting vials and tubes. Affix the small ID labels to each sample vial as indicated in the following table and diagram.

Serum and plasma samples are identified by using color-coded polypropylene caps for the cryovials. Red caps are used to identify serum samples and purple caps are used to identify plasma samples.

B. Labeling Aliquot Vials

Great care must be taken when labeling aliquot vials. It is critical that the small ID labels applied to the aliquot vials match the participant ID label on the *T1DGC Blood Collection Form*. It also is extremely important that labels are applied firmly and correctly oriented on the vial to minimize labels falling off during shipping and/or storage.

Attach the label to the vial when the vial is at room temperature and leave the cap on the vial when labeling. Apply the label to the vial so that the long edge of the label is parallel to the floor when the vial is held in an upright position. That is, the bar-code and readable form of the participant ID on the label should be placed **vertically** rather than horizontally on the vial. The label should not trail off the bottom of the vial or over the cap. (See Diagram on next page).

While holding the vial in an upright position, affix the colored portion of the label to the vial first. Wrap the clear tail around the perimeter of the vial. The end of the clear tail should overlap the colored portion of the label. Press **firmly** on the entire label. Verify that all edges of the label adhere to the vial. Freezer tape is not required, but can be used.

When possible, allow newly labeled (empty) vials to set at room temperature for several hours prior to subjecting them to colder temperatures. Labels applied to empty vials 24 – 48 hours in advance of use have better adhesion to the vials.

DIAGRAM FOR LABEL PLACEMENT

LABELING SCHEME

Label type	Use
Large labels	Label each of 3 or 4 tubes collected per participant Label for EDTA tube after plasma aliquoted
Father – blue stripe Mother – pink stripe Proband – purple stripe Affected sib(s) – green stripe Unaffected sib(s) – yellow stripe Case – orange stripe Control – gray stripe	
Small vial labels	
Father – blue stripe	Label 5 2-ml cryovials (serum storage – red cap) Label 4 2-ml cryovials (plasma storage – purple cap)
Mother – pink stripe	Label 5 2-ml cryovials (serum storage – red cap) Label 4 2-ml cryovials (plasma storage – purple cap)
Proband – purple stripe	Label 5 2-ml cryovials (autoantibodies and serum storage – red cap) Label 4 2-ml cryovials (plasma storage – purple cap)
Affected sib(s) – green stripe	Label 5 2-ml cryovials (autoantibodies and serum storage – red cap) Label 4 2-ml cryovials (plasma storage – purple cap)
Unaffected sib(s) – yellow stripe	Label 5 2-ml cryovials (serum storage – red cap) Label 4 2-ml cryovials (plasma storage – purple cap)
Case – orange stripe	Label 5 2-ml cryovials (autoantibodies and serum storage – red cap) Label 4 2-ml cryovials (plasma storage – purple cap)
Control – gray stripe	Label 5 2-ml cryovials (serum storage – red cap) Label 4 2-ml cryovials (plasma storage – purple cap)

C. Aliquoting Samples

Samples for each participant are aliquoted as outlined below.

1. 7.5-ml red top tube: After centrifuging, the serum and the clot should be separated; if not, re-centrifuge for an additional 10 minutes. Unscrew the cap and aliquot serum promptly. For each participant, pipette 0.5-ml aliquots into each of 5 labeled cryovials, using a fresh plastic transfer pipette for each individual. If there is serum remaining after the 5 cryovials have been filled, do not discard it; top off each of the aliquots with additional serum. Re-cap the red top tube and dispose of the capped tube in a biohazard box (*i.e.*, sharps container).

2. 4.9-ml purple top tube: After centrifuging, the plasma should be promptly separated from the cells. Pipette the plasma in 0.5-ml aliquots into each of the 4 labeled cryovials for storage, using a fresh plastic transfer pipette for each individual. If there is plasma remaining after the 4 cryovials have been filled, do not discard it; top off each of the aliquots with additional plasma. **(NOTE: Take special care not to disturb the buffy coat on the cell pack when aliquoting the plasma samples as this will impact the DNA yield adversely.)**

3. The cell pack remaining after plasma is aliquoted from the EDTA tube is shipped to the DNA Repository for DNA extraction. The tube is re-capped and re-labeled with a new, large participant ID label (if needed) following centrifuging and aliquoting processes. The EDTA cell pack is shipped at ambient temperature with the green or yellow top tubes sent daily to the DNA Repository.

ALIQUOTING SCHEME

Tube	Vial(s)	Amount	Use
7.5-ml red top	5 2-ml cryovials (proband, affected sib, case)	0.5 ml	autoantibodies (1) serum storage (4)
	5 2-ml cryovials (all other family members, control)	0.5 ml	serum storage (5)
4.9-ml purple top	4 2-ml cryovials (each participant)	0.5 ml	plasma storage (4) cell pack for DNA (1)

Note: The cell pack in the EDTA tube is shipped to the DNA Repository for DNA extraction. After all plasma is aliquoted, the EDTA tube is re-capped, re-labeled with a new large participant ID label (if needed), and shipped daily at ambient temperature with the green or yellow top tubes to the DNA Repository.

D. Aliquoting Quality Control Samples

1. The Clinic Coordinator identifies the QC participants and notifies the nurse/technician collecting blood. (Note that participants who return to the clinic for a second blood collection are never selected as a QC participant.) Labels for the QC participants are enclosed in a separate envelope and include large labels for the additional tube to be collected and small vial labels for the QC samples to be aliquoted. For ASP and trio families, the envelopes are labeled with QC-Red "N" or QC-Purple "N", where N is the sequential number of QC IDs within a network. Separate QC label envelopes for the case/control study are labeled Case QC Red "N" or Control QC Purple "N" where N is the sequential number of QC IDs within a network. Envelopes are opened consecutively within the clinic.

2. Complete Question 7 ("Is participant quality control?") and Question 8 ("Which quality control?") on the *T1DGC Blood Collection Form: Original Collection*. Indicate the type of quality control participant by marking the response "QC-Red" **or** "QC-Purple".

3A. A QC-Red participant must always be a proband, an affected sibling, or a case at

least 16 years old (or large for age). For QC-Red participants, label the 7.5-ml red-top tube with a large ID label from the QC envelope and also affix a large QC ID label to page 3 of the *T1DGC Blood Collection Form: Original Collection* (Question 9). Purple-striped QC vial labels (if QC participant is proband), green-striped QC vial labels (if QC participant is affected sibling), or orange-striped QC vial labels (if QC participant is case) are placed on each of 5 2-ml cryovials (1 blind duplicate sample for autoantibodies and 4 storage samples). Only the proband (Participant -03), the first affected sibling (Participant -04), and the case (Participant 7, CAS) should be selected as a QC-red participant. Any additional affected siblings (Participants -07, -08, and -09) should not be selected as a QC-red participant.

3B. After centrifuging the 7.5-ml red top QC tube, transfer 0.5 ml to each of the 5 appropriately labeled 2-ml cryovials, using a fresh plastic transfer pipette for each individual. If there is serum remaining after the 5 cryovials have been filled, do not discard it; top off each of the aliquots with additional serum.

4A. A QC-Purple participant can be any participant in an ASP or trio family, or a control that is at least 16 years old (or large for age). For QC-Purple participants, label one 4.9-ml purple tube with a large label from the QC envelope and also affix a large QC ID label to page 3 of the *T1DGC Blood Collection Form: Original Collection* (Question 9). Place the appropriate color striped label for the selected family member (father-blue; mother-pink; proband-purple; affected sibling-green; unaffected sibling-yellow, or control-gray) on each of 4 2-ml cryovials (plasma storage samples). Additional affected siblings (Participants -07, -08, and -09) should not be selected as a QC-purple participant.

4B. After centrifuging the 4.9-ml purple-top QC tube, transfer 0.5 ml to each of the 4 appropriately labeled 2-ml cryovials, using a fresh plastic transfer pipette for each individual. If there is plasma remaining after the 4 cryovials have been filled, do not discard it; top off each of the aliquots with additional plasma. Take special care not to disturb the buffy coat on the cell pack as this can impact the DNA yield.

4C. The cell pack in the EDTA tube is shipped to the DNA Repository for DNA extraction. After all plasma is aliquoted, the EDTA tube is re-capped, re-labeled with a new large QC ID label (if needed), and shipped at ambient temperature with the green or yellow top tubes to the DNA Repository.

E. General Comments for Aliquoting Samples

1. The plastic transfer pipettes are graduated in 0.25 ml increments. The approximate capacity is 1 ml. **Two** pipettes should be used for each participant: one to transfer serum and one to transfer plasma.

2. Be careful not to disturb cells when drawing plasma into a pipette. If cells mix with the plasma, re-centrifuge the sample to insure obtaining the maximum amount possible. When using pipettes, avoid drawing red cells into the bulb.

3. Seal or cap all vials immediately; samples should not be allowed to stand open.

VII. RE-COLLECTION OF BLOOD SAMPLES

A. Purpose

In some cases, it may be necessary to contact participants to return to the clinic for a second blood collection. Reasons for a re-collection include: inability to obtain sample(s) during initial clinic visit (including failure to obtain serum samples on a proband, affected sibling or a case); loss of sample(s) due to local freezer failures or shipping errors; failure of the green top (sodium heparin) or yellow top (CPDA) sample to produce a viable cell line for future DNA samples; or low DNA yield from the EDTA cell pack when participant refused cell line. Only one attempt at re-collection should be made for any one participant.

B. Procedure

The *T1DGC Blood Collection Form: Re-collection* should be used to record the second blood collection. The form is formatted and completed in the same way as the *T1DGC Blood Collection Form: Original Collection*, with two exceptions. The reason for the re-collection is recorded (Question 2) and there is no section for quality control samples.

Participants who return to the clinic for a second collection are not selected for quality control purposes. The procedures for blood collection, sample processing and aliquoting are the same as outlined above for the original collection. There is a separate *T1DGC Blood Collection Form: Re-collection* for the Case/Control study.

For a re-collection, labels from the participant's initial clinic visit should be used to label tubes and cryovials. If labels have been discarded or the number of labels is inadequate for the second blood collection, the clinic should contact the Regional Network Center and the Network staff contact the Coordinating Center for additional labels. This should be done well in advance of the participant's re-collection visit.

APPENDIX A
BLOOD COLLECTION FORM: ORIGINAL COLLECTION
INSTRUCTIONS FOR COMPLETION

The *T1DGC Blood Collection Form: Original Collection* is to be completed by the nurse or technician at the time of the blood collection. There is a separate form *T1DGC Blood Collection Form: Original Collection (Case/Control)* that should be used for the cases and controls. The form is completed in the same way, following the instructions provided below.

INSTRUCTIONS:

1. Apply a participant ID label to every page and record clinic ID and secondary ID on every page.

2. Record the date of blood collection (Question 1).

3. Before collecting blood, ask the participant, "Do you have any bleeding disorders?" If the participant answers affirmatively, collect blood under the supervision of a physician.

4. Indicate whether any blood was collected (mark "Yes" or "No"), then follow the appropriate skip pattern. When blood is not collected, record the reason (Question 2).

5. Record the time blood was collected, using a 24-hour clock (Question 3).

6. Record the time that the samples BEGIN the centrifuging process, using a 24-hour clock (Question 4).

7. Record the time that the sample vials were placed in the freezer, using a 24-hour clock (Question 5). All serum and plasma samples **must** be frozen within 90 minutes

of the blood collection.

8A. Instructions are provided for processing, aliquoting, labeling and storing samples (Question 6).

8B. For the green top or yellow top tubes (Question 6a), mark “Yes” if any tube is collected and mark “No” if no tube is collected. For Question 6b, record the number of green top or yellow top tubes collected (1 or 2) only if “Yes” was marked for Question 6a.

8C. If participant consented to cell line, mark “Yes” for Question 6c. Mark “No” If participant did not consent to cell line and place a pre-printed “DNA Only – No Cell Line” label on the participant’s green top or yellow top tube(s) before shipping to DNA Repository.

8D. The serum aliquots for autoantibody analysis and storage are listed with the amount of sample requested (Question 6d). Due to the number of storage vials, each vial is not listed separately on the form. Mark “Yes” if any vials are filled and “No” if none are filled. For Question 6e, record the number of vials filled only if “Yes” was marked for Question 6d.

8E. The plasma aliquots for plasma are listed with the amount of sample requested (Question 6f). Due to the number of storage vials, each vial is not listed separately on the form. Mark “Yes” if any storage vials are filled and “No” if none are filled. For Question 6g, record the number of vials filled only if “Yes” was marked for Question 6f.

8F. The cell pack from the 4.9-ml purple top (EDTA) tube is shipped to the DNA Repository for DNA extraction; cell packs are shipped daily at ambient temperature with the cell line samples. Mark “Yes” if the cell pack is available and “No” if it is not.

9A. If the participant has not been selected as a QC participant, mark "No" to the question "Is participant quality control?" (Question 7) and skip to Question 11.

9B. If the participant has been selected as a QC participant, mark "Yes" to the question "Is participant quality control?" (Question 7). Indicate whether the participant was selected as QC-Red or QC-Purple (Question 8). Attach one of the large ID labels from the QC label set in the space provided (Question 9) and complete the aliquoting section (Question 10) in the same manner as above.

9C. **COMPLETE ONLY THE SECTION OF THE FORM THAT PERTAINS TO THE TYPE OF QC PARTICIPANT INDICATED (Question 10).** For example, if the participant was selected as QC-Red, indicate vials that are filled ("Yes") or empty ("No") for the serum samples only. **Do not** enter any information for the plasma samples for QC-Red participants; leave this section blank.

If the participant was selected as QC-Purple, indicate vials that are filled (mark "Yes") or empty (mark "No") for the plasma samples and cell pack only. **Do not** enter any information for the serum samples for QC-Purple participants; leave this section blank.

10. Record the nurse or technician 5-digit ID number on page 5 for the staff member collecting the blood (Question 11) and processing the blood (Question 12). In some clinics, this may be the same individual.

11. Enter the 5-digit ID of the person editing the form (Question 13).

APPENDIX B

BLOOD COLLECTION, ALIQUOTING AND SAMPLE SHIPMENT

SUPPLIES LIST

Only Sarstedt supplies will be used for blood collection in the T1DGC. Supplies are ordered from Sarstedt using the master account number provided by the Network Coordinator.

CATALOG NUMBER	DESCRIPTION
01.1613.100	7.5 ML S-MONOVETTE (SODIUM HEPARIN) (CS/500; PKG/50; MIN ORDER: 50)
01.1610.001	8.5 ML S-MONOVETTE (CPDA) (CS/500; PKG/50; MIN ORDER: 50) **UNITED KINGDOM NETWORK USE ONLY**
01.1601.100	7.5 ML S-MONOVETTE (SERUM) (CS/500; PKG/50; MIN ORDER: 50)
04.1931.100	4.9 ML S-MONOVETTE (EDTA PLASMA) (CS/500; PKG/50; MIN ORDER: 50)
85.1638.035	NON-SAFETY MULTIFLY NEEDLE WITH ADAPTER (21G X 0.75"; 200 mm tubing) (CS/1000; PKG/100; MIN ORDER: 100)
85.1638.235	SAFETY MULTIFLY NEEDLE WITH ADAPTER (21G X 0.75"; 200 mm tubing) (CS/1000; PKG/100; MIN ORDER: 100)
85.1640.035	NON-SAFETY MULTIFLY NEEDLE WITH ADAPTER (23G X 0.75"; 200 mm tubing) (CS/1000; PKG/100; MIN ORDER: 100)
85.1640.235	SAFETY MULTIFLY NEEDLE WITH ADAPTER (23G X 0.75"; 200 mm tubing) (CS/1000; PKG/100; MIN ORDER: 100)
85.1638.005	NON-SAFETY MULTIFLY NEEDLE WITH ADAPTER (21G X 0.75"; 60 mm tubing) (CS/1000; PKG/100; MIN ORDER: 100)

APPENDIX B (CONT.)

BLOOD COLLECTION, ALIQUOTING AND SAMPLE SHIPMENT

SUPPLIES LIST

CATALOG NUMBER	DESCRIPTION
85.1638.205	SAFETY MULTIFLY NEEDLE WITH ADAPTER (21G X 0.75"; 60 mm tubing) (CS/1000; PKG/100; MIN ORDER: 100)
85.1640.005	NON-SAFETY MULTIFLY NEEDLE WITH ADAPTER (23G X 0.75"; 60 mm tubing) (CS/500; PKG/100; MIN ORDER: 100)
85.1640.205	SAFETY MULTIFLY NEEDLE WITH ADAPTER (23G X 0.75"; 60 mm tubing) (CS/500; PKG/100; MIN ORDER: 100)
85.1373	S-MONOVETTE NEEDLE (21G x 1”) (CS/500; PKG/100; MIN ORDER: 100)
85.1441	S-MONOVETTE NEEDLE (22G x 1”) (CS/500; PKG/100; MIN ORDER: 100)
72.609	2 ML SC MICROTUBE (CRYOVIAL): NO CAP (CS/5000; PKG/500; MIN ORDER: 1000)
65.716.008	SCREW CAP FOR MICROTUBE, VIOLET (CS/10000; PKG/1000; MIN ORDER: 1000)
65.716.003	SCREW CAP FOR MICROTUBE, RED (CS/10000; PKG/1000; MIN ORDER: 1000)
86.1172	TRANSFER PIPETTE (3.5 ML, graduated PE) (CS/5000; PKG/1000; MIN ORDER: 1000)
95.064.997	FIBERBOARD BOXES (to hold 2-ml microtubes) (CS/120; 10/PK; MIN ORDER: 10)

APPENDIX B (CONT.)

BLOOD COLLECTION, ALIQUOTING AND SAMPLE SHIPMENT

SUPPLIES LIST

SHIPPING CONTAINERS

Asia-Pacific: Provided by World Courier

European: Provided by World Courier

North American:

95.064.928	MAILER SYSTEM (cell line samples) (CS/50; MIN ORDER: 50)
95.064.929	GEL PACKS (cell line samples) (CS/12: MIN ORDER: 12)
96.064.927	SHIPPING CONTAINERS (autoantibody, storage and cell pack samples) (CS/6: MIN ORDER: 6)
96.064.930	ABSORBENT PADS (autoantibody, storage and cell pack samples) (PK/100: MIN ORDER: 100)

NOTE: Gel packs should be kept at room temperature. Do not refrigerate or freeze before use in cell line/cell pack shipments!

United Kingdom:

78.898	POLYPROPYLENE MAILING CONTAINER WITH ABSORBENT LINER (cell lines)
65.679.004	YELLOW CAP FOR MAILING CONTAINER (cell lines)

APPENDIX B (CONT.)

BLOOD COLLECTION, ALIQUOTING AND SAMPLE SHIPMENT

SARSTEDT CONTACTS

ASIA-PACIFIC NETWORK:

Place all orders to Sarstedt Australia at Sarstedt Australia Pty. Ltd., 16 Park Way Technology Park, South Australia, 5098 (Phone: 0061-8-8349-6555; FAX: 0061-8-8349-4041)

EUROPEAN NETWORK:

Place all orders to Mr. Feuerbach at Sarstedt Germany, Rommeldorfer St., 51588 Numbrecht, Germany (Phone: +49-2293305; FAX: +49-2293305122 or +49-2293305280)

NORTH AMERICAN NETWORK:

Place all orders to Sarstedt USA, 1025 St James Church Road, Newton, NC 28658 (Phone: 800-257-5101; FAX: 828-465-4003)

UNITED KINGDOM NETWORK:

Place all orders to Mr. Feuerbach at Sarstedt Germany, Rommeldorfer St., 51588 Numbrecht, Germany (Phone: +49-2293305; FAX: +49-2293305122 or +49-2293305280)

APPENDIX B (CONT.)

GENERAL BLOOD COLLECTION SUPPLIES AND EQUIPMENT

Blood Collection Supplies

Alcohol wipes
Emesis basin
Tourniquets
Gauze
Bandaids
Biohazard boxes/bags
Syringes
Freezer (-70^{o}C preferred; -20 ^{o}C acceptable)
Centrifuge (refrigerated)
Test tube racks
Timer
Low temperature freezer tape (to reinforce storage boxes)
Squeeze bottle
Disposable gloves

Shipping Supplies

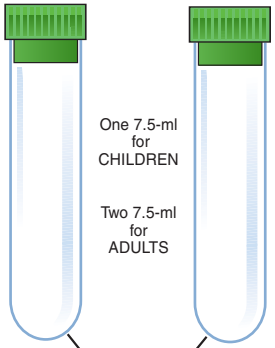
Dry ice
Biohazard labels
Insulated shipping containers
Gel packs
Ziplock bags

APPENDIX C
BLOOD COLLECTION FLOW CHARTS

TYPE 1 DIABETES GENETICS CONSORTIUM BLOOD FLOW CHART

FILLING PRIORITY: ❶ ❹ ❷ ❸

7.5-ml GREEN (Sodium Heparin) | **7.5-ml GREEN (Sodium Heparin)**



One 7.5-ml for CHILDREN

Two 7.5-ml for ADULTS

Stand at ROOM TEMPERATURE

DO NOT chill, centrifuge, or aliquot

Cell Line

GREEN-top tube

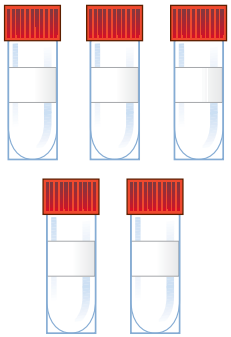
Ship DAILY at ambient temperature → **DNA Repository**

7.5-ml RED (serum) | **4.9-ml PURPLE (EDTA plasma)**

STAND 30 - 60 min. | **ICE 30 - 60 min.**

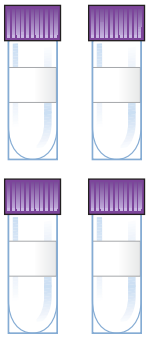
CENTRIFUGE

0.5 ml each *(5 samples)*



Autoantibodies and Serum Storage 2-ml cryovials

0.5 ml each *(4 samples)*



Plasma Storage 2-ml cryovials

Cell Pack

DNA

FREEZE

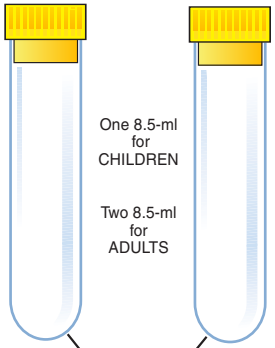
Ship MONTHLY on dry ice → **Autoantibody and Sample Storage Laboratory**

Ship DAILY at ambient temperature → **DNA Repository**

TYPE 1 DIABETES GENETICS CONSORTIUM BLOOD FLOW CHART (UK)

FILLING PRIORITY: ❶ ❹ ❷ ❸

8.5-ml YELLOW (CPDA) **8.5-ml YELLOW (CPDA)**



One 8.5-ml for CHILDREN

Two 8.5-ml for ADULTS

Stand at ROOM TEMPERATURE

DO NOT chill, centrifuge, or aliquot

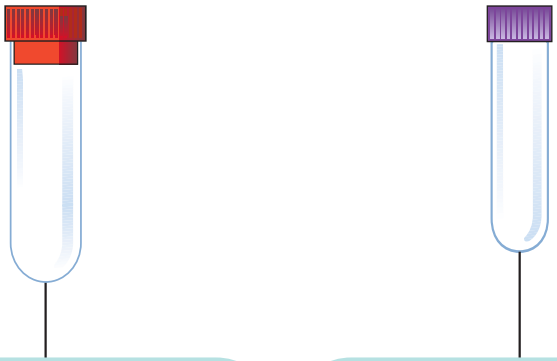
Cell Line

YELLOW-top tube

Ship DAILY at ambient temperature

DNA Repository

7.5-ml RED (serum) **4.9-ml PURPLE (EDTA plasma)**



STAND 30 - 60 min.

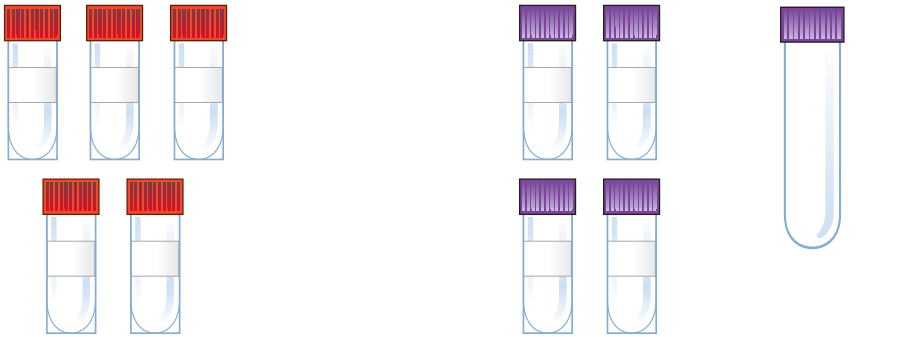
ICE 30 - 60 min.

CENTRIFUGE

0.5 ml each *(5 samples)*

0.5 ml each *(4 samples)*

Cell Pack



Autoantibodies and Serum Storage 2-ml cryovials

Plasma Storage 2-ml cryovials

DNA

FREEZE

Ship DAILY at ambient temperature

Ship MONTHLY on dry ice

Autoantibody and Sample Storage Laboratory

DNA Repository

VII. GENETIC MEASURES

A. BACKGROUND

The etiology of type 1 diabetes is unknown, but it is recognized to be due to both genetic and environmental determinants (1). The genetic basis of type 1 diabetes is complex and likely to be due to genes of both large and small effect. There have been numerous studies investigating genetic susceptibility loci, using both case-control and family study designs. Early studies of disease concordance using twin designs reported higher monozygotic (MZ) than dizygotic (DZ) rates, with MZ rates approaching 50% (2-3). These early studies were likely biased, however, as recruitment of the twins were through advertisement and solicitation, so that affected concordant pairs were more likely to participate than discordant pairs. Population-based twin studies confirmed the increased concordance in MZ pairs, but with the concordance of 30%-40%, and the concordance in DZ pairs only 5%-10% (4-5). Based upon the results of twin studies, susceptibility to type 1 diabetes is determined by genetic risk factors, but less than 50% of the risk is due to the effects of genes. Studies of first and second-degree relatives also support familial aggregation of type 1 diabetes (6-8).

The Consortium will use a well-tested, positional cloning approach to identify genes that influence susceptibility to type 1 diabetes. Positional cloning has been used in studies of many Mendelian and complex disease phenotypes, and is currently considered a standard approach to cloning disease susceptibility genes. By genotyping a comprehensive set of polymorphic markers that are equally-spaced across the genome, and by tracing the familial inheritance of the marker genotypes, it is statistically possible to identify regions of the genome that are disproportionately shared by affected family members, as compared to unaffecteds. These regions are called "linkage regions." More sophisticated analyses will seek to identify families within the T1DGC collection who show linkage to different regions of the genome (heterogeneity), and stratify by highly specific individual genetic markers that have been shown to be associated with risk of developing type 1 diabetes. These specific risk markers include HLA loci; single nucleotide polymorphisms (SNPs) clustered around the *CTLA4* (cytotoxic T-lymphocyte-associated protein 4) gene (9) and a SNP in the promoter region of the *INS* (Insulin) gene.

B. GENETIC MARKER TYPING

The Consortium will perform genetic marker typing of study participants to characterize genetic variation at these known markers (landmarks) in the human genome. The genotyping will support two specific analytical modalities:

1. Whole genome scans to identify families that show linkage of disease status to certain regions of the genome, hence focusing the search for susceptibility genes. This analysis seeks to discover broad genomic regions (*e.g.*, 10-20cM in size) where a type 1 diabetes disease susceptibility gene is most likely to be located. With the development of genome-wide SNP marker panels that increase information content and genomic coverage, the Consortium will continue genome-wide linkage scans in families to identify regions containing type 1 diabetes susceptibility genes. These marker panels contain ~6,000 SNPs placed

equidistant in the genome, and are amenable to standard methods of linkage analysis.

2. Stratification of study families and individual participants based on independent markers of genetic risk and assessment of association of type 1 diabetes with these markers. Three regions of the genome have been consistently implicated in risk for type 1 diabetes: HLA (*IDDM1*), *INS* (*IDDM2*) and *CTLA4* (*IDDM7*). Recent evidence suggests that additional genes in the HLA region as well as novel susceptibility loci (PTPN22, IFIH1) contribute to risk of type 1 diabetes. The Consortium will utilize the existing collection of affected sib pair (ASP) families to further explore the genetic information in the HLA region using ~3,000 SNPs, 66 microsatellite polymorphisms, and classical HLA genotypes in the "MHC Fine Mapping Project." Additional candidate genes that have been previously identified contributing to risk of type 1 diabetes are being characterized by performing SNP analysis in the "Rapid Response Project."
3. In addition to performing analyses of ASP families (linkage), the Consortium has designed a genome-wide association project in which ~500,000 SNPs are genotyped in 4,000 cases with type 1 diabetes and 2,500 controls. These samples, obtained from the U.K. and complementary to the Wellcome Trust Case Control Consortium, will provide information that identifies genomic regions containing genes that are associated with risk of type 1 diabetes.

Genetic data will be collected from these classes of genetic markers:

1. Single Nucleotide Polymorphism (SNP) Markers used for genome-wide linkage (~6,000 SNPs) or genome-wide association (~500,000 SNPs)
2. HLA (Human Leukocyte Antigen) Markers
3. Candidate gene polymorphisms (SNPs) in *CTLA4*, *INS*, *PTPN22*, *IFIH1*, and other genes

The genotypes from these classes will constitute the primary genetic data that will be used for identification of linkage regions in the first phase of positional cloning, by linkage mapping and risk stratification. Additional SNPs will be genotyped in a second phase of fine-mapping by the Consortium, but the precise number and identity of markers used for the fine-mapping is unknown at this time and will not be addressed further.

All consenting study participants in the Consortium who provide a sample of blood for genetic analysis will be typed for all classes of genetic markers.

1. Microsatellite (STRP) Marker Typing

Microsatellite markers (also called STRP, Simple Tandem Repeat Polymorphisms) are non-functional markers that consist of variable number of repeats of (usually) two, three, or four nucleotides and are highly polymorphic. They occur frequently in the human genome as a result of normal DNA mutation processes and are not generally believed to be functionally important. Their utility in routine genome scans comes from their high information content, and because they can be typed by semi-

automated, high throughput methods. A variety of chromosome-specific sets of markers optimized for high-efficiency genotyping have been developed.

The Center for Inherited Disease Research (CIDR) is a centralized facility, housed in the Johns Hopkins Bayview Medical Center in Baltimore, which was established to provide genotyping and statistical genetics services for investigators seeking to identify genes that contribute to human disease (http://www.cidr.jhmi.edu). Genotyping at CIDR is performed as a service to the research community. Since the Consortium is funded by NIDDK, the Consortium has applied for, and obtained, use of CIDR genotyping services for the study. Consequently, microsatellite genotyping of the existing collection of untyped families (approximately 600, see Chapter II. Objectives) and all newly recruited families (approximately 2,800; see Chapter II. Objectives) will be genotyped at CIDR, at no cost to the Consortium.

CIDR uses standard methods for genotyping. The CIDR web site provides up-to-date information about exact panel of markers, position, size range, marker type, CEPH sizes and primer pairs. The initial Consortium genome-wide linkage scan was performed by a CIDR marker set containing ~ 400 microsatellite markers with average spacing of 9 cM throughout the genome.

2. Human Leukocyte Antigen (HLA) Locus Genotyping

There are many HLA genotyping strategies, with differing levels of resolution and number of HLA loci considered. In common with other autoimmune diseases, a person's HLA genotype profile can be a significant genetic risk factor for type 1 diabetes susceptibility. In particular, there is important information for type 1 genetic risk at both the class I (A, B, C) and the class II (DR, DQ, DP) loci. The information from the haplotypes defined by A, B, DR, DQ and the existence of novel associations with DP suggested that complete HLA typing is required to fully deconvolute the risk association. In addition, the increase in resolution of susceptibility by sub-typing DRB1 and DQB1 will prove important in defining interactions between HLA and other regions. For example, on DQB1*0302 haplotypes, DRB1*0401 and *0402 (in Caucasians) and *0405 (in Caucasians, African-Americans and Asians) confer susceptibility, while *0403 (in Caucasians and Chinese) and *0406 (in Japanese) are protective. In contrast, other DRB1 alleles appear to be risk neutral. Therefore the Consortium will type the HLA loci HLA-A, B, C, DQA1, DQB1, DPA1, DPB1, DRB1.

To type the loci, the Consortium will use the Dynal reverse dot blot method, implemented on line strips supplied through Roche Molecular Systems (Alameda, CA) as developed by Henry Erlich and Janelle Noble. The following set of seven assays will be utilized for the T1DGC genotyping effort:

1) HLA-A
2) HLA-B
3) HLA-C
4) DQA1/DQB1
5) DPA1/DPB1

6) DRB1gen (also includes *INS* + *CTLA4* SNPs, see below)
7) DRB1sub

With the exception of DRB1, each locus is typed on a single line strip with a single preceding PCR amplification step using one pair of primers. Briefly, after PCR amplification of the variable locus, the denatured product is hybridized to the linear array (line strip) in a Bee Blot machine, and after color development, the strips are scanned and the image processed. From the pattern of amplimer binding to the probes on the line strip, the HLA genotype of the sample can be inferred to 4 digit resolution. DRB1 is more complex, and uses a low resolution assay DRB1gen followed by one or two subtype assays using the one the six subtyping assays (DRB1sub).

3. Single Nucleotide Polymorphism (SNP) Markers

SNPs are non-functional markers that consist of two alternative forms (alleles). SNPs represent the most frequent form of genetic polymorphism in the human and form the basis of the human HapMap. Their utility in routine genome scans comes from their high information content, large numbers in the genome, and ability to be characterized by semi-automated, high through-put methods. CIDR utilizes panels of SNP markers for genotyping of the existing collection of ASP families using ~6,000 SNPs. CIDR, as well as other public and private entities, use larger panels of SNPs for genotyping cases and controls (typically 317,000 or 500,000 markers).

SNPs can be used to provide important information on genomic regions of risk (MHC Fine Mapping), Candidate Genes (Rapid Response, including INS and CTLA4), and genome-wide analysis (genome-wide linkage scan and genome-wide association scan).

C. PROCESSING OF DNA FOR GENETIC ANALYSIS

Participants that meet study eligibility requirements will be interviewed in their local recruiting study clinic to collect their demographic and clinical data, and each participant will be asked to provide blood samples for genetic analysis, biomarker analysis, and for cell-line immortalization and repository storage. For each cell line sample, within 24 hours of collection, the clinic will ship barcode labeled tube(s) of heparin-stabilized or CPDA-stabilized whole blood at ambient temperature to the DNA Repository in their network. After receipt of the blood sample(s) at the repository, staff will extract DNA from a separate aliquot of the leukocytes separated from the whole blood, and will store the DNA under appropriate low temperature conditions.

Periodically, each network DNA Repository will ship quantitated samples of DNA suspended in solution to five separate laboratories for genetic analysis (genotyping):

1. Shipment of DNA samples from network DNA Repository to network HLA Laboratory

2. Shipment of DNA samples from network DNA Repository to CIDR at Johns Hopkins, Baltimore MD, USA.

3. Shipment of DNA samples from network DNA Repository to MHC Fine Mapping Laboratory at the Wellcome Trust Sanger Institute, Cambridge, UK.

4. Shipment of DNA samples from network DNA Repository to Rapid Response Laboratory at the Broad Institute, Massachusetts Institute of Technology, Cambridge, MA, USA.

5. Shipment of DNA samples from network collection of cases and controls to the Genome-Wide Association Study (GWAS) Laboratory (Illumina, Inc., San Diego, CA, USA).

1. Shipments to HLA Laboratories

Shipments of DNA samples to HLA laboratories will occur intra-network (*i.e.*, a DNA Repository will only ship samples for HLA genotyping to the corresponding network HLA laboratory). These shipments may vary in frequency and will occur when the DNA Repository has processed sufficient samples to fill one or more shipping boxes with samples. Each shipment consists of 92 samples. DNA will be supplied to the HLA genotyping laboratories in screw-capped tubes with bar-coded labels. A minimum of 5 ug of DNA will be provided to HLA laboratories, at a suggested concentration of 20 ng per ul (total volume = 250 ul).

2. Shipments to CIDR

On a more infrequent basis, all DNA Repositories in the Consortium will be contacted by the Coordinating Center and requested to ship aliquots of DNA solution to CIDR, Baltimore MD, USA for microsatellite genotyping and/or 6K SNP whole genome scan. The Coordinating Center will use the central study database to generate lists of T1DGC participant identifiers for individuals who have been newly recruited, and who have not had CIDR perform genotyping using their DNA sample. The DNA Repository will ship 120 µg of DNA per sample, diluted to a constant concentration of 100 ng/µl in sterile water. These samples will be shipped to CIDR in plates supplied by CIDR with CIDR barcode labels.

3. Shipments to MHC Fine Mapping Laboratory

Once during the study, all DNA Repositories in the Consortium will be contacted by the Coordinating Center and requested to ship aliquots of DNA solution to the MHC Fine Mapping Laboratory, Wellcome Turst Sanger Institute, Cambridge, UK. The Coordinating Center will use a cutoff date to generate lists of T1DGC participant identifiers for individuals who be included in the MHC Fine Mapping project. The DNA Repository will ship 100 µL of DNA per sample, diluted to a constant concentration of 100 ng/µl (10µg). These samples will be shipped to the MHC Fine Mapping Laboratory in plates.

4. Shipments to Rapid Response Laboratory

Once during the study, all DNA Repositories in the Consortium will be contacted by the Coordinating Center and requested to ship aliquots of DNA solution to the Rapid Response Laboratory, Broad Institute, Massachusetts Institute of Technology, Cambridge, MA, USA. The Coordinating Center will use a cutoff date to generate lists of T1DGC participant identifiers for individuals who be included in the Rapid Response project. The DNA Repository will ship 50 µL of DNA per sample, diluted to a constant concentration of 100 ng/µl (5 µg). These samples will be shipped to the Rapid Response Laboratory in plates.

5. Shipments to Genome Wide Association Laboratory

For the initial Genome-Wide Association Analysis, cases with type 1 diabetes collected as part of the Wellcome Trust/JDRF collection at the University of Cambridge (UK Grid) and controls from the British 1958 Birth Cohort (B1958BC) will be shipped to Illumina, Inc., for SNP genotyping. The Consortium and Illumina staff will coordinate the selection of samples, the aliquoting of samples, and the shipment of samples to Illumina. Genotype data will be sent to dbGaP (NIH) and to the GWAS Analytic team at the University of Cambridge (Professor David Clayton) for quality control analyses and statistical genetic analyses. Cleaned genetic data will be returned to the Consortium Coordinating Center and control data returned to the B1958BC.

D. STUDY DATABASE

As described in Chapter II, Objectives, the total collection of T1DGC families will derive from three sources. There are approx 1,200 families who have already been recruited and genotyped; approx 600 families have been recruited and for whom there is stored DNA, but who have not previously been genotyped; and approx 2,800 new ASP families, 1,600 new trio families, 2,050 cases and 2,050 controls will be recruited under the auspices of this protocol. The study database, housed at the Coordinating Center, will aggregate as much genetic and phenotypic data as possible from the participants recruited prior to the Consortium, and will include all phenotypic and genotype data collected from newly recruited participants.

E. PRIVACY AND CONFIDENTIALITY OF PARTICIPANT GENETIC DATA

The collection and aggregation of participant genetic data into a central study database, and the subsequent release of the data to consortium-internal and -external researchers, requires sensitivity to concerns about the use of the data, and diligence to protect the privacy and confidentiality of study participants. This is especially true when a study has a truly global reach and must deal with cultural and ethnic sensitivities (10).

In addition to a comprehensive multi-layered informed consent process, the Consortium has taken additional specific steps to protect the phenotype and genotype data of individuals. The Coordinating Center has a special role in ensuring that data collection is appropriate, and that privacy and confidentiality are maintained during data collection, analysis, and distribution, and in reporting study results.

1. Anonymity of Study Participants

Local clinics will collect and use personal contact information to recruit and schedule study participants, but no information that could uniquely identify participants will be collected on study paper-based forms. Regional Network Centers will randomly distribute sets of study barcode labels to clinics within their network for the purposes of uniquely labeling study artifacts collected from a study participant (*i.e.*, paper forms and specimen tubes). These label sets contain anonymous barcode labels with preprinted study participant identifiers conforming to a prescribed standard format. Label sets will be used by a clinic as needed, and the clinic will have sole and private discretion in the assignment of the preprinted anonymous study identification labels to participating families. The local recruitment clinic will retain records to link a study participant identifier to personal contact information. All other sites, including laboratories and the Coordinating Center, will use only the anonymous study identifier and will never have access to contact information. The demographic and phenotypic information collected for an individual will not include information that could be used to indirectly infer the identity of a participant, for example local postal code or a more granular geographic identifier. Hence the data sets will conform to data privacy standards that mandate de-identification. Detailed recruitment or sample tracking reports will only display the anonymous T1DGC participant identifier.

2. Analytical Data Sets

Periodically, phenotype and genetic raw data will be extracted from the participant collection database at the Coordinating Center and used to create secondary databases and data sets for analysis. The analysis will involve preliminary checks of the data quality and integrity followed by statistical analyses of the cleaned data. The clean analytical data sets will be used to both conduct Consortium-level analyses on the data and prepare data sets for distribution to Consortium internal researchers or to authorized external researchers.

To provide an extra level of confidentiality of data, a second family analytical identifier (AID) will be assigned to each study participant, as the first step of the creation of a new analytical data set within the Coordinating Center. AIDs will be assigned to participants using a randomization scheme that randomizes across clinics within a network, and across study recruitment periods. The source network of each participant will still be encoded within the new AID, but the identifier will differ from the study participant identifier during data collection. A single key file will link the data collection study participant identifier to the AID. This file will reside on a secured server within the Coordinating Center, and have file permissions that restrict access to designated data management staff within the Coordinating Center. Analyses on newly collected families and participants within the Coordinating Center will use the AIDs if there is no requirement to access raw collection data and/or collection study participant identifiers. The use of the AIDs as identifiers in distributed data sets is described in the sub-section on distribution of data sets below.

3. Data from Pre-Consortium Families

This protocol does not cover the recruitment and collection of data from type 1 diabetes families for which there is already genome scan/genetic marker data (approx 1200 families), or for families that have been recruited and for whom there is stored DNA. Aliquots of the stored DNA solution for the pre-existing families will be sent to a variety of genotyping facilities, during the study.

The Coordinating Center will aggregate phenotype and genotype data from both these groups of families as available and will assign unique analytical identifiers (AIDs) to the family participants, in addition to existing anonymous identifiers assigned under the original recruitment protocol. These AIDs will provide consistency with data from the newly collected families that are recruited under this protocol, as well as providing an extra level of confidentiality.

4. Distribution of Data Sets from Coordinating Center to Researchers

The Coordinating Center will be required to distribute data sets to network PI/researchers and to other researchers who have applied for (and received permission) to analyze certain subsets of data. All data sets will be shipped to researchers with study participants identified using the anonymous, randomized AID. If a data set is distributed to a Contributing Investigator and contains families from the investigator's clinic, upon request, the investigator will be given the translation keys to translate the AIDs to data collection study participant identifiers as assigned within the local network clinic. The Coordinating Center may also directly translate the study identifiers for those families within the data set itself. Contributing Investigators will not be provided with the keys for translation of AIDs for participants recruited outside their clinic. Non-Contributing Investigator internal Consortium researchers and researchers external to the Consortium will only have access to the AIDs and will not be provided with the translation key maps between the AIDs and the study participant identifiers.

5. Inferences from the Genetic Data of a Study Participant

1. Inference of Family Relationships

In the course of analysis of collected family genetic data, it will be necessary to check that the inheritance of genetic markers within a pedigree is consistent with Mendelian segregation. These checks are used to detect errors in data for quality control purposes. In some situations there may be genetic evidence that the self-reported pedigree relationships do not represent the true biological relationships. These discrepancies between the reported and probable biological relationships will often be detectable with high confidence, given the number of independent genetic markers that will be genotyped for a study participant. While family relationships may be adjusted in analytical data sets based on these results, *no genetic-based pedigree relationship testing results will be reported back to any participant, or to the clinics that recruited them.*

2. Inference of Ethnic Ancestry

The multiple independent marker genotypes collected for a participant may permit detailed inference of ethnic ancestry. For example, the predominant ethnic ancestry of an individual may be inferred and also their percentage of ethnicity admixture. The self-

reported ethnicity of a participant or family based on answers provided during completion of study forms may not in fact constitute their predominant ancestry. In a similar way to the inference of family relationships, adjustments may be made in analytical data sets, *no genetic-based ethnicity testing results will be reported back to any participant, or to the clinics that recruited them.*

6. Revocation of Informed Consent and Withdrawal from the Study

The Coordinating Center will respect every participant's wishes, as articulated in the informed consent, regarding the use and distribution of his/her samples. A study participant may revoke their informed consent at any time, and request that their specimens be destroyed and their data purged from study databases and data sets. The Coordinating Center will communicate the appropriate laboratories and clinic to arrange for sample destruction, and will purge both raw collected data and analytical data from its databases and data sets. The Coordinating Center will coordinate removal of the participant data from electronic copies of data sets in possession of internal and external researchers.

7. Security of Data Systems

The Coordinating Center will use secure computer systems and applications to manage study data collection and analysis. The specific computer infrastructure security measures that will be in place are described in Chapter VII, Data Management.

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SAMPLE STORAGE AND SHIPPING
TABLE OF CONTENTS

I. SAMPLE STORAGE AT CLINIC

A. Overview

Shipment of T1DGC samples occurs daily and monthly, depending upon the type of sample. Whole blood for cell lines (one or two samples for each participant, depending on age) and the cell pack from the EDTA plasma sample are maintained at room temperature and shipped to the DNA Repository within 24 hours of collection. Autoantibody samples (one each for the proband, the affected sibling, and the case) and long-term storage samples (up to 5 serum and 4 plasma per participant) are stored in a freezer and shipped monthly.

B. Guidelines for Freezing Serum and Plasma Samples

1. All cryovials are to be frozen immediately after aliquoting; do not allow vials to sit out. The preferred freezer temperature is -70^{o}C, although -20^{o}C is acceptable for short-term sample storage (*i.e.*, one month).

2. Cryovials must be frozen upright in the storage boxes that will hold the samples when they are shipped to the laboratory.

3. Record time of freezing samples on the *T1DGC Blood Collection Form*. Samples must be placed in the freezer **within 90 minutes** of blood collection.

4. Update the shipping forms daily as samples are stored.

C. Procedure for Packing Serum and Plasma Samples for Storage

Each participant's serum samples (maximum of 5 with red cap) and plasma samples (maximum of 4 with purple cap) are stored and shipped **together**.

Each storage box has 100 spaces for samples. Before packing the boxes for long-term storage, wrap a length of freezer tape around the outside corners of the box's lid to reinforce it. When fully packed, the box may be slightly crowded.

Since each participant should have a total of 9 samples, all of the samples for as

many as 10 participants can be stored in one box (*i.e.*, a total of 90 samples per storage box). **DO NOT DIVIDE A FAMILY'S SAMPLES ACROSS TWO BOXES.** Within a box, pack the samples in order of the date collected, from the upper left hand corner to the lower left hand corner. Case and control samples may be included in the boxes with the family samples and are placed in the boxes in the same manner. They should be placed at the end of a family's samples so they do not divide the family's samples.

For each participant, pack the **serum** samples first and then pack the **plasma** samples. Begin at the first sample position on the first row of the box and place successive samples moving to the right and then moving down a row. Serum samples will occupy the first five spaces in each row. For all participants with a full set of storage samples (5 serum and 4 plasma), only the last space in the row will be empty (Figure 1). In this figure, all 10 participants have a full complement of vials.

If a participant has fewer than the maximum number of serum and plasma samples, begin filling in the row, leaving a blank space for any missing storage samples. Serum samples should occupy the first five spaces and plasma the next four spaces. In Figure 2, participant #2 has three serum samples and two plasma samples. Participant #5 has two serum and one plasma sample. Participant #7 has three serum samples and **no** plasma samples. Participant #9 has one serum sample and one plasma sample.

As a participant's samples are added to the storage box, place a vial label on the top of the box lid, starting in the upper left hand corner of the box. To the right of the label write **in ballpoint ink** the number of serum and plasma samples enclosed for the respective ID (*i.e.*, 5–S; 4–P). The ID labels should be placed on the lid as described here and illustrated in Figure 3. Vial labels for the first five participants' samples (*i.e.*, participants 1-5) should be in a column on the left side of the box lid and the vial labels for the second five participants' samples (*i.e.*, participants 6-10) should be in a column on the right side of the box lid. If a vial label for the participant's samples is not available, write the **full 7-digit ID**, **in ballpoint ink**, in the location the label should occupy.

1st ppt's samples (Father: Family 1)	S	S	S	S	S	P	P	P	P	■
2nd ppt's samples (Mother: Family 1)	S	S	S	S	S	P	P	P	P	■
3rd ppt's samples (Proband: Family 1)	S	S	S	S	S	P	P	P	P	■
4th ppt's samples (Affected: Family 1)	S	S	S	S	S	P	P	P	P	■
5th ppt's samples (Unaffected: Family 1)	S	S	S	S	S	P	P	P	P	■
6th ppt's samples (Father: Family 2)	S	S	S	S	S	P	P	P	P	■
7th ppt's samples (Mother: Family 2)	S	S	S	S	S	P	P	P	P	■
8th ppt's samples (Proband: Family 2)	S	S	S	S	S	P	P	P	P	■
9th ppt's samples (Affected: Family 2)	S	S	S	S	S	P	P	P	P	■
10th ppt's samples (Unaffected: Family 2)	S	S	S	S	S	P	P	P	P	■

Figure 1. Packing diagram for storage samples. "S" indicates a serum cryovial, "P" indicates an EDTA plasma cryovial and "■" indicates an empty space. "ppt's" = participant's. Color of letters indicates color of the cryovial cap.

1st ppt's samples (Father: Family 1)	S	S	S	S	S	P	P	P	P	■
2nd ppt's samples (Mother: Family 1)	S	S	S	■	■	P	P	■	■	■
3rd ppt's samples (Proband: Family 1)	S	S	S	S	S	P	P	P	P	■
4th ppt's samples (Affected: Family 1)	S	S	S	S	S	P	P	P	P	■
5th ppt's samples (Unaffected: Family 1)	S	S	■	■	■	P	■	■	■	■
6th ppt's samples (Father: Family 2)	S	S	S	S	S	P	P	P	P	■
7th ppt's samples (Mother: Family 2)	S	S	S	■	■	■	■	■	■	■
8th ppt's samples (Proband: Family 2)	S	S	S	S	■	P	P	P	P	■
9th ppt's samples (Affected: Family 2)	S	■	■	■	■	P	■	■	■	■
10th ppt's samples (Unaffected: Family 2)	S	S	S	S	S	P	P	P	P	■

Figure 2. Packing diagram for storage samples where fewer than the maximum numbers have been collected for 2nd, 5th, 7th and 9th participants. "S" indicates a serum cryovial, "P" indicates a plasma cryovial, and "■" indicates an empty space. "ppt's" = participant's. Color of letters indicates color of the cryovial cap.

When a box has been filled, the labels affixed and the number of storage samples (serum and plasma) recorded for each participant, place a vertical strip of freezer tape over each column of labels on the top of the box. This will prevent the labels from falling off during long-term storage.

Figure 3. Placement of participant ID labels and sample counts on the top of the storage box lid.

D. Procedure for Quality Control Samples

The duplicate (i.e., quality control or QC) EDTA cell packs will be shipped daily (at ambient temperature) with the original cell pack and cell line samples. Serum and plasma QC samples will be shipped monthly with original samples (i.e., in the same month as they are collected).

Samples should not be placed adjacent to the original samples; place QC samples at the end of the shipment as indicated in Figure 4. Each set of QC samples (serum or plasma) should occupy a separate row. That is, do not combine samples from a QC-Red participant with those from a QC-Purple participant to fill an entire row. For a QC-Red participant, the first five spaces in the row will be filled and the remaining five spaces will be left empty. For a QC-Purple participant, the first five spaces in the

row will be left empty, the next four spaces will be filled with the samples and the last space will be left empty.

1st ppt's samples (Father: Family 1)	S	S	S	S	S	P	P	P	P	■
2nd ppt's samples (Mother: Family 1)	S	S	S	S	S	P	P	P	P	■
3rd ppt's samples (Proband: Family 1)	S	S	S	S	S	P	P	P	P	■
4th ppt's samples (Affected: Family 1)	S	S	S	S	S	P	P	P	P	■
5th ppt's samples (Father: Family 2)	S	S	S	S	S	P	P	P	P	■
6th ppt's samples (Mother: Family 2)	S	S	S	S	S	P	P	P	P	■
7th ppt's samples (Proband: Family 2)	S	S	S	S	S	P	P	P	P	■
8th ppt's samples (Affected: Family 2)	S	S	S	S	S	P	P	P	P	■
9th ppt's samples (QC-Red)	S	S	S	S	S	■	■	■	■	■
10th ppt's samples (QC-Purple)	■	■	■	■	■	P	P	P	P	■

Figure 4. Packing diagram for storage samples, with quality control samples included. "S" indicates a serum cryovial, "P" indicates an EDTA plasma cryovial and "■" indicates an empty space. "ppt's" = participant's. Color of letters indicates color of the cryovial cap.

II. SAMPLE SHIPPING

All T1DGC samples must be packaged and shipped in compliance with the 46th edition of the International Air Transport Association (IATA) *Dangerous Goods*

Regulations. Samples for T1DGC are classified as Category B (diagnostic specimens or clinical specimens) and must comply with the IATA Packing Instruction 650 (Appendix C). Effective January 1, 2005, packages containing diagnostic specimens must have a diamond-shaped label with "UN 3373" inside. Either "Diagnostic Specimens" or "Clinical Specimens" must be clearly marked on the package (adjacent to the UN 3373 label) and on the waybill.

Re-collection samples should be included with samples from original collections.

A. Schedule for Shipping Cell Line and EDTA Cell Pack Samples

Daily shipments are required for green top (sodium heparin) or yellow top (CPDA) tubes and EDTA cell pack (purple top) samples. Blood should be received at the DNA Repository **within 24 hours** of collection (or as close to this time as possible, considering geographic and budgetary constraints). Overnight shipment to the laboratory is arranged via courier by clinic staff.

B. Cell Line and EDTA Cell Pack Sample Packaging and Shipment

Ship cell line and EDTA cell pack samples at room temperature in double-boxed styrofoam 8-slot tube holders. To help maintain room temperature, surround the box assembly with gel packs (**stored at room temperature between uses**) and place the assembly inside a larger styrofoam shipping container. **DO NOT REFRIGERATE GEL PACKS AS THIS WILL COMPROMISE THE VIABILITY OF THE SAMPLE! DO NOT USE DRY ICE AS FREEZING WILL DESTROY THE CELLS!**

C. Schedule for Shipping Autoantibody, Storage, and Serum and Plasma Quality Control Samples

Autoantibody, storage and serum and plasma quality control samples are shipped **monthly** to the Regional Autoantibody and Storage Laboratory, preferably on a Monday or Tuesday. Samples should be held in clinic freezers for a **maximum** of 30 days to: (1) minimize loss of samples at the local level due to freezer failure; (2) minimize degradation of samples stored at less than -70^{o}C; and (3) ensure that autoantibody analysis remains current by providing a consistent flow of samples to the

laboratory. To minimize the risk of catastrophic loss of samples, shipments should never exceed 500 samples.

Clinics are assigned a specific shipping date (*e.g.*, the first Monday of each month) and shipping dates will rotate so that network laboratories are receiving samples each week. Clinics should provide laboratories with 24 hours advance notice of intent to ship. Appendix A provides the laboratory contact information for each network.

D. Frozen Sample Packaging and Shipping

Packaging and shipping of frozen samples is the responsibility of each clinic.

1. Samples must be frozen for at least twenty-four hours before they are shipped.

2. Frozen samples are shipped in the storage boxes in which they have been stored in the freezers at the clinics.

3. The boxes with frozen samples must be placed so that samples are upright in the supplied insulated shipping container and surrounded with dry ice pellets. At least 10 pounds (4.5 kg) of dry ice is necessary to keep the samples frozen for up to 48 hours; 15-20 pounds (7-9 kg) is recommended.

4. Label each shipment with "CONTENTS TO REMAIN FROZEN".

E. Sample Packaging and Shipping

1. The two clinic shipping forms (*Face Sheet* and *Contents Sheet*) must be enclosed or attached with each shipment. Instructions for the completion of these forms are located in Appendix B. Use a separate *Face Sheet* for each shipping container of samples.

2. Samples must be shipped by air courier for arrival at the laboratory by the following morning. On the day of shipment, the primary nurse or technician should notify the laboratory that the samples have been shipped to arrive by air courier the following morning. (This will vary by network; due to differences in

time zones, the technician may need to call the laboratory the morning that the shipment will be arriving.) The technician will also provide the laboratory with the courier service used and the courier's reference number.

3. **If the shipment is not received by noon, the laboratory personnel should contact the Regional Network Center and the Clinic Coordinator of the pertinent clinic immediately. This permits the clinic to put a trace on the missing samples and, hopefully, locate them before the sample integrity is compromised.**

4. Shipments **MUST** be made according to the shipping schedule.

5. The clinics must request that laboratories return the containers as soon as possible, with expenses covered as determined by the Regional Network Center. Return need not be by air courier and the clinics should provide the laboratories with a return address shipping label.

III. DESTRUCTION OF T1DGC SAMPLES

T1DGC samples should be destroyed or discarded **only** with written instructions from the study Coordinating Center located at Wake Forest University. **All samples should be retained until the clinic and/or laboratories receive the *T1DGC Notification to Destroy Samples* form.** (See Appendix D for a copy of the form and instructions for completion.) The Coordinating Center initiates the form after notification by the Network Coordinator. The sample(s) to be destroyed are confirmed prior to forwarding the form to the appropriate clinic and/or laboratory.

Valid reasons for destroying or discarding samples include the following: (1) appropriate consent not obtained from participant at time of blood collection; (2) participant subsequently withdrew consent; (3) participant determined to be ineligible after blood collection; (4) consent not obtained for cell line; and (5) other miscellaneous reasons. The "Other" reasons category includes frozen samples that were lost or delayed in transit and were received thawed or mislabeled tubes where identification of

the sample is in question. The laboratory **should never** discard or destroy samples that arrive unlabeled without consulting the clinic staff, the Regional Network Coordinator, **AND** the Coordinating Center.

IV. SHIPPING SUMMARY

In summary, samples are shipped as outlined:

Destination	Frequency	Tube or Vial	Mode
Original and Recollection Samples:			
DNA Repository	Daily	Green or yellow top tubes (cell line) EDTA tube (cell pack for DNA)	Ambient temperature
Autoantibody and Storage Laboratory	Monthly	5 2-ml cryovials (autoantibodies/serum storage) 4 2-ml cryovials (plasma storage)	Frozen
QC (Duplicate) Samples:			
DNA Repository	Daily (with original samples)	EDTA tube (cell pack for DNA)	Ambient temperature
Autoantibody and Storage Laboratory	Monthly (with original samples)	5 2-ml cryovials (autoantibodies/serum storage QC) 4 2-ml cryovials (plasma storage QC)	Frozen

APPENDIX A
NETWORK LABORATORY CONTACT
INFORMATION FOR SAMPLE SHIPMENTS

ASIA-PACIFIC NETWORK:

DNA Repository / Autoantibody and Storage Laboratory:

Attention: Nick Homatopoulos/ Ian Nicholson
Victorian Transplantation and Immunogenetics Service (or VTIS)
Australian Red Cross Blood Bank
Cnr Kavanagh and Balston Sts
Southbank
Victoria 3006
Australia

Contact via e-mail:

Michael Varney (mvarney@arcbs.redcross.org.au) with copies to:
Ian Nicholson (inicholson@arcbs.redcross.org.au) **and**
Nick Homatopoulos (nhomatopoulos@arcbs.redcross.org.au)

Phone: 61 3 9341 6309 (Mike Varney) or 61 3 9694 0242 (Ian Nicholson)

EUROPEAN NETWORK:

DNA Repository:

Bernhard O. Boehm, M.D.
Klinikum der Universität Ulm
Kliniken Oberer Eselsberg
Abteilung Innere Medizin I
Robert-Koch-Straße 8
89081 Ulm
Germany

Contact via e-mail:

Bernhard Boehm (bernhard.boehm@uniklinki-ulm.de) **and**
Tina Joss (tina.joss@uniklinki-ulm.de) **and**
Angelika Kurkhaus (angelika.kurkhaus@uniklinki-ulm.de) **and**
Silke Rosinger (silke.rosinger@uniklinki-ulm.de) **and**
(et1dgn.ulm-repository@uniklinki-ulm.de)

Phone: +49-731-500-44515
FAX: +49-731-500-44519

APPENDIX A (CONT.)

NETWORK LABORATORY CONTACT INFORMATION FOR SAMPLE SHIPMENTS

Autoantibody and Storage Laboratory:

Alistair Williams
Diabetes and Metabolism
Medical School Unit
Southmead Hospital
Bristol BS10 5NB
UK

Contact via e-mail: antibody-IGC@bristol.ac.uk
Phone: +44 117 959 5337
FAX: +44 117 959 5336

NORTH AMERICAN NETWORK:

DNA Repository:

Fred Hutchinson Cancer Research Center (FHCRC)
1100 Fairview Ave. North, D2-346
P.O. Box 19024
Seattle, WA 98109-1024

Primary Contact: Gary Olsem
Phone: 206-667-3756
E-mail: golsem@fhcrc.org
Fax: 206-667-5255

Secondary Contact: Heather Risbeck
Phone: 206-667-3756
Email: hrisbeck@fhcrc.org
Fax: 206-667-5255

Laboratory Director: John Hansen, MD
Phone: 206-667-5111
Email: jhansen@fhcrc.org
Fax: 206-667-5255

Shared Email: cgb@fhcrc.org

APPENDIX A (CONT.)

NETWORK LABORATORY CONTACT INFORMATION FOR SAMPLE SHIPMENTS

Autoantibody and Storage Laboratory:

Barbara Davis Center
M20-4201C, Attn: Liping Yu
12801 E. 17th Avenue
Aurora, CO 80010
Telephone: 303-724-6808

Contact: Liping Yu
Phone: 303-315-7108
E-mail: liping.yu@uchsc.edu

UNITED KINGDOM NETWORK:

DNA Repository:

JDRF/WT Diabetes & Inflammation Laboratory
Cambridge Institute for Medical Research
University of Cambridge
Wellcome Trust/MRC Building
Addenbrooke's Hospital, Cambridge, CB2 2XY

Contact via e-mail:

Sarah Nutland (sarah.nutland@cimr.cam.ac.uk) **and**
Helen Stevens (helen.stevens@cimr.cam.ac.uk)

Phone: 44(0)1223 762 106
Fax: 44(0)1223 762 102

Autoantibody and Storage Laboratory:

Alistair Williams
Diabetes and Metabolism
Medical School Unit
Southmead Hospital
Bristol BS10 5NB
UK

Contact via e-mail: antibody-IGC@bristol.ac.uk
Phone: +44 117 959 5337
FAX: +44 117 959 5336

APPENDIX B

CLINIC SHIPPING FORMS: INSTRUCTIONS FOR USE

There are two clinic shipping forms: a *Face Sheet* and a *Contents Sheet*. Copies of these forms are located on the T1DGC web site.

Both forms must be included in any daily shipments (for cell line samples and EDTA cell packs) sent to the DNA Repository and in any monthly shipment (for autoantibody and storage samples) sent to the Autoantibody and Storage Laboratory.

Two copies of each of these forms are created from the originals. The original forms are sent to the laboratory with the sample shipment. Copy #1 is kept at the clinic and Copy #2 is sent to the Regional Network Center.

Both the clinic and the laboratory complete designated portions of the forms when processing the sample shipment. Data from both forms are entered into a web-based specimen tracking system at the laboratory when samples are received. The laboratory forwards the completed original forms to the Regional Network Center for final documentation of the shipment.

FACE SHEET:

A. The clinic completes the top half and the left side of the bottom half of the *Face Sheet*.

B. The full address of the clinic and the laboratory is printed or typed in the area allotted.

C. A Shipping ID Label is placed in the designated space on the form. A second identical Shipping ID Label is placed on the shipping container. Shipping IDs are 11-digit numbers, beginning with the network identifier. (NOTE: There are three shipping labels provided for each **unique** shipping ID. Only two labels are to be

used in any given shipment; one label is placed on the shipping form and one on the shipping container. The third label can be used in the event that one label tears. Alternatively, the third label can be used for local forms. However, the third label should never be used on a subsequent shipment.)

D. The courier or shipping company used (*e.g.*, Federal Express or World Courier) and the reference number ID is recorded on the form.

E. The type of samples included in the shipment (*i.e.*, cell line and/or cell pack **or** autoantibody/storage) is selected.

F. Record the name of the clinic contact and his/her phone number.

G. The following items are recorded on the left side on the bottom part of form by the person preparing the shipment:
(1) clinic ID
(2) date and time the shipment was packed at the clinic
(3) total number of samples packed. The technician should confirm this total by both counting samples and adding the numbers in the "number vials" column on the contents sheets.
(4) number of contents pages included. Number will vary depending on the number of vials in the shipment, since each contents page allows for 6 sample IDs. (NOTE: The *Face Sheet* is not included in the count of contents pages.)
(5) ID of person packing the samples and completing the shipping forms.

H. The right side of the bottom part of the face sheet is to be completed by the laboratory personnel upon arrival of the shipment.

I. The following items are recorded by the person receiving the shipment:
(1) Laboratory ID
(2) date and time the shipment arrived at the laboratory
(3) total number of samples received. The technician should confirm this total by

both counting samples and adding the numbers in the "number vials" column on the contents sheets.

(4) number of contents pages received.

(5) initials of person receiving the samples and completing the shipping forms.

CONTENTS SHEET

The second shipping form is the *Contents Sheet*. More than one contents sheet may be included in each shipment, depending on the number of samples included.

The number of pages attached and each page number should be filled in at the top of the contents pages by the clinic staff. This form should be completed as the samples are collected and stored. The form must be checked against the samples when packaged for shipment at the clinic and when the samples are received at the laboratory.

A. The clinic records the page numbers in the upper right corner of the form.

B. The clinic places one of the bar-coded large ID labels for each participant's samples on the form. This will reduce staff effort and prevent transcription errors at the clinics and laboratories. (NOTE: Each *Contents Sheet* will accommodate labels for 6 participant ID labels. Completely fill all 6 spaces, leaving no blank spaces, as the *Contents Sheet* is completed.)

C. The clinic records the type of samples by marking the vial cap colors for the samples (*e.g.*, red=serum; purple=plasma **or** EDTA cell pack; green/yellow= sodium heparin or CPDA tubes). Mark all that apply.

D. The clinic records the number of samples with that same color vial cap with the same ID in the column labeled "Sent".

E. In the column labeled "Comments on Samples", the clinic marks "Red samples hemolyzed" if serum samples were hemolyzed and/or "Purple samples

hemolyzed" if plasma samples were hemolyzed. These two selections are the only comments that should be marked by clinic staff; the remaining options are to be used by the laboratory upon receipt and inspection of the samples.

F. The laboratory counts and records the number of samples of each vial color in the column labeled "Arrived" for inventory purposes and acknowledgment of arrival. If a tube (or tubes) broke during shipment, record the number of **un**broken tubes received.

If the number of samples sent does not equal the number of samples received, the laboratory staff must contact the clinic staff to resolve the discrepancy. This may involve the clinic sending a corrected version of the *Face Sheet* and/or *Contents Sheet*.

The laboratory should copy the Regional Network Center and the Coordinating Center on all communications with the clinic regarding shipping problems or discrepancies with the shipment.

G. In the column labeled "Comments on Samples", the laboratory should mark the following selections to indicate discrepancies in the number of samples shipped and the condition of samples in the shipment:

(1) Tube(s) broken: if the green or yellow top tubes for cell lines are broken or the EDTA cell pack tube is broken
(2) Samples thawed: if sample shipment is thawed upon receipt at the laboratory
(3) Samples missing: if the number of samples "Sent" by the clinic is not the same number of samples received at the laboratory
(4) Other: if none of the above indicates the problem with the shipment

APPENDIX C

IATA PACKING INSTRUCTION 650

PACKING INSTRUCTION 650

▲ OPERATOR VARIATIONS, AO-03, AS-08, CO-07, CS-07, FX-09, QF-03

General Requirements

Diagnostic specimens must be packed in good quality packagings, which must be strong enough to withstand the shocks and loadings normally encountered during transport, including trans-shipment between transport units and between transport units and warehouses as well as any removal from a pallet or overpack for subsequent manual or mechanical handling.

Packagings must be constructed and closed so as to prevent any loss of contents when prepared for transport which might be caused under normal conditions of transport, by vibration, or by changes in temperature, humidity or pressure.

Primary receptacles must be packed in secondary packagings in such a way that, under normal conditions of transport, they cannot break, be punctured or leak their contents into the secondary packaging. Secondary packagings must be secured in outer packagings with suitable cushioning material. Any leakage of the contents must not substantially impair the protective properties of the cushioning material or of the outer packaging.

Packages must be prepared as follows:

(a) **For liquids:**

- The primary receptacle(s) must be leak-proof and must not contain more than 500 mL.
- There must be absorbent material placed between the primary receptacle and the secondary packaging; if several fragile primary receptacles are placed in a single secondary packaging, they must be either individually wrapped or separated so as to prevent contact between them. The absorbent material, such as cotton wool, must be in sufficient quantity to absorb the entire contents of the primary receptacles and there must be a secondary packaging which must be leak-proof.
- The primary receptacle or the secondary packaging must be capable of withstanding without leakage an internal pressure producing a pressure differential of not less than 95 kPa in the range of -40°C to+55°C (-40°F to 130°F).
- The outer packaging must not contain more than 4 L.

(b) **For solids:**

- The primary receptacle(s) must be sift-proof and must not contain more than 500 g.
- If several fragile primary receptacles are placed in a single secondary packaging, they must be either individually wrapped or separated so as to prevent contact between them and there must be a secondary packaging which must be leak-proof.
- The outer packaging must not contain more than 4 kg.

☞ An itemized list of contents must be enclosed between the secondary packaging and the outer packaging.

☞ Each completed package must be capable of successfully passing the drop test described in 6.6.1 except that the height of the drop must not be less than 1.2 m.

☞ Packages consigned as freight must be at least 100 mm (4 in) in the smallest overall external dimension.

- Each package and the "Nature and Quantity of Goods" box of the air waybill must show the text "DIAGNOSTIC SPECIMEN PACKED IN COMPLIANCE WITH IATA PACKING INSTRUCTION 650".

  With effect from 1 January 2004, each package must also be marked requirements in accordance with 7.1.5.8 to indicate that the shipper has determined that the packaging meets the applicable air transport. The marking must be applied adjacent to the words "Diagnostic Specimens".

  A Shipper's Declaration for Dangerous Goods is not required.

  Provided diagnostic specimens are packed in accordance with this Packing Instruction, no other requirements of these Regulations apply except for the definition in 3.6.2.1.4 and the reporting of dangerous goods accidents and incidents in 9.6.1.

- **Specific Requirements**
  Although exceptional cases (for example, the shipment of whole organs), may require special packaging, the great majority of diagnostic specimens can and must be packaged according to the following guidelines.

  Substances shipped at ambient temperatures or higher: Primary receptacles include those of glass, metal or plastic. Positive means of ensuring a leak-proof seal, such as heat seal, skirted stopper or metal crimp seal must be provided. If screw caps are used these must be reinforced with adhesive tape.

  Substances shipped refrigerated or frozen (wet ice, pre frozen packs, Carbon dioxide, solid [dry ice]): Ice, Carbon dioxide, solid (dry ice) or other refrigerant must be placed outside the secondary packaging(s) or alternatively in an overpack with one or more completed packagings. Interior support must be provided to secure the secondary packaging(s) or packages in the original position after the ice or Carbon dioxide, solid (dry ice) has been dissipated. If ice is used the packaging must be leak-proof. If Carbon dioxide, solid (dry ice) is used the outer packaging must permit the release of carbon-dioxide gas. The primary receptacle must maintain its containment integrity at the temperature of the refrigerant as well as at the temperatures and pressure of air transport to which the receptacle could be subjected if refrigeration were to be lost.

  Substances shipped in liquid nitrogen: Plastic capable of withstanding very low temperatures must be used instead of glass receptacles. Secondary packaging must also withstand very low temperatures and in most cases will need to be fitted over individual primary receptacles. Requirements for shipment of liquid nitrogen must also be observed. The primary receptacle must maintain its containment integrity at the temperature of the refrigerant used as well as at the temperatures and pressure of air transport to which the receptacle could be subjected if refrigeration were to be lost.

  Lyophilized substances: Primary receptacles must be either flame-sealed glass ampoules or rubber-stoppered glass vials with metal seals.

APPENDIX D

T1DGC NOTIFICATION TO DESTROY SAMPLES: FORM AND INSTRUCTIONS FOR USE

T1DGC Notification to Destroy Samples

T1DGC Participant ID

COMPLETED BY COORDINATING CENTER

1. Date

Day - Month - Year

2. Reason for destroying samples

- Consent not obtained 1
- Withdrew consent 2
- Ineligible 3
- Consent not obtained for cell line 5
- Other 4

If other, provide additional information or explanation:

_____

3. Clinic ID associated with participant ID

Clinic ID

4. Type of samples to be destroyed (CHECK ALL THAT APPLY.)

- Serum aliquots 1
- Plasma aliquots 1
- Green top tubes 1
- Cell pack 1
- DNA aliquots 1
- Cell line aliquots 1

5. Number of each sample type to be destroyed **(NOTE: Reflects full inventory of all known participant samples across all laboratories and clinics.)**

Serum aliquots	*Green top tubes	***DNA aliquots
Plasma aliquots	**Cell pack	****Cell line aliquots

* For Network DNA Repositories, this reflects the number of green top tubes received; please destroy all PBLs LCLs and DNA aliquots associated with these samples UNLESS reason for destroying samples is "consent not obtained for cell line"; then, destroy all samples except PBMC.

** Please destroy all DNA aliquots extracted from the cell pack.

*** This reflects the total number of DNA aliquots shipped from Network DNA Repositories to other facilities.

**** For Rutgers or Contributing Investigator Requests, this reflects the number of cell line aliquots received.

T1DGC Participant ID

6. Authorized Coordinating Center signature

_____

7. Date sent to Regional Network Center - -
Day Month Year

COMPLETED BY REGIONAL NETWORK CENTER

8. Regional Network decision
Approved 1
Not approved 2

9. Authorized Regional Network Center signature

_____

10. Date sent to Coordinating Center - -
Day Month Year

COMPLETED BY COORDINATING CENTER

11. Notification sent to following T1DGC study sites (ID completed for applicable sites)

a. Clinic ID

b. Shipping ID Autoantibody and Storage Laboratory ID

c. Shipping ID DNA Repository ID

Shipping ID

d. Shipping ID HLA Genotyping Laboratory ID

T1DGC Participant ID

COMPLETED BY COORDINATING CENTER

11. Notification sent to following T1DGC study sites (ID completed for applicable sites) (Continued)

e. Shipping ID ☐-☐☐☐☐☐☐☐☐☐☐ CIDR ID ☐☐☐

f. Shipping ID ☐-☐☐☐☐☐☐☐☐☐☐ MHC Laboratory ID ☐☐☐

g. Shipping ID ☐-☐☐☐☐☐☐☐☐☐☐ NIDDK Biosample Repository ID (Fisher) ☐☐☐

Shipping ID ☐-☐☐☐☐☐☐☐☐☐☐

h. Shipping ID ☐-☐☐☐☐☐☐☐☐☐☐ NIDDK Genetics Repository ID (Rutgers) ☐☐☐

Shipping ID ☐-☐☐☐☐☐☐☐☐☐☐

i. Shipping ID ☐-☐☐☐☐☐☐☐☐☐☐ Rapid Response Laboratory ID ☐☐☐

j. Other Shipping ID ☐-☐☐☐☐☐☐☐☐☐☐ Laboratory ID **OR** Clinic ID **OR** Request ID ☐☐☐☐

Other Shipping ID ☐-☐☐☐☐☐☐☐☐☐☐ Laboratory ID **OR** Clinic ID **OR** Request ID ☐☐☐☐

Reason for additional Shipping ID

_____

12. Date notification sent to T1DGC laboratory or clinic ☐☐ - ☐☐☐☐☐☐☐☐☐ - ☐☐☐☐
Day Month Year

T1DGC Participant ID

COMPLETED BY T1DGC LABORATORY OR CLINIC

13. T1DGC laboratory or clinic (COMPLETE ONLY ONE.)

Lab ID **OR** Clinic ID

14. Type of samples destroyed (CHECK ALL THAT APPLY.)

Serum aliquots 1
Plasma aliquots 1
Green top tubes 1
Cell pack 1
DNA aliquots 1
Cell line aliquots 1

15. Number of each sample type destroyed (Refer to Question 5 for number and type of sample(s) to be destroyed. Refer to Question 11 for the shipping ID associated with the sample(s) to be destroyed. COMPLETE ALL THAT APPLY TO YOUR FACILITY.)

Serum aliquots | *Green top tubes | ***DNA aliquots

Plasma aliquots | **Cell pack | ****Cell line aliquots

* For Network DNA Repositories, this reflects the number of green top tubes received; please destroy all PBLs LCLs and DNA aliquots associated with these samples UNLESS reason for destroying samples is "consent not obtained for cell line"; then, destroy all samples except PBMC.

** Please destroy all DNA aliquots extracted from the cell pack.

*** This reflects the total number of DNA aliquots shipped from Network DNA Repositories to other facilities.

**** For Rutgers or Contributing Investigator Requests, this reflects the number of cell line aliquots received.

16. Date samples destroyed

Day - Month - Year

17. Authorized laboratory or clinic signature

_____

COMPLETED BY COORDINATING CENTER

18. Date completed notification form received at Coordinating Center

Day - Month - Year

19. Date completed notification form FAXed to Regional Network Center

Day - Month - Year

T1DGC NOTIFICATION TO DESTROY SAMPLES: INSTRUCTIONS FOR USE

The *T1DGC Notification to Destroy Samples* form will be used in cases where it is necessary to destroy study samples. This form is completed by the Coordinating Center and approved by the Regional Network Center prior to the Coordinating Center notifying the necessary laboratories and/or clinic that samples must be destroyed.

Each laboratory or clinic completes a section of the form outlining the samples they destroyed and sends the form to the Coordinating Center. This form is entered into a database at the Coordinating Center and a copy of the form is forwarded to the Regional Network Center.

Completed by Coordinating Center

1. The Coordinating Center records the T1DGC Participant ID on every form page.

2. The Coordinating Center records the date the form is completed in a day-month-year format (Question 1).

3. The Coordinating Center marks one response as to why samples are being destroyed. If the response category "Other" is marked, additional information or an explanation is included (Question 2).

4. The Coordinating Center records the Clinic ID associated with the participant (Question 3).

5. The Coordinating Center marks all types of samples to be destroyed. All applicable samples at all locations are marked (Question 4).

6. The Coordinating Center determines the number of each sample type to be destroyed. This number is based on the information the Coordinating Center has as to how many samples are present across all laboratories and clinics (Question

5).

7. There must be an authorized Coordinating Center signature. Authorized Coordinating Center personnel include Dr. Stephen Rich, Principal Investigator of the T1DGC study; Joan Hilner, Deputy Director for the T1DGC; and Letitia Perdue, Project Manager for the T1DGC (Question 6).

8. The Coordinating Center completes the date the form is sent to the Regional Network center in a day-month-year format (Question 7).

Completed by Regional Network Center

9. The Regional Network Center approves or does not approve the destruction of the participant's samples and marks the correct response (Question 8).

10. There must be an authorized Regional Network Center signature. Authorized Regional Network Center personnel include the Principal Investigator and the Network Coordinator (Question 9).

11. The Regional Network Center completes the date the form is sent back to the Coordinating Center in a day-month-year format (Question 10).

Completed by Coordinating Center

12. The Coordinating Center records the laboratory and/or clinic ID for all applicable sites where participant samples are currently being held. The shipping ID containing the samples that are being destroyed is recorded in order to ensure the correct samples are destroyed. This form is sent to all applicable sites along with a cover letter from Joan Hilner, Deputy Director (Question 11).

13. The Coordinating Center completes the date the form is sent to the T1DGC laboratory or clinic in a day-month-year format (Question 12).

Completed by T1DGC Laboratory or Clinic

14. The T1DGC Laboratory or Clinic completes either the “Lab ID” box or the “Clinic ID” box with their laboratory or clinic ID (Question 13).

15. The T1DGC Laboratory or Clinic determines the number and type of each sample for this participant they currently have in their facility and destroys these samples.

16. All sample types destroyed at this facility are recorded on the form (Question 14).

17. The number of each sample type destroyed is recorded. If no samples were destroyed, a 0 is recorded in the box. The cover letter from Joan Hilner will include the number and type of samples the facility has that need to be destroyed (Question 15).

18. The T1DGC Laboratory or Clinic completes the date the samples were destroyed in a day-month-year format (Question 16).

19. There must be an authorized Laboratory or clinic signature. Authorized Laboratory personnel include the Principal Investigator. Authorized clinic personnel include the Principal Investigator (Question 17).

Completed by Coordinating Center

20. This form is forwarded to the Coordinating Center, who completes the date the form was received at the Coordinating Center in a day-month-year format (Question 18).

21. The Coordinating Center faxes a copy of the form to the Regional Network Center and completes the date this was faxed in a day-month-year format (Question 19).

QUALITY CONTROL
TABLE OF CONTENTS

I. INTRODUCTION

The T1DGC Coordinating Center will perform quality control studies throughout the time period that data are collected. The Coordinating Center will be assisted in the performance of these duties by the Regional Network Centers, the clinics and the Quality Control Committee.

There are two primary purposes for quality control. The most important purpose is to provide feedback to the data collection clinics in order to maintain and improve the quality of the study data over the course of data collection. A secondary purpose is to historically document the level of quality for inclusion in study publications.

Quality control involves the collection of specific types of data and the subsequent analysis of that data. It is primarily a measure of the quality of data either collected by the clinics or samples analyzed by laboratories associated with the study.

Quality control is accomplished in many different ways depending upon the type of data being collected, the type of procedure being analyzed, and the associated outcome variable in question. The quality control measures used in the T1DGC study will assess the reliability and validity of the data and proper adherence to the protocol.

The tools that will be used include:

1. Monitoring:
    a. recruitment efforts
    b. specimen tracking
    c. data completeness
    d. freezer temperatures

2. Internal surveillance:
    a. editing forms (at the clinic and Regional Network Center)
    b. laboratory internal quality control procedures

3. External surveillance:
    a. variability of laboratory measurements, using split pair samples
    b. data entry error rates
    c. data edits

This section has been developed to outline the procedures to be performed in order to assure that quality data are being collected and reported.

II. COORDINATING CENTER RESPONSIBILITIES

The T1DGC Coordinating Center has primary responsibility for monitoring and ensuring the overall quality of the study data. Specific responsibilities of the Coordinating Center in developing and carrying out quality control measures are listed below:

1. Organize and conduct Regional Network Center training sessions to teach standardized data collection protocols.

2. Organize and conduct Regional Network Laboratory (DNA Repositories, Autoantibody and Storage Laboratories, and HLA Genotyping Laboratories) training sessions to teach the T1DGC Specimen Tracking System protocol.

3. Review pilot study data and certify clinic readiness to initiate T1DGC data collection.

4. Maintain an up-to-date file of all completed Regional Network Center data entry certification and clinics certified to collect data.

5. Design protocol and procedures for periodic site visits to the Regional Network Centers and Regional Network Laboratories that check for quality of performance and adherence to T1DGC standardized procedures.

6. Develop a system for monitoring study recruitment and communicate with the

Regional Network Coordinators regarding recruitment progress and issues.

7. Develop a system for promptly processing and analyzing incoming data and generating quality control reports for distribution to the Regional Network Centers and Regional Network Laboratories.

8. Identify problems and notify Regional Network Centers of the quality of performance of network and clinic personnel throughout the entire data collection period.

9. Identify problems and notify Regional Network Laboratories of the quality of performance of their laboratories throughout the entire data collection period.

10. Develop and maintain a system for tracking all T1DGC specimens from collection at the clinics to receipt at the Regional Network Laboratories and from Regional Network Laboratories to receipt at the Regional HLA Laboratories, NIDDK Central Repositories, the Center for Inherited Disease Research, MHC Fine Mapping Laboratory, Rapid Response Laboratory, contributing investigators and other facilities or entities approved by the T1DGC Steering Committee or Access Committee.

11. Report pertinent information to the Quality Control Committee, the Steering Committee and the External Advisory Board.

12. Maintain historical data that describes the quality and performance of the entire T1DGC study.

13. Produce and maintain the study documents related to T1DGC quality control: (1) the reports presented to the Quality Control Committee and Steering Committee during data collection; and (2) documents found in reports to the T1DGC External Advisory Board.

III. REGIONAL NETWORK CENTER RESPONSIBILITIES

Given the study structure, the T1DGC has a two-tiered quality control scheme. Each Regional Network Center maintains all direct contact with the clinics collecting data within their specified region. Thus, quality control measures are implemented by the Regional Network Centers at the clinic level, with specific responsibilities outlined below:

1. Organize and conduct clinic training sessions to teach standardized data collection protocols. Training sessions can be centralized, one-on-one or a combination of these techniques within any given Regional Network.

2. Notify the Coordinating Center when clinic training has been completed and when a pilot study has been performed.

3. Maintain an up-to-date file of all completed Regional Network Center data entry certification, clinics certified to collect data, clinic IDs and clinic staff IDs.

4. Monitor recruitment of each clinic and develop and implement strategies to achieve recruitment goals as needed.

5. Review completeness of form sets upon receipt from clinics and notify clinics of missing forms.

6. Review forms for completeness and notify clinics of missing data and errors in form completion.

7. Develop and implement a system for tracking requests for data forms, data verification or data correction from clinics in accordance with outlined procedures.
8. Design protocol and procedures for periodic site visits that check for quality

of performance and adherence to T1DGC standardized procedures in clinics where specific serious problems have been identified.

9. Review *T1DGC Daily Freezer Temperature Log* from clinics on a monthly basis and notify clinic of problems noted.

10. Monitor clinic compliance with quality control scheme for blood collection and notify clinic if inadequate collection of quality control samples noted.

IV. QUALITY CONTROL COMMITTEE

T1DGC study data is primarily of two types: (1) laboratory and (2) forms. Thus, the Quality Control Committee is comprised of four subcommittees: (1) DNA Repositories, (2) Autoantibody and Storage Laboratories, (3) HLA Genotyping Laboratories, and (4) Forms Data. The overall committee includes members from each of the Regional Network Laboratories, the Regional Network Centers and the Coordinating Center. (A list of the Quality Control Committee members and an organizational chart is located in Appendix A.)

The Quality Control Committee will meet as needed to review the status of the study quality control monitoring. Decisions regarding current and proposed techniques will be discussed, as well as current issues. The committee will be kept abreast of issues through frequent correspondence with the Chair of the Quality Control Committee and the Deputy Director of the Coordinating Center.

V. SITE VISITS

A. Regional Network Center and Laboratories

During the first 6 months of data collection, and annually thereafter as needed, site visits will be made to each of the Regional Network Centers and Regional Network Laboratories. The goals of the site visits are: (1) to observe the Regional Network Center or Regional Network Laboratory under normal operating conditions for adherence to protocol; (2) to identify and resolve any data collection issues at the individual clinics (for Regional Network Center site visits only); (3) to identify and resolve any sample shipment,

handling and analysis procedures (for Regional Network Laboratory site visits only); (4) to increase/improve communication between the Coordinating Center and Regional Network Center and Regional Network Laboratory personnel; and (5) to demonstrate the study's concern for the quality of data collection.

The site visits will be conducted in a single day, unless issues within the Regional Network Center or Regional Network Laboratory necessitate an extended visit. The site visit team for the Regional Network Centers will consist of the Deputy Director (Coordinating Center), Project Manager (Coordinating Center) and, if possible, the Project Officer from NIDDK and/or the JDRF liaison. The site visit team for the Regional Network Center Laboratories will consist of the Chair of the Quality Control Committee, the Deputy Director (Coordinating Center), and, if possible, the Project Officer from NIDDK and/or the JDRF liaison. An agenda is prepared and distributed to the Regional Network Center or Regional Network Laboratory prior to the site visit. (Appendix B contains examples of site visit agendas for Regional Network Centers and each type of Regional Network Laboratory.)

Following the site visits, a formal report is prepared. For Regional Network Center site visits, the report is written by the Deputy Director and Project Manager at the Coordinating Center; the Chair of the Quality Control Committee prepares the site visit reports for the Regional Network Laboratories. Site visit reports are distributed to the Chair of the Steering Committee, the Chair of the Quality Control Committee, the Deputy Director of the Coordinating Center, the Project Officer at NIDDK, the JDRF liaison, and the Regional Network Center or Regional Network Laboratory visited. These individuals will discuss these reports on a conference call, if required; this group will make recommendations for the follow-up and correction of problem areas in a timely manner. The Principal Investigator at the Regional Network Center or Regional Network Laboratory will be asked to respond in writing in a timely manner regarding the resolution of any major problems.

B. Data Collection Clinics

Due to the large number of clinics within the Regional Network Centers, annual site visits to all clinics are not planned. However, Regional Network Centers may identify certain clinics where continued or serious issues regarding data collection or sample shipments require a site visit. In this event, the Regional Network Center will confer with the Coordinating Center and develop an agenda for the site visit. The site visit will include observation of collection of blood and completion of forms for a family. (Appendix C contains sample check sheets for blood collection and shipping procedures.)

Following the site visit, the Network Coordinator will prepare a formal report to be distributed to the Chair of the Steering Committee, the Chair of the Quality Control Committee, the Deputy Director of the Coordinating Center, the Project Officer at NIDDK, the JDRF liaison and the Principal Investigator and Clinic Coordinator of the clinic visited. These individuals will discuss the report on a conference call with the Network Coordinator and/or Network Principal Investigator, if required; this group will make recommendations for the follow-up and correction of problem areas in a timely manner. Each Clinic Coordinator and Clinic Principal Investigator will be asked to respond in writing in a timely manner regarding the resolution of any major problems.

VI. QUALITY CONTROL PROCEDURES

This section details the quality control procedures that are to be carried out for specified components.

A. Identifying Participants for Duplicate Blood Collection

The Clinic Coordinator is responsible for identifying the T1DGC participants for whom the quality control duplicate blood collection will be performed. The participants selected are referred to as "QC participants". A *T1DGC Participant and QC Selection Log* has been developed to assist in the selection and tracking of quality control participants. In the event that the additional sample cannot be collected on the identified participant, the nurse or technician collects the duplicate sample on the next appropriate participant.

Given the overall volume of blood being collected, the additional quality control tube is collected only in participants that are at least 16 years old (or large for their age). The additional serum and plasma volume required for quality control is split between two participants: QC-Red for autoantibodies and serum storage and QC-Purple for plasma storage and DNA extraction from the cell pack. A QC-Red participant must be an affected individual (*i.e.*, must have type 1 diabetes). A QC-Purple participant in an ASP or trio family can be any age (or size) eligible individual. In the Case/Control Study, the QC-Purple participant must be a control.

The quality control sampling for the QC-Red participant within each clinic is outlined below:

1. There is no QC-Red collected during the clinic's pilot study.
2. An affected individual (proband, affected sibling or case) from the first two T1DGC collections will have an additional serum tube collected. The selected individuals should not be in the same family.
3. After the collection of the first two QC-Red samples, every 10th affected participant will have an additional serum tube collected.
4. After the collection of an additional five QC-Red samples (for a total of seven QC-Red samples), every 20th affected individual will have an additional serum tube collected.
5. For clinics with primarily pediatric populations, a QC-Red sample should be collected from every age (or size) eligible participants to provide adequate duplicate samples.

The quality control sampling for the QC-Purple participant within each clinic is outlined below:

1. There is one QC-Purple collected during the clinic's pilot study.
2. Any age (or size) eligible individual from the first two T1DGC collections will have an additional plasma tube collected. These participants should not be in the same family.
3. After the collection of the first two QC-Purple samples, every 10th participant will

have an additional plasma tube collected.

4. After the collection of additional five QC-Purple samples (for a total of seven QC-Purple samples), every 20th participant will have additional plasma tube collected.

Once a participant is identified as a QC-Red or QC Purple participant, the Clinic Coordinator should provide the appropriate label set to the nurse or technician. The nurse will place a quality control ID label on the Blood Collection Form, the duplicate sample, the duplicate aliquots (for serum and plasma) and the shipping forms. (See Appendix D for a schematic of the duplicate blood collection sampling procedures and the contents of the QC label sets.)

The quality control ID label will have the same color scheme and participant identifier as the T1DGC ID (*i.e.,* if an affected sibling is selected as a quality control participant, the QC ID label will be green with an -04 as the participant identifier.)

B. Regional Network Laboratories

The Coordinating Center will receive laboratory results for examined participants on a monthly basis from each type of laboratory as outlined below:

1. DNA Repositories: data for the DNA yield from the EDTA cell pack and/or cell line and for the cell line transformation success/failure.
2. Autoantibody and Storage Laboratories: data for autoantibody measures (GAD65 and IA-2ic) on probands, affected siblings and cases.
3. HLA Genotyping Laboratories: data for HLA-A, B, C, DP, DQ, DRB1 and subtypes and CTLA4 and INS SNPs for all participants

The quality of performance in the DNA Repositories will be based largely on the cell line transformation rate and the DNA yield from cell packs and /or cell lines. Further, those using the DNA (*e.g.*, the HLA Genotyping Laboratories) will report any issues with the quality of the samples to the Coordinating Center. The Chair of the Quality Control

Committee and the Deputy Director at the Coordinating Center will investigate any noted problems regarding DNA quality.

To assess the quality of the measures from the Autoantibody Laboratories Laboratories, a two-pronged system will be implemented. First, univariate analyses will be conducted on the monthly data results uploaded to the Coordinating Center. Within each laboratory, comparison of data results over time will be recorded. Based on these analyses, summary statistics (*e.g.*, means, variances) and out-of-range values will be obtained and, if necessary, investigated further.

Second, duplicate measures will be performed on an approximate 5% random sample of participants for autoantibody measures. Duplicate serum samples will be sent by the clinics to the laboratory in the sample shipments. To the extent possible, the laboratory will be blinded as to which samples were paired.

In addition to graphical inspection of the data, reliability will be assessed using correlation coefficients and the technical error measurement for autoantibody measures. (The technical error is the square root of the pooled between measures variance as a percent of the sample mean: ((Sqrt(Σ d^2/2n))/sample mean)* 100.) The technical error is compared to the laboratories internal coefficient of variation. If there is evidence of high technical error then the laboratory will be contacted and queried for an explanation.

HLA genotyping quality control is assessed by two separate procedures: (1) continuous blind quality control where four randomly selected samples from a single pedigree are incorporated on each new plate of 92 samples; and (2) an annual blind QC panel exercise of 92 samples chosen from production pedigree samples previously typed by the T1DGC HLA Laboratories, and simultaneously, independently, re-typed by all HLA Laboratories. The first procedure provides a low level, on-going check of intra-laboratory consistency that can alert the Coordinating Center and HLA Laboratory to a sustained drop in genotyping quality. The second procedure provides a measure of inter-laboratory consistency and accuracy as well as intra-laboratory consistency. All inter-and intra-

laboratory discrepancies are thoroughly investigated and resolved.

For the first procedure, duplicate HLA genotype measures will be performed on a random 5% of samples. Under the direction of the Coordinating Center, the DNA Repositories will provide duplicate DNA samples within each set of 92 samples sent to the HLA Genotyping Laboratories. To the extent possible, the laboratory will be blinded to the pairing of the original and duplicate samples. The proportion of discordant allele calls will be assessed.

For the second procedure, each laboratory genotypes an identical set of 92 samples, with approximately the same number of samples contributed from each of the networks. The 92 samples are included on a single plate with 4 negative controls, as is the case with T1DGC production samples.

More detailed information regarding external and internal quality control procedures are contained in the laboratory-specific *T1DGC Laboratory Manual of Operations*.

C. Shipping and Data Collection Forms

1. Shipping Forms

The clinics will forward a copy of their shipping forms to the Regional Network Center as part of standard documentation. These forms include: (1) a copy of the shipping forms sent with the daily shipment of cell line and EDTA cell packs to the DNA Repositories; and (2) a copy of shipping forms sent with the monthly shipment of blood samples to the Autoantibody and Storage Laboratories.

Upon receipt of the samples, laboratory staff completes the shipping forms with the necessary information and enters the data into the specimen tracking system. The laboratory staff makes a copy of the shipping forms for their records and sends the original shipping forms to the Regional Network Center. The Regional Network Center staff verifies that data entry of the forms was performed accurately.

2. Data Collection Forms Review

Each Regional Network Center is required to submit a 5% random sample of form sets to the Coordinating Center on a quarterly basis for a manual quality control review. A list of randomly generated ID numbers for each clinic will be supplied by the Coordinating Center. The manual review of forms by staff of the Coordinating Center will entail a page-by-page review of the following items:

1. form completion;
2. affixed T1DGC ID and quality control labels, when applicable;
3. interviewer IDs;
4. skip patterns observed;
5. data collection errors corrected according to study protocol;
6. ethnicity and study coding; and
7. overall form consistency and preparedness for data entry.

A report of errors and/or recommendations for improvement will be sent to the Regional Network Center and the Deputy Director of the Coordinating Center following each review.

3. Duplicate Data Entry

All study forms are entered at the Regional Network Centers. Following manual review, the 5% random sample of participant form sets sent by the Regional Network Center on a quarterly basis will be data entered at the Coordinating Center to estimate the data entry error rate. A field-by-field comparison will be made between the original and the re-entered record at the Coordinating Center. A report that indicates which fields were discordant and form-specific error rates will be generated. The first-pass error rates will be adjudicated (via the hard-copy of the form) for data entry errors before final reports are sent to the Regional Network Center.

The resulting error rates will be summarized and forwarded to the Regional Network Center for review. **All** forms from the time period being evaluated where the random sample error rate is 0.50% or greater will be re-entered. The double entry of the 5% sample will be an ongoing process so that the Coordinating Center can identify specific problems. Double entry analysis initially will occur quarterly; however, this will be

reassessed in view of the volume of re-entry required in the Regional Network Centers.

D. Error, Warning and Informational Messages

The T1DGC Data Entry System requires a minimum number of completed fields before a form can be accepted. Validation checks in the form of error, warning and informational messages are applied during data entry. Insofar as possible, corrections will be made as the data are entered.

An error message will display for data values that are critical and must be corrected before data is saved. A warning message will display for data values that should be verified and/or edited by the clinic; however data are able to saved if a warning message is displayed. An informational message will display if the data is out of the "expected" range; entry should be checked at the Regional Network Center, but data does not have to be confirmed by the clinic.

E. Query System

The T1DGC Query System was created to resolve data editing questions. It is to be used as a tool for the Regional Network Centers to record and identify sources of action taken to correct data collection or data entry errors or to correct or verify out-of-range or unexpected database values at either the Regional Network Center or clinic level. The responses that the Regional Network Centers enter into this system are used to create reports for the Forms Data Quality Control Committee, the Steering Committee and the External Advisory Board.

The Query System is dynamic, allowing the Regional Network Centers to identify at one time the entire list of queries for each family ID. Queries are created from the warning messages seen at the time of data entry, as well as cross-form validation checks that appear on the Irregularities Report.

The Regional Network Center first determines that the query is not a data entry error. Once this is confirmed, the Regional Network Center marks the query as "RNC –

Data to be reviewed." All queries marked as "RNC – Data to be reviewed" are sent back to the clinic for resolution.

The clinic and the Regional Network Center can either verify or edit queries. The user can filter queries that have been verified so they no longer appear in the Query System. The Project Managers at the Coordinating Center are responsible for reviewing queries that have been verified on a monthly basis. If a query has been verified and it is considered pertinent information for the T1DGC, the Project Manager changes the status of the query and notifies the Regional Network Center that verification of this query is unacceptable. Once a query has been verified by the Coordinating Center Project Manager, the query will be removed from other reports (*i.e.,* the Irregularities Report)." See Appendix C of **Chapter XI**, *Data Entry System,* for detailed instructions in the use of the T1DGC Query System.

APPENDIX A
QUALITY CONTROL COMMITTEE

ALL SUB-COMMITTEES

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APPENDIX A (CONT.)
QUALITY CONTROL COMMITTEE

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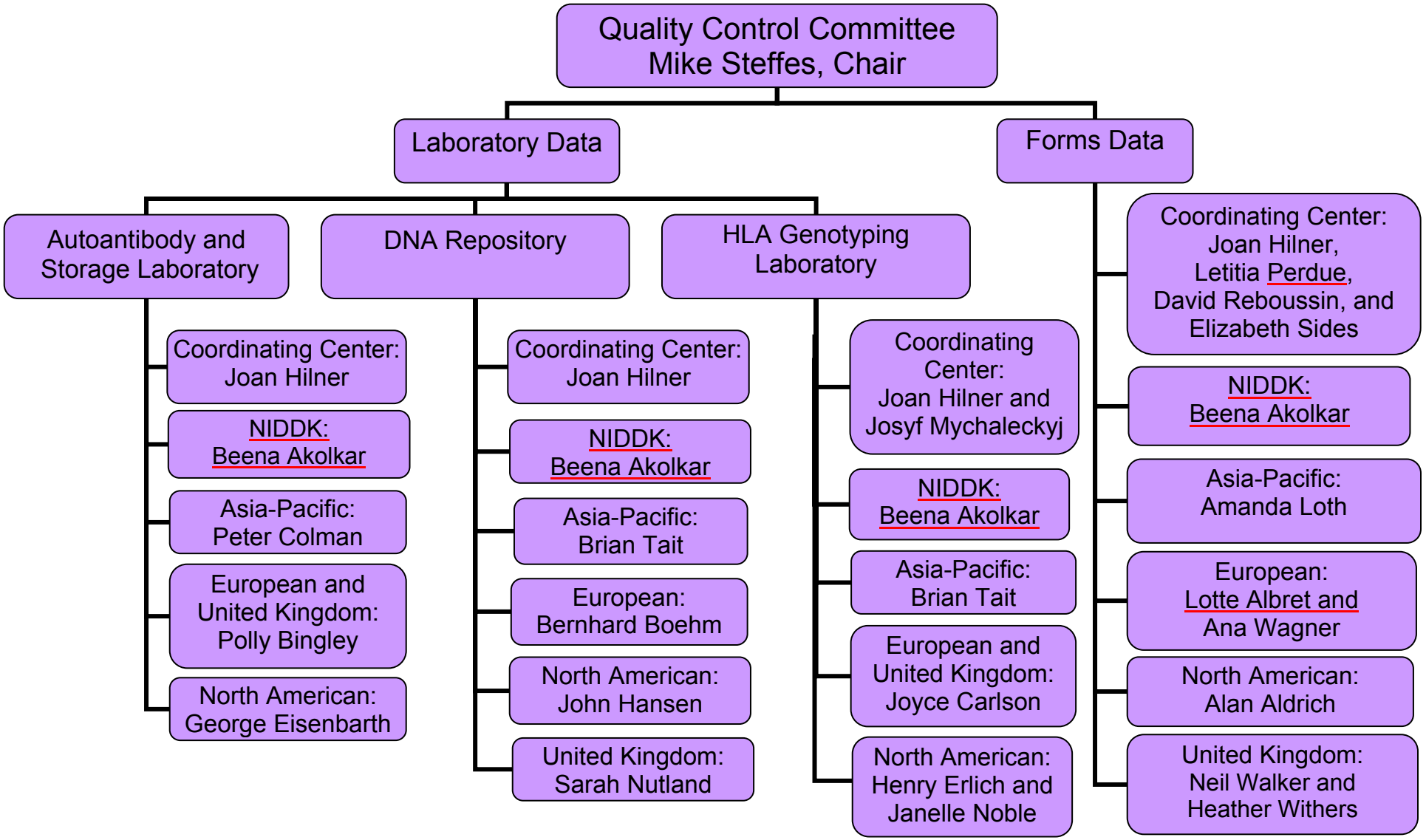
Quality Control Committee
Mike Steffes, Chair
Laboratory Data
Forms Data
Autoantibody and Storage Laboratory
DNA Repository
HLA Genotyping Laboratory
Coordinating Center: Joan Hilner
NIDDK: Beena Akolkar
Asia-Pacific: Peter Colman
European and United Kingdom: Polly Bingley
North American: George Eisenbarth
Coordinating Center: Joan Hilner
NIDDK: Beena Akolkar
Asia-Pacific: Brian Tait
European: Bernhard Boehm
North American: John Hansen
United Kingdom: Sarah Nutland
Coordinating Center: Joan Hilner and Josyf Mychaleckyj
NIDDK: Beena Akolkar
Asia-Pacific: Brian Tait
European and United Kingdom: Joyce Carlson
North American: Henry Erlich and Janelle Noble
Coordinating Center: Joan Hilner, Letitia Perdue, David Reboussin, and Elizabeth Sides
NIDDK: Beena Akolkar
Asia-Pacific: Amanda Loth
European: Lotte Albret and Ana Wagner
North American: Alan Aldrich
United Kingdom: Neil Walker and Heather Withers

APPENDIX B

SITE VISIT AGENDAS

AGENDA
REGIONAL NETWORK CENTER
SITE VISITS

I. Observation of Family Collection (if possible)

II. Review of Recruitment
- A. Goals
- B. Recruitment Strategies and Materials
- C. Changes to Projections (through current fiscal period)

III. Review of Data Entry/ Edits
- A. Missing Data
- B. Errors
- C. Data Entry Flow (time from collection to entry)

IV. Review of Logs
- A. Daily Freezer Temperature Log
- B. Discarded ID Log
- C. Participant and QC Selection Log/ Adequacy of QC Sampling
- D. Data Editing Log
- E. Other Network Center or Clinic Logs (e.g., Staff IDs, Clinic IDs, etc)

V. Storage of Forms
- A. Data Collection Forms from Clinics
- B. Shipping Forms from Laboratories
- C. Layered Portion of Informed Consent Forms from Clinics
- D. IRB Approvals/Informed Consents

VI. Study Documents
- A. Manual of Operations
- B. Protocol

VII. T1DGC Label Sets
- A. Label Storage at Network Center
- B. Systems for Distribution to Clinic and Tracking
- C. Estimated Need for Additional Label Sets

VIII. Miscellaneous
- A. Communication with Clinics
- B. Communication with Coordinating Center
- C. “Problem Clinics”
- D. Reimbursement/ Invoicing
- E. Adverse Events
- F. Application to Eligibility Committee
- G. Notification to Destroy Sample Forms

Agenda for the Site Visit to the DNA Repository for the North American Regional Network (Eric Mickelson, Principal Investigator): Thursday, May 13, 2004

Visitors: Beena Akolkar, PhD, NIDDK
Joan Hilner, MPH, MA, RD, Wake Forest University
Michael Steffes, MD, PhD, University of Minnesota

Local Participants: Eric Mickelson, Ji Pei and Emily Villegas

8:00 Introductions

8:05 Review the Agenda

8:10 Review Plan of the Consortium – Transformation of Peripheral Blood Cells, Isolation of DNA

Several laboratories throughout the world will be transforming peripheral blood mononuclear cells for the Consortium, extracting DNA from transformed cells, storing DNA and (in some cases) shipping to other locations for analyses (including HLA genotyping).

Current plan for North America includes samples from clinical centers affiliated with the North American Regional Network.

Expected Numbers of Samples from Affected Sib-Pairs: 1,100 families with an average of 5/family: 5,500 samples transformed over 3 years. DNA to be extracted from a maximum 5,500 EDTA cell packs.

Shipments

What are the expected times for transport from distant sites (e.g., Canada)?
Shipments completed to date (specific issues to be discussed, if necessary).

9:00 Method for Transformation of Peripheral Blood Mononuclear Cells
Method used in Seattle – Overview
Proposed Workflow – Overview
Cost structures for several services: transforming cells, storing transformed cells, extracting DNA, storing DNA and shipping DNA or transformed cells to other locations (repositories or investigators)
Use of fetal calf serum (supplied from the USA)
Capacity to complete transformations with other current and future obligations

10:30 Tour of the Cell Transformation Facility, including Receiving Area

11:30 Discussions among all participants

Agenda for the Site Visit to the Autoantibody and Storage Laboratory for North American Network (Dr. George Eisenbarth, Principal Investigator): May 20, 2004

Visitors: Beena Akolkar, PhD, NIDDK
Joan Hilner, MPH, MA, RD, Wake Forest University
Michael Steffes, MD, PhD, University of Minnesota

Local Participants: George Eisenbarth, MD, PhD and Liping Yu, MD

8:00 Introductions

8:05 Review the Agenda

8:10 Review Plan of the Consortium – Measurements of Islet Antibodies
Three laboratories in Europe, Australia and North America will be measuring antibodies to GAD and IA-2_{ic}. Current plan for North America includes samples from clinical centers affiliated with the North American Network. Expected numbers of samples from affected individuals (type 1 diabetes) to be analyzed for the Consortium: a minimum of 2,200 samples (1,100 families with 2 members on average expected from each family).

Shipments
Well established protocols from shipping samples from the clinics.
Costs of shipping containers back to the clinics.

8:30 Methods for Measuring Islet Antibodies
Methods proposed in Denver – Overview, similarities of the revised method to methods in Bristol and Melbourne. Please present (preferably in tabular form) the similarities and differences between the method in Denver and those in Bristol and Melbourne. Review the radioactive labels used in each assay. Demonstrate that using double label assays in Denver will yield identical assays among the three laboratories. Do you calculate values for the unknowns using a single calibrator -- thereby calculating a ratio for each unknown, which can then be used to infer WHO units? If so, please document how similarly this assay produces results similar to those from the standard curves (with several points on a curve) used in Bristol and Melbourne.

10:00 Review results from the DASP surveys -- Please present the results with the assay which produces results closest to those in Bristol and Melbourne.
Overview of proposed workflow
Cost structures for shipping samples to other locations.

11:00 Tour of the Laboratory, including Receiving Area

11:30 Review of T1DGC Specimen Tracking System (Liping Yu and Dustin Williams)

Agenda for the Site Visit to the HLA Genotyping Laboratory for the Asia-Pacific Regional Network (Dr. Brian Tait, Principal Investigator), March 11, 2004

Visitors: Joan Hilner, MPH, MA, RD, Wake Forest University
Michael Steffes, MD, PhD, University of Minnesota

Local Participants: Brian Tait, Mike Varney, Anthony Louey, others as deemed appropriate

13:30 Introductions

13:35 Review the Agenda

13:40 Review Plan of the Consortium – Isolation of DNA and Completion of HLA Typing

Several laboratories throughout the world will complete HLA genotyping using kits from Roche Molecular Systems in Alameda, CA (i.e., everyone will be using the same method). The DNA extracted from collected blood or transformed cells will be analyzed in an identical manner using 96-well plates with consistent reporting protocols to the Coordinating Center at Wake Forest University. To provide DNA promptly, the Melbourne HLA Genotyping Laboratory will be extracting and utilizing DNA from EDTA-anti-coagulated blood (frozen cell pack).

Expected Numbers of Samples in the Asia-Pacific Regional Network: 200 affected sib-pair families with an average of 5/family plus up to 2,160 trios with 3/family over 2 year data collection period; 7,480 samples forwarded to the HLA Genotyping Laboratory in Melbourne, Australia

14:00 Tour of HLA Genotyping Facility, including Storage Area

14:30 Methods and resources
Method used currently in Melbourne – Overview
Specific items for discussion include the following:
- Methods used and volume of samples genotyped in past three years
- Experience of personnel in using various methods for HLA genotyping
- Participation in HLA workshops and verification of results by third-party laboratories
- Success in using DNA provided by other laboratories for HLA genotyping or for other techniques or procedures
- Systems used to receive and track the inventory of samples
- Turnaround time to complete HLA analyses
- Experience with SCORE to interpret results and determine HLA genotypes
- Procedures utilized to report results to other entities, including coordinating centers for clinical studies or trials

Specific items for discussion include the following (cont.):
- Progress of certification studies to demonstrate proficiency of the

laboratory in the methods of the Consortium
Facilities available for the method of the Consortium

16:00 Progress and preparation for assaying samples sent in the first quarter of 2004
Demonstration that the laboratory has the facilities and trained personnel to complete the assays in a timely manner.
Summary of the experience of the laboratory to complete similar work in an efficient manner from receipt of samples to reporting results to the Coordinating Center.

16:30 Adjourn

APPENDIX C

SITE VISIT CHECK SHEETS

- **Blood Collection**
- **Blood Handling, Storage and Shipping**
- **Interviewing**

T1DGC

BLOOD COLLECTION CHECK SHEET

CLINIC ID _____ DATE _____

OBSERVER(S) _____ TECHNICIAN ID_____

		S	U
A.	**Equipment, environment**		
1.	Isolated room, professional environment.	☐	☐
2.	Equipment, forms, supplies adequate (needles, vacutainers, bandaids, alcohol swabs, gauze, tourniquet, ice bath, ammonia, inhalants, butterfly needles, butterfly adapter, syringes).	☐	☐
B.	**Procedure**		
1.	Label checked.	☐	☐
2.	Participant prepared, procedure explained.	☐	☐
3.	Bleeding disorders queried and recorded.	☐	☐
4.	Needle, adapter, vacutainer prepared.	☐	☐
5.	Tourniquet applied properly.	☐	☐
6.	Vein palpated, cleansed, and dried.	☐	☐
7.	Venipuncture technique.	☐	☐
8.	Tubes filled in proper order and inverted.	☐	☐

		S	U
9.	Tourniquet released as soon as flow starts in last tube.	☐	☐
10.	Total tourniquet time within 2 minute limit.	☐	☐
11.	Vacutainers filled.	☐	☐
12.	Stasis obtained.	☐	☐
13.	Needle disposed properly.	☐	☐
14.	Tubes labeled properly.	☐	☐
15.	Form completed accurately.	☐	☐
16.	Other	☐	☐

COMMENTS:

S = Satisfactory
U = Unsatisfactory

T1DGC

BLOOD HANDLING, STORAGE, SHIPPING

CHECK SHEET

CLINIC ID _____ DATE _____

OBSERVER(S) _____ TECHNICIAN ID_____

		S	U
A.	**Equipment**		
1.	Equipment, supplies adequate.	☐	☐
2.	Equipment working correctly, centrifuge at 4°C.	☐	☐
3.	Daily record of freezer temperature up-to-date.	☐	☐
4.	Biohazard labels available.	☐	☐
5.	Other	☐	☐
B.	**Procedure**		
1.	Tubes labeled accurately.	☐	☐
2.	Tubes:		
	Red top tube to rack at room temperature 30-60 minutes.	☐	☐
	Purple top tube to ice water 30-60 minutes.	☐	☐
	Green/yellow top tube(s) at room temperature until shipped (daily).	☐	☐
3.	Centrifuge balanced.	☐	☐

		S	U
4.	Centrifuge operation.	☐	☐
5.	Aliquoting equipment ready, vials labeled and organized, biohazard labels available.	☐	☐
6.	Proper specimen volumes in respective vials.	☐	☐
7.	Vial filling priority observed.	☐	☐
8.	Sealing of vials.	☐	☐
9.	Cell pack in purple top tube saved for shipment with green top tube; purple top tube re-labeled, if needed	☐	☐
10.	Completion of blood collection form.	☐	☐
11.	Freezer organization and storage.	☐	☐
12.	Time constraints observed throughout procedure (90 minute maximum from drawing to freezing).	☐	☐
13.	Disposal of red top tubes and contaminated equipment.	☐	☐
14.	Other	☐	☐

C. Shipping

1.	Knowledge of shipping schedule for the laboratory.	☐	☐

		S	U
2.	Dry ice available.	☐	☐
3.	Shipping supplies adequate (for daily ambient and monthly frozen shipments).	☐	☐
4.	Specimens for labs packed properly (for daily ambient and monthly frozen shipments); adherence to IATA regulations.	☐	☐
5.	Serum and plasma specimens remain frozen while being packed.	☐	☐
6.	Shipping forms complete properly.	☐	☐
7.	Other	☐	☐

COMMENTS:

S = Satisfactory
U = Unsatisfactory

T1DGC
INTERVIEWING
CHECK SHEET

CLINIC ID _____ DATE _____

OBSERVER(S) _____ INTERVIEWER ID _____

	RATING Circle one: 1 = Yes (satisfactory) 2 = No (unsatisfactory)		**COMMENTS Continue on reverse if necessary**
I. Communication Skills			
Maintained:			
A. Adequate eye contact with participant	1	2	_____
B. Neutral attitude	1	2	_____
C. Non-judgmental voice tone and manner	1	2	_____
D. Good rapport with participant	1	2	_____
E. Professional, confident, competent manner	1	2	_____
II. Interviewing Techniques			
A. Good pacing and tempo; maintained pace while allowing the participant time to answer	1	2	_____
B. Probes			
1. Appropriate use of repetition and neutral probes	1	2	_____
2. Appropriate verification of responses	1	2	_____
C. Phrasing and pronunciation			
1. Clear, easily understood phrasing of sentences	1	2	_____
2. Proper pronunciation of medical terminology	1	2	_____

T1DGC
INTERVIEWING
CHECK SHEET

CLINIC ID _____ DATE _____

OBSERVER(S) _____ INTERVIEWER ID _____

	RATING Circle one: 1 = Yes (satisfactory) 2 = No (unsatisfactory)		**COMMENTS Continue on reverse if necessary**
III. Interviewing Procedures			
A. Recorded responses correctly	1	2	_____
B. Made notations in margin as appropriate	1	2	_____
C. Skip patterns followed correctly	1	2	_____
D. Other interviewer instructions followed correctly:			
1. Interviewer instructions not read aloud	1	2	_____
2. Response categories read correctly, where appropriate	1	2	_____
3. Cue cards used appropriately	1	2	_____
4. When two alternate phrasings are given, appropriate one chosen	1	2	_____

APPENDIX D

DUPLICATE BLOOD COLLECTION SAMPLING SCHEME AND CONTENTS OF BLOOD COLLECTION QUALITY CONTROL LABEL SETS

Duplicate Blood Collection Sampling Scheme

Quality Control – Red (Serum):
Age-or Size-Eligible Affected Participants

Total QC-Red collected

Pilot Study

NO QC-Red sample collected → 0 QC-Red samples for pilot study

Study Families

Affected participants from first two collections will have a QC-Red sample collected; participants should not be in the same family → 2 QC-Red samples on study participants

↓

After first 2 QC-Red samples collected, every 10th affected participant will have a QC-Red sample collected → 7 QC-Red samples on study participants

↓

After a **total** of 7 QC-Red samples have been collected, every 20th affected participant will have a QC-Red sample collected → Until study is complete

Quality Control – Purple (Plasma and Cell Pack):
Age-or Size-Eligible Participants

Total QC-Purple collected

Pilot Study

QC-Purple sample collected on one participant during pilot study → 1 QC-Purple sample for pilot study

Study Families

First 2 collections will have a QC-Purple sample collected from each; participants should not be in the same family → 2 QC-Purple samples on study participants

↓

After first 2 QC-Purple samples collected, every 10th participant will have a QC-Purple sample collected → 7 QC-Purple samples on study participants

↓

After a **total** of 7 QC-Purple samples have been collected, every 20th participant will have a QC-Purple sample collected → Until study is complete

Note: All QC participants must be age- or size-eligible.

CONTENTS OF BLOOD COLLECTION QUALITY CONTROL LABEL SETS

ASP AND TRIO FAMILIES

QC-Red (Proband/Affected Sibling ONLY)

Large ID Labels
3 for proband (purple–striped)
3 for affected sibling (green–striped)
(1 label for blood tube, 1 for blood collection form and 1 for shipping form)

Small ID Labels
6 for proband (purple-striped)
6 for affected (green-striped)
(1 label for autoantibodies, 4 for storage and 1 for top of storage box)

QC-Purple (Any family member)

Large ID Labels
6 for every family member
(2 labels for blood tube, 1 for blood collection form and 2 for shipping forms)

Small ID Labels
5 for every family member
(4 for storage and 1 for top of storage box)

CASE-CONTROL STUDY

QC-Red (Case ONLY)

Large ID Labels
3 for case (orange–striped)
(1 label for blood tube, 1 for blood collection form and 1 for shipping form)

Small ID Labels
6 for case (orange-striped)
(1 label for autoantibodies, 4 for storage and 1 for top of storage box)

QC-Purple (Control ONLY)

Large ID Labels
6 for control (gray–striped)
(2 labels for blood tube, 1 for blood collection form and 2 for shipping forms)

Small ID Labels
5 for control (gray–striped)
(4 for storage and 1 for top of storage box)

ADVERSE EVENT REPORTING

TABLE OF CONTENTS

I. PURPOSE

This chapter provides the clinics and networks with information regarding study policy on adverse event reporting. It is expected that few, if any, adverse events related to the study protocol will occur throughout the exam period. However, if such an event occurs, the following guidelines will assist the clinics in proper handling and reporting of the incident.

II. ADVERSE EVENTS

An adverse event is defined as both an expected side effect that is of a serious nature or an unexpected side effect/event regardless of severity. In the case of the Type 1 Diabetes Genetics Consortium (T1DGC), the expected risks associated with the study are related to the blood collection. Inserting a needle for blood sampling can be associated with some discomfort and bruising and, although very rarely, with inflammation and infection of the arm veins. These risks are considered to be minimal and are addressed in the protocol and the informed consent forms.

Pre-specified adverse events that must be reported include: excessive bleeding at the phlebotomy site; excessive bruising at the phlebotomy site; infection attributed to the phlebotomy; and thrombophlebitis attributed to the phlebotomy

There may be other adverse events associated with the clinic visit (*e.g.*, falling or other injury) that also should be reported if they meet the definition provided above. An incident that occurs prior to, during, or after the blood collection that is considered a "normal" occurrence of such a procedure (*e.g.,* fainting, nausea, etc.) is not documented as an adverse event and the form need not be completed.

III. ADVERSE EVENT GRADING

All adverse events that occur are graded both by attribution and severity of the incident. Attribution of the event is graded by its relation to the study protocol and is designated as one of the following: (1) unrelated to the protocol; (2) possibly related to

the protocol; (3) probably related to the protocol; or (4) definitely related to the protocol. Any event that is reported to either the Principal Investigator or his/her designated research staff by the participant or medical staff caring for the participant is evaluated and graded by the Principal Investigator and/or research staff according to one of these categories. Once relation to the protocol is determined, it is documented as such on the *T1DGC Adverse Event Report* that is completed at the clinic.

Adverse events are also graded based on the severity of the event. They are graded as being (1) mild; (2) moderate; or (3) severe. The following descriptions are used to determine the severity of the adverse event:

- Mild: The symptom or event did not require treatment.
- Moderate: The symptom or event resolved with treatment.
- Severe: The symptom or event resulted in the inability to carry on normal activities and required professional medical attention.

IV. ADVERSE EVENT REPORTING

Regardless of the severity, all adverse events reported to the clinic staff or Principal Investigator are documented, and the *T1DGC Adverse Event Report* is completed and submitted to the clinic's Internal Review Board (IRB) and/or Ethics Committee (EC), the Regional Network Center and the Coordinating Center. The report includes a description of the event, when and how it was reported, as well as any official chart records or documentation to corroborate the event or the reporting of the event. Clinics must know and follow the adverse event reporting policies of the local IRB or EC. (The *T1DGC Adverse Event Report* is located on the web site. Instructions for completing the report are located in Appendix A of this chapter.)

Any severe and/or unanticipated adverse event should immediately be reported to the safety officers and IRB or EC at the local clinic, the Regional Network Center and the Coordinating Center. All other adverse events are reported in a timely fashion to the safety officers and IRB or EC (*i.e.*, within 2 weeks of the date of the event). All adverse

events are summarized annually and submitted to the IRB or EC at the local clinic, Regional Network Center and Coordinating Center.

The Coordinating Center reports any action resulting in temporary or permanent suspension of this study (*e.g.*, IRB or EC actions or actions by the investigators or co-investigators) to the NIDDK Project Officer.

APPENDIX A
ADVERSE EVENT REPORT:
INSTRUCTIONS FOR COMPLETION

CLINIC INSTRUCTIONS:

1. Place the participant's bar-coded ID label in the box designated "Participant ID Number."

2. Record the clinic ID and the clinic staff ID number in the designated boxes.

3. Record the date that the adverse event occurred. Date is recorded with day first, month second (month written out), and year third.

4. Record the location at which the adverse event occurred (*e.g.,* the clinic or at home).

5. Mark "Yes" if a physician was required, and in the space below, record the name of the physician who responded. Mark "No" if a physician was not required. The name of the physician is left blank if "No" is recorded.

6. Mark "Yes" if the participant was able to continue with the study interview/exam after the adverse event. Mark "No" if the adverse event prevented the participant from continuing the exam.

7. In the space provided for "Summary and Outcome of Adverse Event", describe the adverse event in a clear and concise manner. Provide specific details (*e.g.*, where, when, why, etc.) as well as the outcome of the event. Related documentation may be included if necessary.

8. Determine relation of the adverse event to the study protocol (*i.e.,* unrelated, possibly related, probably related, and definitely related) and mark the appropriate box.

9. Grade the severity of the adverse event as mild, moderate or severe, according to the descriptions listed below (from this chapter), and mark the appropriate box.

- Mild: The symptom or event did not require treatment.
- Moderate: The symptom or event resolved with treatment.
- Severe: The symptom or event resulted in the inability to carry on normal activities and required professional medical attention.

10. Make a copy of the completed form and send to the Regional Network Center for review.

REGIONAL NETWORK INSTRUCTIONS:

11. The Regional Network Center records the date when the report is received under the section "For Regional Network Center Use".

12. The Regional Network Center reviews and signs the report, records the date it is sent to the Coordinating Center and forwards a copy of the report to the Coordinating Center for final review.

COORDINATING CENTER INSTRUCTIONS:

13. The Coordinating Center records the date on the form when the report is received under the section "For Coordinating Center Use". The form is reviewed and signed. "Yes" is marked if an action is required and "No" if no action is required. If "Yes" is marked, a summary of the action taken is recorded.

14. The Coordinating Center keeps a copy and returns the completed form to the Regional Network Center, who retains a copy of the completed form and forwards the original back to the clinic.

REGIONAL NETWORK CENTER RESPONSIBILITIES
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I. PURPOSE

This chapter is designed for use by the Regional Network Centers. While the *Type 1 Diabetes Genetic Consortium* (*T1DGC) Manual of Operations* (MOO) is written for the clinics and the Regional Network Centers, this chapter outlines the specific responsibilities of the staff at the Regional Network Center. These include: (1) overseeing the operations of the clinics on a day-to-day basis; (2) assisting clinics with regulatory issues and T1DGC requirements and supplying necessary documentation to the Coordinating Center; (3) ensuring that family recruitment and subsequent data collection are occurring at the clinics; (4) supporting the clinics throughout the exam period; and (5) entering and transmitting data to the Coordinating Center.

Problems and questions that arise that cannot be resolved at the clinic level are brought to the attention of the Regional Network Center. Likewise, the Regional Network Center will request assistance from the Coordinating Center for unresolved issues.

II. RECRUITMENT

A. Recruitment Goals

Each Network has a recruitment goal as outlined in **Chapter III**, *Recruitment.* The Regional Network Center is responsible for aiding the clinics in their efforts to reach the overall T1DGC goal of 2,800 affected sib-pair (ASP) families; 1,600 trio families; 2,050 cases; and 2,050 controls.

In each network, there are gender-specific goals (as well as race- and ethnic-specific goals in the North American Network) that must be met and reported to the National Institutes of Health (NIH) on a quarterly basis. Real-time recruitment reports are provided on the T1DGC web site to aid in recruitment monitoring and for quarterly reporting to the NIH. Participants are not counted as completed in recruitment reports until all necessary exam forms have been data entered and cell line samples have been received and data entered at the Network DNA Repository.

The Regional Network is responsible for working with each network clinic to set an overall recruitment goal, as well goals for specific time periods. The Regional Network Center monitors the number of recruited participants in each individual clinic. If particular clinics are having difficulty in recruiting participants or meeting their goal, it may be necessary for staff from the Regional Network Center to site visit the particular clinic in order to assess the problem, and develop reasonable solutions or provide suggestions for recruitment.

B. Recruitment Materials

The Regional Network Center is responsible for suggesting recruitment strategies and materials to their clinics (*e.g.*, flyers, brochures, and/or referrals from physicians). Templates for a recruitment brochure and flyer are available on the T1DGC web site and in the appendices of **Chapter III**, *Recruitment*. These may be used by the clinics with appropriate site-specific information inserted. The clinics must submit all recruitment materials to their local Institutional Review Board (IRB) or Ethics Committee for approval. The Regional Network Center may require submission of proof of approval.

III. ELIGIBILITY

The Regional Network Center answers any questions from the clinics about a family's/participant's eligibility status. In ASP families, both the proband **and** the affected sibling must be eligible and participate in order for a family to be included in the study. For trios, the proband must be eligible and participate **and** both biological parents must be available and participate in order for a family to be included. In the Case/Control study, only individuals will participate.

An Eligibility Committee has been established for affected participants that do not meet all of the study criteria (diagnosis before 35 years old, insulin use within 6 months of diagnosis without stopping for 6 months or more), but have other evidence of Type 1 diabetes. The clinic confirms the evidence, completes the appropriate *T1DGC Application to Eligibility Committee* and forwards it to the Regional Network Center. The

staff at the Regional Network Center completes their designated portion of the form and forwards it to the Coordinating Center. Staff at the Coordinating Center will communicate with the Eligibility Committee to determine if the participant can be recruited for the T1DGC. Once a decision is made, the Coordinating Center informs the Regional Network Center, who informs the clinic of the decision. See **Chapter IV**, *Eligibility,* for more information on the Eligibility Committee. The application is data entered at the Coordinating Center.

Up to three additional affected siblings may participate in an ASP family. However, a *T1DGC ASP Application for Additional Affected Sibling* must be completed for approval of inclusion for each additional sibling. This form is completed at the clinic and forwarded to the Regional Network Center. Staff at the Regional Network Center is responsible for approving inclusion of each sibling. Upon approval, the Coordinating Center is notified and labels for each additional affected sibling are generated and sent to the Regional Network Center. (Alternatively, the Regional Network Center may supply each clinic with a number of label sets for families with additional affected siblings in order to decrease the amount of time between application approval and receipt of label set(s).) The application is sent with the entire family form set to the Regional Network Center for data entry.

IV. DATA COLLECTION AND ENTRY

The Regional Network Center is responsible for monitoring the accuracy and completeness of data collected at clinical sites. They are also responsible for data entry of the forms collected from the clinics.

A. Label Sets

Label sets are sent from the Coordinating Center to the Regional Network Centers for distribution to the clinics. Label sets are scanned at the Coordinating Center prior to dispersing to the Regional Network Centers. Likewise, when the Regional Network Center receives the label sets they are scanned prior to shipment to the clinics. See **Chapter XI**, *Data Entry System*, for detailed instructions on scanning

label sets received from the Coordinating Center. Regional Network Centers must notify the Coordinating Center at least two weeks in advance when additional label sets are needed. Network staff should e-mail the appropriate project manager and Teresa Harnish (tharnish@wfubmc.edu) when label sets and/or additional labels for specific participants are needed.

B. Data Form Review and Entry

As families are recruited and examined, the Regional Network Center receives completed form sets from the clinics for data entry. It is the responsibility of the Regional Network Center to review the forms as they arrive; to check for discrepancies and/or missing data fields; and to ensure that form sets are complete and meet the minimal acceptable standards (*i.e.,* proband and affected sibling prior to data entry for ASP families).

In affected sib-pair families, forms sets for **at least** the proband and affected sibling must be completed prior to data entry. In trio families, form sets for the affected child and both biological parents must be completed prior to data entry. Without the following forms on these essential family members who meet eligibility criteria, data cannot be entered and clinics will not be reimbursed: (1) *T1DGC Consent Summary Form; (2)* Layered Portion of the *Informed Consent* (one for each); *(3) T1DGC Eligibility Form*; (4) *T1DGC Exam Form* (one for each); and (5) *T1DGC Blood Collection Form* (one for each). For the case, the forms required for the individual include: (1) Layered Portion of the *Informed* Consent; (2) *T1DGC Eligibility Form* (for Case or Control); (3) *T1DGC Case Exam Form*; (4) *T1DGC Blood Collection Form*. For the control, the forms required for the individual include: (1) Layered Portion of the *Informed* Consent; (2) *T1DGC Eligibility Form* (for Case or Control); and (3) *T1DGC Blood Collection Form*.

The Regional Network Center staff is responsible for contacting clinics to resolve errors or discrepancies and/or missing data fields. A *Data Editing Log* was developed and is available on the web site to aid the Regional Network Center staff in tracking these errors.

C. T1DGC Reports and Query System

The Coordinating Center has created numerous dynamic reports available on the T1DGC Data Entry web site for use by the Regional Network Centers in order to assist in determining the status of a particular family (or family member) and to identify any irregularities that must be corrected. The Regional Network Center and Coordinating Center monitors these reports closely in order to identify and resolve problem areas with a particular network or clinic as quickly as possible.

The T1DGC Query System was created as a dynamic system listing all edits that need to be resolved. The Query System allows the user to sort by network, country, clinic, and family ID. Queries that are not data entry errors originating at the Regional Network Center **must** be sent to the clinic for verification or editing. See **Chapter XI**, *Data Entry System*, for detailed instructions on the T1DGC Query System.

D. Data Entry of *T1DGC Shipping Forms*

In addition to tracking errors on the forms sent from the clinic, Regional Network Center staff is responsible for reviewing and tracking errors on shipping forms that are data entered by laboratory staff. The Regional Network Center receives two copies of each T1DGC Shipping Form. The first copy, sent by the clinic, is a copy of the shipping form that the clinic sent to the laboratory (without receipt of sample included); the second copy, sent by the laboratory, is the completed **original** (with receipt of sample included). The Regional Network is responsible for ensuring receipt of both copies of the form and complete and accurate entry of the form. The Regional Network Center contacts the clinic and/or the laboratory regarding missing forms, data entry errors, or discrepancies in the number of samples sent and received.

E. Requests from Contributing Investigators

The Regional Network Center is responsible for receiving requests from Contributing Investigators for quarterly data freeze data and/or samples and genotyping data sets. The Network Center submits these requests to the Coordinating Center via the data entry website. The Regional Network Center is responsible for reviewing the

requests and ensuring that they are completed correctly and entered in a timely fashion. Requests for samples must be received between either January-February or July-August. See **Chapter XI**, *Data Entry System*, for detailed instructions on submitting requests from Contributing Investigators.

V. REGULATORY ISSUES

A. Informed Consent Forms

The Regional Network Center is responsible for ensuring that the clinics are compliant with all regulatory issues related to data collection for the T1DGC. It is understood that the clinics will follow the regulations set forth by their respective Internal Review Board (IRB) or Ethics Committee (EC), but a current signed *Informed Consent* approved by the local IRB or EC is required by the T1DGC for each participant. In addition, for sites within the United States, the T1DGC requires a signed *Written Authorization* to use and disclose protected health information conforming to United States privacy law (HIPAA regulations), or a combined informed consent/written authorization document on each participant.

All T1DGC informed consent forms are sent to the NIDDK Central Repositories and CIDR for review, prior to the laboratories shipping samples to these locations. Staff at the Regional Network Center and Coordinating Center also will review each clinic's informed consent forms in order to determine that collections are in agreement with the goals of the T1DGC. Any requests for changes to the *Informed Consent* made by the NIDDK Central Repositories, CIDR, the Coordinating Center and/or the Regional Network Center **must** be implemented, and if necessary, participants will be re-consented to permit distribution of samples. In order to minimize the number of clinics who have to modify their informed consent forms, it is strongly suggested that the clinics forward their forms to the Regional Network Center so review of the documents can be completed prior to starting recruitment.

The clinic staff is responsible for sending a copy of the layered portion of the informed consent (with signature covered by a participant ID label) to the Regional

Network Center for data entry. Staff at each clinic maintains the **original** signed informed consent forms, written authorizations (as required in the United States) and **original** copies of data forms.

For ASP and trio families, the Regional Network Center also must recognize that data entry of forms for a particular family cannot be initiated without an appropriately completed *T1DGC Consent Summary Form*. Additionally, for clinics within the United States, the written authorization to use and disclose protected health information must be signed if it is not part of the informed consent document. The clinics can send the *T1DGC ASP Consent Summary Form* when the proband and the affected sibling are consented. For trios, the *T1DGC Trio Consent Summary Form* must be fully complete.

B. Ethics Committee and Internal Review Board Approval Letters

In addition to informed consent forms, the Regional Network Center and Coordinating Center must have a **current** copy of each clinic's EC or IRB approval letter. The Regional Network Center and Coordinating Center also must have on file the date the EC or IRB approval was received and the date the EC or IRB approval will expire. This information will be forwarded on to the NIDDK Central Repositories and CIDR by the Coordinating Center. The Coordinating Center and Regional Network Center are responsible for monitoring each clinic's EC or IRB expiration date and obtaining a new letter of approval before the current one has expired.

C. Office for Human Research Protections (OHRP) and Federalwide Assurances (FWA)

Each T1DGC clinic must register their IRB and receive a FWA number from OHRP in order to verify compliance with the Department of Health and Human Services (DHHS) regulations for the protection of human subjects. The Regional Network Center and Coordinating Center are responsible for assisting clinics obtain this approval by either: (1) determining if the clinic's IRB is already registered and the institution has a FWA number; (2) helping the clinic to register their IRB and receive a FWA number; or (3) helping the clinic locate another institution and sign an Unaffiliated Investigator Agreement stating that the institution with the approved IRB and FWA number is

responsible for the clinic without a FWA number. Each clinic's FWA number is kept on file at the Regional Network Center and the Coordinating Center.

VI. CLINIC OPERATIONS

A. Training and Certification

The Regional Network Center staff is responsible for attending the training sessions conducted by the Coordinating Center staff. During this training, all aspects of the T1DGC study (*e.g.,* recruitment strategies, eligibility criteria, exam form administration, blood collection and shipping, and data entry) are reviewed and discussed.

The Regional Network Centers then are responsible for training the staff at each clinic. Training models are network-specific; training may be completed at a Regional Network Center centralized training session or members of the Regional Network Center may visit each site to train clinic staff. Training should include review of data collection schema, recruitment goals and strategies, eligibility requirements, interviewing instructions and practice, blood collection and processing, sample storage and processing, quality control and a review of the T1DGC forms. Clinic IDs and staff ID numbers, assigned by the Regional Network Center, are provided to all clinic staff and are kept on file at the Regional Network Center and the Coordinating Center.

The Regional Network Centers and the Coordinating Center are responsible for certifying readiness of clinic staff to initiate T1DGC data collection. Certification consists of successful completion of a pilot study, including data forms, blood collection (including a quality control sample for plasma) and laboratory shipments. The pilot study is intended to assess the readiness of the clinic to begin data collection for the T1DGC; as such, poor performance during the pilot signals a need to re-train prior to initiating data collection. However, recruitment of T1DGC participants cannot commence until the Regional Network Center and Coordinating Center have the following documentation: (1) FWA Number; (2) EC/IRB Approval Letter; (3) EC/IRB

Approval Date (if not apparent from the letter); (4) EC/IRB Expiration Date (if not apparent from the letter); and (5) Blank Copies of the Informed Consent Forms.

Training of new clinic staff should be performed by existing clinic staff with varying degrees of consultation with the Regional Network Center, if desired or needed. Staff turnover at the Regional Network Center will also require training and certification of new personnel by other staff members at the Regional Network Center.

B. Manual of Operations and Forms

Staff at the Regional Network Center must be proficient in the use of the *T1DGC Manual of Operations* (*MOO*) and the data forms. Regional Network Centers are notified by the Coordinating Center when updates to the *T1DGC MOO* and/or data forms are made. The *T1DGC MOO* is web-based, and each Regional Network Center must have a printed copy of the most updated version of the manual at their site. Additionally, it is the Regional Network Center's responsibility to ensure that the clinics are using and referring to the most updated version of the *T1DGC MOO* and data forms. For sites without Internet access, the Regional Network Center distributes printed copies of the *MOO* and data forms and sends copies to the clinics. For sites with Internet access, the Regional Network Center notifies the clinics of such changes via phone call or e-mail and requests that the clinics print the updated chapters.

C. Reimbursement for Completed Examinations

Regional Network Centers invoice the Coordinating Center on a monthly basis. Only examined families with all required data on the proband **and** the affected sibling (or, in trios, the affected child **and** both biological parents) are eligible for reimbursement. Required data includes: *T1DGC Consent Summary Form,* Layered Portion of *Informed Consent* (for all required family members)*, T1DGC Eligibility Form, T1DGC Exam Form* (for required family members), *T1DGC Blood Collection Form* (for required family members) and cell line samples on participating family members. In the Case/Control study, examined individuals with all required data are eligible for reimbursement. For the case, required data includes: Layered Portion of *Informed*

Consent, T1DGC Eligibility Form, *T1DGC Case Exam Form*, *T1DGC Blood Collection Form* and a cell line sample. For the control, required data includes: Layered Portion of *Informed Consent, T1DGC Eligibility Form, T1DGC Blood Collection Form* and a cell line sample.

On a monthly basis, the Coordinating Center will supply the Regional Network Centers with a list of all participants who the Coordinating Center confirms as eligible for reimbursement. The Regional Network Center must supply the Coordinating Center with a detailed invoice, listing the participants they believe to be eligible for reimbursement. Funds will be forwarded from the Coordinating Center to the Regional Network Center and the Regional Network Center is responsible for reimbursing each clinic in their network.

D. Contact with Coordinating Center and Clinics

Weekly conference calls are held between a Project Manager located at the Coordinating Center and the Regional Network Center Coordinator and/or other designated staff members to identify problems and resolve issues. Additionally, the Coordinating Center Project Manager is available throughout the week via phone, FAX and e-mail. Each year, the Deputy Director of the Coordinating Center and a Project Manager from the Coordinating Center will site visit each network. The Network Coordinator also is responsible for participating in monthly calls with the Deputy Directory, the Project Managers and the Network Coordinators from all networks (*i.e.,* Network Coordinators' calls).

Regional Network Centers also must be in regular contact with each clinic within their network. The frequency of this contact is established by the staff at the Regional Network Center. Contact can include phone calls and e-mail on a clinic-specific basis, newsletters, network-wide conference calls, web site notifications, and/or Network Meetings. Regional Network Center staff may need to perform site visits to specific clinics throughout the data collection period.

E. Clinic Close-Out

Regional Network Centers are responsible for assisting each of clinics within their network with close-out. The Regional Network Center Coordinators will work with each clinic to: identify all remaining families needing completion, provide regular communication regarding the status of data irregularities and reports, ensure all possible re-collections have occurred, ensure all samples have been received at the network laboratories, and determine procedures for destroying or redistributing T1DGC materials remaining at the clinic after close-out. The Regional Network Center Coordinators will update the Coordinating Center about the status of close-out activities on a regular basis via the *Clinic Close-Out Form* and frequent communications with the Project Managers. Refer to **Chapter XIV**, *Close-Out,,* for detailed information regarding adverse events.

VII. ADVERSE EVENTS

An adverse event is defined as both an expected side effect that is of a serious nature or an unexpected side effect/event regardless of severity. For the T1DGC, these incidents are anticipated to be infrequent. However, appropriate procedures must be in place if an adverse event occurs. All adverse events reported by the clinics are graded both by attribution and severity of the incident at the clinic site. Refer to **Chapter IX**, *Adverse Event Reporting,* for detailed information regarding adverse events.

The clinic staff completes the *T1DGC Adverse Event Report* and forwards it to the Regional Network Center. The Regional Network Center is responsible for reviewing the incident and signing and dating the form before forwarding to the Coordinating Center for final review. After review at the Coordinating Center, it is sent back to the Regional Network Center where a copy is retained and the Regional Network sends a copy of the form back to the clinic. Instructions for completing the form are located in Appendix A of **Chapter IX**, *Adverse Event Reporting.*

DATA ENTRY SYSTEM

TABLE OF CONTENTS

I. INTRODUCTION

The data management system used for data collection in the Type 1 Diabetes Genetics Consortium (T1DGC) utilizes a web browser-based interface, with electronic data stored and managed centrally at the Coordinating Center. This model was chosen both for its rapid, efficient collection of clinical information using the existing technology of the Internet, as well as the ease of use and familiarity with web browsers. User-friendly screens, identical to the data collection forms, have been developed using hypertext mark-up language (HTML). Participant data entered by Regional Network Center staff resides on a Microsoft Windows NT server at the Coordinating Center with *Cold Fusion* software enabling connectivity to the back-end SQL server database.

The web-based data management system can be used with any PC with a compatible browser (*e.g.*, Internet Explorer 5.5.2). There are two reasons for using Internet Explorer 5.5.2 (or higher versions) for the data entry system: (1) in some cases, the web-based forms are dynamically generated; and (2) using a non-compliant browser may hinder certain system functions.

The web-based system allows the user to interact with all phases of the research data. Family initialization, validating eligibility, and entry of each of the study forms are available in this application. Depending on security access, users may be allowed to enter and edit data as well as view reports. (Appendix A provides an overview of the data entry web site.)

II. DATABASE MANAGEMENT SYSTEM (DBMS)

A. Login

Once Internet Explorer 5.5.2 browser (or a compatible version) is invoked on the client computer, the following URL is entered:

http://www.T1DGCDataEntry.org/

The page loads and the system prompts the user to enter his/her username and password into the appropriate fields (Figure 1). The system is password-protected in order to prevent unauthorized access. Once a valid username and password combination are entered and verified, the user clicks on the **login** button below these fields and the system proceeds to the main screen. The Coordinating Center provides a username and password for each person in the study prior to the start of data collection. Username will always be the first initial of your first name and entire last name. Passwords must be a minimum of 6 characters, mixed case (upper and lower), and alphanumeric. Account passwords must be kept confidential. Username and password will always be the same as on the main T1DGC web site.

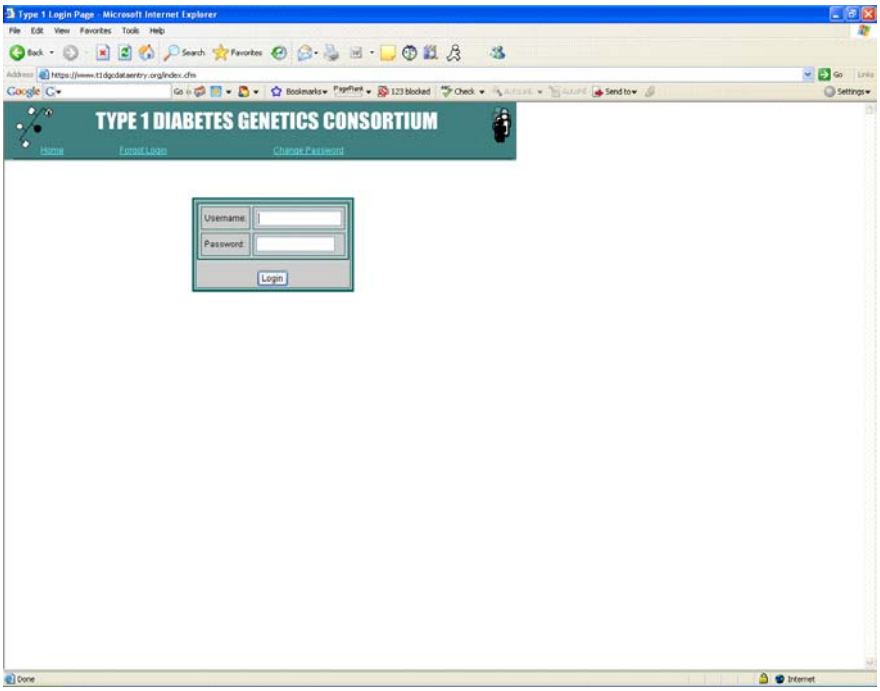


Figure 1. Login window for T1DGC data entry system.

If the user forgets his/her username or password, he/she selects the "Forgotten Login" option (Figure 2). After entering his/her e-mail address, the system e-mails the password to the documented e-mail address. To further enhance security, data encryption techniques during transmission are employed throughout the web application. If the user is unsure of the e-mail registered on the web site, the user can

select the appropriate project manager and e-mail the request. The project manager will e-mail the user the e-mail address registered to the user.

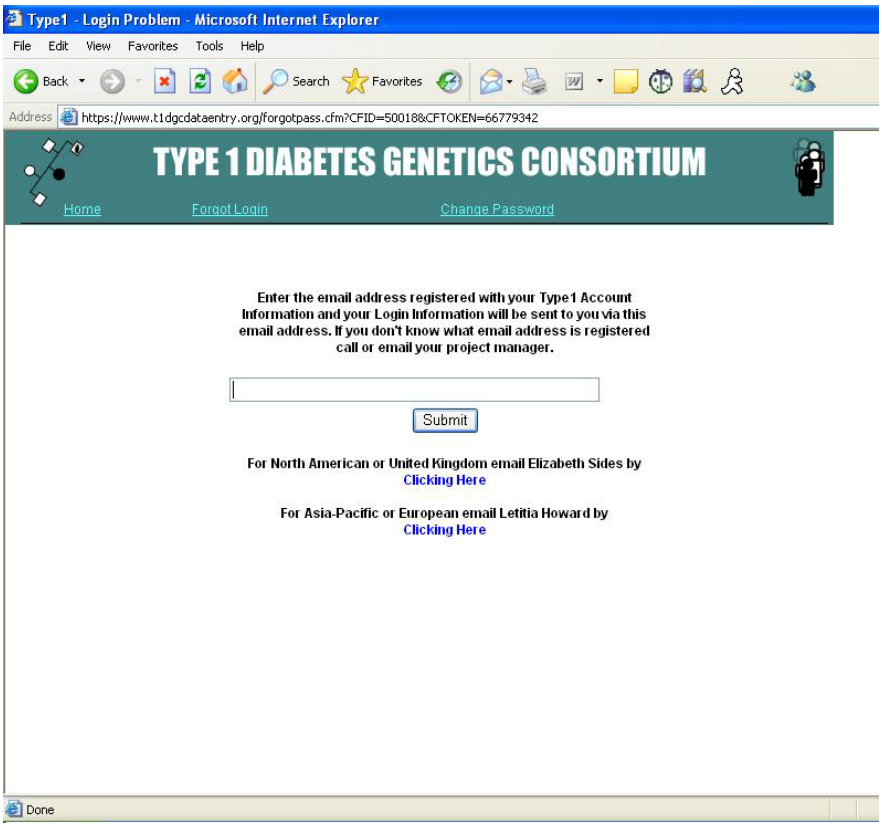


Figure 2. Forgot Login for T1DGC data entry system.

If the user unsuccessfully enters their username and password three consecutive times, the system will lock the user out of the web site. The user should contact Dustin Williams (dtwillia@wfubmc.edu) and their Network Project Manager to unlock the account.

B. Administrative Functions

Depending on the security level that was set when the account was created, a user can change his/her password, scan family ID bar-codes into the system, enter a request from a Contributing Investigator for data and/or samples, and/or enter a Contributing Investigator request for genotyping data sets.

1. Change Password

To change a password, the user chooses “Change Password” before login; or at first login, selects “Administration” from the upper navigational menu and selects “Change Password” on the list of administrative options. After selecting “Change Password,” the user is instructed to enter the username, the old password, and a new password, and to verify the new password (Figure 3). The user clicks on the **Change Password** button. Changing your password on the data entry web site will automatically change your password on the main T1DGC web site, and vice versa.

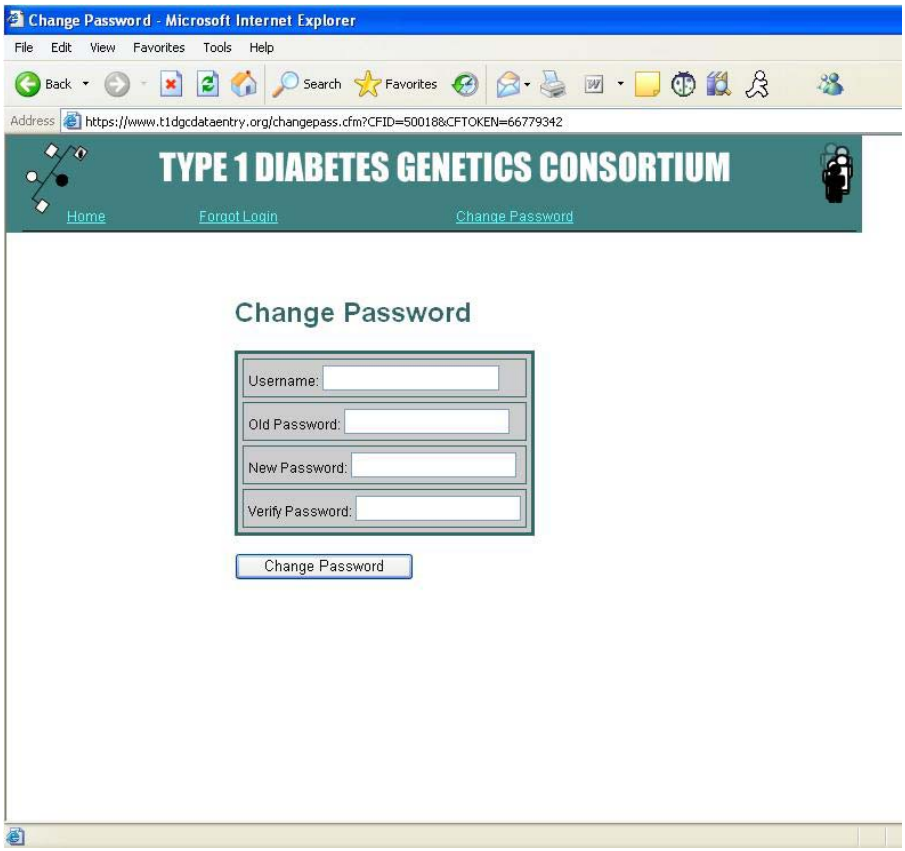


Figure 3. Changing password for login.

If username and previous password match a record in the database, the Coordinating Center changes the password of the account to the new password entered. Passwords must be a minimum of 6 characters, mixed case (upper and lower), and alphanumeric. Account passwords must be kept confidential. Do not create passwords that are based on the user’s first or last name.

2. Family ID Bar-code Maintenance

Family IDs must be scanned at the Coordinating Center and the Regional Network Center to initiate a valid range of family IDs in the data entry system. The term "scanned out" refers to family IDs scanned from the label sets generated at the Coordinating Center prior to shipping to the Regional Network Center. The term "scanned in" refers to family IDs scanned from the same label sets when they arrive at the Regional Network Center. All family ID label sets must be "scanned out" and "scanned in." QC label sets do not have to be either "scanned out" or "scanned in."

To scan family ID bar-codes into the system, the user selects "Family ID Bar-code Maintenance" from the list of administrative options. The user enters the number of family IDs to be scanned and clicks **Add**. The user then scans each family ID and clicks **Save** (Figure 4). The newly entered family IDs will appear to the right of the screen under the search options. The user will be able to view and delete records, but not edit.

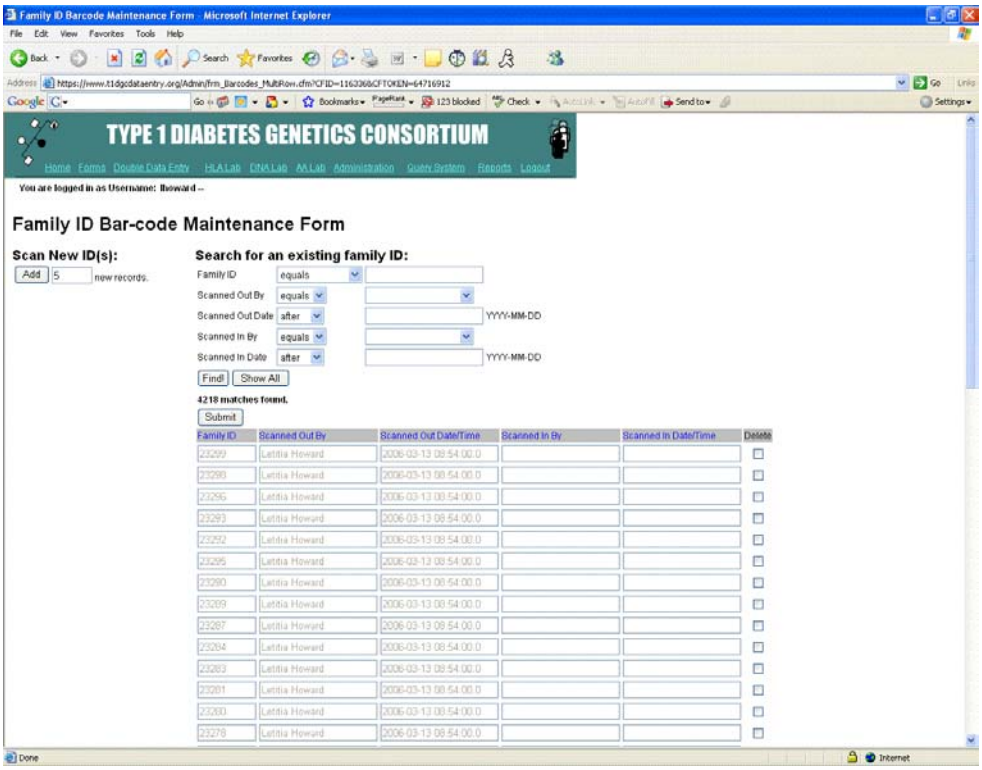


Figure 4. Family ID Bar-code Maintenance Form.

To search for an existing family ID in the system, the user enters specific search criteria and clicks **Find!**. The user can search by: family ID; who scanned out one or more family IDs (at the Coordinating Center); the date the family IDs were scanned out (at the Coordinating Center); who scanned in one or more family IDs (at the Regional Network Center); or the date the family IDs were scanned in (at the Regional Network Center).

If searching by family ID, the user enters the family ID and selects one of the following options: “equals”, “less than” or “greater than”. If searching by who scanned out the family IDs, the user selects a name from the drop down menu. If searching by date that the family IDs were scanned out, the user enters the date and selects from the following options: “equals”, “less than” or “greater than”. The same search options exist for family IDs scanned in by the Regional Network Center. The user can view all family IDs that have scanned with the specific search criteria by clicking **Show All**.

3. Contributing Investigator Request for Quarterly Freeze data and/or samples

The T1DGC study database is frozen on a quarterly basis (January 1, April 1, July 1 and October 1). A Contributing Investigator may request the most recent data set at any time. Samples must be requested in either January –February or July-August. All requests for samples and/or data from a Contributing Investigator must be submitted to the investigator’s respective Regional Network Center. Investigators requesting information should complete the *T1DGC Contributing Investigator Request for Quarterly Data and Samples Form* and submit the form to the Regional Network Center (via FAX or as an e-mail attachment.

The Regional Network Center submits this request to the Coordinating Center by selecting “Administration” from the upper navigational menu on the T1DGC data entry web site and selecting “Request for Data and/or Samples.” The user is directed to the Contributing Investigator Request for Data and/or Samples page (Figure 5). The user selects whether this is a new request. If the request is not new, the original Request ID (assigned by the system) is entered.

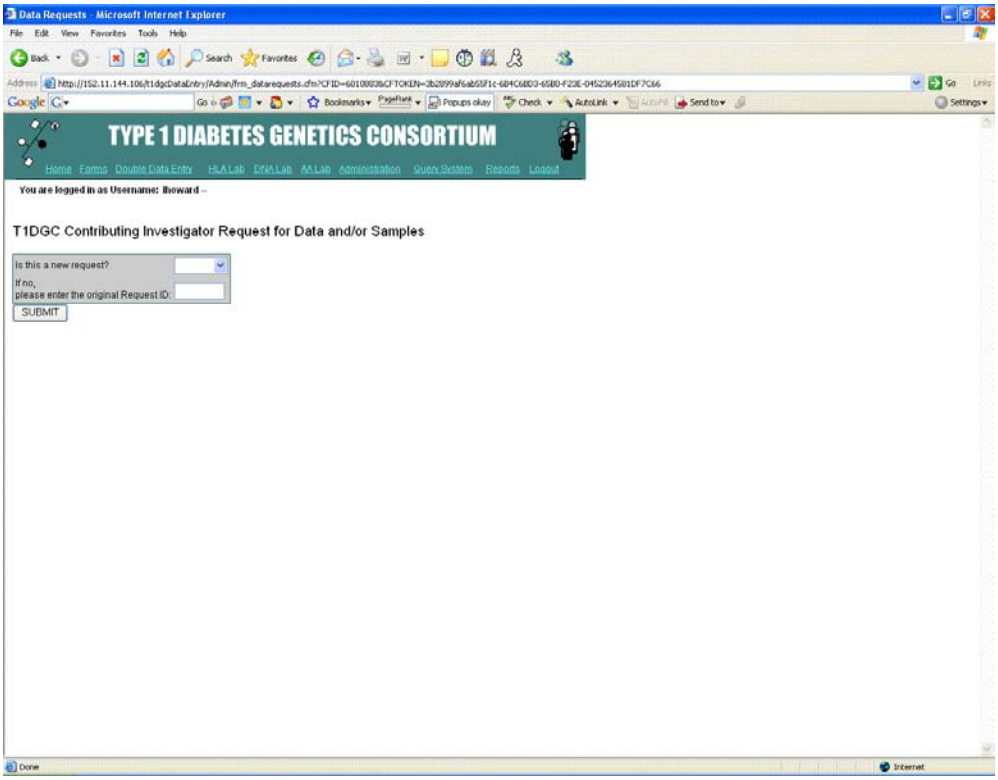


Figure 5. Contributing Investigator Request for Quarterly Freeze data and/or samples.

The Request ID is a 4-digit number assigned automatically assigned by the system. All communication regarding the request should include the Request ID. Regardless of whether this is a new ore previously submitted request, the user is directed to the Contributing Investigator Selection page and asked to identify the Contributing Investigator(s) affiliated with the request and the date of the request (Figure 6).

Multiple investigators can be selected by holding down the 'Ctrl' key and selecting the investigator with the mouse. If multiple dates are identified on the form(s) received at the Regional Network Center, the latest date should be entered.

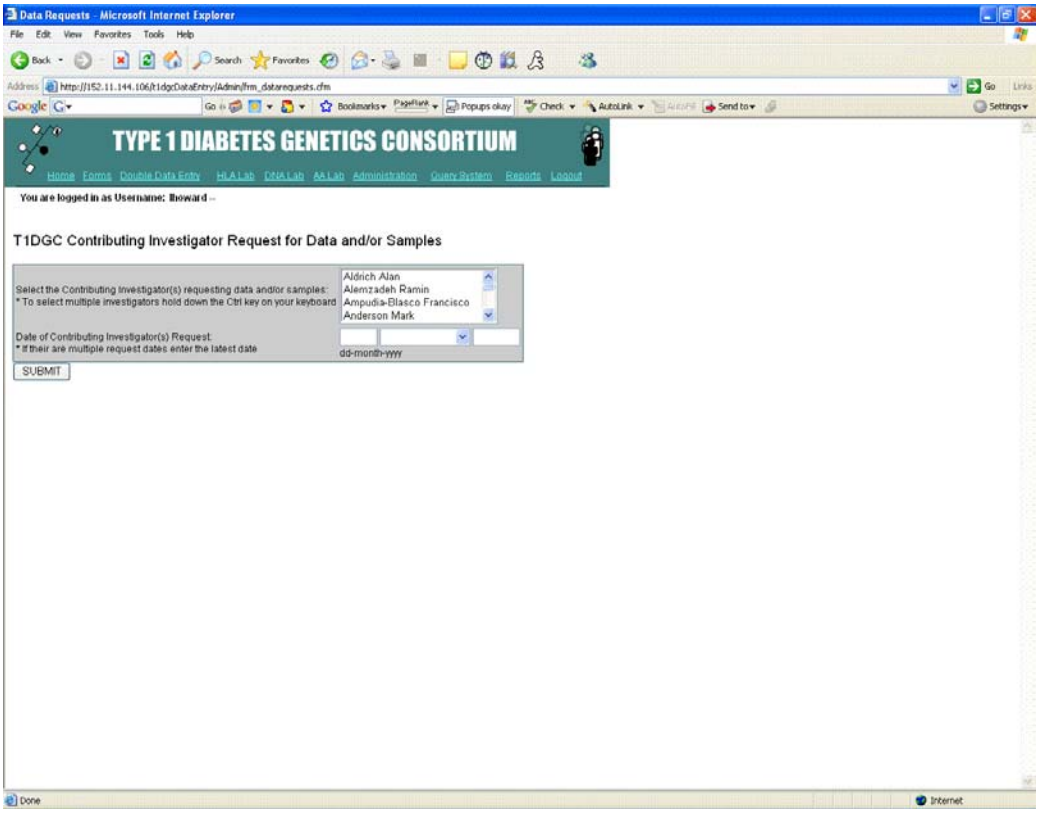


Figure 6. Contributing Investigator Selection Page.

The user is then directed to the Clinic and Resources Selection Page (Figure 7). The system lists the clinic IDs affiliated with the investigator(s) selected on the previous page. The user selects the clinics where data and/or samples are requested by checking the box underneath the clinic or by selection "Check All." The user can uncheck all clinic IDs by selecting "UnCheck All."

The user identifies whether data, samples or both are being requested. If only data or only samples are being requested, the user completes only one of the next two questions (i.e., "data set requested" or "samples requested"). If samples are requested all information on the form must be completed or the form will not be saved. If just data is requested, the user is not required to put a shipping address in the form. All other fields are required.

If the clinic ID associated with the Contributing Investigator is not listed, the Network Center should contact the Coordinating Center Project Manager for their network.

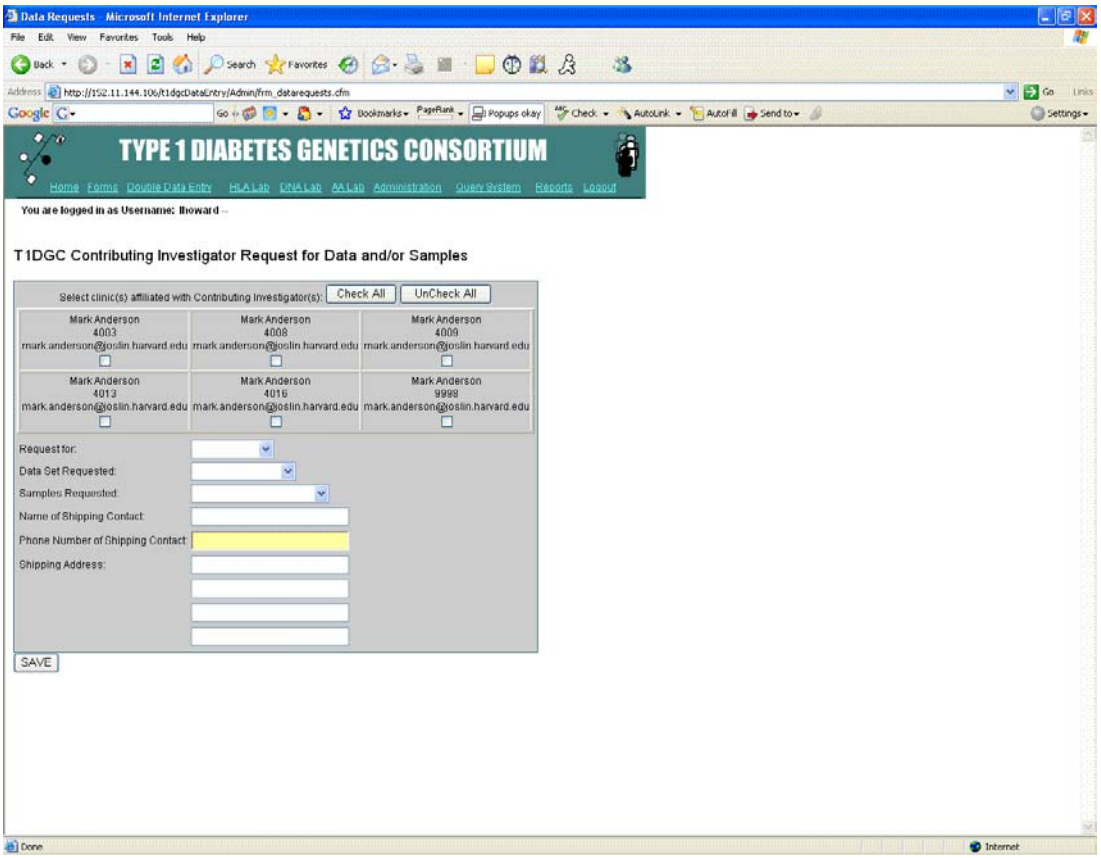


Figure 7. Clinic and Resources Selection Page.

If the data is saved the Contributing Investigator Request for Quarterly Freeze data and/or samples page is re-displayed with "Your request ID is XXXX and it has been sent to the CoC" at the top of the page (Figure 8).

An e-mail is automatically generated to the Regional Network Center, the Coordinating Center and the Contributing Investigator. The Coordinating Center will process the request, preparing a data set and/or shipping manifest to be forwarded to the Network DNA Repository. The Coordinating Center will notify the Contributing Investigator via e-mail when the data set is available on the T1DGC web site. The DNA

Repository will complete the *T1DGC Shipping Form: Shipments to Contributing Investigators* when the samples are shipped. The entry of this form into the Specimen Tracking system will generate an automatic e-mail that is sent to the Regional Network Center, the Coordinating Center and the Contributing Investigator.

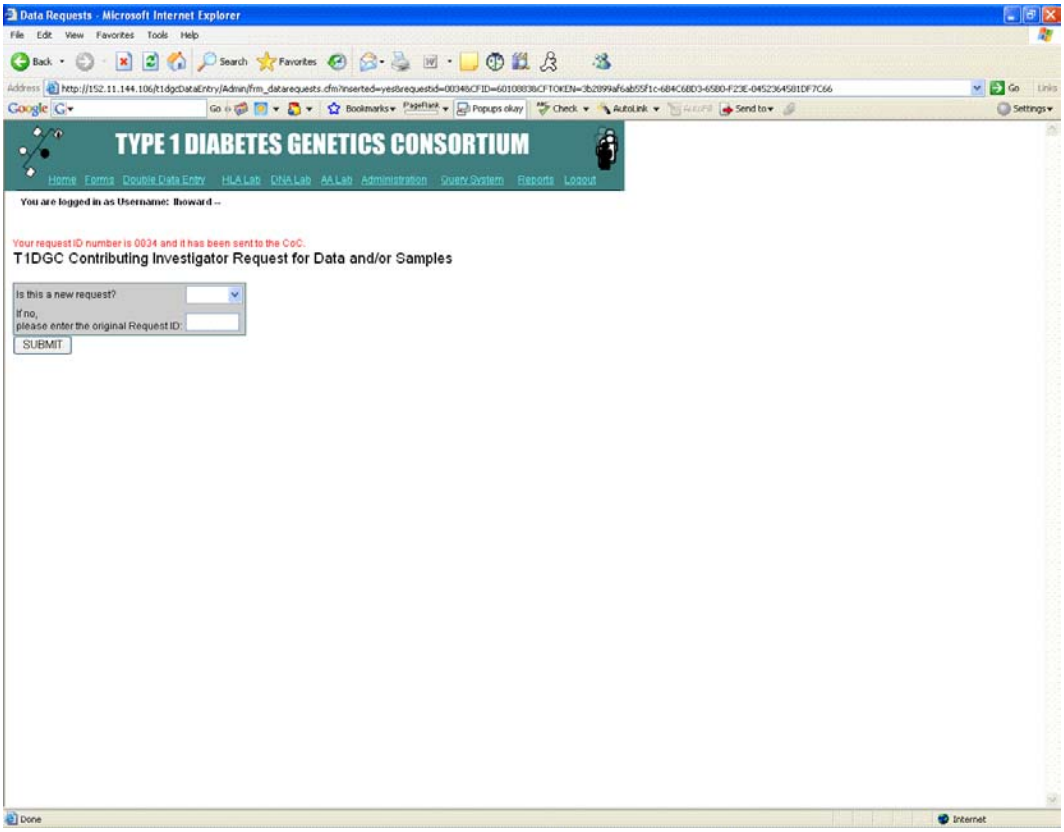


Figure 8. Contributing Investigator Request has been saved.

4. Contributing Investigator Request for Genotyping data sets

Gentoyping data sets from sample submissions to CIDR, the MHC Fine Mapping Laboratory and the Rapid Response Laboratory and other genotyping laboratories as determined by the T1DGC are made available to Contributing Investigators. Contributing Investigators will be notified when these data sets are available.

The Regional Network Center submits this request to the Coordinating Center by selecting “Administration” from the upper navigational menu on the T1DGC data entry web site and selecting “Request for Genotyping Data Sets.” The user is directed to the

Contributing Investigator Request for Genotyping Data Sets page (Figure 9). The user selects whether this is a new request. If the request is not new, the original Request ID (assigned by the system) is entered.

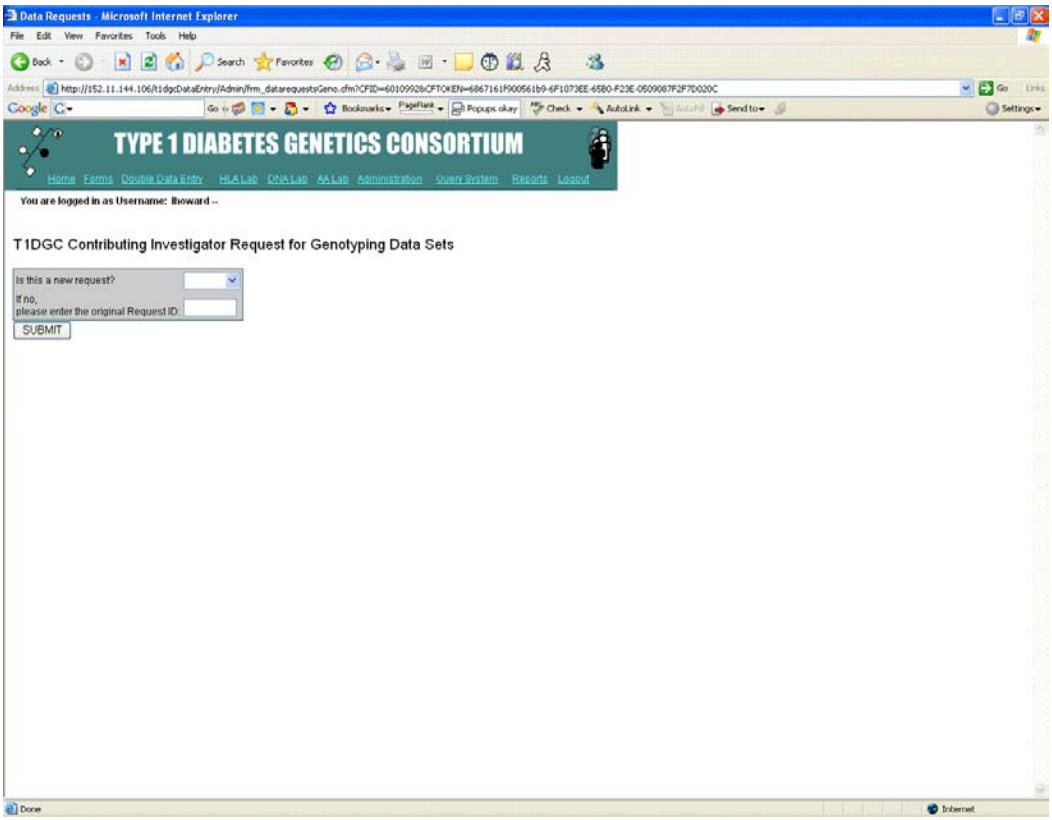


Figure 9. Contributing Investigator Request for Genotyping data sets.

The Request ID is a 5-digit number (in contrast to the 4-digit number that is assigned to Contributing Investigator Requests for Quarterly Freeze data and/or samples) assigned automatically assigned by the system. All communication regarding the request should include the Request ID. Regardless of whether this is a new ore previously submitted request, the user is directed to the Contributing Investigator Selection page and asked to identify the Contributing Investigator(s) affiliated with the request and the date of the request (Figure 10).

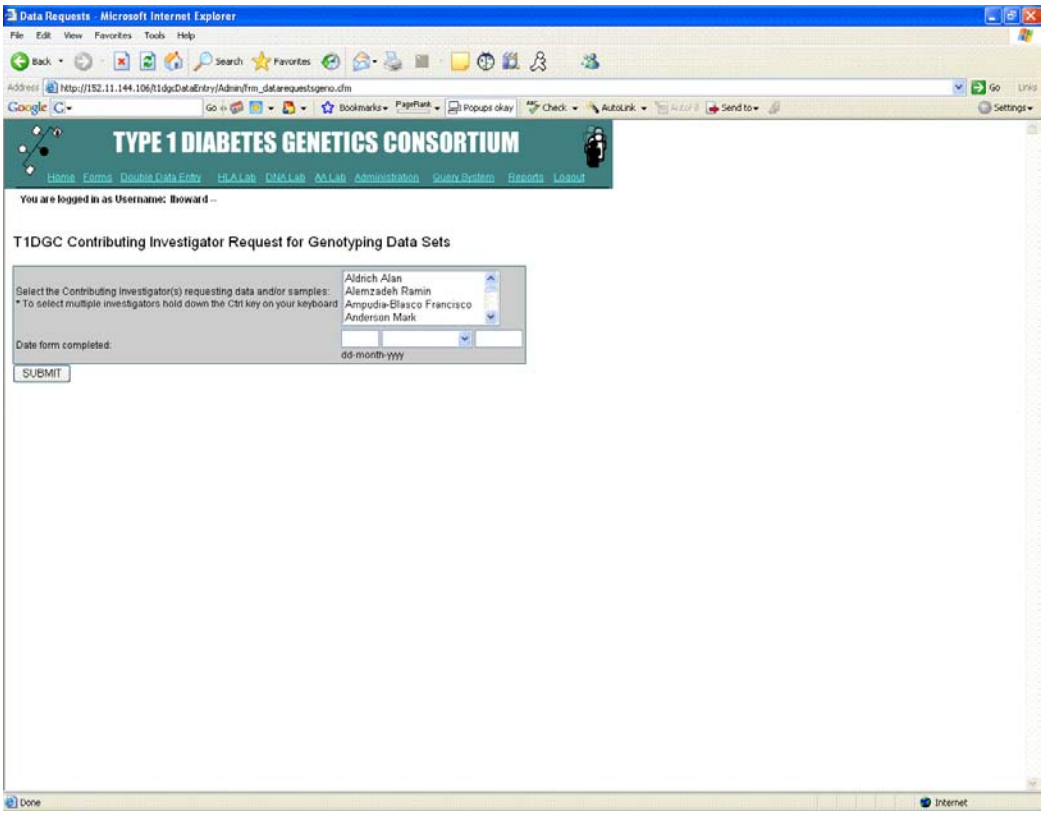


Figure 10. Contributing Investigator Selection Page.

Multiple investigators can be selected by holding down the 'Ctrl' key and selecting the investigator with the mouse. If multiple dates are identified on the form(s) received at the Regional Network Center, the latest date should be entered.

The user is then directed to the Clinic and Data Set Selection Page (Figure 11). The system lists the clinic IDs affiliated with the investigator(s) selected on the previous page. The user selects the clinics where data and/or samples are requested by checking the box underneath the clinic or by selection "Check All." The user can uncheck all clinic IDs by selecting "UnCheck All."

The user identifies which data set is requested and the type of data set that is requested. The user should mark all data sets or types of data sets that are apply. At least one data set and one type of data set is required.

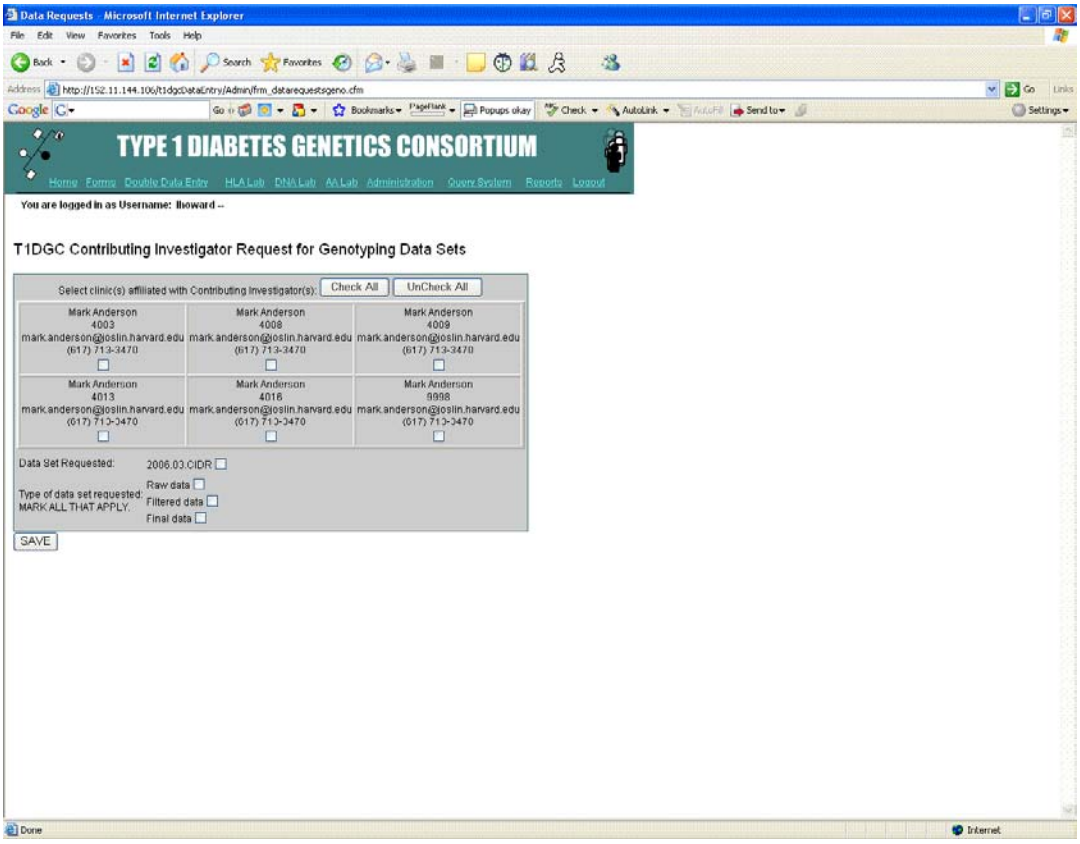


Figure 11. Clinic and Data Set Selection Page.

If the clinic ID associated with the Contributing Investigator is not listed, the Network Center should contact the Coordinating Center Project Manager for their network.

If the data is saved the Contributing Investigator Request for Quarterly Freeze data and/or samples page is re-displayed with "Your request ID is XXXX and it has been sent to the CoC" at the top of the page (Figure 12).

An e-mail is automatically generated to the Regional Network Center, the Coordinating Center and the Contributing Investigator. The Coordinating Center will process the request, preparing a data set. The Coordinating Center will notify the Contributing Investigator via e-mail when the data set is available on the T1DGC web site.

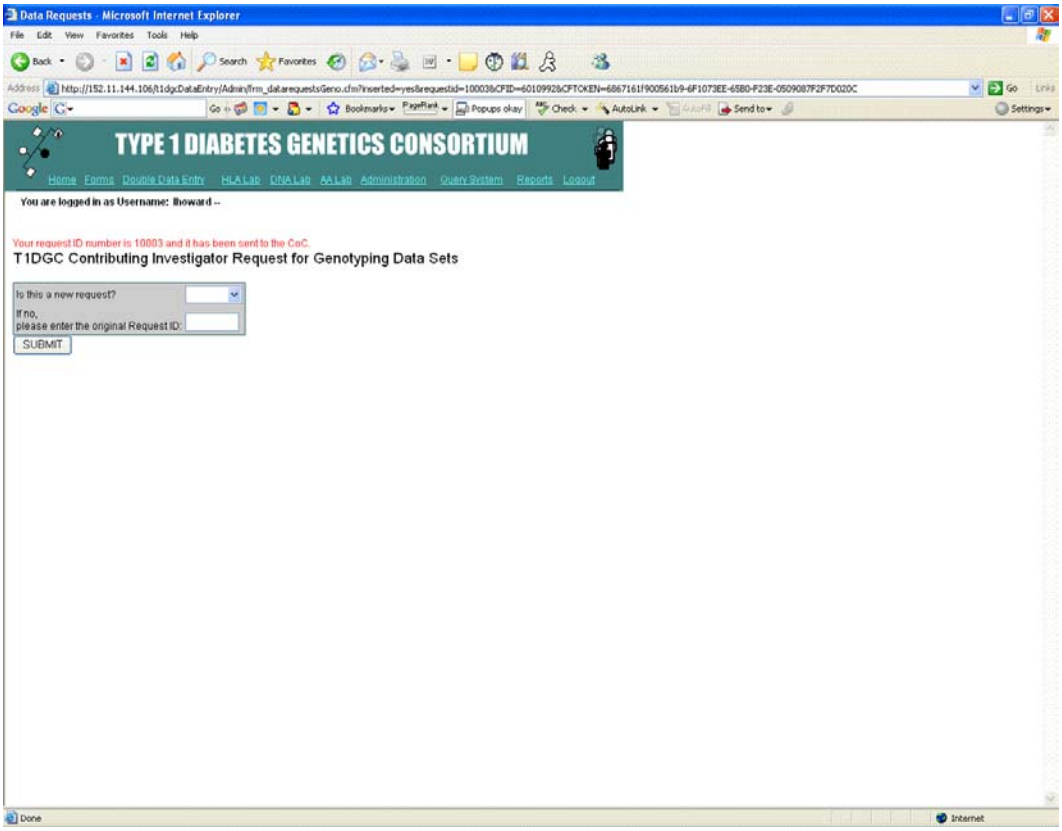


Figure 12. Contributing Investigator Request has been saved.

III. DATA ENTRY OF FORM SETS

A. General Instructions for Data Entry

Individuals entering data must be familiar with the following operations of the database management system:

1. Each screen displays a certain number of fields or slots where data from T1DGC forms are entered. These fields may appear on the screen as boxes of a different color from the screen background. Other fields are called "radio buttons", "list boxes", and "check boxes." These fields allow the user to select from several choices. If information has been omitted on the forms, do not enter the data. For more on missing data, see item 7.

2. Move from field to field by using the “Tab” key, or by clicking on another field with the mouse.

3. All data entry must be done with the “Caps Lock” key on. Data entered in lower case will not be saved.

4. Correct keying errors in a specific field by backspacing over the error and re-typing the data. If a mistake is made after moving to a new field, use the mouse, Shift-Tab or Tab keys to move to the field that needs correction.

5. At the end of a screen, check entries to be sure they are correct. Save each form after it is entered. To save the entered form data, click on the **Save Data** button at the top or bottom of the screen.

6. Each time a Family ID is entered, the system checks that the ID is valid. If the ID is invalid, access to the forms will be denied.

7. The database system sets all data items to “missing” by default. Numeric and date fields, for which no data have been entered, are assigned a NULL value. If an answer is missing on the paper form, do not change the value on the screen.

8. If data are invalid on the paper form, **do not** enter any information in the field and consult the Clinic Coordinator. Record these discrepancies on the *T1DGC Data Editing Log*, documenting the current date, participant or family ID, clinic ID, form name, question number, interview date, and the nature of the discrepancy. Once these discrepancies are resolved, entry of the data can occur.

9. The system will note that data are out of "expected" ranges and "valid" ranges. For example, the expected range for interview dates are between the years of 2004-2006. You may encounter valid values outside the expected range. In such cases, the system will note this with an orange mark next to the field in question, but entry **is** permitted. The user has to select whether to correct the value or save with errors. Data values that are missing and must be answered are noted with a red mark next to the field in question, and the user must correct the value

before data are saved. All data requiring correction **must** be corrected at the clinic level. The Regional Network Center staff **cannot** correct data without consulting the clinic where the forms originated.

B. Family and Form Selection

Once the user is logged in, he/she is asked to scan or enter a Family ID from the bar-coded label (Figure 13). Scanning the IDs is the preferred method; manual entry of IDs is possible, but discouraged. If the bar-code scanner is inoperable and manual entry is necessary, do not enter the hyphens that appear on the bar-coded ID label.

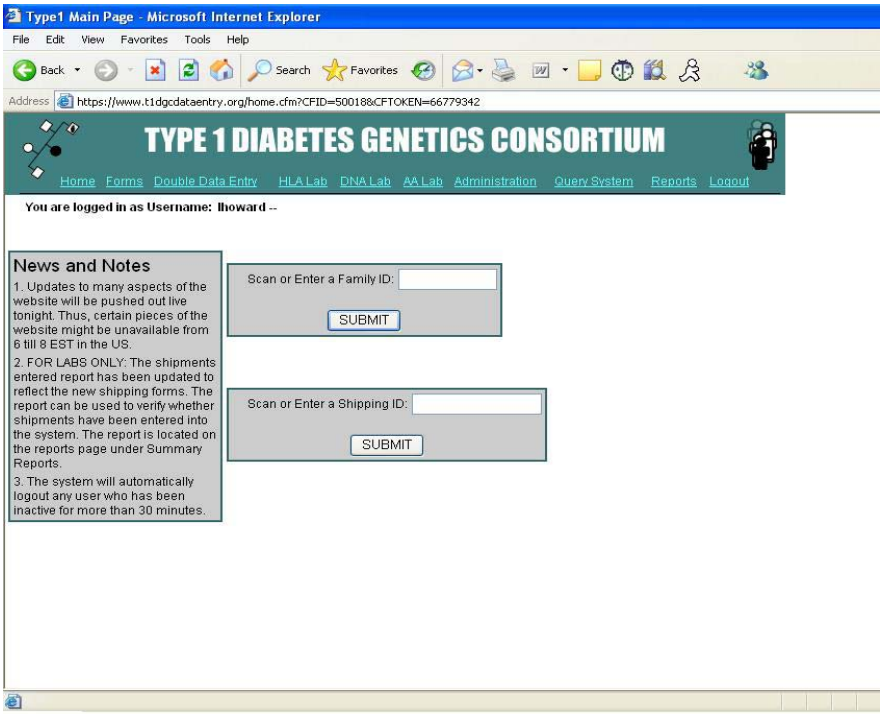


Figure 13. Scanning family IDs from bar-coded labels.

After scanning the bar-code, the system processes the Family ID, testing for validity. (Appendix B provides an overview of the data entry web site form flow.) If a Family ID is invalid, the user will not be able to enter the forms (Figure 14). The user should confirm the bar-code was read correctly and matches the written ID. If the label was read correctly, the user should contact the Coordinating Center to resolve the problem.

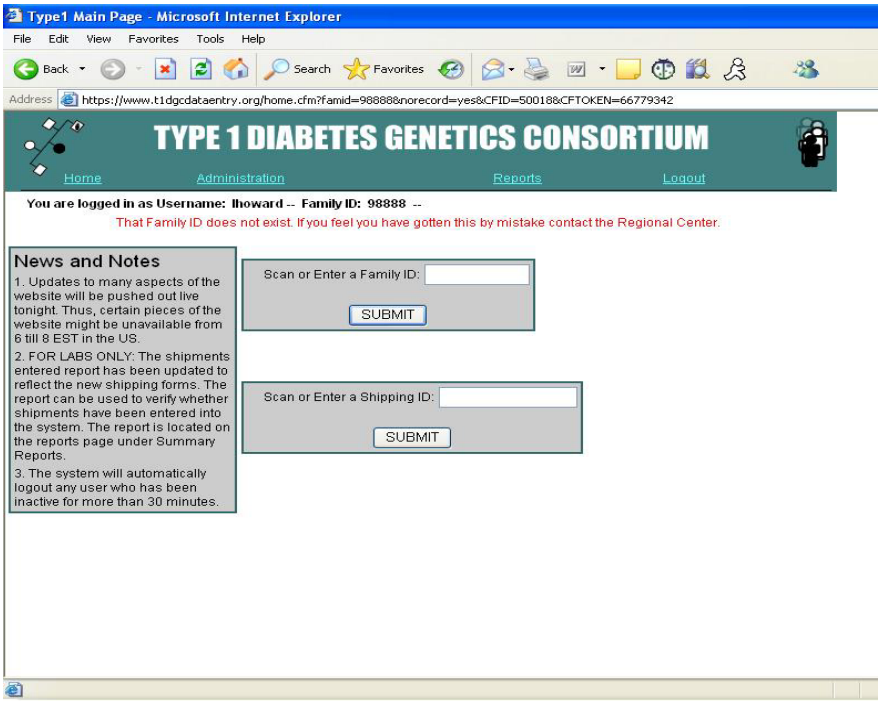


Figure 14. Entry of an Invalid ID.

Once the Family ID is entered, the system automatically determines if this is a previously initialized family. If the ID has not been entered previously, the user may have to select whether an ASP or trio family is being initialized in the system (Figure 15). This screen will only appear in networks where trio families are being collected in conjunction with ASP families. The user is then able to access and complete the required data entry forms. If the family was initialized during a prior data entry operation (*i.e.,* family type has already been selected), the user is not prompted again for type of family.

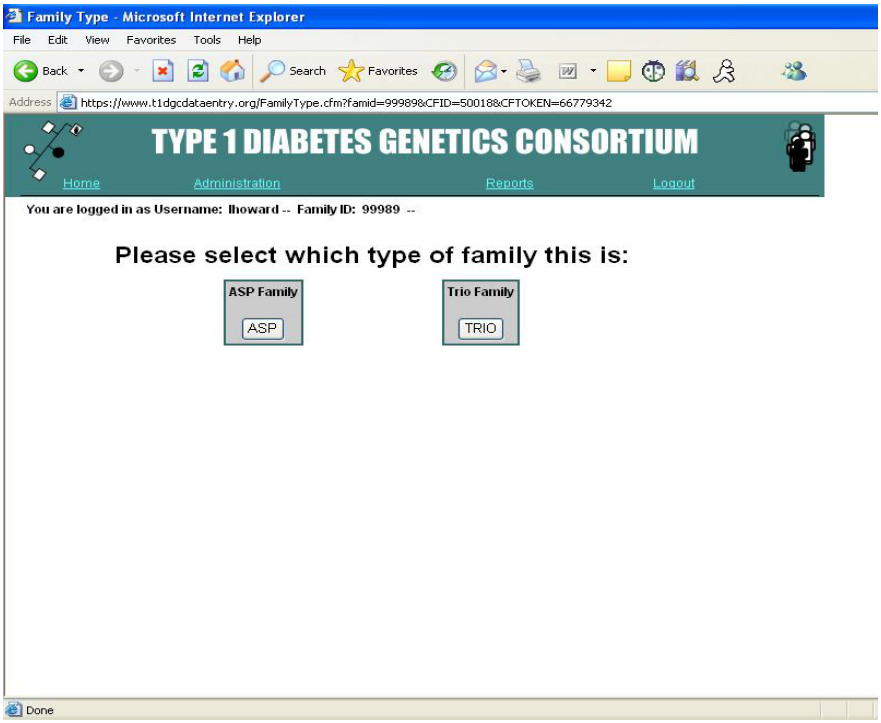


Figure 15. Selection of family type.

C. North American Trio Pre-Eligibility Form

Note: This section applies only to trio families collected in the North American Network.

If a trio family is selected In the North American Network, the *T1DGC North American Trio Pre-Eligibility Form* will appear and must be entered prior to entering the *T1DGC Eligibility Form* (Figure 16).

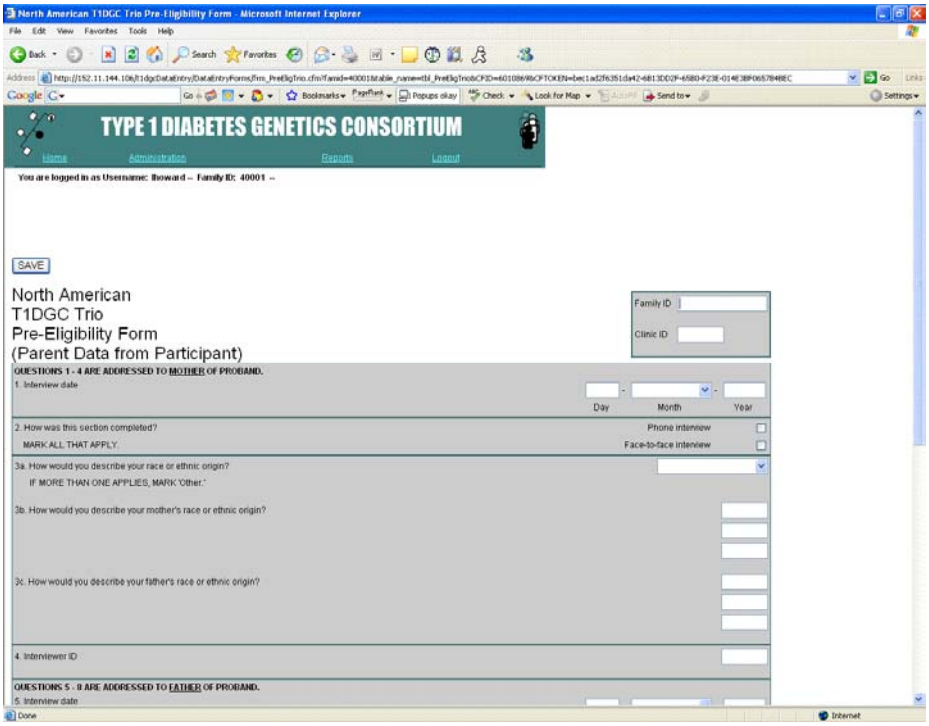


Figure 16. North American T1DGC Trio Pre-Eligibility Form.

D. Consent Summary Forms

1. Data Entry of Consent Summary Form

For new families, the *T1DGC Consent Summary Form* is entered first (Figure 17).

Data entry of forms for a family cannot be initiated without an appropriately completed *T1DGC Consent Summary Form*. For ASP families, the form must contain both the bar-coded ID label for the proband and the affected sibling, the date the *Informed Consent* was signed **and** the consent status. For trios, the bar-coded ID label, the date the *Informed Consent* was signed **and** the consent status must be complete for the proband, father and mother.

For clinics within the United States, *Written Authorization* must be obtained in addition to the *Informed Consent*. Consult the Clinic Coordinator if any of these data are missing on the *T1DGC Consent Summary Form*. Information must be obtained from the clinic to correct the forms prior to entry of the data.

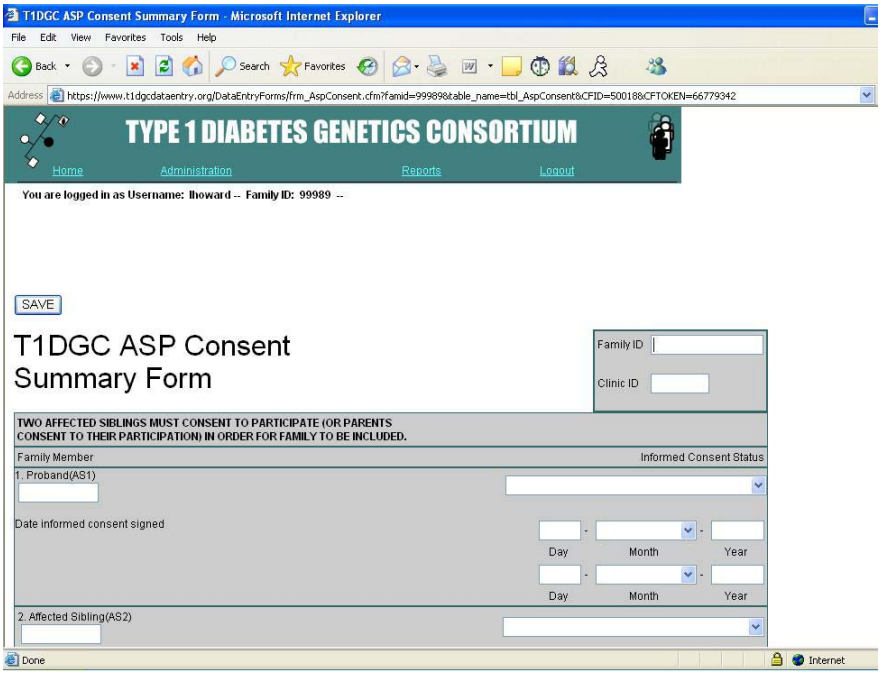


Figure 17. Entry screen for *T1DGC ASP Consent Summary Form*.

2. *Consent Summary Form* Warnings and Errors

a. Warnings (Orange Dots):

(i) If data entered are out of an "expected" range, the form is redisplayed with an orange dot at the top describing the potential mistake (Figure 18).

(ii) Confirm that the data on the form matches that entered on the web page.

(iii) If the data match, press the "Save with Warnings" button. If the data do not match, correct the discrepant data and press the "Save" button.

b. Errors (Red Dots):

(i) If data entered are out of an "expected" range or is blank and the field is **required**, the form is redisplayed with a red mark at the top describing the potential error (Figure 18).

(ii) Confirm that the data on the form matches that entered on the web page.

(iii) If the data match and are valid, the Coordinating Center should be contacted.

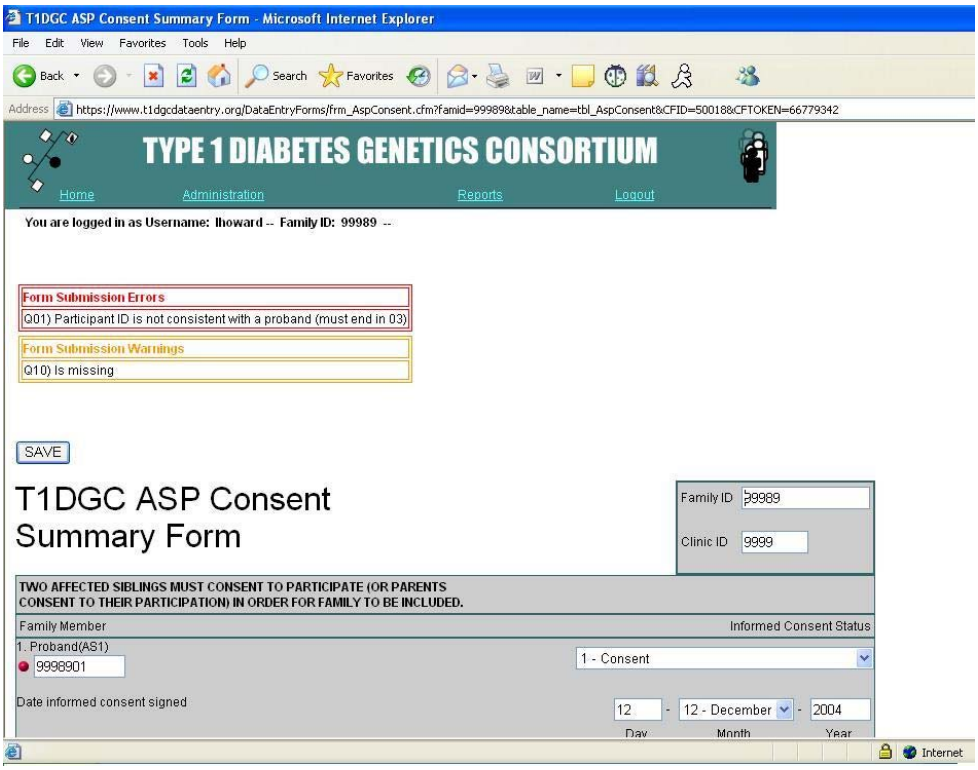


Figure 18. ASP Consent Summary Form with Warnings and Errors.

Warnings and error messages will appear if data entered are out of "expected" ranges for all forms, as they do for the *Consent Summary Form*.

E. Informed Consent Database

Once you have entered the required data on the *T1DGC Consent Summary Form*, the user is taken to the Consent Selection Page (Figure 19). The user sees the name and participant ID of every family member where information was entered on the *Consent Summary Form*. Once a user clicks on a family member, he/she is taken to the layered portion of the consent for this person (Figure 20). The user enters the layered portion and clicks "Save." If errors are made on the entry of information on this page, it cannot be modified. Regional Network Center staff can view previously entered layered portions of the participant's consent form; however any changes to the layered

portion of the participant's consent form must be e-mailed to the Network Project Manager at the Coordinating Center for correction.

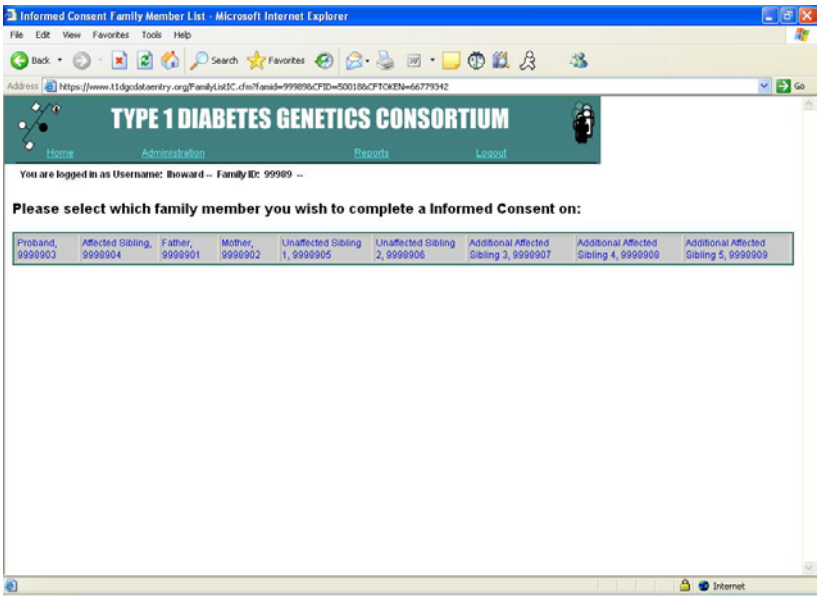


Figure 19. Informed Consent Selection Page.

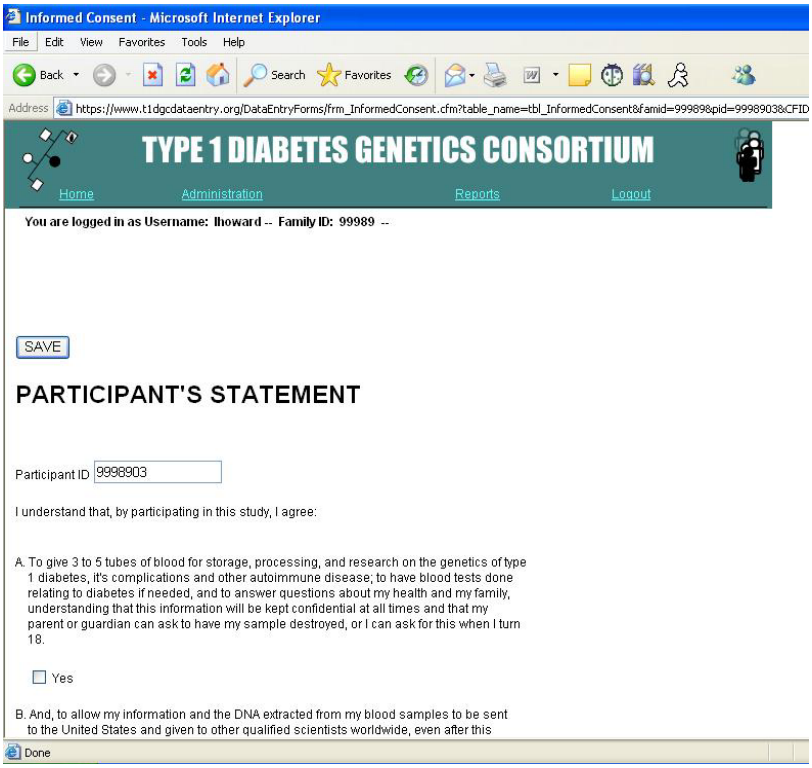


Figure 20. Informed Consent Database.

F. Eligibility Forms

After completing and submitting the required data on the *T1DGC Consent Summary Form*, **one** of the two *T1DGC Eligibility Form*s is entered. The system directs the user to the *T1DGC Eligibility Form* page and the user must select one of the two *T1DGC Eligibility Forms* (Figure 21). Either the *T1DGC Eligibility Form (Administered to Proband)* is entered (Figure 22 or the *T1DGC Eligibility Form (Administered to Guardian)* is entered (Figure 23).

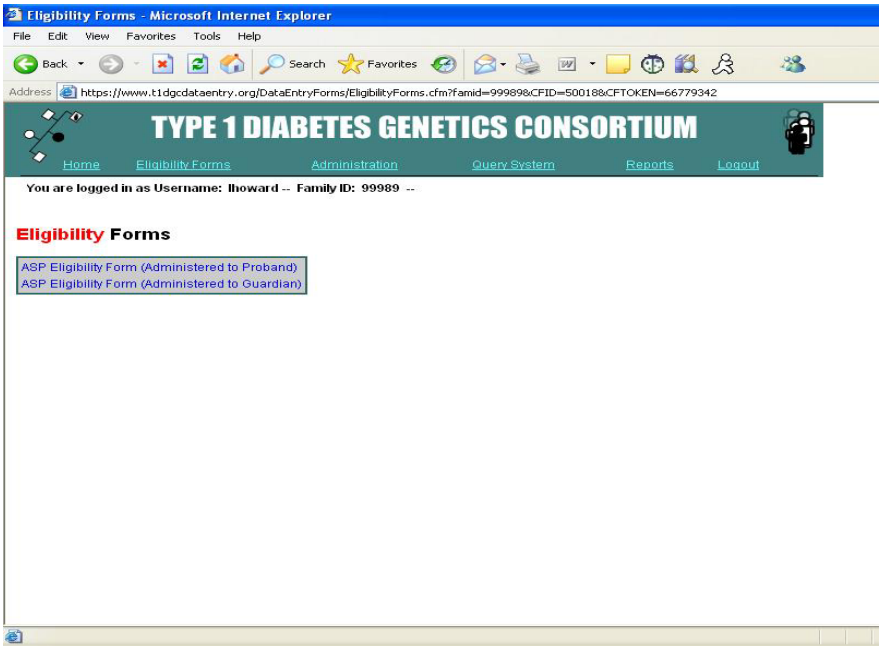


Figure 21. Selection of *T1DGC ASP Eligibility Form.*

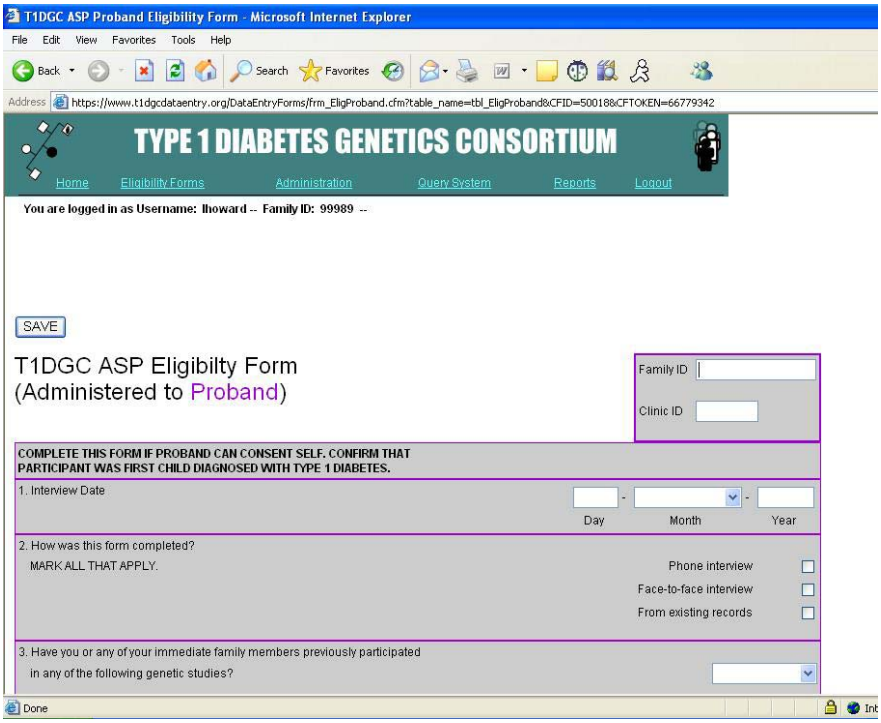


Figure 22. Entry screen for *T1DGC ASP Eligibility Form* (Proband).

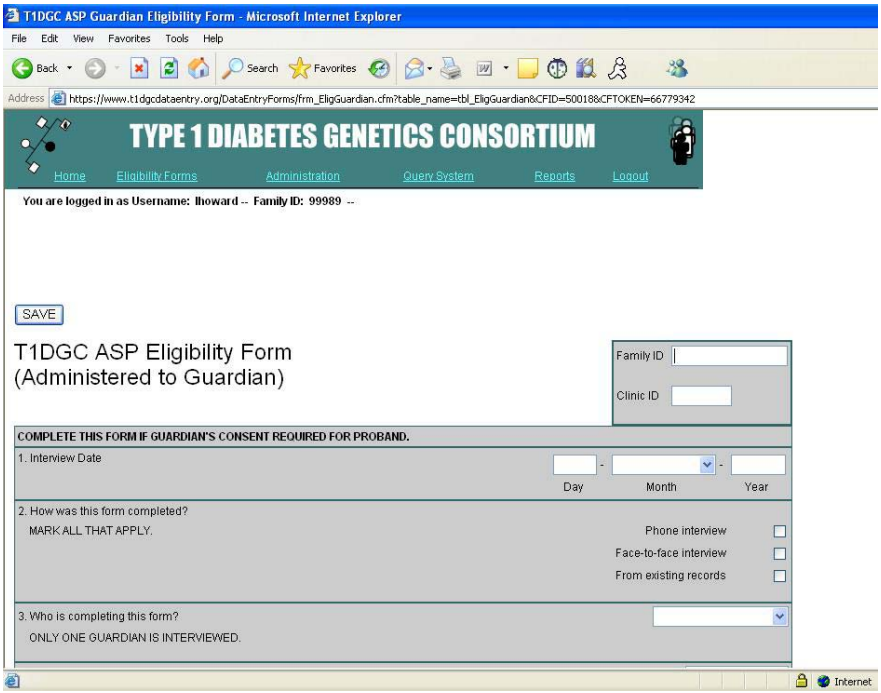


Figure 23. Entry screen for *T1DGC ASP Eligibility Form* (Guardian).

G. Core Data Entry Forms

Upon completion of the eligibility form, the remainder of the "Core Data Entry Forms" can be accessed and entered. The system directs the user to the "Core Data Entry Forms" page that lists all the forms that must be data entered for the proband and the affected sibling in ASP families (Figure 24); or in trio families, the proband and both biological parents. Note that forms for these essential participants must be entered before entering forms for any other family members. That is, entry of the *T1DGC Exam Form* and the *T1DGC Blood Collection Form* for the proband and the affected sibling must be entered for ASP families before proceeding to data entry for mother, father or unaffected siblings.

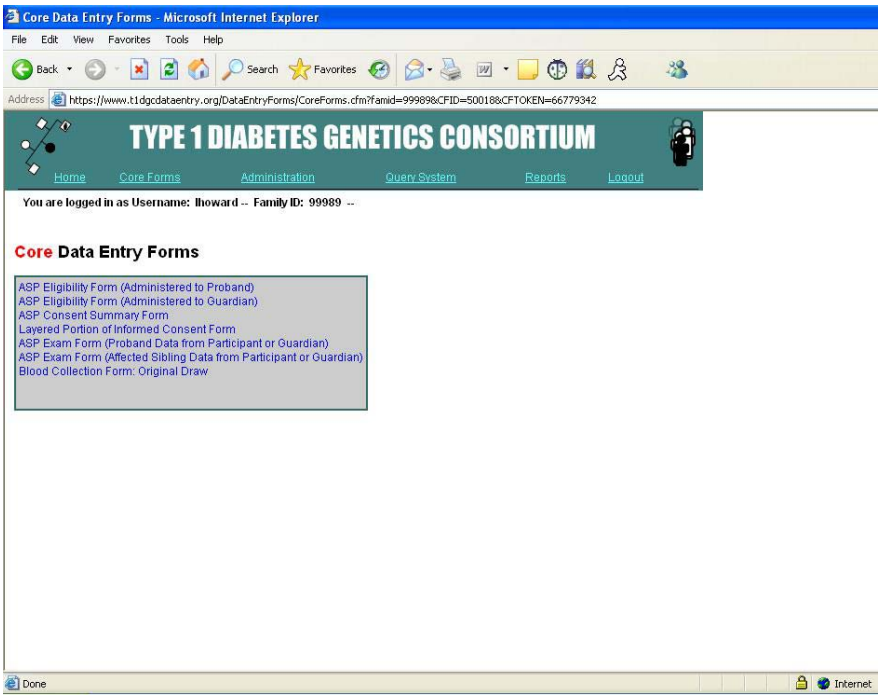


Figure 24. List of core data entry forms for ASP families.

To data enter a form, locate the desired form in the list, place the mouse over the form title and click the mouse button. The form to complete is presented. If the form has been entered, it is displayed with any previously entered information per family or participant ID.

H. Data Entry Forms

After completion of the Core Data Entry Forms, a list of all data entry forms for all members of the family is shown (Figure 25). Complete the remainder of the data entry.

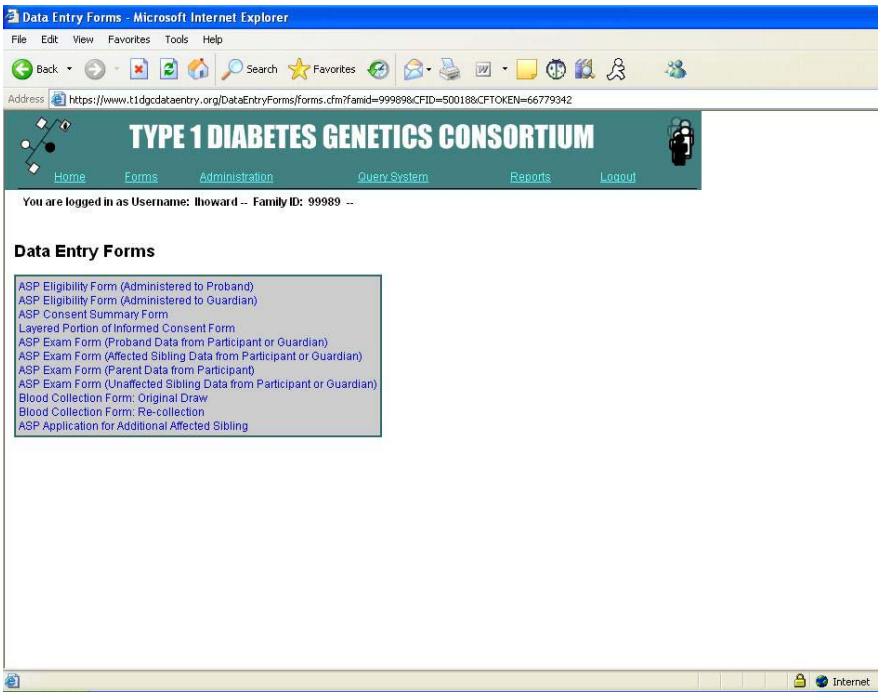


Figure 25. List of all ASP data entry forms.

If the same form is completed on multiple family members as in the case of the *T1DGC Blood Collection Form, T1DGC ASP Exam Form (Affected Sibling Data), T1DGC Exam Form (Parent Data), T1DGC ASP Exam Form (Unaffected Sibling Data)* and *T1DGC ASP Application for Additional Affected Sibling,* the system will prompt the user to select the family member for which the form is completed (Figure 26).

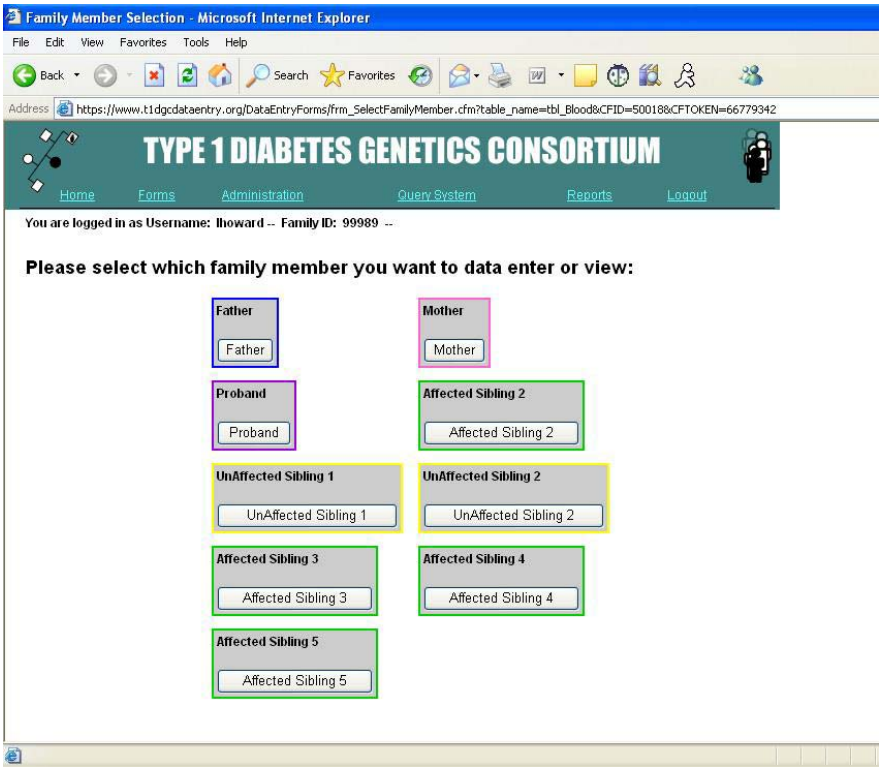


Figure 26. Family Selection for *T1DGC Blood Collection Form*.

I. *T1DGC ASP Application for Additional Affected Sibling*

If information has been entered on the *T1DGC ASP Consent Summary* regarding additional affected siblings, the *T1DGC ASP Application for Additional Affected Sibling* will be a form listed on the Data Entry Forms page. The user will be prompted to select "Affected Sibling 3", "Affected Sibling 4" or "Affected Sibling" (Figure 27). The *T1DGC ASP Exam Form (Affected Sibling Data)* and *T1DGC Blood Collection Form* must also be completed for each additional affected sibling.

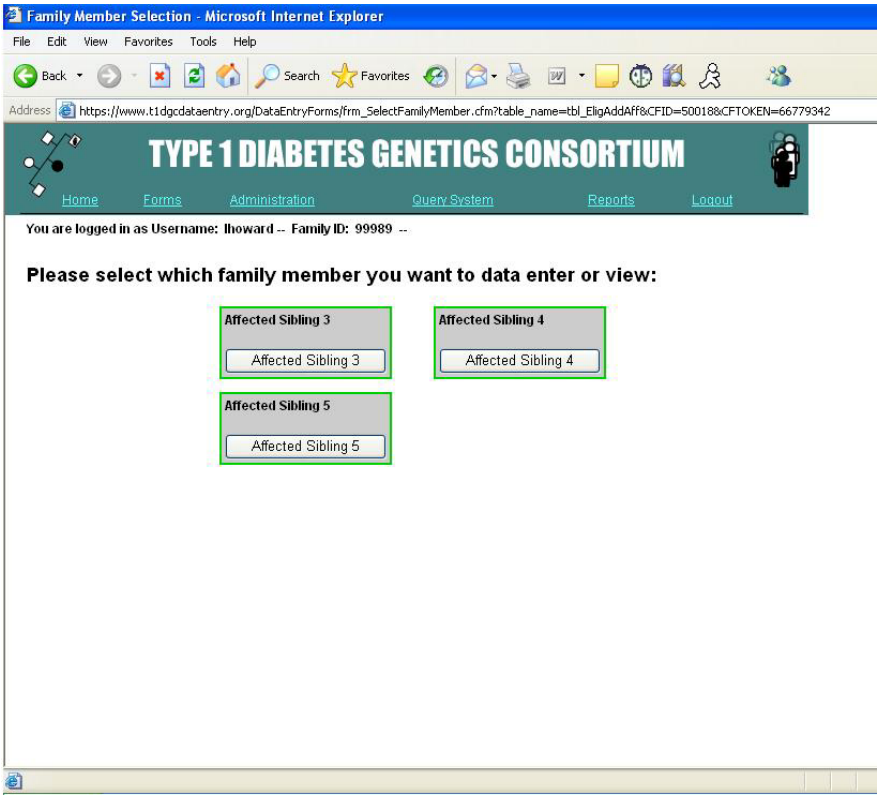


Figure 27. Family Selection for *T1DGC ASP Application for Additional Affected Sibling.*

IV. DATA VALIDATION PROCEDURES

The database management system performs several validation checks during the entry process, both before and after data are submitted. Data must: (1) match the correct type (*e.g.,* numeric data in numeric fields); (2) be in the correct range of valid responses; and (3) be left blank when the paper form field is missing. Data that fail the established validation checks generate messages, or prompts, that describe the problem and required actions on the part of the user.

Once data entry of all the fields on the form is completed, pressing **Save** begins the data validation process (see Section IIID2). If a data item is categorized as a critical field, it cannot be saved until the data can be validated. Any errors in critical fields that are detected during the validation process are displayed at the top of the screen in red. The user must correct the values in order to continue. Warnings displayed in orange do not have to be corrected in order to continue. However, the user should confirm the

correct value has been entered and follow-up with the Clinic Coordinator to confirm the response.

All questions have pre-assigned missing values for the purpose of data entry. The data entry screens require a set degree of completeness before a form is accepted. Should the forms be incomplete, the missing value is entered into the database.

V. CLINIC SHIPPING FORMS

A. Data Entry by Laboratories

The *T1DGC Clinic Shipping Forms* for specimen shipments from clinics are data entered by the laboratory receiving the samples. The Regional Network Center staff is responsible for ensuring the shipping forms have been entered correctly. Any errors found by Regional Network Center staff should be corrected on the data entry screen and the laboratory should be notified. **Chapter XII,** *Specimen Tracking and Inventory System* provides detailed instructions for completion and entry of the shipping forms.

B. Review of Shipping Forms by Regional Network Centers

The Regional Network Centers will receive two copies of the *T1DGC Clinic Shipping Form*, one partially completed (received from the clinic) and one fully completed (received from the receiving laboratory). The Regional Network Center should confirm they have received two copies of each shipping form. After the completed *T1DGC Clinic Shipping Forms* have been received by the laboratory, the Regional Network Center should review the form to ensure entry was completed accurately.

Once the user is logged in, he/she scans the Shipping ID from the *T1DGC Clinic Shipping Form – Face Sheet* (Figure 13) in the box labeled "Enter or Scan a Shipping ID." If the laboratory has previously entered the shipment, the user will be directed to the Shipping Form Selection Page (Figure 28). If the shipping form has not previously been entered, the user will be directed to a blank Face Sheet. The Regional Network

Center staff should contact the T1DGC laboratory and ask them to enter the shipping form.

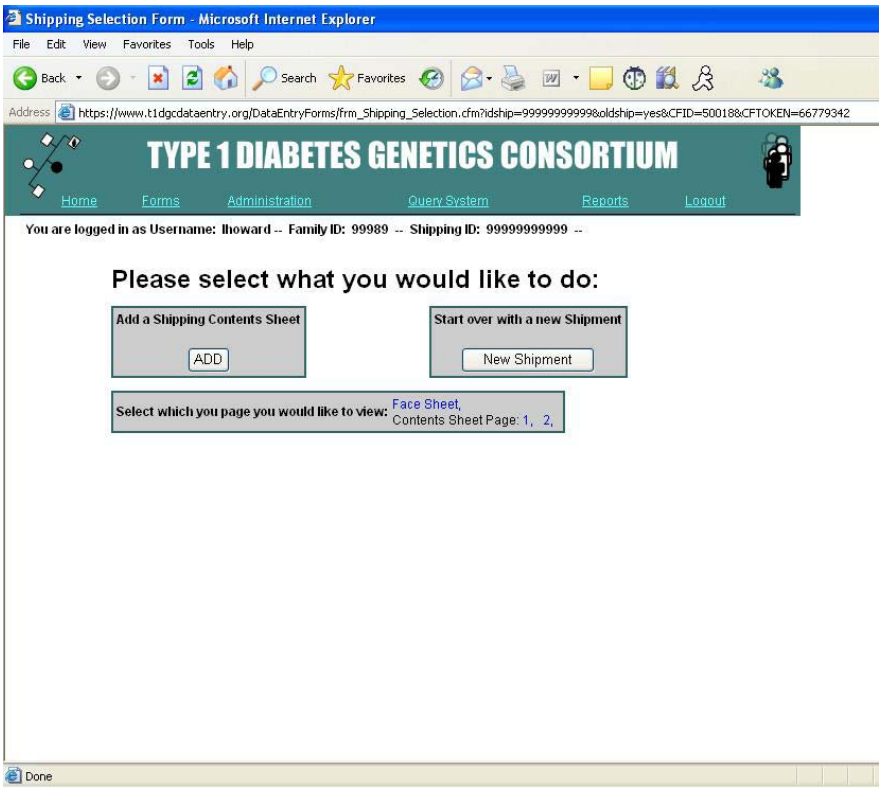


Figure 28. Shipping Form Selection Page.

The user has three options:

1. Add a Shipping Contents Sheet;
2. Start over with a new Shipment; or
3. Select a page they would like to view.

Regional Network Center staff should view the Face Sheet (Figure 29) and each Contents Sheet (Figure 30) in order to ensure entry is complete and the paper version of the form matches exactly to the information in the system. If the information on the hard copy of the shipping forms does not correspond with the information in the system, the Regional Network Center staff must contact the laboratory to correct the entry. The Regional Network Center should **never** update the information entered into the *T1DGC Clinic Shipping Form* without consulting the shipping clinic and the receiving laboratory.

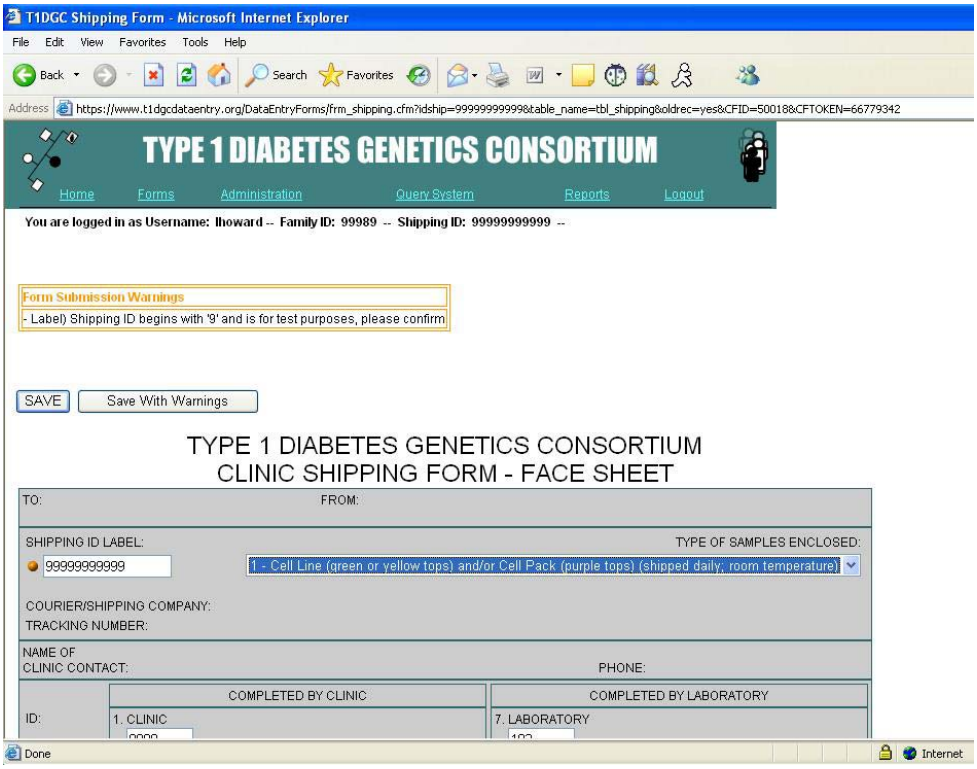


Figure 29.*T1DGC Clinic Shipping Form* – Face Sheet.

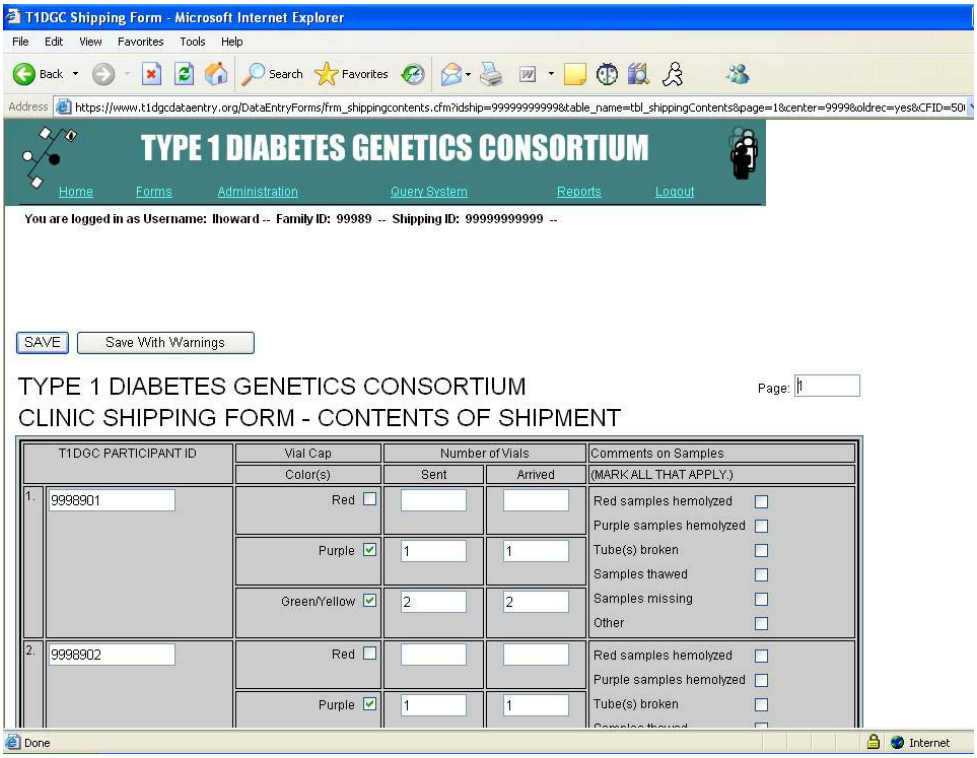


Figure 30.*T1DGC Clinic Shipping Form* – Contents Sheet.

VI. QUERY SYSTEM

The T1DGC Query System has been created in order to resolve data editing questions. This is to be used as a tool for the Regional Network Centers to record and identify sources of action taken to correct mistakes or clarify unexpected database values. The responses the Regional Network Centers enter into this system will be used to create reports for the Steering Committee, Forms Data Committee, and External Advisory Board.

The Query System is a dynamic system that updates within 30 minutes after a query has been corrected. Updating data forms within the query system will update the database (*i.e.*, if you correct a question on a form while you are in the query system, the next time you pull up this form, whether or not you are in the query system, the form will be corrected). The process that updates the query data tables is run every 30 minutes and starts at 15 and 45 minutes after the hour. Any changes in the underlying data will be reflected in the query system after the next run. The Regional Network Centers can use the query system as a tool shortly after data forms have been entered into the database (*i.e.*, within the same timetable as described above).

A. Query System Responses

Queries can be answered ten ways (Figure 31):

1. RNC - Data edited: This is selected if a data entry error occurred at the Regional Network Center; the Regional Network Center must go into the form and correct the data entry error; however, this query does not need to be sent to the clinic.

2. RNC - Data to be reviewed: This is selected if the query is not a data entry error and thus, has to be sent to the clinic to be corrected or verified. Queries marked as “to be reviewed” will be listed in the Query System Report that must be sent to the clinic in order to verify or edit the query.

3. RNC - Verified: This is selected when the Regional Network Center has reviewed the form and verified the form was entered correctly into the system. *(NOTE: Previously, Regional Network Centers were instructed to select this option when they had already received information from the clinic that the information was correct. Queries marked this way do not have to be changed to "Clinic-Verified," but should be marked accordingly in the future.)*

4. Clinic - Edited: This is selected when the clinic has reviewed the form and found the form was recorded incorrectly, edited the form, and returned the edited forms and Query System Report to the Regional Network Center. In order to enter this into the query system, a valid clinic staff ID must also be entered at the top or bottom of the screen. Clinic - Edited can be marked without receipt of the Query System Report, provided that a corrected version of the form has been received.

5. Clinic - Verified: This is selected when the clinic has reviewed the form and verified the form was recorded correctly. When the Query System Report has been returned to the Regional Network Center, this can be selected. In order to enter this into the query system, a valid clinic staff ID must be entered at the top or bottom of the screen. Clinic - Verified can be marked without receipt of the Query System Report, provided that the Regional Network Center has received written confirmation (via e-mail, fax, or mail).

6. Defer for future processing: This is selected when the Regional Network Center does not wish to address this query immediately. This could be because the Regional Network Center has already asked the clinic about this query and does not wish to ask the same question at this time. However, this query will continue to appear if no action has been taken to correct the issue.

7. Unanswered: This can be selected as a way for the Regional Network Center to confirm they have looked at the query or as another option for "Defer for future processing."

8. Past Verified: This option is no longer active. In the past, this appeared next to queries that have been verified in the past by the Clinic or Regional Network Center. The value is an automated, display only response and can not be selected; however if a query had been verified in the past, but the status of the query has changed, the Regional Network can change queries marked as "Past Verified" to another option.

9. CoC: Must Correct: The Coordinating Center marks this response if a query has been selected as "RNC – Verified" or "Clinic – Verified"; however needs to be edited or corrected. The Regional Network Center cannot select this option. If this selection is marked, the Regional Network Center should review the form to confirm data entry and then must go back to the clinic in order to resolve the query. This is considered a crucial field that must be correct.

10. CoC: Clinic Verify: The Coordinating Center marks this response if a query has been selected as "RNC – Verified"; however needs to be verified at the clinic level. The Regional Network Center cannot select this option. If this selection is marked, the Regional Network Center must go back to the clinic in order to verify the query. Verification of data entry (RNC-Verified) is not sufficient.

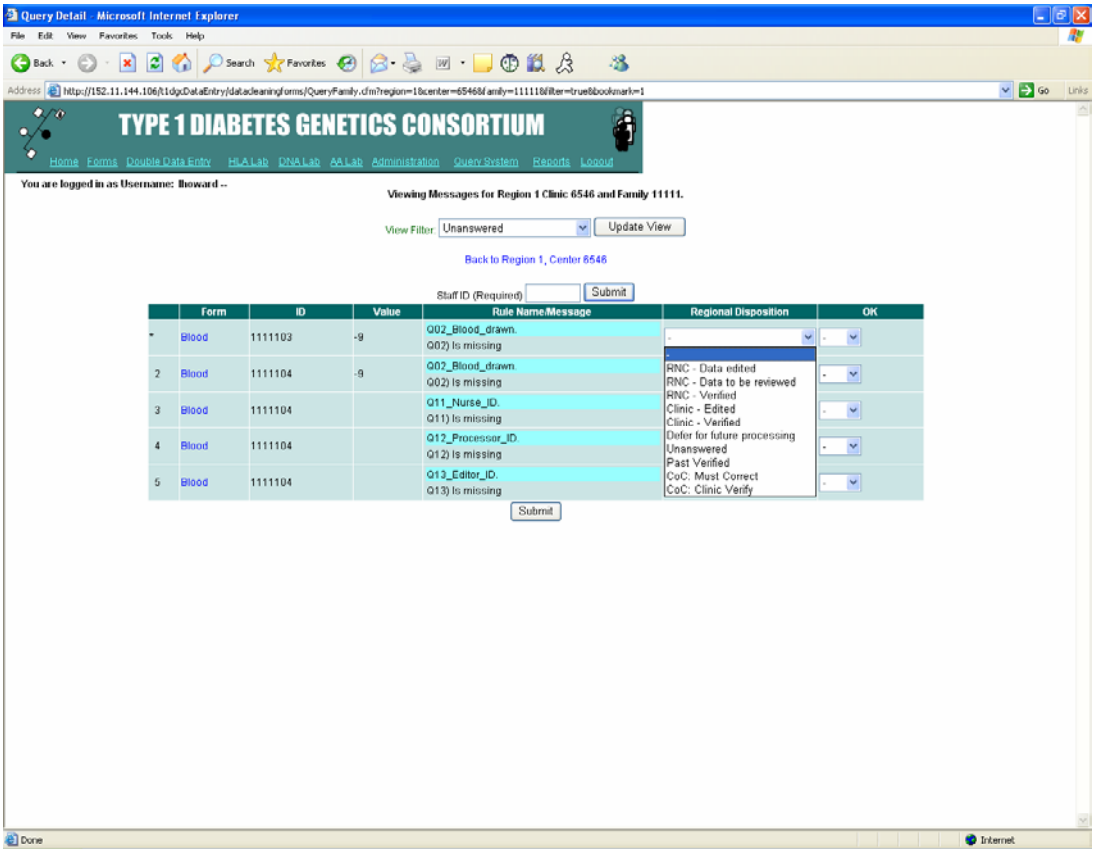


Figure 31. Regional Dispositions.

B. Filtering the Query List

The query list can be filtered to only display certain types of queries, depending on the filtering system the user selects. When a user first opens the query system, the default filter displays all queries. However, the user can modify the list of queries thirteen ways in order to display only certain queries (Figure 32):

1. All: This will show all queries in the query system.

2. All but Past Verified: This will show all queries except those that have been verified in the past by a clinic or the Regional Network Center and are marked as “Past Verified”

3. RNC - Data edited: This will show all queries that have been marked as “RNC-data edited” (*i.e.,* a data entry error has occurred).

4. RNC - Data to be reviewed: This will show all queries that have been marked as to be reviewed by the clinic (this will be the same information that is in the Query System Report).

5. RNC - Verified: This will show all queries that have been marked as "RNC - Verified" (*i.e.,* the Regional Network Center has confirmed that the data entry system entry reflects what is on the data form).

6. Clinic - Edited: This will show all queries that have been marked as "Clinic - Edited" (*i.e.,* clinic has sent a revised copy of the form and the Regional Network Center will or has modified the data entry system accordingly).

7. Clinic - Verified: This will show all queries that have been marked "Clinic - Verified" (*i.e.,* the clinic has verified the information is correct through the Query System Report or written documentation).

8. Defer for future processing: This will show all queries the Regional Network Center has marked "Defer for future processing" (*i.e.,* the Regional Network Center has decided not to respond to this query at this time).

9. Unanswered: This will show all queries where a response to a query has not been entered or "Unanswered" has been selected.

10. Past Verified: This will show all queries that the clinic or Regional Network Center has verified in the past.

11. CoC: Must Correct: This will show all queries the Coordinating Center has reviewed and must be corrected by either the Regional Network Center or clinic.

12. CoC: Clinic Verify: This will show all queries the Coordinating Center has reviewed and must be verified by the clinic rather than the Regional Network Center.

13. CoC: This will show all queries marked as "CoC: Must Correct" or "CoC: Clinic Verify." This allows the Regional Network Center to identify queries previously resolved, but that need to be resolved by another method.

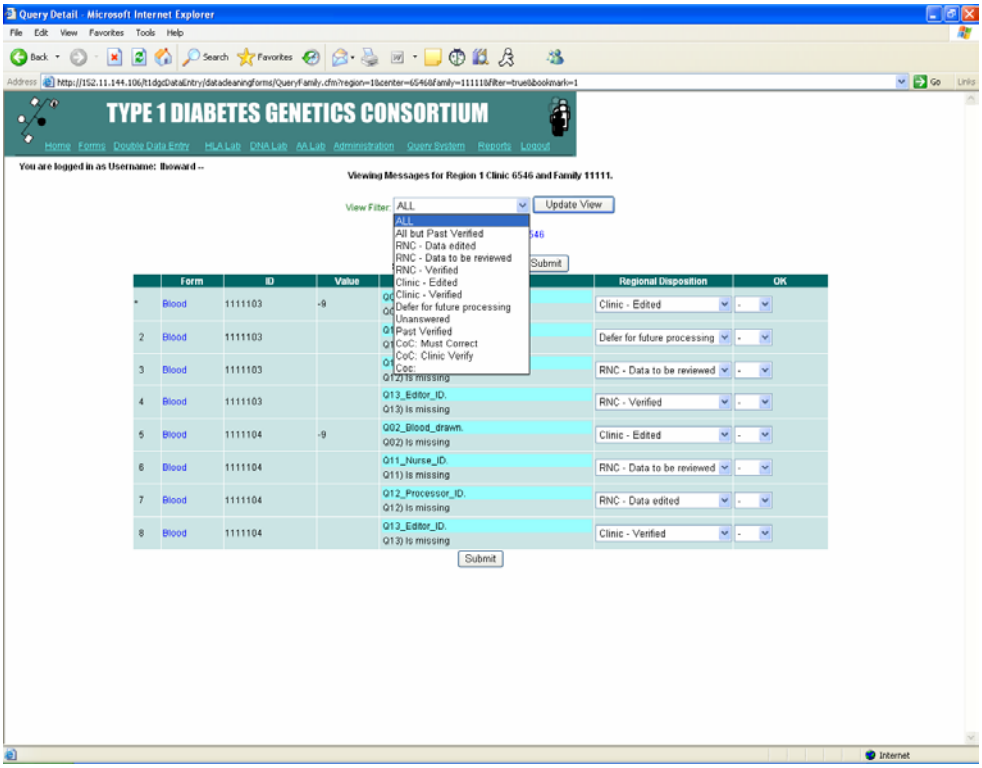


Figure 32. Ways to Filter the T1DGC Query System.

The user can filter the queries at any level of the query system: region, clinic, family or within the family data form queries. Once the user selects the way to filter the system, the user must click "Update View." The system does not filter automatically once the user selects one of the above choices. Once a user has filtered the query system, in order to change the filter, the user must select the new way to filter the system and click "Update View." As the user moves between the levels (region, clinic,

family, family data forms), the system remembers the filtering selection the user made and will carry the filter selection throughout each level.

c. Query System Basics

Every thirty minutes, the Query System will be updated to include all forms that have been entered.

1. Log-on to the T1DGC Data Entry Web Site.

2. Click on the link at the top of the page entitled “Query System.”

3. The system recognizes the user as belonging to a specific network and will display the total number of queries for the user’s network. The user should click on the message count in order to see the list of clinics (Figure 33).

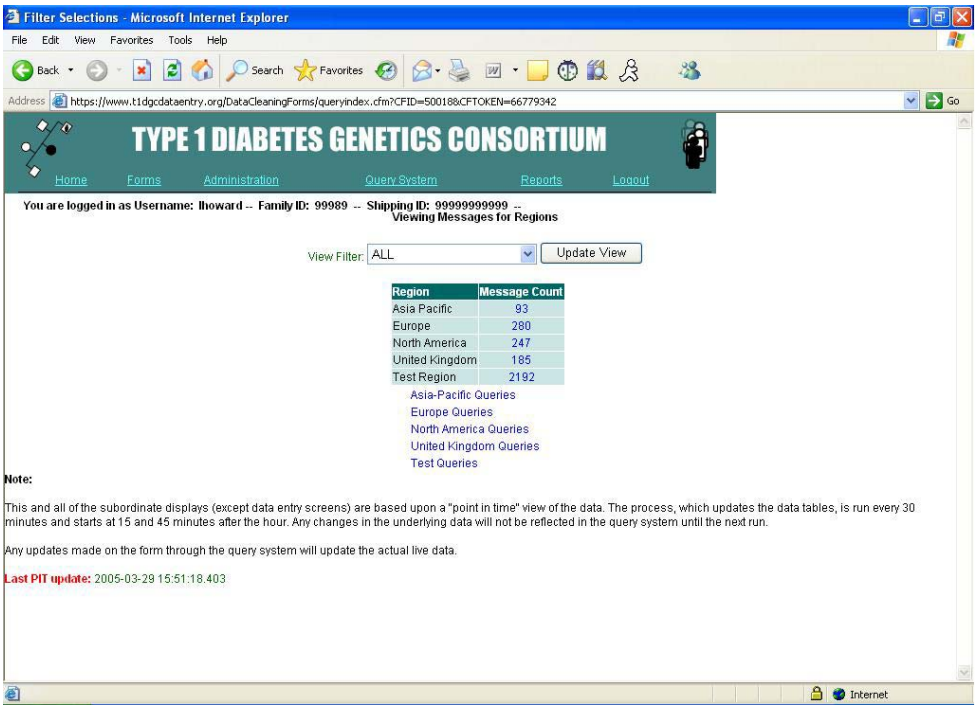


Figure 33. Query System Home Page with List of Networks.

4. The user will see the location of the clinics, clinic IDs and the number of queries for each clinic (Figure 34).

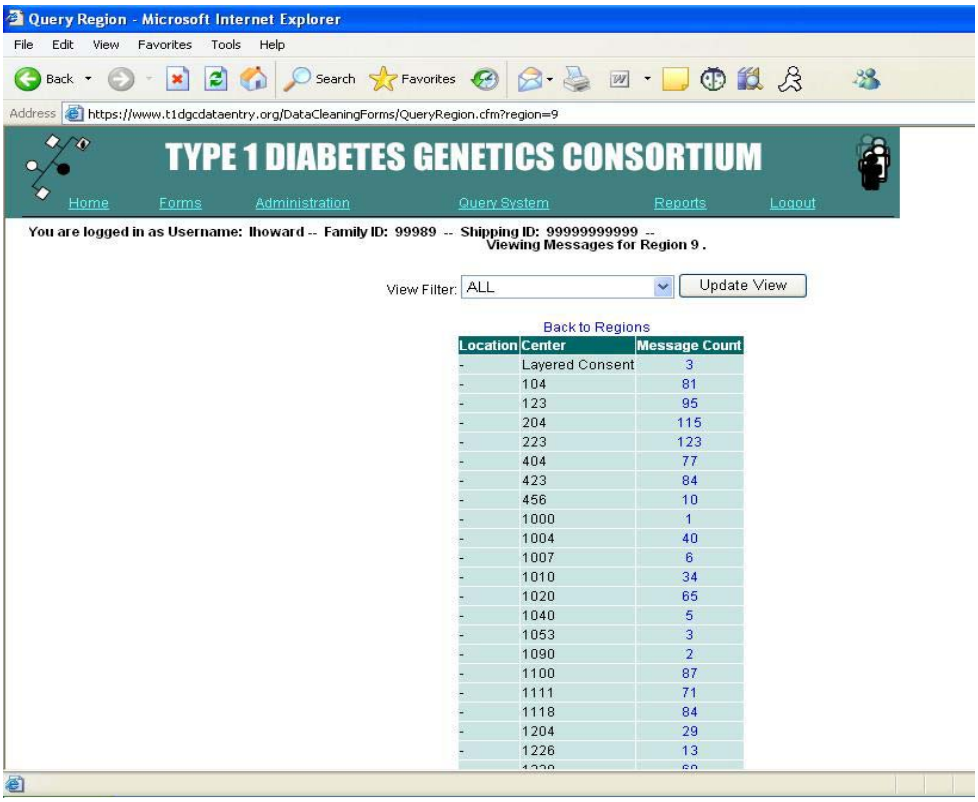


Figure 34. Query System List of Clinics.

5. The user can view the family IDs to which these queries apply by clicking on the message count for a particular clinic. A separate listing is present for any queries on the Shipping Forms since these may contain multiple family IDs. Family IDs are associated with the clinic where the *T1DGC Consent Summary Form* is completed (Figure 35).

6. The user will see a list of family IDs and the number of queries for each family ID. The user can see the list of queries by clicking on the message count for a particular family ID (Figure 36).

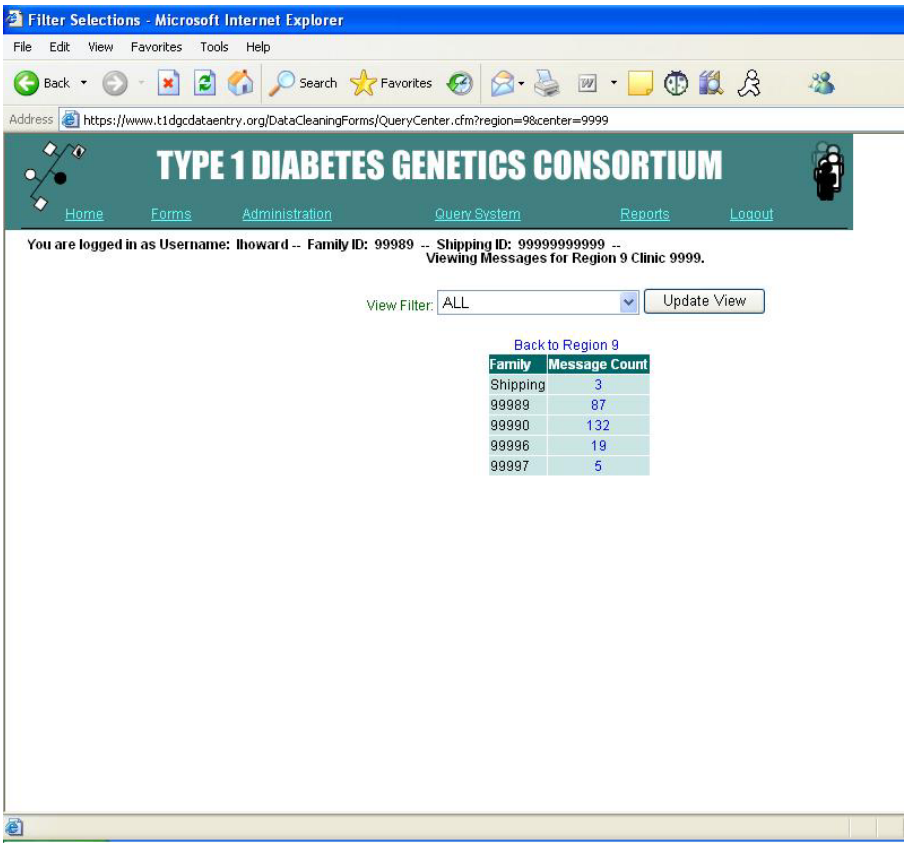


Figure 35. Query System List of Family IDs associated with a clinic.

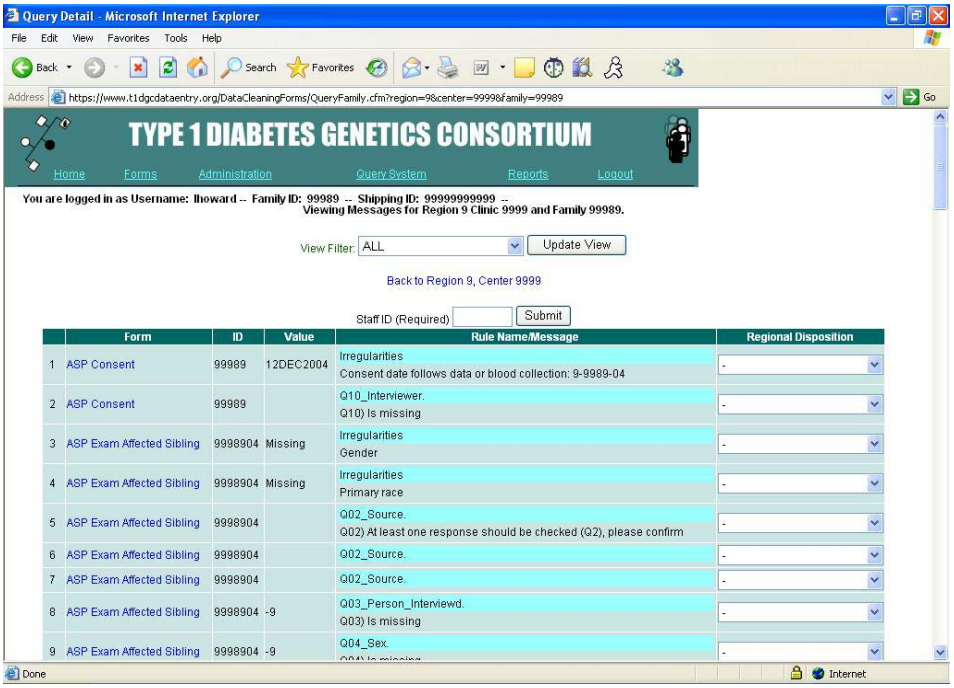


Figure 36. List of Queries associated with a Family ID.

7. In order to see the queries that must be answered, filter the query list to either “Unanswered” or “All but Past Verified,” and click “Update View.” To view all queries the Coordinating Center has reviewed, but not approved, filter the query list to “CoC” and click “Update View.”

8. Queries are listed with certain information in order to better help the user determine the query:

   a. *Form:* The form on which the query appears. The query system also contains cross-form checks. Cross-form queries will appear twice in the query list, once for each form (*i.e.,* if date of birth isn’t recorded the same on the Eligibility Form and the Exam Form, this query will appear under both forms). The query response on the forms in cross-form checks should be the same for both forms.

   b. *ID*: This lists the family or participant ID relevant to the form. For the Consent Summary Form and Eligibility Forms, this will be the family ID; for all other forms, the participant ID will appear in this column.

   c. *Value:* This is the value that has been entered in the T1DGC data entry system. This value should be checked against the forms by the Regional Network Center.

   d. *Rule Name/Message:* This will list the warning or error that was displayed during data entry. If this is a cross-form check, the rule name is displayed as “Irregularities” and follows with information specific to the problem encountered on the form.

e. *Regional Disposition:* This is the column the Regional Network Center and/or Coordinating Center will update according to how the query was resolved.

f. *OK:* This lists whether the Coordinating Center has reviewed the query once a response has been marked. If "Yes" is entered, the response is approved. If the Coordinating Center determines further action is needed, the Coordinating Center will update the "Regional Disposition" field.

D. Resolving Queries at the Regional Network Center

The Regional Network Center should have the copy of the family form set on hand when entering information into the query system in order to accurately portray how the query is resolved.

When a query is reported, the Regional Network Center first ensures the information was correctly entered into the database. The user should refer to the specified form and check what is on the form against what is reported in the "Value" column.

The user can also see the actual data entered into the system by clicking on the form link. Data may be corrected by accessing the form here.

1. Data Entry Errors "RNC - Data edited" – Data Forms

If a data entry error was made, the user can correct the data entry system by clicking on the form link. The user is required to scan/enter the relevant family or participant ID for validation (Figure 37). This will take the user directly to the form. The form is displayed exactly as in the normal data entry system, with the addition of a link to take the user back to the list of queries for the family (Figure 38).

Information already entered in the form is re-displayed as well as any warnings or errors previously displayed. Accessing and correcting the form through the query system updates the data entry form in the records.

A suggested strategy is to mark all queries that are data entry errors, filter the system to show only queries marked as “RNC-data edited” and print this page. This will allow the user to mark the queries that have been corrected as they make the corrections. Should multiple queries affect the same form, those corrections can be made together once the form has been displayed.

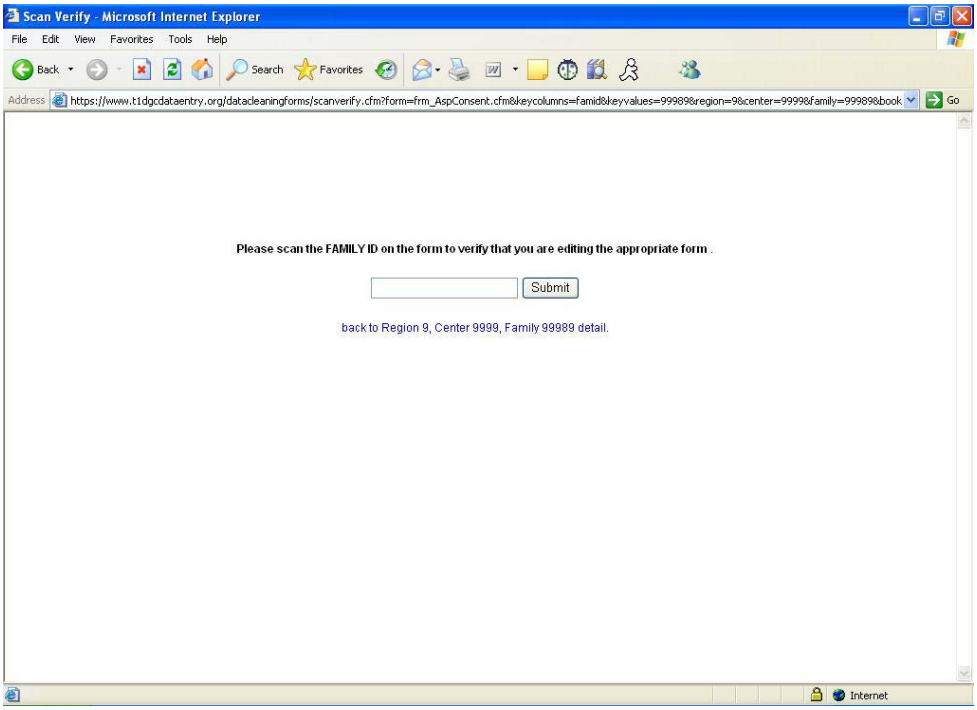


Figure 37. Enter the family or participant ID for validation.

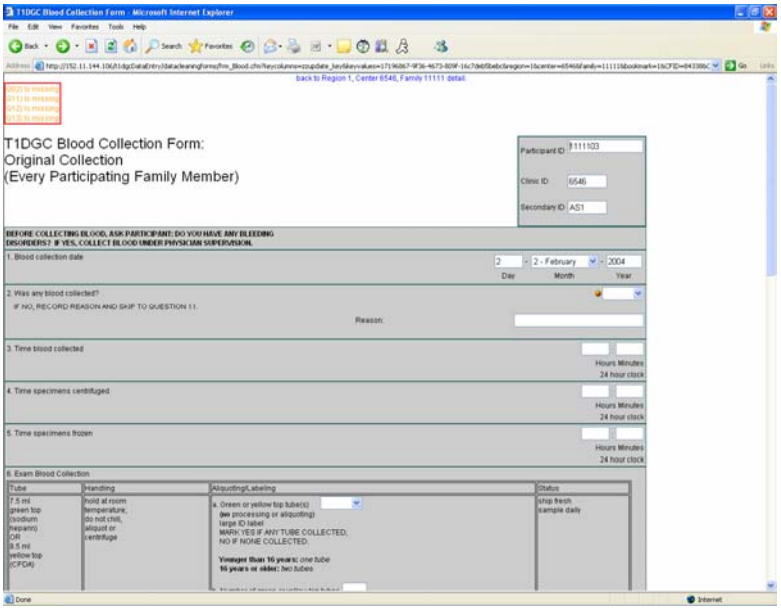


Figure 38. Correction of forms within the T1DGC Query System.

Once the form has been corrected, the user clicks “Save corrections” at the bottom of the page. If the corrections have been saved, “Record inserted” will appear at the top left hand side of the page (Figure 39). If errors (red dots) remain, the record cannot be inserted and “Record inserted” will not appear on the page. The user can return to the list of queries by clicking “back to Region x, Clinic x, Family x detail.”

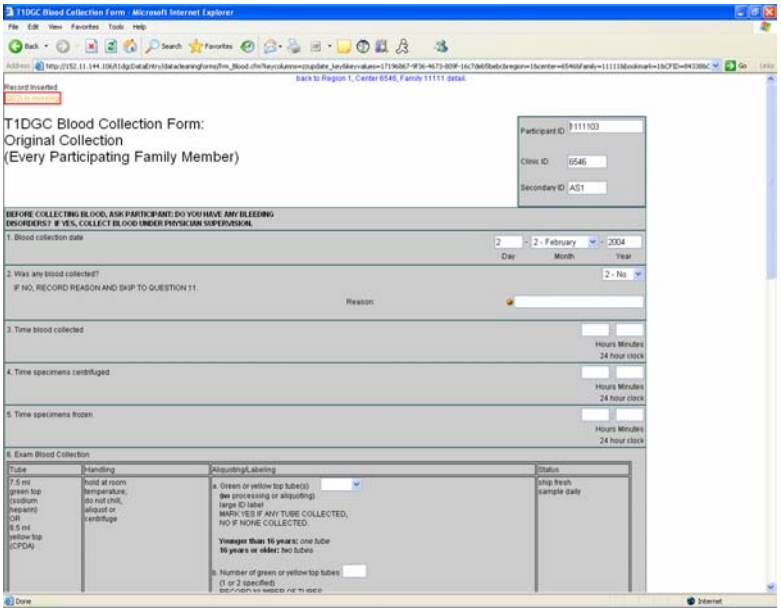


Figure 39. Corrections entered and saved in the database.

2. Queries confirmed by the Regional Network Center "RNC – Verified"

In some cases, the Regional Network Center may already know that the information in the database is correct. The Regional Network Center does not need to re-confirm a query with the clinic in cases such as these. The Regional Network marks queries as "RNC-Verified" only for cases where the Regional Network Center is sure the information is correct. Queries marked this way are reviewed by the Coordinating Center. If the Coordinating Center determines the query must be resolved at the clinic level, the Coordinating Center will update the "Regional Disposition" appropriately.

3. "Defer for Future Processing"

The Regional Network Center can mark "Defer for future processing" without sending the query to the clinic. This can be marked if the Regional Network Center has already asked the clinic about this query, but has not yet received a response and doesn't want to ask the clinic the same question twice. Queries marked as "Defer for future processing" will continue to appear until they are resolved. When filtering by "Unanswered," queries marked as "Defer for Future Processing" will not appear on the list.

4. Clinic Shipping Forms

Clinic Shipping are identified by the clinic ID rather than the Family ID. All clinic shipping forms are grouped together within a clinic. To view Clinic Shipping Form queries, click on "Shipping" from the family ID list (Figure 35). This will display all shipping queries for a clinic (Figure 40).

If a data entry error was made on a Clinic Shipping Form, the user can correct the data entry system by clicking on the form link. The user is required to scan/enter the relevant **shipping** ID for validation (Figure 41). This will take the user directly to the form. The form is displayed exactly as in the normal data entry system, with the addition of a link to take the user back to the list of queries for the family (Figure 42). Information already entered in the form is re-displayed as well as any warnings or errors previously displayed. Accessing and correcting the form through the query system

updates the data entry form in the records. Should multiple queries affect the same form, those corrections can be made together once the form has been displayed.

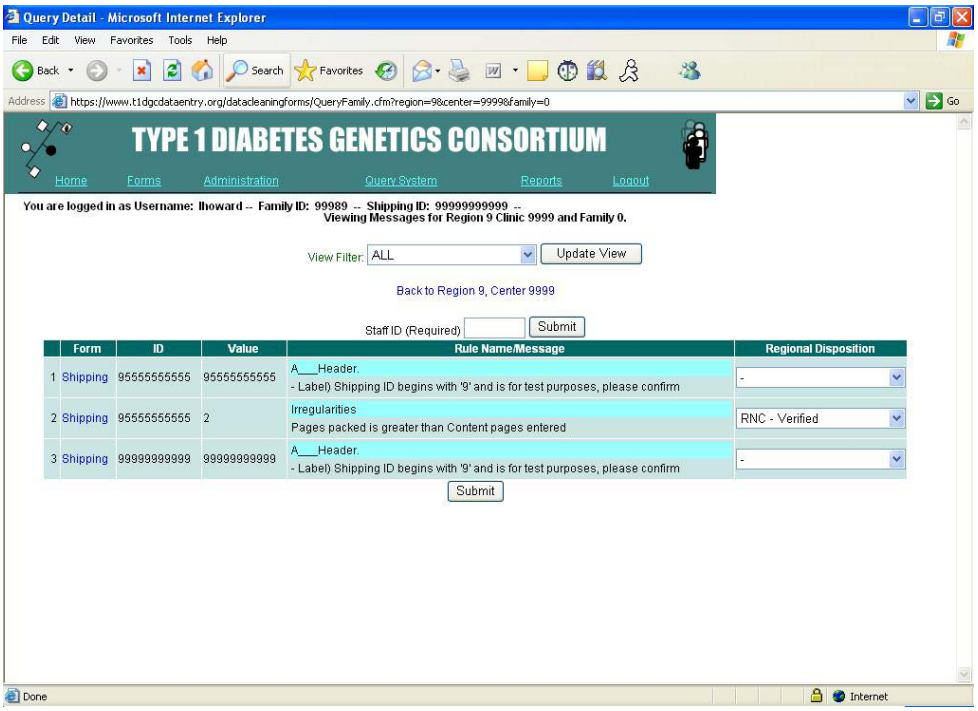


Figure 40. Query System for Shipping Forms

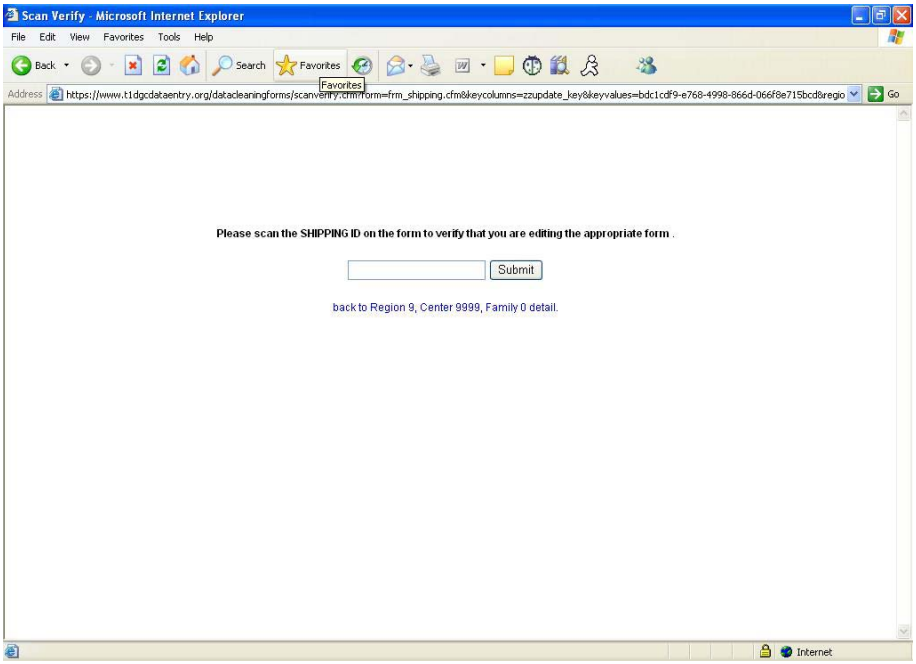


Figure 41. Enter Shipping ID to edit form

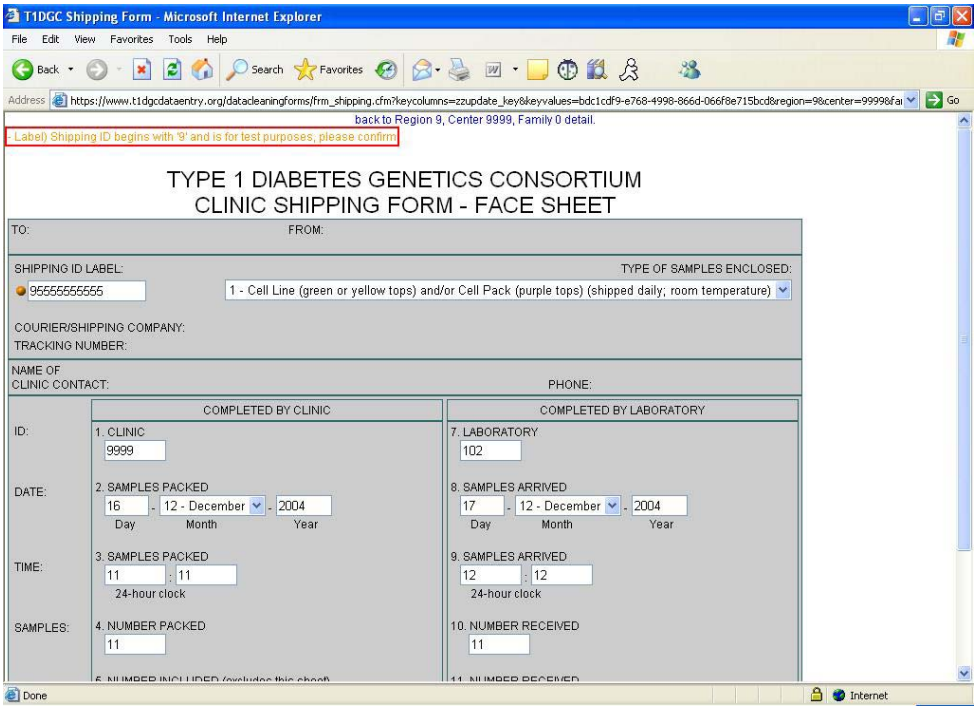


Figure 42. Correcting a Shipping Form through the Query System.

Once the form has been corrected, the user clicks “Save corrections” at the bottom of the page. If the corrections have been saved, “Record inserted” will appear at the top left hand side of the page. If errors (red dots) remain, the record cannot be inserted and “Record inserted” will not appear on the page. The user can return to the list of queries by clicking “back to Region x, Clinic x, Family x detail.”

5. Sending Queries to the Clinic “RNC - Data to be reviewed”

If the user determines a particular query is not a data entry error or is unaware of the circumstances surrounding the query, this query must be sent to the clinic for correction or verification. All queries that are not data entry errors should be marked “RNC - Data to be reviewed,” unless the Regional Network Center is aware of a special circumstance and can verify the query. The queries that are marked as “RNC – Data to be reviewed” will comprise the Query System Report that can be printed or e-mailed to clinic staff. The Query System Report is located on the “home page” of the query system.

Once the Regional Network Center has determined which queries need to be sent to the clinic, the Query System Report can be printed or saved to the user's computer (Figure 43). If the report is printed and sent in the post, the report will print one clinic on each page (*i.e.*, clinic 1020 and 1030 queries will not print on the same page). The Regional Network Center can save the report to their computer and open the report in a Microsoft Excel document in order to modify the report and send the report via e-mail to the clinic staff.

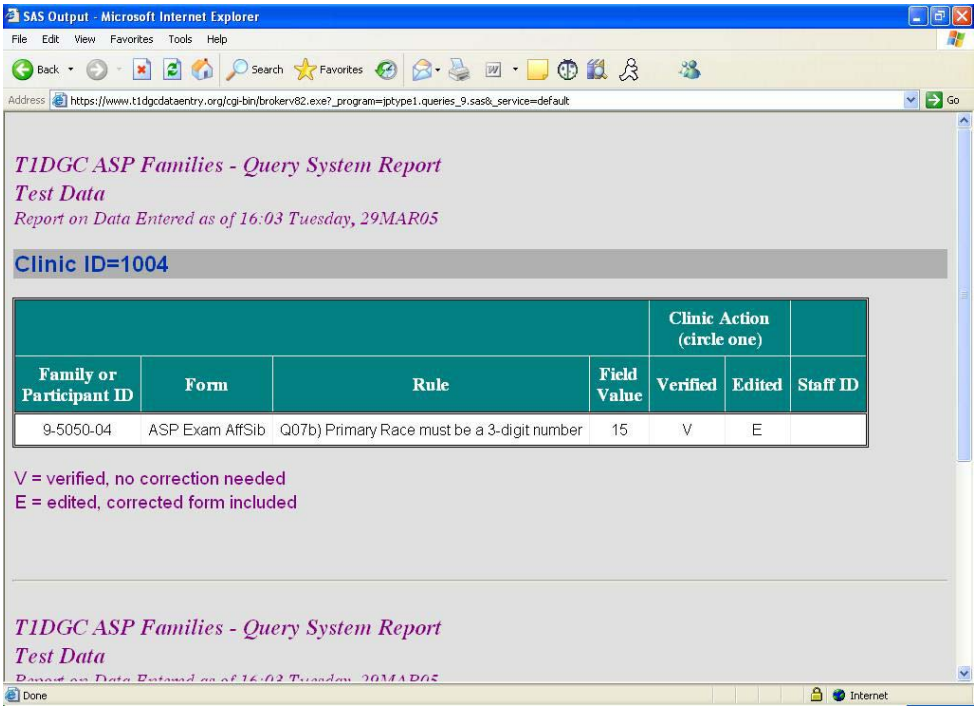


Figure 43. Query System Report.

The Regional Network Center should send this report as early as possible to the clinic staff to allow plenty of time for the clinic to correct or verify the list of queries and return the information back to the Regional Network Center for data entry. Once the Network Query System Report has been sent to the clinics, the Regional Network Center should set a reasonable deadline for the information to be received back at the Network Center (*i.e.*, one or two weeks).

Likewise, queries can be sent to clinic staff via e-mail without using the Query System Report. Queries cannot be corrected or confirmed with clinic staff over the phone; some type of written documentation must exist (for corrections, this must be the corrected form).

E. Resolving Queries at the Clinic

The queries that have been marked "RNC - Data to be reviewed" create a report listed on the home page of the query system, Query System Report. This report lists queries by clinic ID. The report lists family or participant ID, form, the query (rule), and the value. There is a place for the clinic staff to circle either "verified" or "edited" and to record their staff ID.

When the clinic receives the report, the clinic should pull all of the family and/or participant information and forms and review each of the queries. All queries that refer to data that are correct as is (*i.e.,* data is permanently missing or correct in its present form) should be marked "verified" and the staff ID must be recorded. Any queries that require a form to be edited should be marked "edited" and the staff ID must be recorded. Edited forms must be corrected, copied and sent to the Regional Network Center for data entry. (The clinic does not have to copy and send the entire form, but rather can send only the page that contains the corrected information.)

F. Entering Queries at the Regional Network Center the Clinic Has Resolved

When the completed report is received from the clinic, the Regional Network Center staff should check to ensure that each query has been answered, staff IDs have been recorded appropriately, and queries marked as edited are accompanied by the documented corrected form.

If all documents appear to be in order, the Regional Network Center should update the query system by selecting either "Clinic - Edited" or "Clinic - Verified." Clinic-edited corresponds to "edited" on the report. Clinic-verified corresponds to "verified" on the report. A valid staff ID must be entered at the top or bottom of the screen for "Clinic

- Edited" or "Clinic - Verified" to be entered. Queries marked "Clinic - Edited" should have accompanying form corrections.

A suggested strategy is to set the filter to "RNC - Data to be reviewed" and match the records in the Query System Report to the records in the query system and enter the clinic responses. Then reset the filter to "Clinic - Edited" to display those records that need correction. Multiple corrections affecting the same form can be made together once the form has been displayed.

If there are corrections to be made to the form, the user can correct the data entry system by clicking the form link. The user is required to scan/enter the relevant family or participant ID (see Section D1). This will take the user directly to the form. The form is displayed exactly as in the rest of the data entry system; the information already entered in the form is re-displayed, as well as any warnings or errors previously displayed. Accessing and updating the form through the query system updates the data entry of the form in the records.

All queries marked as "Clinic – Verified" will be reviewed by the Coordinating Center. The Coordinating Center will update the "Regional Disposition" field appropriately for queries that must be corrected and cannot be verified.

H. Confirming Verification at the Coordinating Center

The Coordinating Center reviews each query that is verified at either the Regional Network Center or clinic level. There are certain essential fields that must be corrected and cannot be verified (see Appendix C for a list of queries that must be corrected). Other fields should only be verified at the clinic level, and cannot be verified at the Regional Network Center.

The Coordinating Center has three options when reviewing queries that have been verified: instruct the Regional Network Center to send the query back to the clinic and/or lab for correction; instruct the Regional Network Center to send the query to the

clinic for correction or verification; or approve the verification. For guidelines as to the type of queries fitting into each of these categories, see Appendix.

1. Critical Fields "CoC: Must Correct"

The Coordinating Center has designated certain fields that cannot be left blank or incorrect. If the Regional Network Center or clinic verifies any queries in these critical fields, the Coordinating Center will instruct the Regional Network Center to send the query back to the clinic and/or laboratory (for some Shipping Form problems) for correction. A corrected version of the form must be received and re-entered at the Regional Network Center. Once the correction has been made, the Regional Network Center should update the "Regional Disposition" to "Clinic – Edited."

2. Queries that must be Verified by the Clinic "CoC: Clinic Verify"

The Coordinating Center has designated certain fields that cannot be verified by the Regional Network Center, but must be verified at the clinic level. If the Coordinating marks a query as "CoC: Clinic Verify" the query must be sent to the clinic, the Regional Network Center cannot verify this query. Documentation of verification by the clinic must be received at the Regional Network Center. Once the verification has been received, the Regional Network Center should update the "Regional Disposition" to "Clinic – Verified."

3. Approved Verification Queries

The Coordinating Center will review each of the queries. The Coordinating Center will mark "Yes" in the "Ok" column for queries that have been resolved correctly and no further action is required. Once these queries have been approved by the Coordinating Center, they will be removed from reports.

Occasionally there may be queries in the first two categories that are special circumstances. The Regional Network Center should communicate the circumstances with their Network Project Manager in order for the verification to be approved.

I. Useful Tips

1. When filtering the query system, the user must select the type of filter to apply and click "Update View."

2. When answering a query, once the proper choice has been made the staff ID must be completed (if required) and "Submit" must be selected in order for the query response to be accepted for each query. The "Submit" button will save all information entered in the query system. If a valid staff ID is not entered, **none** of the queries entered will be saved in the query system.

3. When a user first opens the query system, filtering by "unanswered" will allow the user to view only queries that have not been answered. As each query is answered, it will disappear off of the screen.

4. Similarly, when the Query System Reports are returned from the clinic, filtering by "RNC-data to be reviewed" will reveal the report subset and the queries will disappear from the screen once changed to either "Clinic-Edited" or "Clinic-Verified."

5. In order to view all queries they Coordinating Center has reviewed, but not approved, filter by "CoC." This allows the Regional Network Center to view all queries that have been answered but require further attention.

6. Using the "Back to" selection centered above the top of the tables throughout the query system marks the clinic or family that the user was just working on with a star. Clicking the "back" button on the web browser will not star the clinic or family last viewed.

VII. REPORTS

To view online reports, the user selects "Reports" from the upper navigational menu. Reports are divided into three sections: Recruitment, QC, and Statistical (Figure 44). To view a report, the user clicks on the name of the desired report to view and is taken directly to the report.

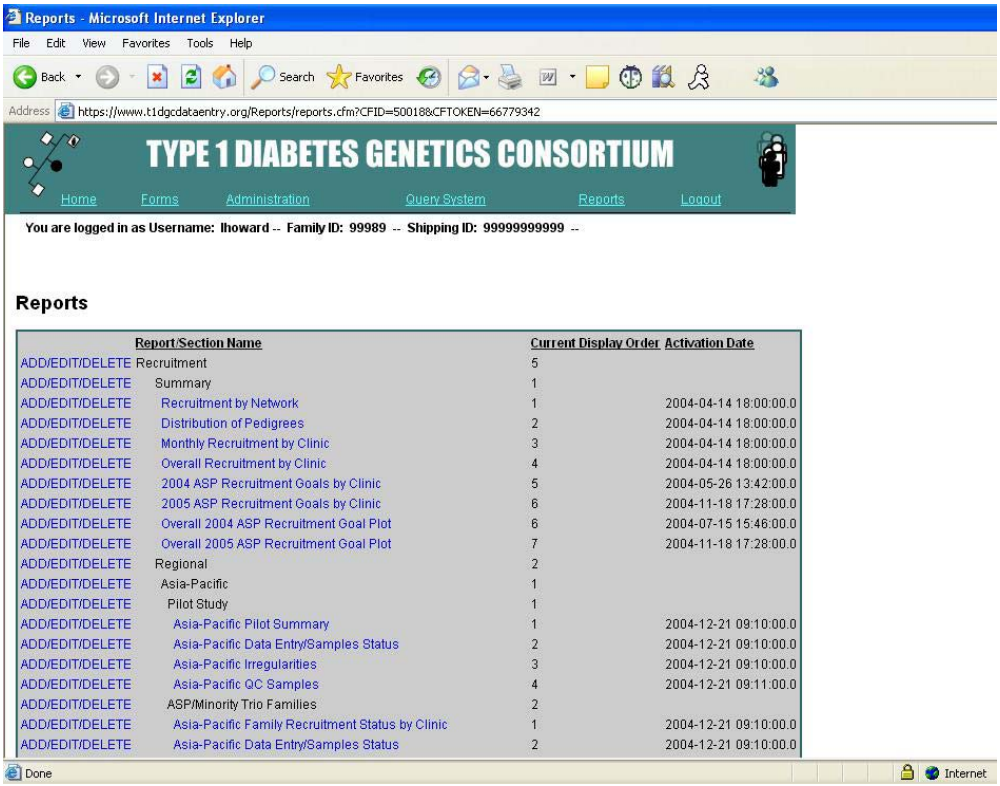


Figure 44. List of Online Reports

1. Monitoring of Reports

Monitoring of study data occurs at both the Coordinating Center and the Regional Network Center in order to achieve and maintain a high level of quality and comparability of data collection worldwide. Some of the monitoring and quality control reports are transmitted to the Regional Network Centers for immediate action and attention; other quality control and monitoring reports are generated for the Quality Control Committee, Project Office, Steering Committee, External Advisory Board, and Data and Safety Monitoring Committee on an as-needed basis.

2. Participant Shipments Report

The Participant Shipment Report was created to allow the user to determine all shipping IDs associated with a participant. The user selects "Participant Shipments" from the list of reports and is directed to enter the participant ID and the shipments and/or HLA plates to search for the participant ID (Figure 45). Participant IDs should be scanned or entered without any dashes (*e.g.*, 1000101). The user can check the shipments and/or HLA plates they want to have displayed or if no forms are checked, the report will default and display all the associated shipping IDs and HLA plates. The Participant Shipments Report lists all associated shipping IDs and/or HLA plates where the participant ID is listed. The number and type of samples included in each shipment is also displayed (Figure 46).

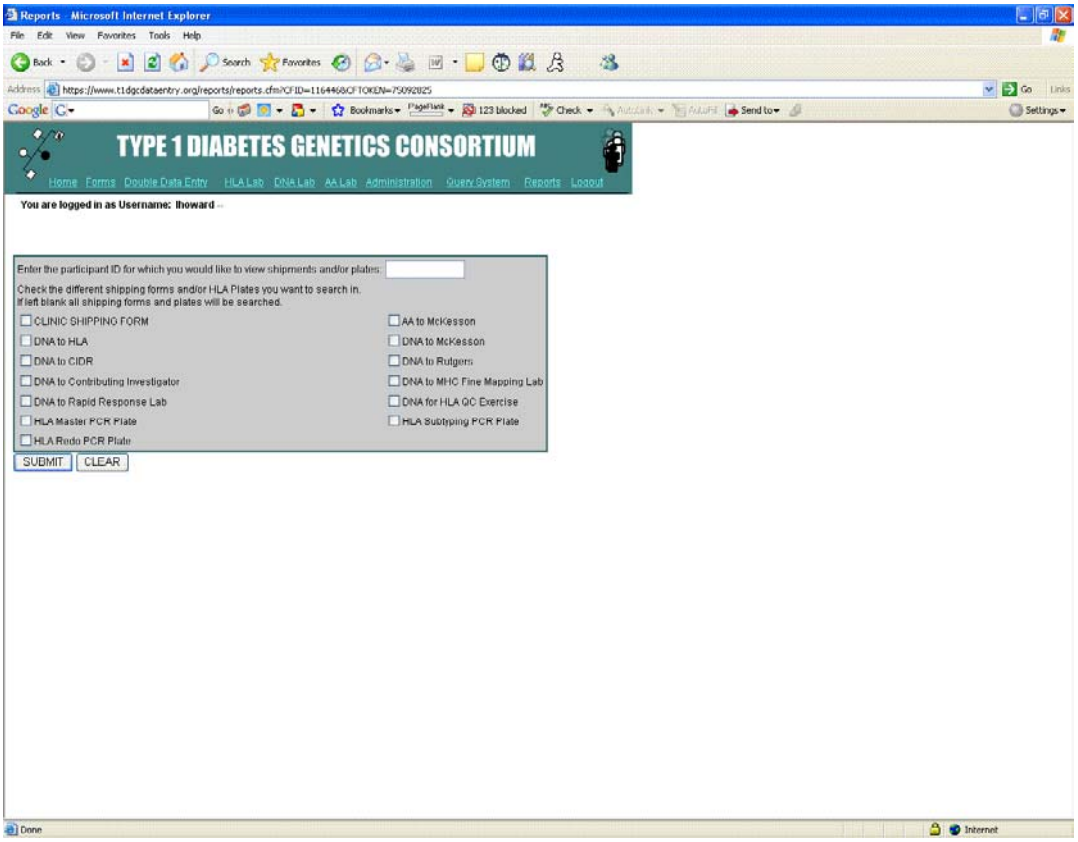


Figure 45. Entering a Participant ID into the Participant Shipments Report.

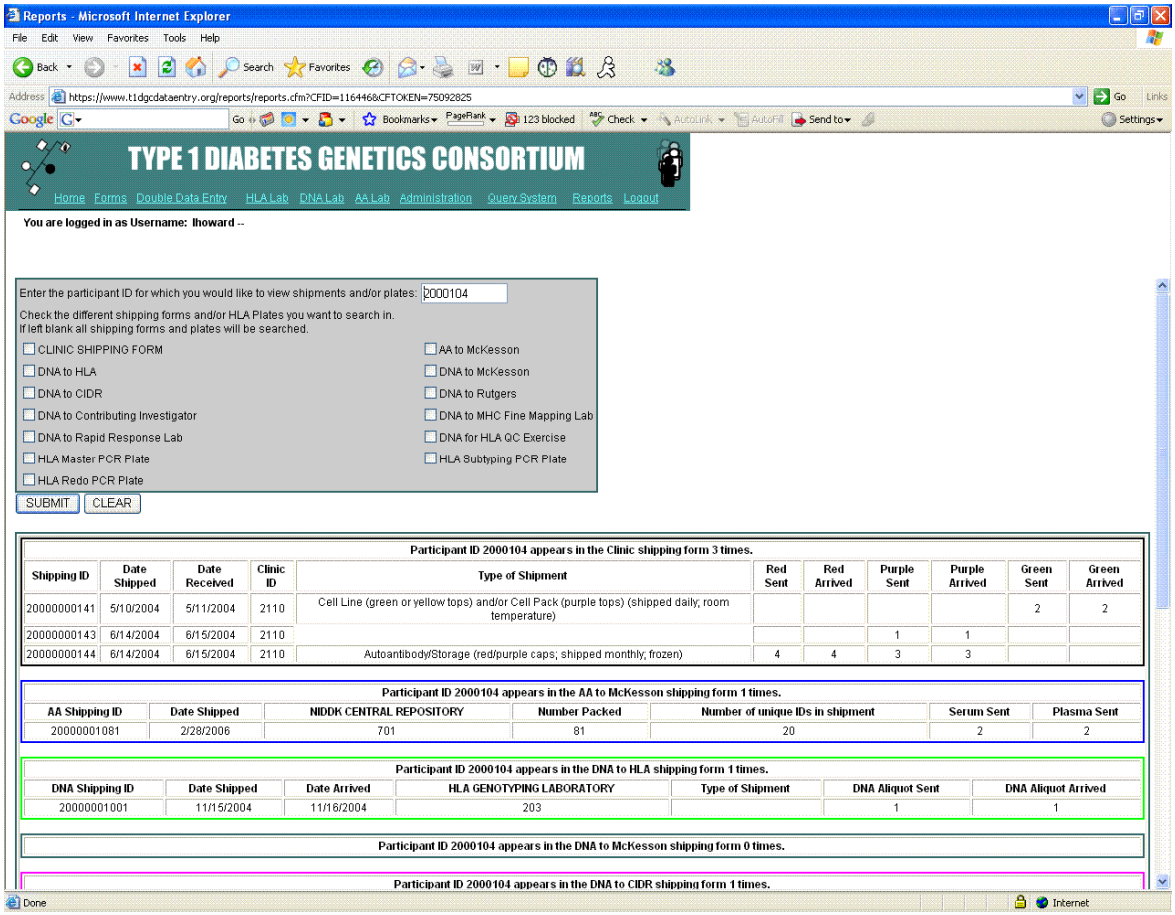


Figure 46. Participant Shipments Report listing all shipments associated with a participant.

VIII. SECURITY

Normally, data are transmitted across the Internet as plain text. It is possible, though highly unlikely, for someone to monitor this traffic, and using the proper equipment, reconstruct the individual pieces into the original data. Due to this threat, we employ a digital server certificate from Verisign, Inc. This certificate allows communications between the web server and the client system to be encrypted. This encryption is as advanced as is now allowable by the United States government. This is the same mechanism used by the banking industry and for electronic commerce. We feel strongly that this system provides more than adequate security against unauthorized use.

Restricted areas of the web site are protected by user login. Prior to gaining access to the restricted area, the user is required to enter a username and password that is checked against a database. If the combination is correct, a "flag" is set to allow the user to enter certain areas of the web site. If a user's username or password is entered incorrectly 3 times or more they are locked out of the system and must call or e-mail Dustin Williams at the Coordinating Center (dtwillia@wfubmc.edu). For security purposes, once a user has successfully logged into the system, inactivity for a period of 20 minutes automatically forces the user to re-authenticate prior to using the system again. It is strongly recommended that users log out of the system before leaving their work area for any extended period.

The Coordinating Center is protected by a Cisco firewall that limits the source and type of traffic coming into the institution. This product remains under constant monitoring and control.

IX. DATABASE MANAGEMENT SYSTEM (DBMS) SOFTWARE UPDATES

Throughout the T1DGC study, the Coordinating Center will periodically update the database management system. If significant changes are made to the system, all Regional Network Center staff are notified via the main page of the web site (Figure 47).

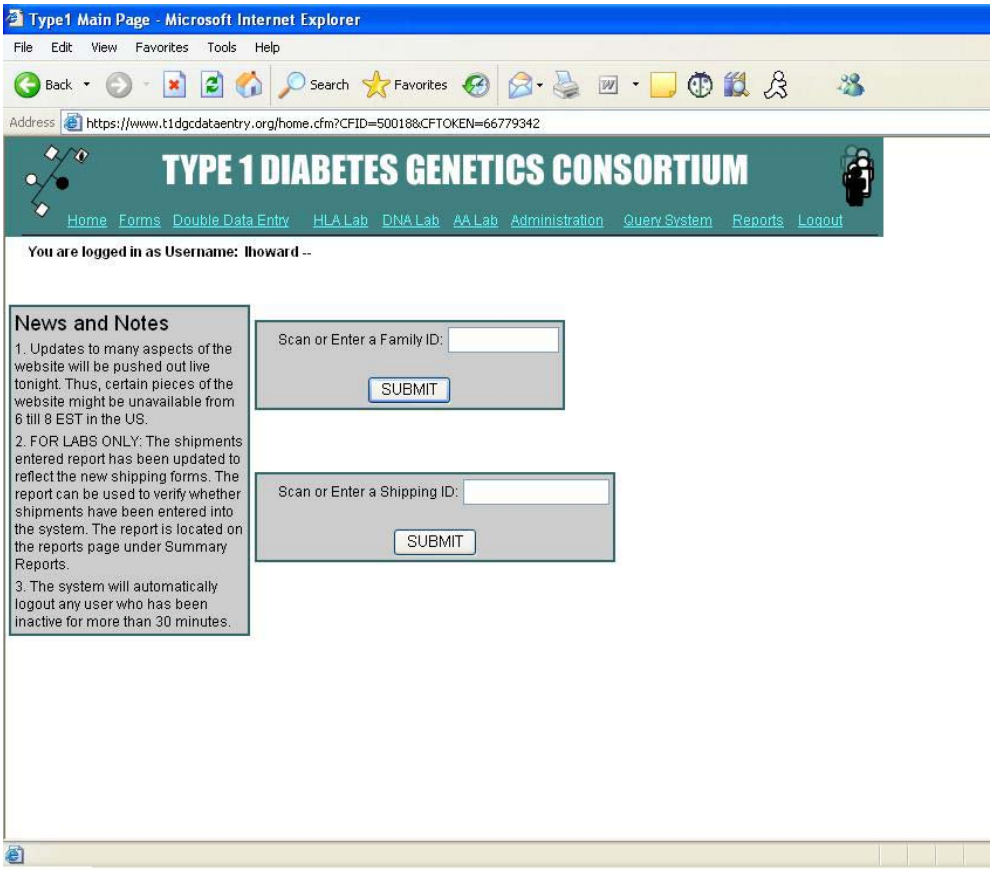


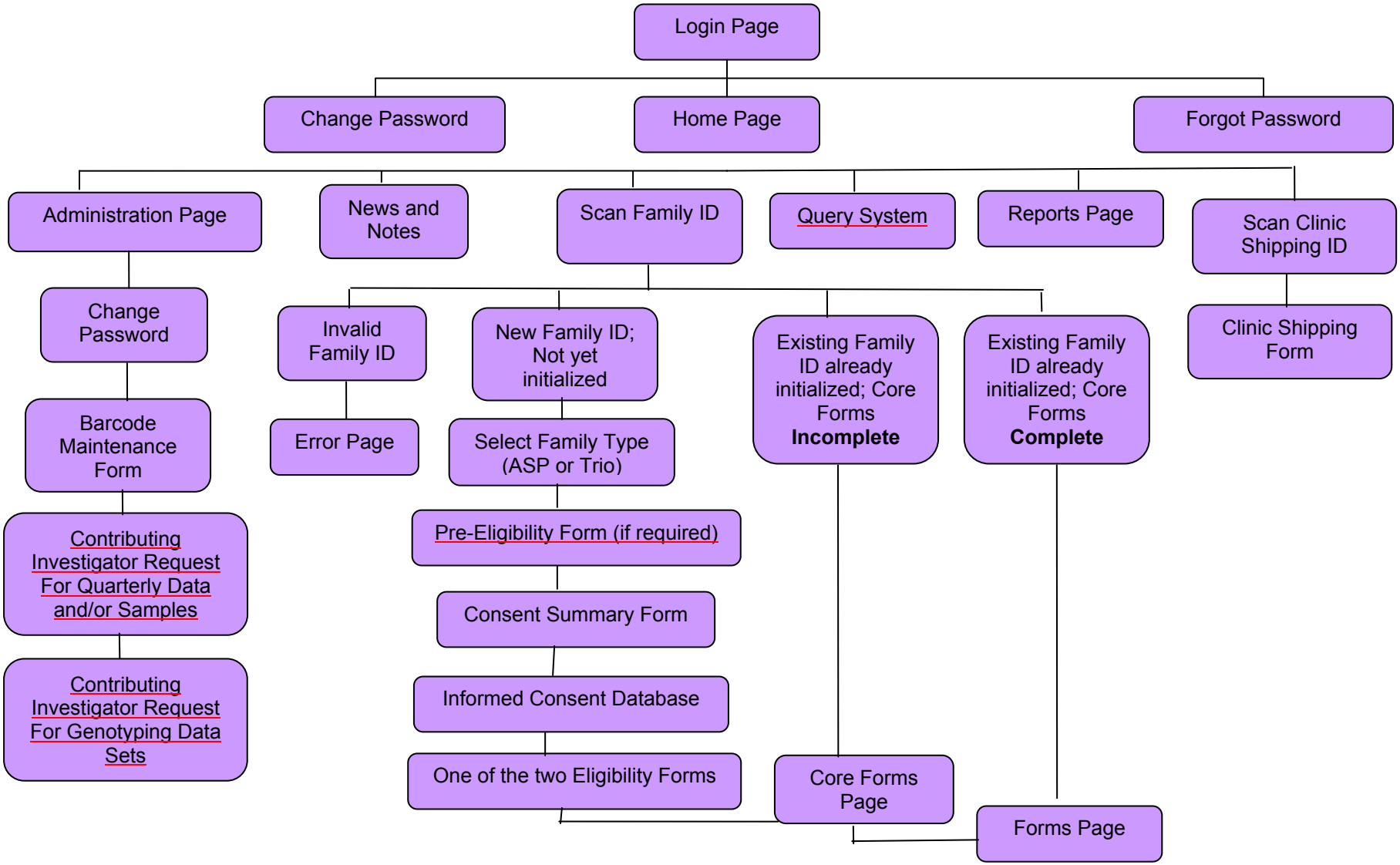
Figure 47. Home page with sample news.

X. DISASTER RECOVERY

All data, programs, code, and documents associated with the T1DGC project are backed up to a DLT tape library every night. These tapes are kept indefinitely and are located in a fireproof cabinet that remains locked at all times. Periodically, copies of tapes are moved to an off-site location for storage. In the event that there is loss of any data, the information can be restored from tape in a matter of hours. The entire computer facility is provided with conditioned power, UPS capability and environmental sensors with notification protocols.

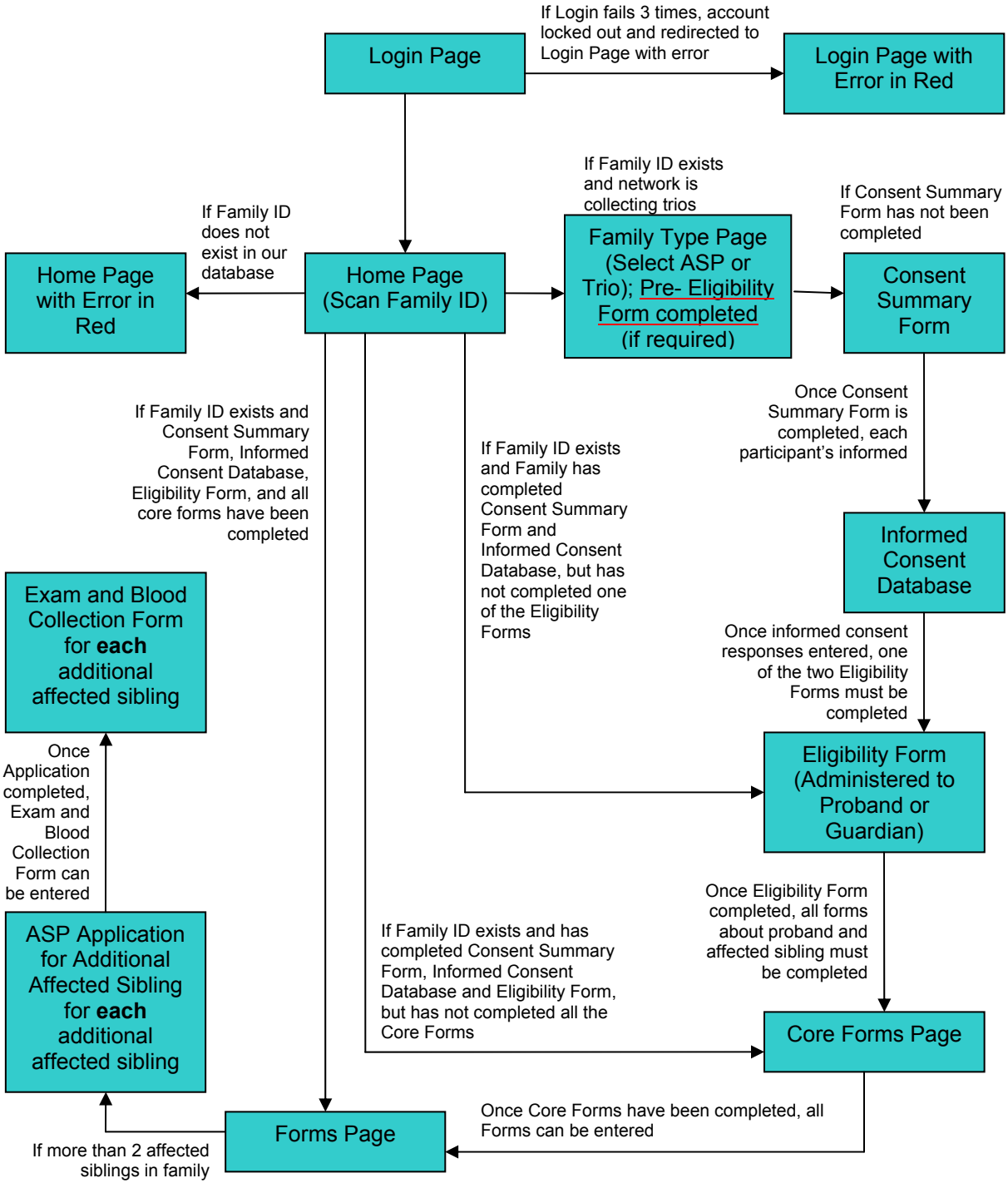
APPENDIX A

DATA ENTRY WEB SITE FLOW CHART



APPENDIX B

DATA ENTRY WEB SITE FORMS FLOW



APPENDIX C

QUERY SYSTEM RESPONSES

Form	Question	Rule Message	Who Can Verify Query
Blood	2	Should be missing, see blood collected	RNC, Clinic
Blood	3	Appears out of range	RNC, Clinic
Blood	4	Appears out of range	RNC, Clinic
Blood	4	Appears out of range (before time collected)	RNC, Clinic
Blood	4	Missing	RNC, Clinic
Blood	5	Appears out of range	RNC, Clinic
Blood	5	Appears out of range (before time collected)	RNC, Clinic
Blood	5	Missing	RNC, Clinic
Blood	6a	Confirm no	Clinic
Blood	6a	Should be missing, see blood collected	RNC, Clinic
Blood	6c	Conflicts with green tubes collected (6a)	RNC, Clinic
Blood	6c	Should be missing, see blood collected	RNC, Clinic
Blood	6d	Should be missing, see blood collected	RNC, Clinic
Blood	6e	Appears out of range	RNC, Clinic
Blood	6f	Confirm no	RNC, Clinic
Blood	6g	Appears out of range	Clinic
Blood	6h	Confirm no	RNC, Clinic
Blood	6h	Confirm yes, conflicts with Q6f	Must be corrected
Blood	6h	Should be missing, see blood collected	RNC, Clinic
Blood	7	Missing	Must be corrected
Blood	7	Should be missing, see blood collected	RNC, Clinic
Blood	10c	10c is no, 10e is yes	Must be corrected
Blood	10e	Confirm no	RNC, Clinic
Blood	10e	Missing	RNC, Clinic
Blood	11	Missing	Must be corrected
Blood	12	Missing	Must be corrected
Blood		Cell line samples inconsistent	Must be corrected
Blood		Cell pack collection missing	Must be corrected
Blood		Clinic ID inconsistent	RNC, Clinic
Blood		QC plasma samples inconsistent	Must be corrected

Blood		Samples inconsistent	Must be corrected
Blood		Serum samples inconsistent	Must be corrected
Blood Redraw	7a	Confirm no	Clinic
Blood Redraw	7c	Missing	Must be corrected
Blood Redraw	7h	Confirm Yes, conflicts with Q7f	Must be corrected
Blood Redraw		Cell line samples inconsistent	Must be corrected
Consent Summary	1	Consent data appears out of range	Must be corrected
Consent Summary		Consent date after exam date	Must be corrected
Elig Additional Affected Sibling	35	Appears out of range	RNC, Clinic
Elig Guardian	14	Time of diagnosis earlier than proband	RNC, Clinic
Elig Guardian	21	Confirm don't know	RNC, Clinic
Elig Guardian	25	Confirm don't know	RNC, Clinic
Elig Guardian	27	Should be missing, check Q26	RNC, Clinic
Elig Proband	9	Appears out of range	RNC, Clinic
Elig Proband	13	Appears out of range	RNC, Clinic
Elig Proband	13	Time of diagnosis earlier than proband	RNC, Clinic
Elig Proband	23	Appears out of range (less than elder sib)	RNC, Clinic
Elig Proband	29	Appears to be before interview date	RNC, Clinic
Elig Proband		Clinic ID inconsistent	RNC, Clinic
Exam Affected	7a	Should be no or not applicable	Must be corrected
Exam Affected	9	Confirm don't know	RNC, Clinic
Exam Affected		Clinic ID inconsistent	RNC, Clinic
Exam Parent	5	Appears out of range	RNC, Clinic
Exam Parent	6a	Should be no or not applicable	Must be corrected
Exam Parent	9b	Onset day is missing	RNC, Clinic
Exam Parent	14a	Confirm don't know	RNC, Clinic
Exam Parent	15a	Confirm don't know	RNC, Clinic
Exam Parent	16a	Appears out of range	RNC, Clinic
Exam Parent	16d	Appears out of range	RNC, Clinic
Exam Parent	16d	Appears out of range	RNC, Clinic
Exam Proband	7a	Should be no or not applicable	Must be corrected
Exam Proband	9	Confirm don't know	RNC, Clinic
Exam Proband	11a1	Confirm don't know	RNC, Clinic
Exam Proband	11a2	Confirm don't know	RNC, Clinic
Exam Proband	11a3	Confirm don't know	RNC, Clinic
Exam Proband	11b1	Confirm don't know	RNC, Clinic
Exam Proband	11b2	Confirm don't know	RNC, Clinic
Exam Proband	11b3	Confirm don't know	RNC, Clinic
Exam Proband	11c	Confirm don't know	RNC, Clinic

Exam Proband	12a1	Confirm don't know	RNC, Clinic
Exam Proband	12a2	Confirm don't know	RNC, Clinic
Exam Proband	12a3	Confirm don't know	RNC, Clinic
Exam Proband	12b1	Confirm don't know	RNC, Clinic
Exam Proband	12b2	Confirm don't know	RNC, Clinic
Exam Proband	12b3	Confirm don't know	RNC, Clinic
Exam Proband	12c	Confirm don't know	RNC, Clinic
Exam Proband	12c1	Appears out of range	RNC, Clinic
Exam Proband	12c4	Appears out of range	RNC, Clinic
Exam Proband	13	Appears to be out of range	RNC, Clinic
Exam Proband		Clinic ID inconsistent	RNC, Clinic
Exam Unaffected		Clinic ID inconsistent	RNC, Clinic
Shipping (Clinic)	3	Appears out of range	RNC, Clinic
Shipping (Clinic)	4	Appears out of range	RNC, Clinic
Shipping (Clinic)	5	Appears out of range	RNC, Clinic
Shipping (Clinic)	8	Arrived date 2 more than packed date	RNC, Clinic
Shipping (Clinic)	10	Number received not equal to number sent	Must be corrected
Shipping (Clinic)	11	Pages received not equal to number included	Must be corrected
Shipping (Clinic)		Clinic ID inconsistent	RNC, Clinic
Shipping (Clinic)		Pages packed greater than pages entered	Must be corrected
Shipping (Clinic)		Arrived doesn't match number sent or comments	Must be corrected
Shipping (Clinic)		Cell line samples inconsistent	Must be corrected
Shipping (Clinic)		Cell pack samples received above limit	Must be corrected
Shipping (Clinic)		Number received not equal to number sent	Must be corrected
Shipping (Clinic)		Plasma samples received above limit	Must be corrected
Shipping (Clinic)		Purple arrived appears out of range	Must be corrected
Shipping (Clinic)		QC Plasma samples inconsistent	Must be corrected
Shipping (Clinic)		Samples inconsistent	Must be corrected
Shipping (Clinic)		Serum samples inconsistent	Must be corrected
Shipping (Clinic)		Tubes broken, shouldn't be checked	Must be corrected

SPECIMEN TRACKING AND INVENTORY SYSTEM

TABLE OF CONTENTS

Page

I. INTRODUCTION

The purpose of this chapter is to provide detailed instructions to the DNA Repositories and the Autoantibody and Storage Laboratories for the specimen shipping and tracking system used in the Type 1 Diabetes Genetics Consortium (T1DGC). The information that follows also will be useful to clinic and Regional Network staff and should guide staff at each critical point in the specimen tracking process. It is crucial to the success of the T1DGC that all staff involved, directly or indirectly, follows the outlined tracking procedures. (Appendix A provides an overview of the specimen tracking process.)

II. SHIPMENTS FROM CLINICS TO LABORATORIES

A. Types of Specimen Shipments

1. There are three types of specimen shipments from the clinics:
   (a) cell line samples (green or yellow top tubes);
   (b) cell pack samples from the EDTA plasma tubes (purple top tubes); and
   (c) serum (red top) and plasma (purple top) samples for autoantibody analysis in the proband and the affected sibling and long-term storage samples for all participants.

2. Cell line samples are shipped at ambient temperature for arrival at the DNA Repository within 24 hours of collection (or as close to this time as possible, given geographic constraints). Green top (sodium heparin) tubes are used in all networks with the exception of the United Kingdom Network where yellow top (CPDA) tubes are used to collect the cell line samples.

3. The cell pack that remains after aliquoting the EDTA plasma is frozen (in the re-capped collection tube) and shipped monthly to the DNA Repository for DNA extraction.

4. Serum samples (maximum of 5 per participant) and plasma samples (maximum of 4 per participant) are placed in storage boxes (with a 10x10 grid) and frozen;

the frozen samples are shipped monthly to the Autoantibody and Storage Laboratory. (Appendix B provides the specific requirements for sample placement within the box and labeling the top of the storage boxes.)

5. The Autoantibody and Storage Laboratory staff is responsible for selecting one serum sample for each proband (purple-striped label) and affected sibling(s) (green-striped labels) included in the shipment. The selected serum samples are analyzed for autoantibodies. All other serum and plasma samples included in the shipment are placed into a freezer for storage in the boxes in which they were shipped. (Appendix C provides information regarding the T1DGC scheme for participant identifiers.)

B. Completing Shipping Forms at the Clinics

1. The clinic staff completes two *T1DGC Shipping Forms* when shipping specimens to the laboratories: the *Face Sheet* and the *Contents Sheet.* Both forms are completed for each specimen shipment and are included in the shipping container. (The T1DGC data forms are located on the T1DGC web site: www.t1dgc.org).

2. The clinic staff affixes a bar-coded Shipping ID label on the *Face Sheet* and the shipping container. Shipping IDs identify each unique shipment and are associated with a set of participant IDs through the *Contents Sheet*. Shipping IDs are 11-digit numbers that begin with the network identifier (*i.e.*, 1=Asia-Pacific; 2=European; 4=North American; and 5=United Kingdom). **The system for entry of the *Shipping Forms* cannot be accessed without a Shipping ID label on the *Face Sheet.***

3. The clinic staff completes the upper portion of the *Face Sheet* as follows:
   (a) full address of the clinic and the laboratory;
   (b) Shipping ID Label in the designated space on the form (and a second identical Shipping ID Label on the shipping container);

(c) courier or shipping company used (*e.g.*, Federal Express or World Courier) and the reference or tracking number;

(d) type of samples included in the shipment (*i.e.*, cell line, cell pack **or** autoantibody/storage); and

(e) name of the clinic contact and his/her phone number.

4. The clinic staff completes the left side of the lower portion of the *Face Sheet* as follows:

(a) clinic ID;

(b) date and time the shipment was packed at the clinic;

(c) total number of samples packed, confirmed by both counting samples and adding the numbers in the "number vials" column on the contents sheets;

(d) number of contents pages included; and

(e) ID of person packing the samples and completing the shipping forms.

5. The clinic staff completes the *Contents Sheet* by affixing a unique, bar-coded participant ID label that will match the bar-coded Participant ID label on the specimen(s) included in the shipment.

6. More than one *Contents Sheet* may be included in each shipment, depending on the number of samples included. The number of pages attached and each page number should be filled in at the top of the contents pages by the clinic staff (*e.g.*, Page 1 of 6, Page 2 of 6, etc.).

7. The clinic staff records the number of each type of sample included in the shipment (*e.g.*, red cap=serum sample; purple cap or top=EDTA plasma sample OR cell pack; green/yellow top=sodium heparin or CPDA cell line sample). The clinic staff also indicates whether the serum and/or plasma samples were hemolyzed by marking the appropriate check boxes in the column labeled “Comments on Samples”.

8. The clinic staff makes two copies of each completed *Face Sheet* and *Contents Sheet*. The original set of shipping forms is included with the samples shipped to the laboratory. One copy is retained at the clinic. The second copy is forwarded from the clinic to the Regional Network Center.

C. Completing Shipping Forms at the Laboratories

1. When the shipment is received at the laboratory, verify contents of the shipment and record the specified information on the lower right portion of the *Face Sheet*. The following items are recorded by the person receiving the shipment:
   (a) laboratory ID;
   (b) date and time the shipment arrived at the laboratory;
   (c) total number of samples received, confirmed by both counting samples and adding the numbers in the "number vials" column on the *Contents Sheets*;
   (d) number of contents pages received; and
   (e) initials of person receiving the samples and completing the shipping forms.

2. Complete the *Contents Sheet* by counting and recording the number of samples of each vial color in the column labeled “Arrived” for inventory purposes and acknowledgment of arrival.

3. In the column labeled “Comments on Samples”, mark the following selections to indicate discrepancies in the number of samples shipped and the condition of samples in the shipment:
   (a) Tube(s) broken: if the green or yellow top tubes for cell lines are broken or the EDTA cell pack tube is broken. If a tube (or tubes) broke during shipment, record the number of **un**broken tubes received.
   (b) Samples thawed: if sample shipment is thawed upon receipt at the laboratory. If samples thawed, record the total number of samples received.

(c) Samples missing: if the number of samples "Sent" by the clinic is not the same number of samples received at the laboratory.

(d) Other: if none of the above indicates the problem with the shipment. Record any specific comments in the margin of the form.

D. Data Entry of Shipping Forms at Laboratories

1. Go to the T1DGC data entry site (https://www.t1dgcdataentry.org). Laboratories need the T1DGC bar-code scanner and a computer with an Internet connection and compatible browser (*e.g.*, Internet Explorer 5.5.2 or higher version).

2. When you access the web site, the first page you encounter is the Log-in Page (Figure 1). Enter your unique lab username and password and click the Login button to access the Specimen Tracking data entry system.

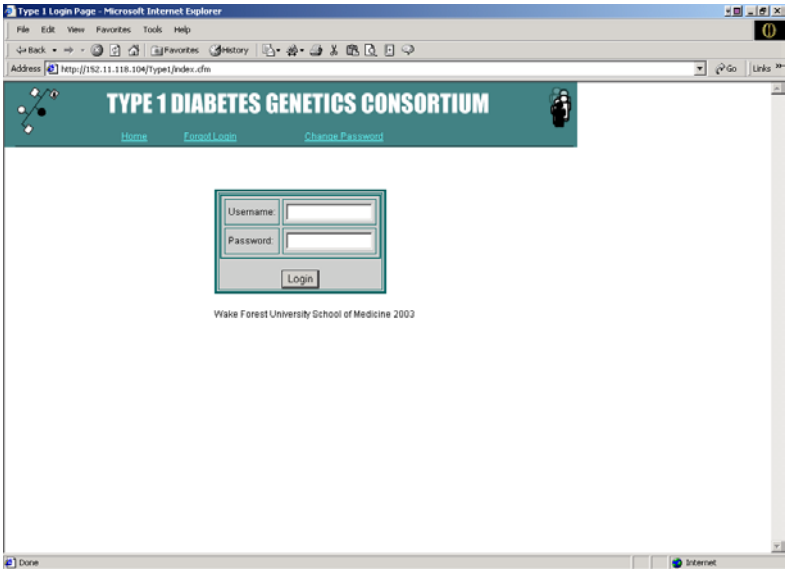


Figure 1. Log-in page.

3. Position the cursor in the box titled "Enter or Scan a Shipping ID" (Figure 2). Scan the bar-coded Shipping ID label from the *Face Sheet*. This will take you to a data entry screen for the *Face Sheet*.

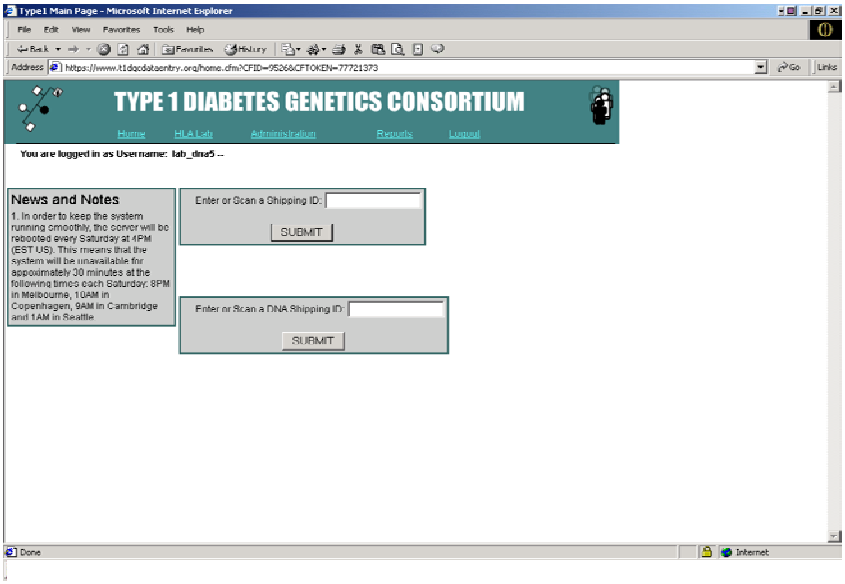


Figure 2. Scan shipping ID from bar-coded labels.

4. If this shipment has never been entered, the *Shipping Form - Face Sheet* will be displayed. Data enter the entire form (except the "TO:" and "FROM:" address fields at the top of the page) and press the "Save" button at the bottom of the page (Figure 3).

5. *Shipping Form - Face Sheet* Warnings and Errors

   (a) Warnings (Orange Dots):

      (i) If data entered are out of an "expected" range, the form is redisplayed with an orange dot at the top describing the potential error (Figure 4).

      (ii) Confirm that the data on the form matches that entered on the web page.

      (iii) If the data match, scroll to the bottom and press the "Save with Warnings" button. If the data do not match, correct the discrepant data and press the "Save" button.

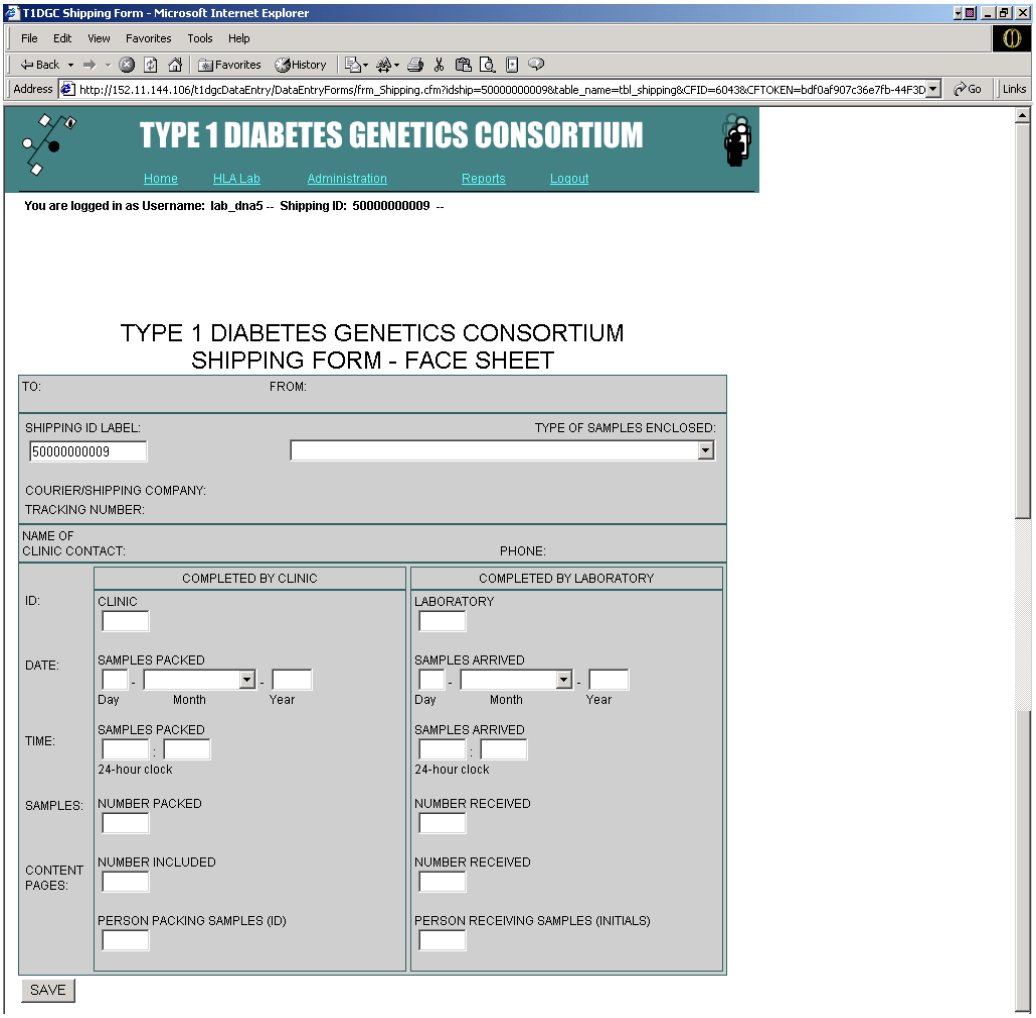


Figure 3. *T1DGC Shipping Form - Face Sheet.*

(b) Errors (Red Dots):

(i) If data entered are out of an “expected” range or is blank and the field is **required**, the form is redisplayed with a red mark at the top describing the potential error.

(ii) Confirm that the answer on the form matches the web page.

(iii) If the data match, the laboratory must confirm the response with the clinic that shipped the samples. Lab staff **cannot** correct data on shipping forms without consulting the clinic.

(iv) If the laboratory confirms that the data are valid, the Coordinating Center should be contacted.

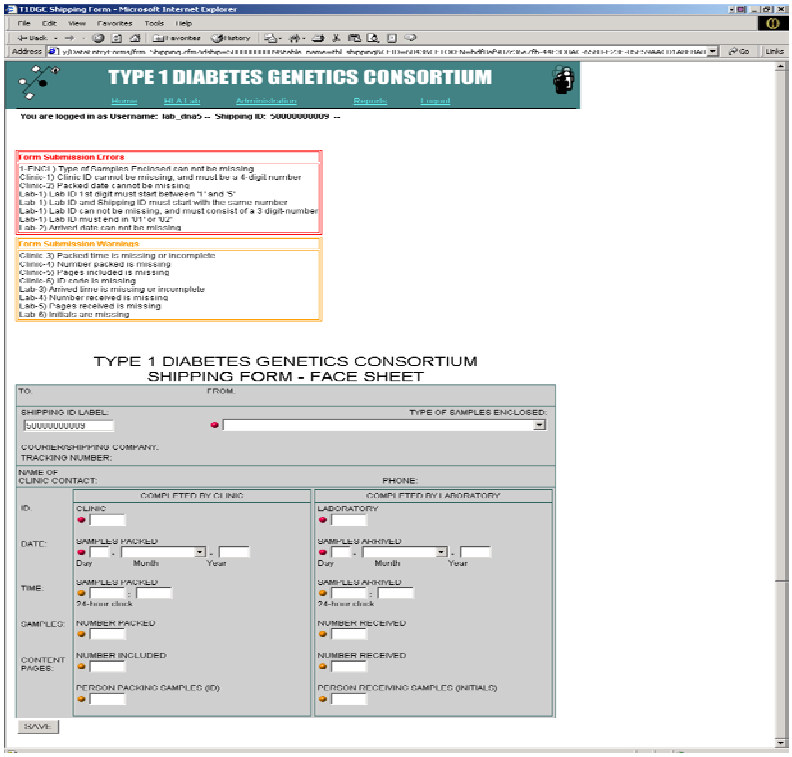


Figure 4. *Shipping Form – Face Sheet* with warnings and errors.

6. *Shipping Form - Contents Sheet*

(a) After a successful save of the *Face Sheet*, the system displays the shipping form *T1DGC Shipping Form - Contents Sheet* (Figure 5).

(b) Data enter the entire **page** and press the **Save** button at the bottom of the page.

(c) The *Contents Sheet* included with the shipment may be more than one page, depending on the number of samples included in the shipment. That is, if specimens for more than six participants are included in a shipment, one or more additional *Contents Sheets* will be associated with the *Face Sheet*. **The *Contents Sheets* are entered and saved one page at a time.**

(d) Warning and error messages will appear if data entered are out of "expected" range as discussed previously for *Face Sheet*.

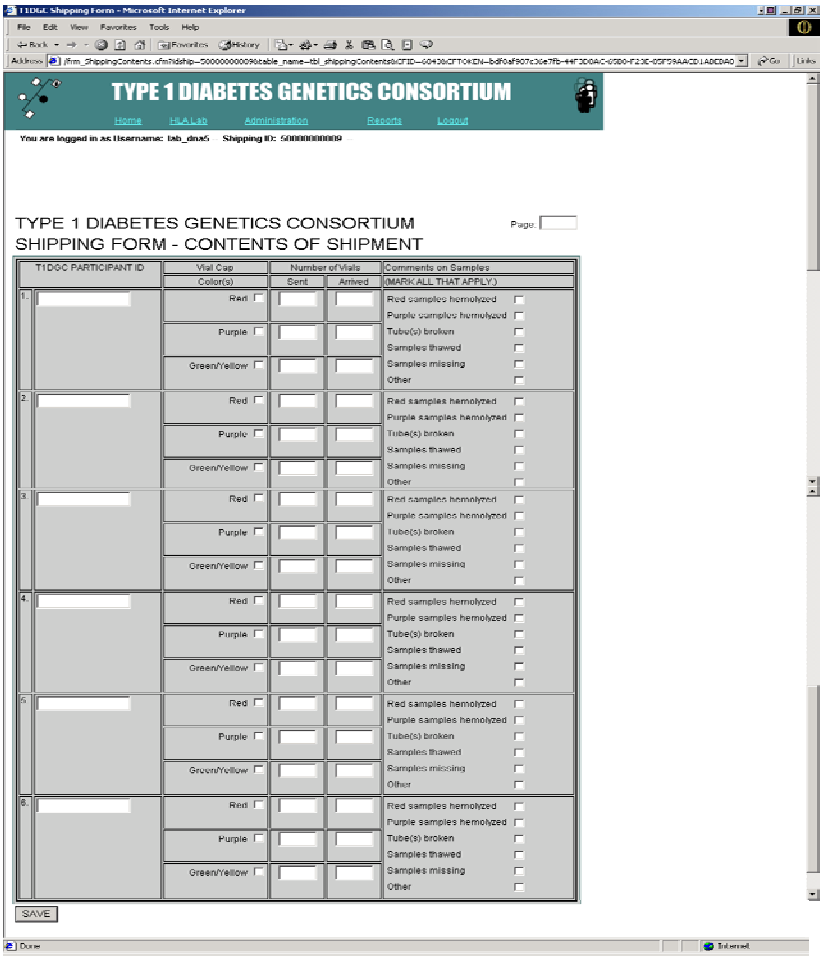


Figure 5. *T1DGC Shipping Form - Contents Sheet.*

7. Shipping Form Selection Page

(a) After a successful save of a *Contents Sheet*, the Shipping Form Selection Page is displayed (Figure 6).

(b) The user has three options from this page:

(i) "Start over with a new shipment" which returns the user to the screen with the box titled "Enter or Scan a Shipping ID" (Figure 2).

(ii) "Add a Shipping Contents Sheet" which opens up a blank Contents Sheet (Figure 5).

(iii) "View a Shipping form page" which displays previously entered shipping forms and what is currently saved in the database for the *Face Sheet* or any *Contents Sheet*.

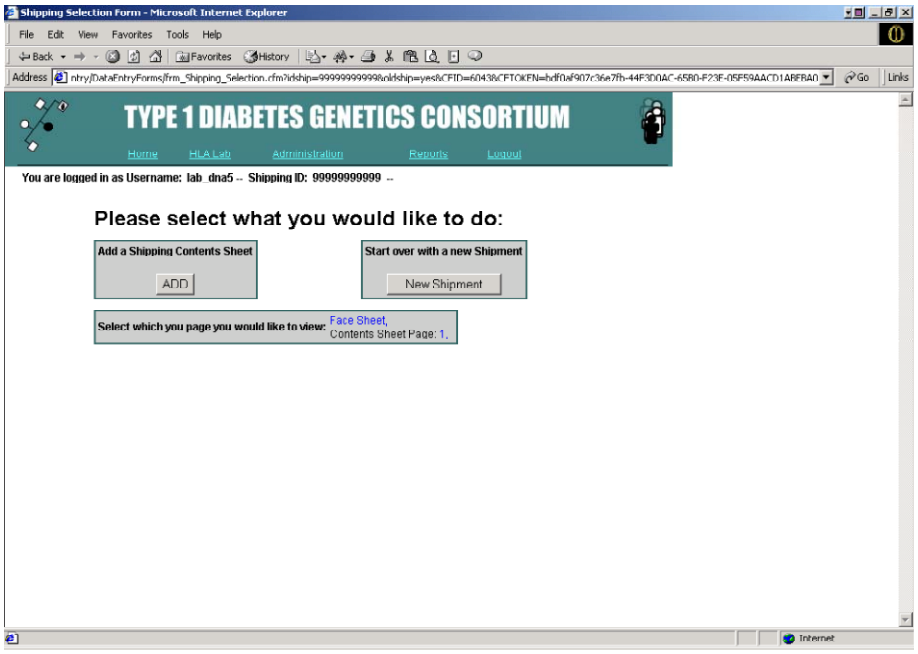


Figure 6. Shipping Form Selection Page.

8. Log Out

   (a) Log out when you are not using the system.

   (b) The system will automatically log you out when there has been 20 minutes of inactivity.

9. Once the receiving process and data entry for the shipment has been completed, make a copy of the forms for retention at the laboratory and forward the completed original shipping forms to the Regional Network Center as final documentation of the shipment. The original shipping forms can be batched weekly (or on a schedule specified by the Regional Network Center) via regular postal service. (Appendix D provides the contact and shipping information for the Network Coordinators.)

E. Verifying Shipping Form Data Entry at the Regional Network Center

1. Each sample shipment generates two versions of each shipping form at the Regional Network Center: one forwarded by the clinic, indicating completion of the form when the shipment was sent (clinic version); and the original from the

laboratory, indicating completion of the form when the shipment was received (laboratory version).

2. The Regional Network Center must verify laboratory entry of *Shipping Forms* for all clinic shipments. The Regional Network Center will contact laboratories regarding any *Shipping Forms* received from the clinics that do not appear in the Specimen Tracking system.

3. The Regional Network Center also is responsible for verifying that all information has been entered correctly. The Regional Network Center staff can modify the shipping form at any point in the shipping process if information has been entered incorrectly, but must communicate with the laboratory and the clinic about any changes. Changes must be reflected on all copies of the shipping forms (clinic, laboratory and Regional Network Center) as follows: mark through the incorrect data with two horizontal lines, record and circle the correct data, and initial and date the correct response.

4. The *T1DGC Blood Collection Forms* received from the clinics are data entered at the Regional Network Center. These data form the basis for a comparison of samples collected in the clinic with samples that were shipped from the clinic and received at the laboratory (obtained from the shipping forms).

5. Discrepancies between blood collection and shipping forms are forwarded from the Coordinating Center to the Regional Network Center for resolution with the clinics and/or receiving laboratories.

III. SHIPMENTS FROM DNA REPOSITORY TO OTHER LABORATORIES

A. Overview

1. The DNA Repository is responsible for generating bar-coded ID labels and a shipping record for cell line and/or DNA samples shipped elsewhere. The bar-coded labels for such samples are either the T1DGC participant ID (preferred), or

a local laboratory ID that is associated with the participant ID in a database available to the Coordinating Center.

2. The Coordinating Center provides a web-based application for recording all IDs for samples shipped from the DNA Repository for receipt at other locations. The Coordinating Center also provides the DNA Repository with the Shipping ID labels to be used for all shipments from a Network Repository to another facility or laboratory.

3. At this time, planned sample shipments from the DNA Repository to other sites include the following:
   (a) DNA sample to the Network HLA Genotyping Laboratory (Appendix E provides contact information and shipping addresses for all of the T1DGC HLA Genotyping Laboratories);
   (b) DNA sample to CIDR for genome scan;
   (c) cell line sample to the NIDDK Central Repository (located in the United States);
   (d) cell line and/or DNA sample for participants contributed by a specific investigator; and
   (e) DNA sample to investigators with approval from the T1DGC Access Committee.

   The T1DGC Specimen Tracking: DNA Repository Flow Chart in Appendix D provides an overview of this process.

B. Completing DNA Shipping Forms for Shipments to Other Laboratories

1. The DNA Repository staff completes two *T1DGC DNA Shipping Forms* when shipping specimens to the laboratories: the *Face Sheet* and the *Contents Sheet.* Both forms are completed for each specimen shipment and are included in the shipping container. (Data forms are on the T1DGC web site: www.t1dgc.org).

2. The DNA Repository staff affixes a bar-coded Shipping ID label on the *Face Sheet* and the shipping container. Shipping IDs identify each unique shipment and are associated with a set of participant IDs through the *Contents Sheet*. Shipping IDs are 11-digit numbers that begin with the network identifier (*i.e.*, 1=Asia-Pacific; 2=European; 4=North American; and 5=United Kingdom). **The system for entry of the *Shipping Forms* cannot be accessed without a Shipping ID label on the *Face Sheet.***

3. The DNA Repository completes the upper portion and the left side of the lower portion of the *Face Sheet*.

4. The DNA Repository staff completes the *Contents Sheet* by affixing a unique, bar-coded participant ID label that will match the bar-coded Participant ID label on the specimen(s) included in the shipment.

5. More than one *Contents Sheet* may be included in each shipment, depending on the number of samples included. The number of pages attached and each page number should be filled in at the top of the contents pages by the DNA Repository staff (*e.g.*, Page 1 of 6, Page 2 of 6, etc.).

6. The staff records the number of each type of sample included in the shipment (*e.g.*, DNA and/or cell line).

7. The DNA Repository staff makes two copies of each completed *Face Sheet* and *Contents Sheet*. The original set of shipping forms is included with the samples shipped to the receiving laboratory. One copy is retained at the DNA Repository. The second copy is forwarded to the Regional Network Center from the DNA Repository.

C. Data Entry of Shipping Forms at DNA Repositories

1. Go to the T1DGC data entry site (https://www.t1dgcdataentry.org).

2. Enter your unique lab username and password on the Log-in Page and click the Login button to access the Specimen Tracking data entry system (Figure 7).

3. Position the cursor in the box titled “Enter or Scan a DNA Shipping ID” (Figure 8). Scan the bar-coded DNA Shipping ID label from the *Face Sheet*. This will take you to a data entry screen for the *Face Sheet*.

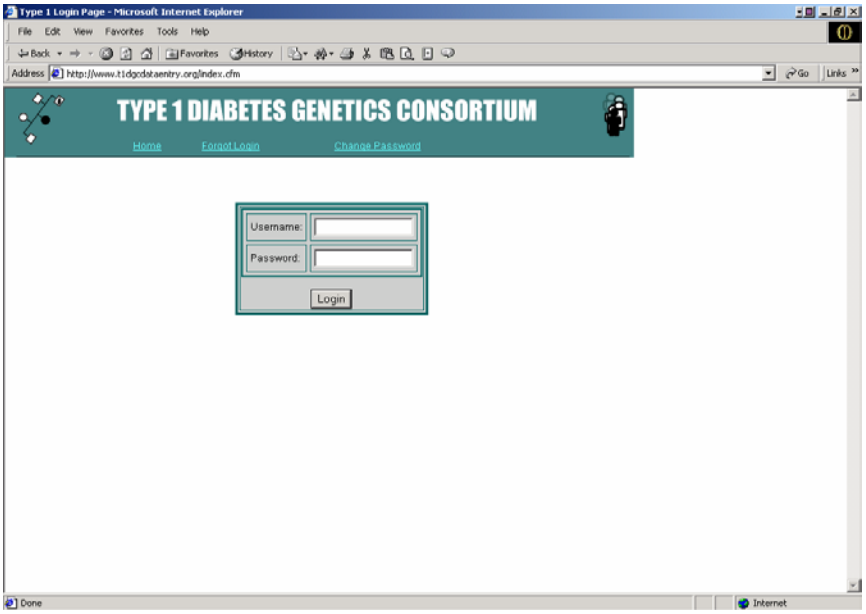


Figure 7. Log-in page.

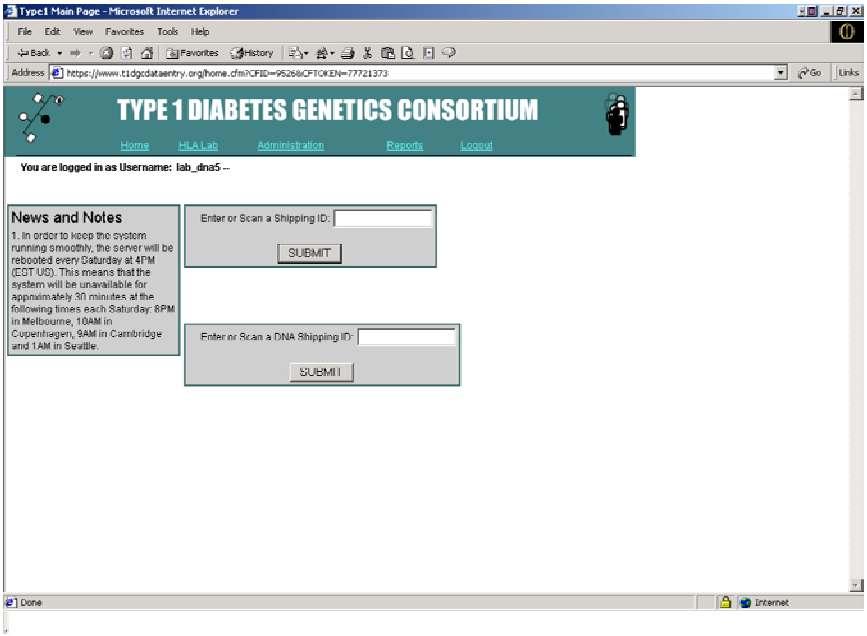


Figure 8. Scan shipping ID from bar-coded labels.

4. If this shipment has never been entered, the DNA Shipping Form Face Sheet will be displayed. Data enter the upper portion and the left side of the lower portion of the form and press the “Save” button at the bottom of the page (Figure 9).

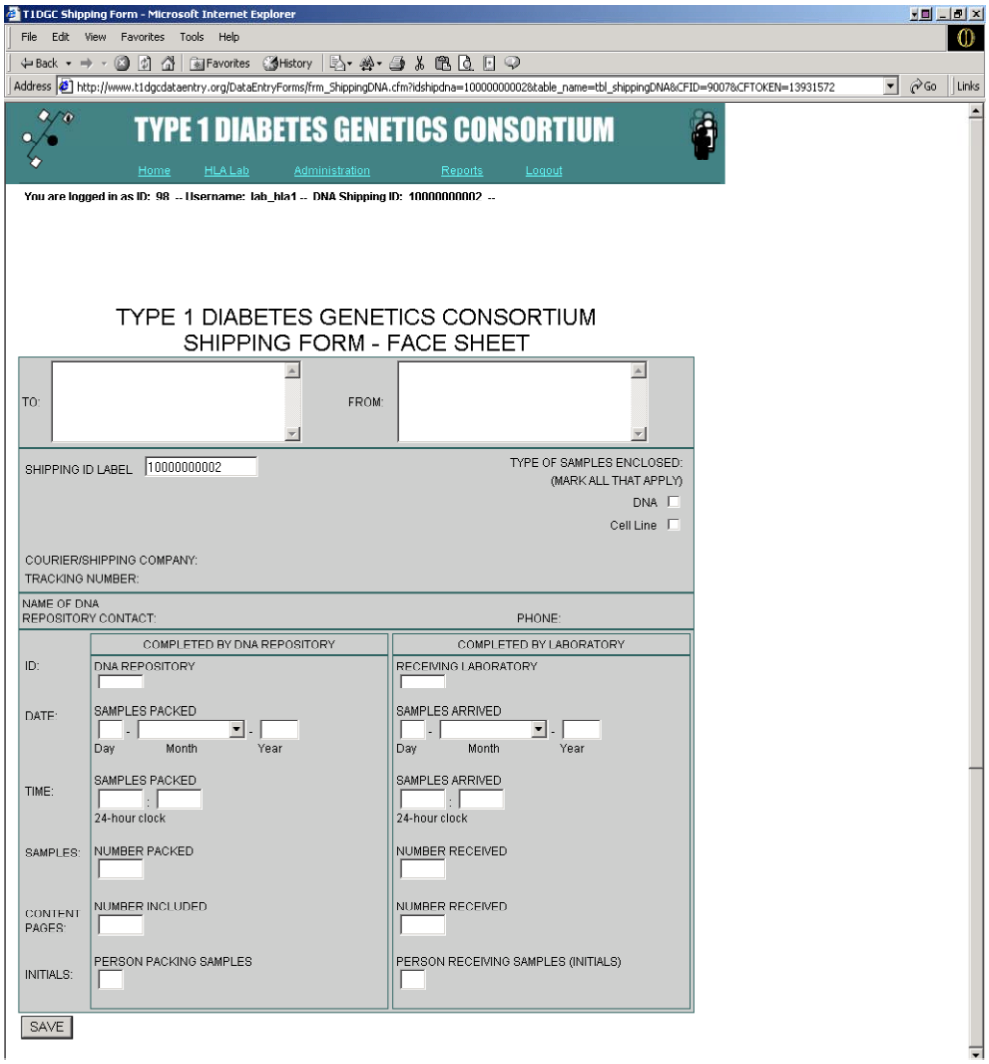


Figure 9. *DNA Shipping Form - Face Sheet.*

5. *Shipping Form - Face Sheet* Warnings and Errors

(a) Warnings (Orange Dots):

(i) If data entered are out of an “expected” range, the form is redisplayed with an orange dot at the top describing the potential error (Figure 10).

(ii) Confirm that the data on the form matches that entered on the web page.

(iii) If the data match, scroll to the bottom and press the “Save with Warnings” button. If the data do not match, correct the discrepant data and press the “Save” button.

(b) Errors (Red Dots):

(i) If data entered are out of an “expected” range or is blank and the field is **required**, the form is redisplayed with a red mark at the top describing the potential error.

(ii) Confirm that the answer on the form matches the web page.

(iii) If the data match and the laboratory confirms data are valid, the Coordinating Center should be contacted.

6. *Shipping Form - Contents Sheet*

(a) After a successful save of the Face Sheet, the system displays the shipping form *T1DGC Shipping Form - Contents Sheet* (Figure 11).

(b) Data enter the entire **page** and press the **Save** button at the bottom of the page.

(c) The *Contents Sheet* included with the shipment may be more than one page, depending on the number of samples included in the shipment. That is, if specimens for more than six participants are included in a shipment, one or more additional *Contents Sheets* will be associated with the *Face Sheet*. **The *Contents Sheets* are entered and saved one page at a time.**

(d) Warning and error messages will appear if data entered are out of “expected” range as discussed previously for *Face Sheet*.

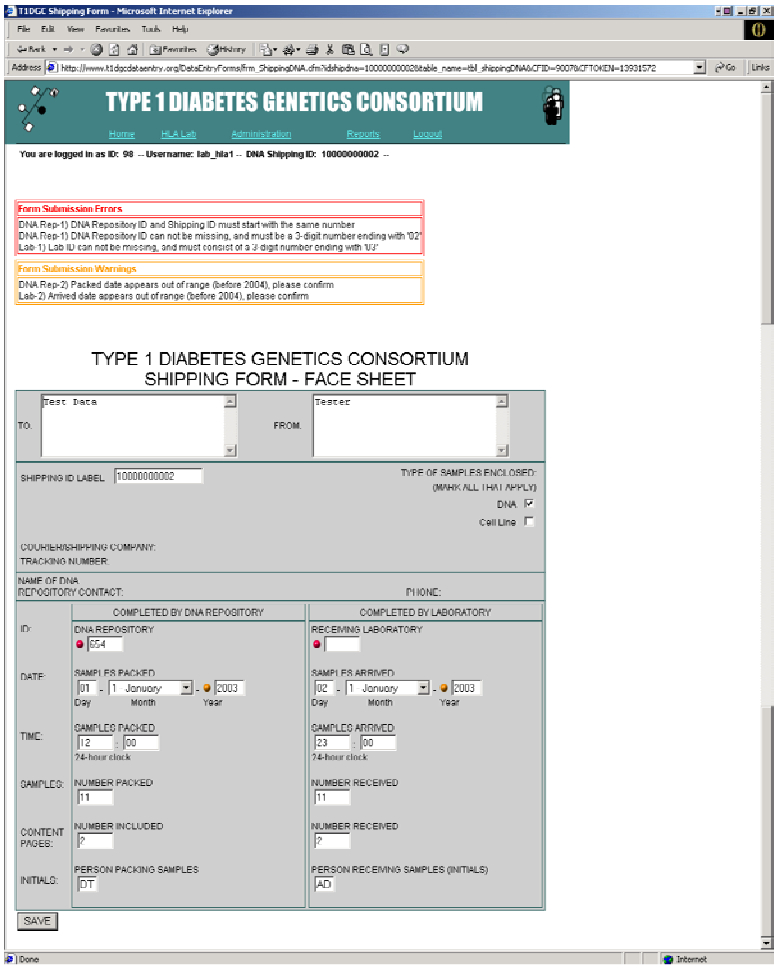


Figure 10. *Shipping Form – Face Sheet* with warnings and errors.

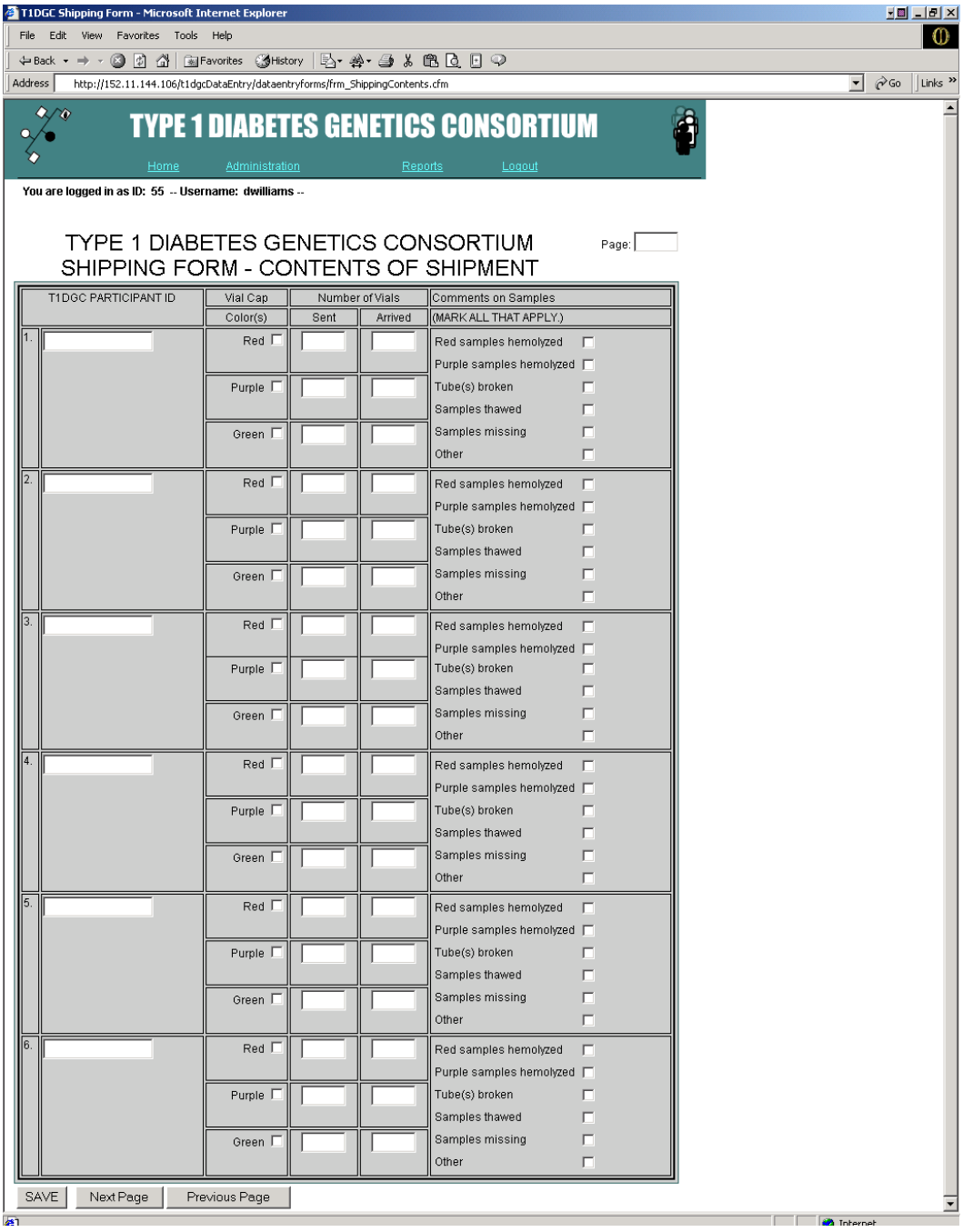


Figure 11. *T1DGC Shipping Form - Contents Sheet.*

7. Shipping Form Selection Page

(a) After a successful save of a *Contents Sheet*, the Shipping Form Selection Page is displayed (Figure 12).

(b) The user has three options from this page:

(i) "Start over with a new shipment" which returns the user to the screen with the box titled "Enter or Scan a Shipping ID" (Figure 8).

(ii) "Add a Shipping Contents Sheet" which opens up a blank Contents Sheet (Figure 11).

(iii) "View a Shipping form page" which displays previously entered shipping forms and what is currently saved in the database for the *Face Sheet* or any *Contents Sheets*.

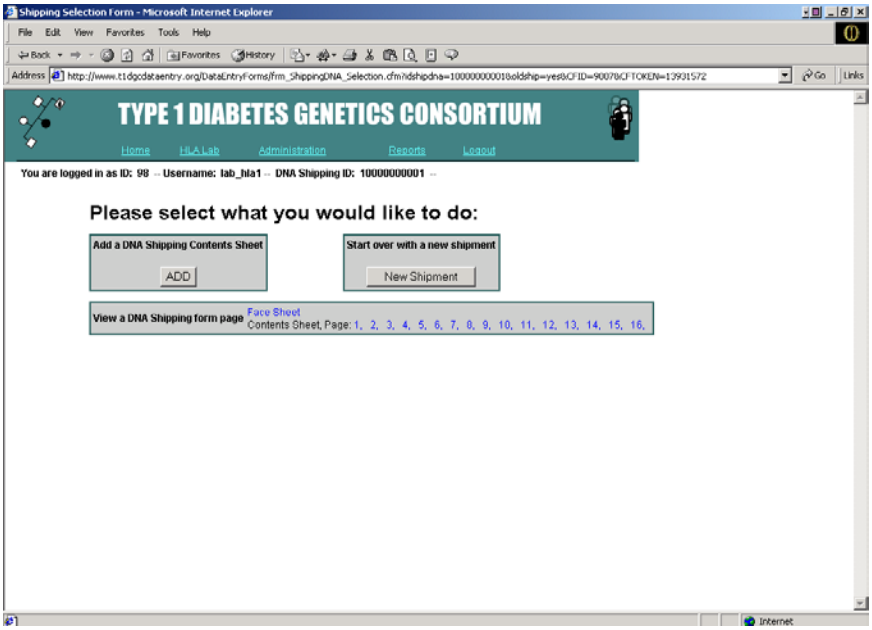


Figure 12. Shipping Form Selection Page.

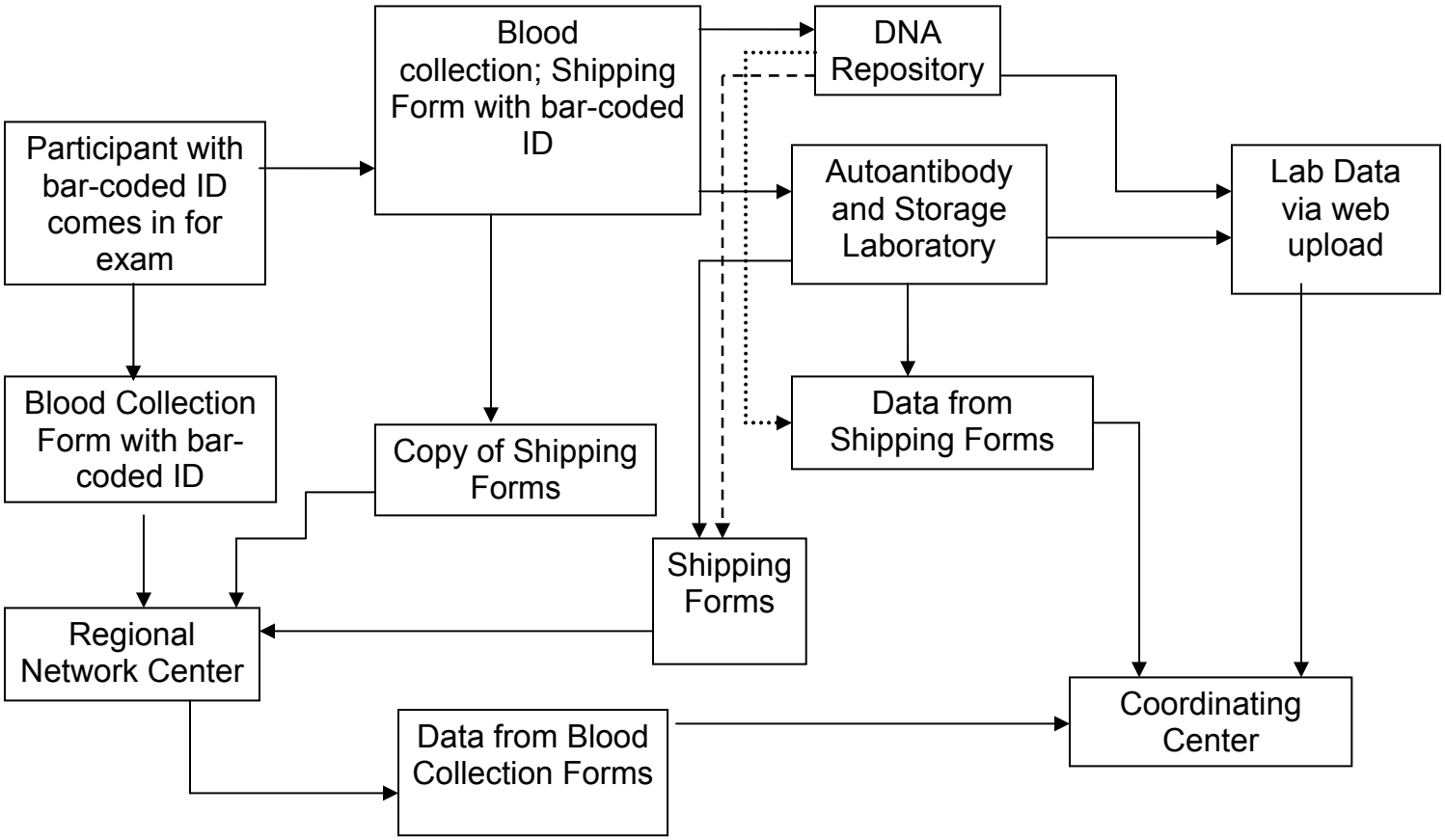
8. Log Out

(a) Log out when you are not using the system.

(b) The system will automatically log you out when there has been 20 minutes of inactivity.

APPENDIX A

T1DGC SPECIMEN TRACKING FLOW CHART



APPENDIX B
AUTOANTIBODY AND STORAGE SAMPLES:
GUIDELINES FOR PACKING AND LABELING STORAGE BOX

1. Each participant's serum samples (maximum of 5 2-ml cryovials sealed with red cap) and plasma samples (maximum of 4 2-ml cryovials sealed with purple cap) are stored and shipped together.

2. Each storage box has 100 spaces for samples (*i.e*, 10 x 10 grid). Since each participant should have a total of 9 samples, all of the samples for as many as 10 participants can be stored in one box (*i.e.*, a total of 90 samples per storage box). **A FAMILY'S SAMPLES SHOULD NOT BE DIVIDED ACROSS TWO BOXES.**

3. Within a box, samples are packed in order of the date collected, from the upper left hand corner to the lower left hand corner.

4. For each participant, **serum** samples are packed first and then the **plasma** samples are packed. Sample placement begins at the first sample position on the first row of the box and successive samples are placed by moving to the right and then moving down a row.

5. Serum samples will occupy the first five spaces in each row. For all participants with a full set of storage samples (5 serum and 4 plasma), only the last space in the row will be empty (Figure 1). In this figure, all 10 participants have a full complement of vials.

6. If a participant has fewer than the maximum number of serum and plasma samples, the row is filled by leaving a blank space for any missing storage samples.

7. Serum samples should occupy the first five spaces and plasma the next four spaces. In Figure 2, participant #2 has three serum samples and two plasma samples. Participant #5 has two serum and one plasma sample. Participant #7 has three serum samples and **no** plasma samples. Participant #9 has one serum sample and one plasma sample.

1st ppt's samples (Father: Family 1)	S	S	S	S	S	P	P	P	P	■
2nd ppt's samples (Mother: Family 1)	S	S	S	S	S	P	P	P	P	■
3rd ppt's samples (Proband: Family 1)	S	S	S	S	S	P	P	P	P	■
4th ppt's samples (Affected: Family 1)	S	S	S	S	S	P	P	P	P	■
5th ppt's samples (Unaffected: Family 1)	S	S	S	S	S	P	P	P	P	■
6th ppt's samples (Father: Family 2)	S	S	S	S	S	P	P	P	P	■
7th ppt's samples (Mother: Family 2)	S	S	S	S	S	P	P	P	P	■
8th ppt's samples (Proband: Family 2)	S	S	S	S	S	P	P	P	P	■
9th ppt's samples (Affected: Family 2)	S	S	S	S	S	P	P	P	P	■
10th ppt's samples (Unaffected: Family 2)	S	S	S	S	S	P	P	P	P	■

Figure 1. Packing diagram for storage samples. "S" indicates a serum cryovial, "P" indicates an EDTA plasma cryovial and "■" indicates an empty space. "ppt's" = participant's. Color of letters indicates color of the cryovial cap.

1st ppt's samples (Father: Family 1)	S	S	S	S	S	P	P	P	P	■
2nd ppt's samples (Mother: Family 1)	S	S	S	■	■	P	P	■	■	■
3rd ppt's samples (Proband: Family 1)	S	S	S	S	S	P	P	P	P	■
4th ppt's samples (Affected: Family 1)	S	S	S	S	S	P	P	P	P	■
5th ppt's samples (Unaffected: Family 1)	S	S	■	■	■	P	■	■	■	■
6th ppt's samples (Father: Family 2)	S	S	S	S	S	P	P	P	P	■
7th ppt's samples (Mother: Family 2)	S	S	S	■	■	■	■	■	■	■
8th ppt's samples (Proband: Family 2)	S	S	S	S	■	P	P	P	P	■
9th ppt's samples (Affected: Family 2)	S	■	■	■	■	P	■	■	■	■
10th ppt's samples (Unaffected: Family 2)	S	S	S	S	S	P	P	P	P	■

Figure 2. Packing diagram for storage samples where fewer than the maximum number have been collected for 2nd, 5th, 7th and 9th participants. "S" indicates a serum cryovial, "P" indicates a plasma cryovial, and "■" indicates an empty space. "ppt's" = participant's. Color of letters indicates color of the cryovial cap.

8. As a participant's samples are added to the storage box, a vial label is placed on the top of the box lid, starting in the upper left hand corner of the box. To the right of the label, the number of serum and plasma samples enclosed for the respective ID is recorded **in ballpoint ink** (*i.e.*, 5–S; 4–P).

9. Vial labels for the first five participants' samples (*i.e.*, participants 1-5) should be in a column on the left side of the box lid and the vial labels for the second five participants' samples (*i.e.*, participants 6-10) should be in a column on the right side of the box lid. If a vial label for the participant's samples was not available, the **full 7-digit ID** is recorded **in ballpoint ink** in the location the label should occupy.

APPENDIX C
T1DGC PARTICIPANT IDENTIFIERS

I. IDENTIFICATION SCHEME

A. Overview

The T1DGC uses a bar-code system to label all paper forms and specimens, with a human readable version of the identifier (ID) printed underneath the bar-code on the same bar-code label. When the bar-code is scanned, Regional Network Center staff can see the human-readable form of the ID encoded within the bar-code on data entry screens. The human-readable form of the bar-code ID (the participant ID) is the unique identifier for an individual participating in the T1DGC.

All communications between clinics, Regional Network Centers, and the Coordinating Center regarding the forms and specimens for individuals and families in the study will refer to the participant ID. Clinics come into contact with bar-codes as sets of labels per family to attach to paper copies of forms and specimen tubes for the individual. Laboratories see the bar-codes on specimen tubes received from clinics or from the Network DNA Repository.

After eligibility has been determined, clinic staff draws a family label set from the stack of available label sets at the clinic. After the labels are attached to forms and specimens, the family ID is assigned to the family. Should the family (or participant) choose to withdraw from the study, the family ID is not reassigned to another family or family member. If a blood re-collection is necessary, the forms and blood collection tubes are labeled with the same participant ID as previous forms and tubes.

B. Technical Specifications

The specifications have been created using a Code 39 + mod 43 checksum bar-code format, with a human-readable version of the ID printed underneath the bar-code on the same bar-code label. The vertical lines in the bar-code are the encoding of the ID that can be read by a bar-code scanner.

1. Finalized Bar-code Format

The finalized bar-code format for the study is:

Attribute	Size	Allowed Value Range
Network Code	char(1)	1 - 9
Family Code	char(4)	0001 - 9999
Individual Code	char(2)	01 - 99

The human-readable form of the bar-code, printed on labels will be:

X-XXXX-XX for example: 1-1001-01

The separate components of the bar-code are discussed below. The actual bar-code lines do not encode the '-' (hyphen) separators; for the example above, the human readable ID 1-1001-01 is actually read by a scanner as 1100101; the hyphens are automatically included in the human-readable form on labels, in reports, and on data entry screens.

2. Network Code

Each network in the consortium has been assigned a single digit Regional Network Center Code. The digits are assigned alphabetically:

Asia Pacific	1
Europe	2
Latin America	3
North America	4
United Kingdom	5
Pilot Studies	8 (Reserved for pilot studies in all networks)
Coordinating Center	9 (Reserved for testing and Coordinating Center use)

If other networks join the T1DGC, their codes will be assigned starting at 6.

2. Family Code

Family code numbering starts at 0001 within each network with a maximum of 9999, allowing for 9999 maximum families that can be recruited in a single network. ***Since the same range of family codes is used within each network, the unique ID for a family in the study is a combination of network code + family code.***

Family codes will not necessarily be sequential across families seen in a clinic. For example, if family ABC were assigned family ID 2-0012 and then family XYZ enters the clinic for their exam immediately after family ABC, family XYZ ***does not have to be assigned*** identifiers 2-0013. The label sets may be split up across the multiple clinics in a network, and certain family codes within each network will be reserved for special purposes such as quality control and internal checking. Clinics will not need to be concerned with these reserved family IDs, and will use the next available label set as directed.

3. Participant Identifier

The individuals within an eligible participating family are assigned individual codes according to their family relationships. The following table lists the standard codes for family individuals:

Participant Identifier	**Relationship**
01	Father
02	Mother
03	Affected Sib1 (Proband)
04	Affected Sib 2
05	Unaffected Sib 1
06	Unaffected Sib 2
07	Affected Sib 3
08	Affected Sib 4
09	Affected Sib 5

Every father in every network will have an individual code of 01, every mother 02 and so on. ***The unique ID for an individual in the study is a combination of network code + family code + individual code.***

In addition to the individual code within the overall bar-code, the individual members of a family can easily be identified from the colored stripes on the labels. The following table lists the standard bar-code color stripes for individual family members:

Bar-code Color Stripe	**Relationship**
Blue	Father
Pink	Mother
Purple	Affected Sib1 (Proband)
Green	Affected Sib 2
Yellow	Unaffected Sib 1
Yellow	Unaffected Sib 2
Green	Affected Sib 3
Green	Affected Sib 4
Green	Affected Sib 5

There will be some repetition in label stripe color. In these cases, such as multiple affected siblings or unaffected siblings, the individuals will have different participant identifiers, but the same label color.

A third level of family individual identifiers, secondary IDs, are recorded on forms by clinic staff. The corresponding Secondary IDs are shown in the table below.

Secondary IDs	Relationship
FA	Father
MO	Mother
AS1	Affected Sib 1 (Proband)
AS2	Affected Sib 2
UN1	Unaffected Sib 1
UN2	Unaffected Sib 2
AS3	Affected Sib 3
AS4	Affected Sib 4
AS5	Affected Sib 5

The Secondary IDs have 2 or 3 characters – for example father is FA, while unaffected sibling 1 is UN1. For FA and MO clinics leave a blank box. The attached bar-code contains the full individual ID (X-XXXX-XX), the label has the colored stripe and relationship indicating a certain family member.

D. Rationale

The participant ID format strikes a balance between having a long confusing string of redundantly encoded information with the need for a quick visual check on source network and family for a sample or form. Since clinics generally manage and ship family specimens as a unit within the same box, a quick way to identify and count family specimens without the need for constant cross-referencing of random single code identifiers is necessary. A visual check of family ID helps clinics prepare the boxes appropriately. Similarly, receiving laboratories will benefit from a visual way to recognize family specimens since they will typically be stored in freezers, in boxes or racks with adjacent freezer addresses.

The network is encoded in the Participant ID to create the unique key for a family across all networks. This scheme of network code + family code in the identifier also enables the Coordinating Center to quickly identify the source network for an individual/family.

APPENDIX D

T1DGC NETWORK COORDINATORS

Asia-Pacific Network:
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Fax: +45-4443-7313
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Fax: +44-01223-336996
E-mail: hw258@cam.ac.uk

APPENDIX E

T1DGC HLA GENOTYPING LABORATORIES

Asia-Pacific Network:
Brian Tait, PhD
Victorian Transplantation and Immunogenetics Services (VTIS)
Australian Red Cross Blood Service
C/O Royal Melbourne Hospital
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Royal Parade
Parkville 3050
Phone: 61 3 9348 1966
Fax: 61 3 9348 1278
E-mail: alouey@arcbs.redcross.org.au

European Network:
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Polygenic Disease and DNA Extraction Facility
National Biobanking Platform Clinical Chemistry
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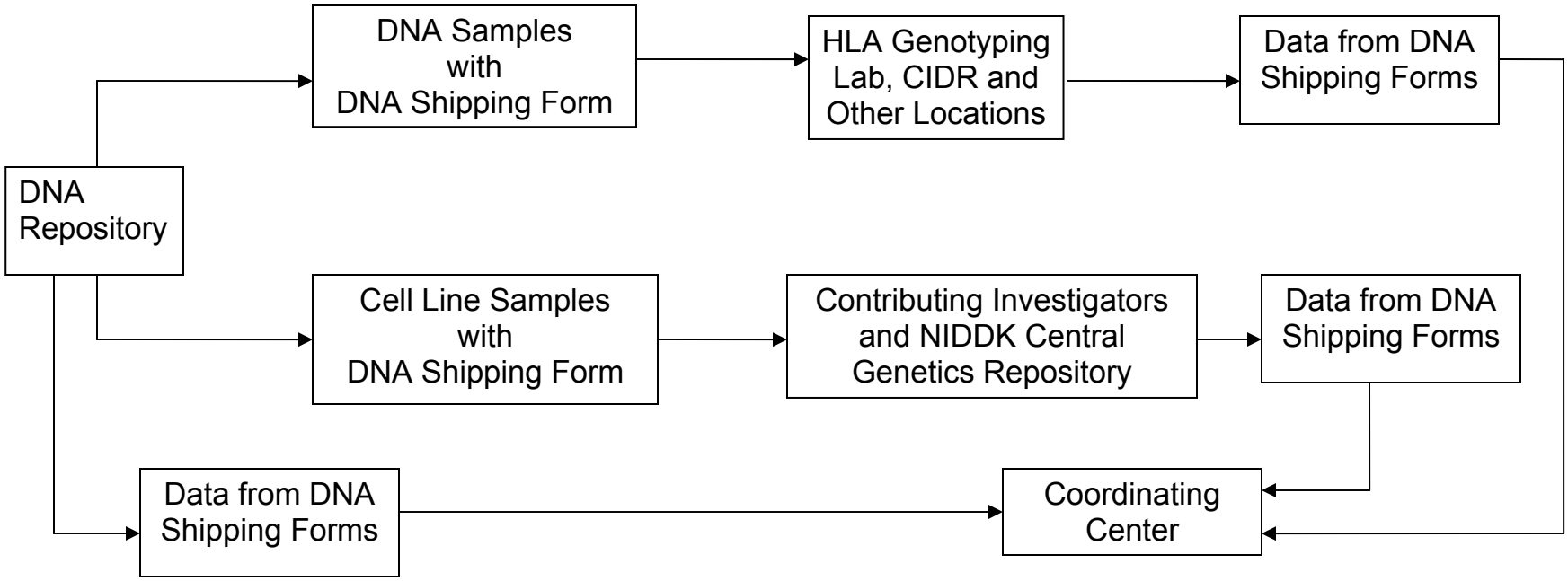
Fax: 44(0) 1223 762102
Email: helen.rance@cimr.cam.ac.uk

APPENDIX F

T1DGC SPECIMEN TRACKING:

DNA REPOSITORY FLOW CHART



HLA GENOTYPING LABORATORY SYSTEM
TABLE OF CONTENTS

I. INTRODUCTION

The purpose of this chapter is to provide detailed instructions to the HLA Genotyping Laboratories for the HLA Lab System used in the Type 1 Diabetes Genetics Consortium (T1DGC). The information that follows also will be useful to the DNA Repositories and should guide staff at each critical point in the shipment and receipt of DNA specimens. It is crucial to the success of the T1DGC that all staff involved, directly or indirectly, follows the outlined procedures.

II. SHIPMENTS FROM DNA REPOSITORY TO HLA GENOTYPING LABORATORY

A. Completing DNA Shipping Forms at DNA Repository

1. The DNA Repository staff completes a *DNA Repository Shipping Form – Face Sheet: Shipments to the HLA Genotyping Laboratory* when shipping specimens to the HLA Genotyping Laboratory. The *DNA Repository Shipping Form: Shipments to the HLA Genotyping Laboratory* is posted on the T1DGC web site (http://www.t1dgc.org) on the Data Collection Forms page.

2. For DNA shipments to the HLA Genotyping Laboratory, the DNA Repository staff will complete the left portion of the *T1DGC DNA Repository Shipping Form – Face Sheet: Shipments to the HLA Genotyping Laboratory.* The *Contents Sheet* is generated on-line as the bar-coded participant ID labels are scanned. A paper copy of this form will be printed after all IDs have been scanned and saved. Both the completed Face Sheet and the printed Contents Sheet are included in the shipping container.

3. The DNA Repository staff affixes a bar-coded DNA Shipping ID label on the *Face Sheet* and the shipping container. DNA Shipping IDs identify each unique shipment and are associated with a set of participant IDs through the *Contents Sheet*. DNA Shipping IDs are 11-digit numbers that begin with the network identified (*i.e.,* 1=Asia-Pacific; 2=European; 4=North American; and 5=United

Kingdom). **The system for entry of the *DNA Shipping Forms* cannot be accessed without a DNA Shipping ID label on the *Face Sheet*.**

Sequential bar-coded Shipment ID labels are provided by the T1DGC Coordinating Center. Each sheet has 10 unique Shipping IDs, with three labels printed for each Shipping ID. Only two of the labels are used for each shipment; one label is placed on the *T1DGC DNA Repository Shipping Form – Face Sheet* and another identical label will be placed on the shipping container for the samples. The third label can be used if one of the labels tears; otherwise, **the extra label should be discarded after shipping**. Alternatively, this label may be used for an internal log, but **should not be used it on subsequent shipments**.

4. The DNA Repository staff completes the upper portion of the *Face Sheet* as follows:
   a. full address of the HLA Genotyping Laboratory (receiving laboratory) and the DNA Repository (shipping laboratory) printed or typed in the area allotted;
   b. DNA Shipping ID Label in the designated space on the form (and a second identical DNA Shipping ID Label on the shipping container);
   c. courier or shipping company used (*e.g.*, Federal Express or World Courier) and the reference or tracking number;
   d. type of shipment (*i.e.*, original sample shipment or replacement sample shipment); and
   e. name of the DNA Repository contact and his/her phone number.

5. The DNA Repository staff completes the left side of the lower portion of the *Face Sheet* as follows:
   a. DNA Repository ID;
   b. date and time the shipment was packed at the DNA Repository;
   c. total number of samples packed, confirmed by counting the samples; and

d. initials of person packing the samples and completing the shipping form.

6. The DNA Repository staff data enters the information completed on the *Face Sheet.*

7 The DNA Repository staff generates the *Contents Sheet* on-line by scanning the bar-coded participant ID labels.

8 The DNA Repository staff records the number of DNA aliquots for each participant included in the shipment. (Only 1 DNA aliquot per participant should be sent to the HLA Genotyping Laboratory.)

9. Once the DNA Repository has entered and saved the *Contents Sheet*, the DNA Repository user should print all *DNA Repository Shipping Contents Sheets*. The staff should make two copies of the *Face Sheet* and *Contents Sheet.* The original set of shipping forms is sent to the Coordinating Center. One set is included in the shipment and one is retained by the DNA Repository for their records.

B. Completing DNA Shipping Forms at HLA Genotyping Laboratory

1. When the shipment is received at the HLA Genotyping Laboratory, verify contents of the shipment and record the specified information on the lower right portion of the *Face Sheet*. The following items are recorded and entered into the specimen tracking system by the person receiving the shipment:
   a. HLA Genotyping Laboratory ID;
   b. date and time the shipment arrived at the HLA Genotyping Laboratory;
   c. total number of samples received, confirmed by counting the samples; and
   d. initials of person receiving the samples and completing the shipping form.

2. Check the participant ID for each sample against the *Contents Sheet* and enter the number “1” for each DNA aliquot in the column labeled “DNA aliquot received” for inventory purposes and acknowledgement of arrival.

3. If a DNA aliquot vial is leaking, record the total number of samples received and mark the box in the column labeled “Samples Leaking.”

4. If there are other discrepancies in the number of samples shipped or irregularities in the condition of the sample, mark the box in the column labeled “Other.” Record any specific comments in the margin of the printed form.

5. Once the HLA Genotyping Laboratory has entered and saved the *Contents Sheet*, the HLA Lab user should print all *DNA Repository Shipping Contents Sheets*. The staff should make a copy of the *Face Sheet* and *Contents Sheet.* The original set of shipping forms is sent to the Coordinating Center and the copy is retained by the HLA Genotyping Laboratory for their records.

III. T1DGC HLA LAB SYSTEM

A. Web Site

Go to the T1DGC data entry site (https://www.t1dgcdataentry.org). Laboratories need the T1DGC bar-code scanner and a computer with an Internet connection and compatible browser (*e.g.*, Internet Explorer 5.5.2 or higher version) to use this web-based system.

B. Log-in Page

1. When the HLA Lab user accesses the web site, the first page encountered is the Log-in Page (Figure 1).

2. Each laboratory staff member is assigned a unique username and password to be used to access the system. The username and password are entered on the Log-in Page.

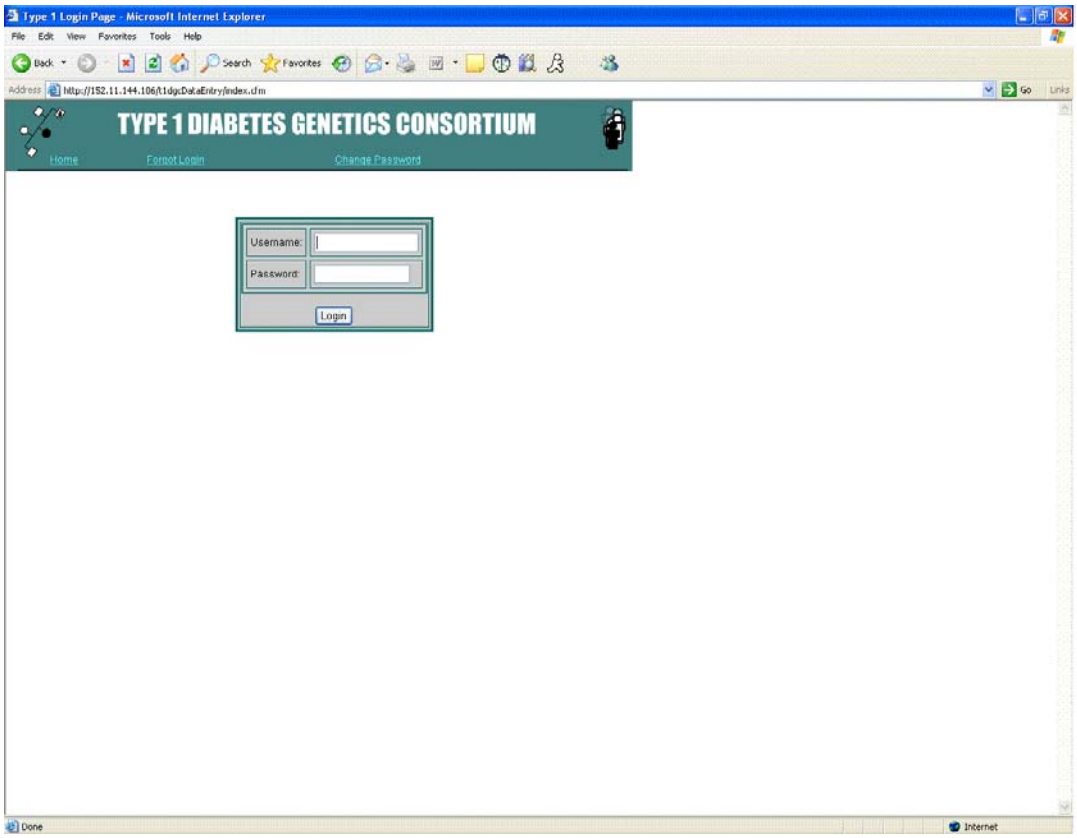


Figure 1. Log-in Page.

C. T1DGC HLA Lab System Home Page

1. Upon a successful log-in, the T1DGC HLA Lab System Home Page will be displayed (Figure 2).

2. From this page, HLA Lab users have several options:

   a. *Receipts*

      (i) **DNA Shipping Form**: enter (or check previously entered) *DNA Repository Shipping Forms: Face Sheet* and/or *Contents Sheet);*

      (ii) **Ethnicity Report**: generate the ethnicity information for participants on a specified Master Plate Grid;

   b. *Plate Management*

      (i) **Master Plate Grid**: create a Master Plate Grid from eligible shipping IDs;

      (ii) **Master Plate Grid Report**: print a copy of the Master Plate Grid;

(iii) **Sub-typing Plate Grid**: create a Sub-typing Plate Grid (or multiple plates) from a specified Master Plate Grid;

(iv) **Sub-typing Plate Grid Report**: print a copy of the Sub-typing Plate Grid and associated Master Plate Grid for a specified Sub-typing Plate Grid;

(v) **Sub-typing Plate Grid Details Report**: print a list of the all Sub-typing Plate Grids and assay, well assignment and participant IDs, for a specified Master Plate Grid;

(vi) **Sub-typing-to-Master Grid Report:** print the Sub-typing Plate Grid with the Master Plate Grid well assignment beneath each participant ID and assay;

(vii) **Redo Plate Grid:** create a Redo Plate Grid;

(viii) **Redo Plate Grid Report:** print a copy of the Redo Plate Grid and associated Parent Plate Grid for a specified Redo Plate Grid;

(ix) **Redo-to-Master Plate Grid Report:** print the Redo Plate Grid with the Parent Plate Grid well assignment beneath each participant ID and locus;

(x) **Cancel Plate Grid:** used on rare occasions to cancel a specified Master Plate Grid, Sub-typing Plate Grid, and/or Redo Plate Grid;

(xi) **HLA Sample File Download**: download the text files used in StripScan (for a specified Plate Grid);

c. *Data Management*

(i) **HLA File Upload**: upload data (xml file) from SCORE to the Coordinating Center via the web (test file and final upload);

(ii) **Probe Binding Report**: download report containing the probe binding and pixel value results for each assay;

(iii) **HLA Lab Shipment Report**: view and print report containing comprehensive information about each plate including date received, number of redos, status, and links to associated sub-typing and master plate grids;

(iv) **HLA Lab Grid Report**: view and print report containing information about the status of each plate logged into the HLA Lab System;

(v) **T1DGC HLA Plate Status**: view and print report summarizing all plates logged into the HLA Lab System;

d. *Administration*

(i) **HLA Software Support**: download updated versions of SCORE or StripScan; or

(ii) **Request for Replacement**: request a replacement sample or view list of all requested replacement samples.

3. The HLA Lab user can always return to this page by clicking on the “HLA Lab” link at the top of the page.

Figure 2. HLA Lab System Home Page.

D. DNA Shipping Form

1. Clicking on the "DNA Shipping Form" link will display a page with a box titled "Enter or Scan a DNA Shipping ID" (Figure 3). Position the cursor in the box.

2. Scan the bar-coded DNA Shipping ID label located on the *Face Sheet*. The ID must be 11 digits and should start with the Network identifier (*i.e.*, 1=Asia-Pacific; 2=European; 4=North American; and 5=United Kingdom). **The system for entry of the *DNA Shipping Form* cannot be accessed without a DNA Shipping ID label on the *Face Sheet.***

3. After scanning the DNA Shipping ID, press "Submit" to proceed.

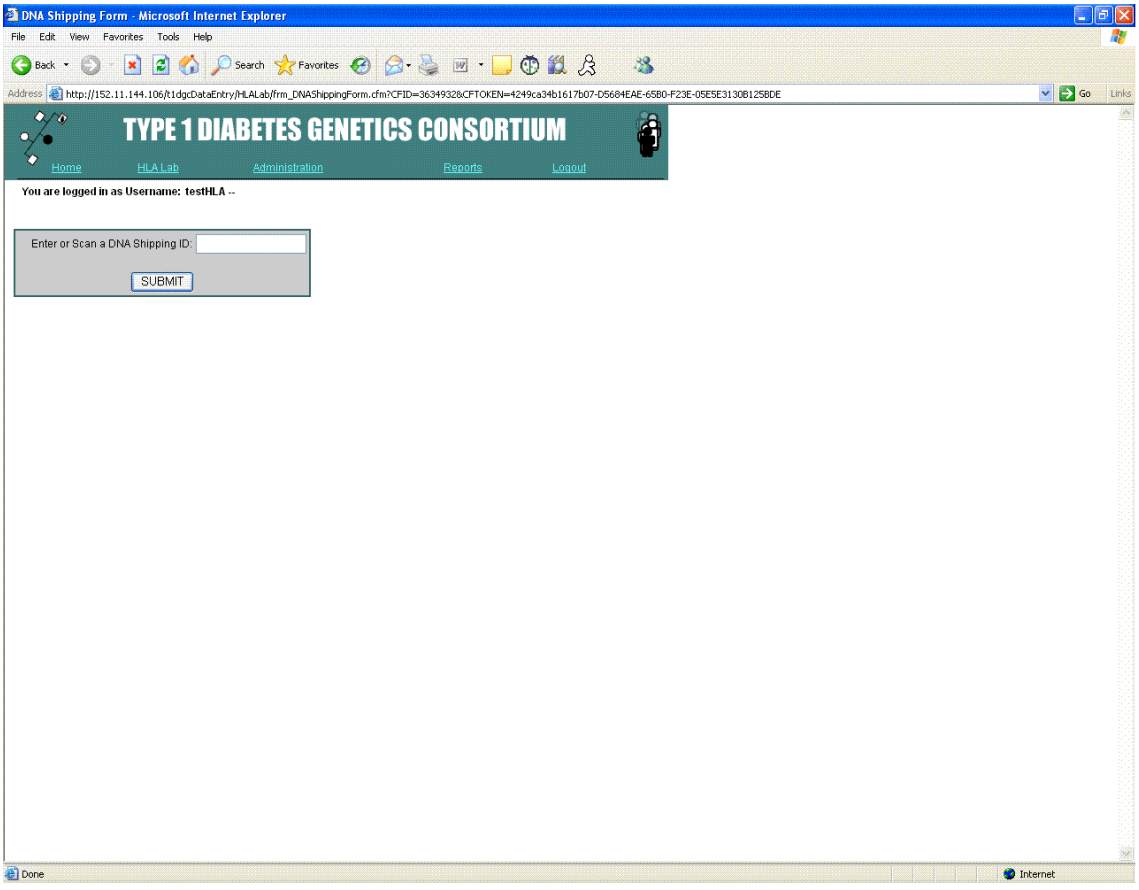


Figure 3. Scan DNA Shipping ID from bar-coded labels.

4. DNA Shipping Form Selection Page

a. When the HLA Lab user enters a DNA Shipping ID, the DNA Shipping Form Selection Page will appear (Figure 4).

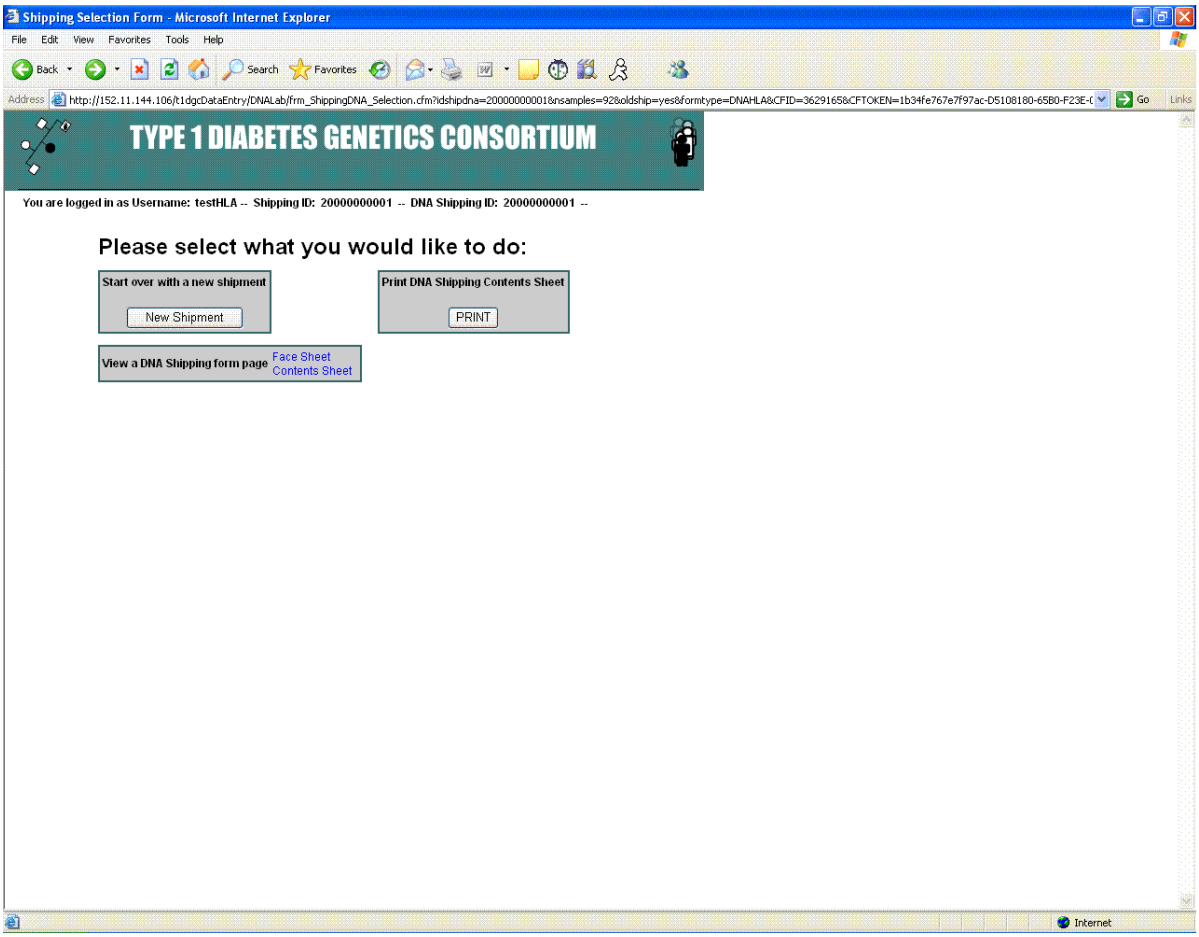


Figure 4. Shipping Form Selection Page.

b. If a shipment has not been entered, a blank *DNA Shipping Form - Face Sheet* will be displayed. This should not occur if the DNA Repository entered the data recorded on the form at the time of shipment. If a blank *Face Sheet* is displayed, the HLA Genotyping Laboratory should enter the **entire** form and contact the Coordinating Center who will in turn contact the DNA Repository to ensure that this does not occur in future shipments.

c. The HLA Lab user has three options from this page:

(i) “Start over with a new shipment” which returns the HLA Lab user to the screen with the box titled “Enter or Scan a DNA Shipping ID”.

(ii) “Print DNA Shipping Contents Sheet” which displays what is currently saved in the database on the *Contents Sheet* and allows the HLA Lab user to print this information.

(iii) “View a DNA Shipping form page” which displays previously entered shipping forms and what is currently saved in the database for the *Face Sheet* or *Contents Sheet*.

d. The HLA Lab user will select option (iii) in order to data enter the part of the DNA Shipping Form they completed after receipt of samples.

5. *DNA Shipping Form - Face Sheet*

a. The DNA Repository staff will enter the data recorded on the *DNA Repository Shipping Forms* at the time of receipt of the shipment. When the HLA Genotyping Laboratory staff scans the DNA Shipping ID and selects Face Sheet, the *Face Sheet* displayed will be populated with the data entered at the DNA Repository (Figure 5).

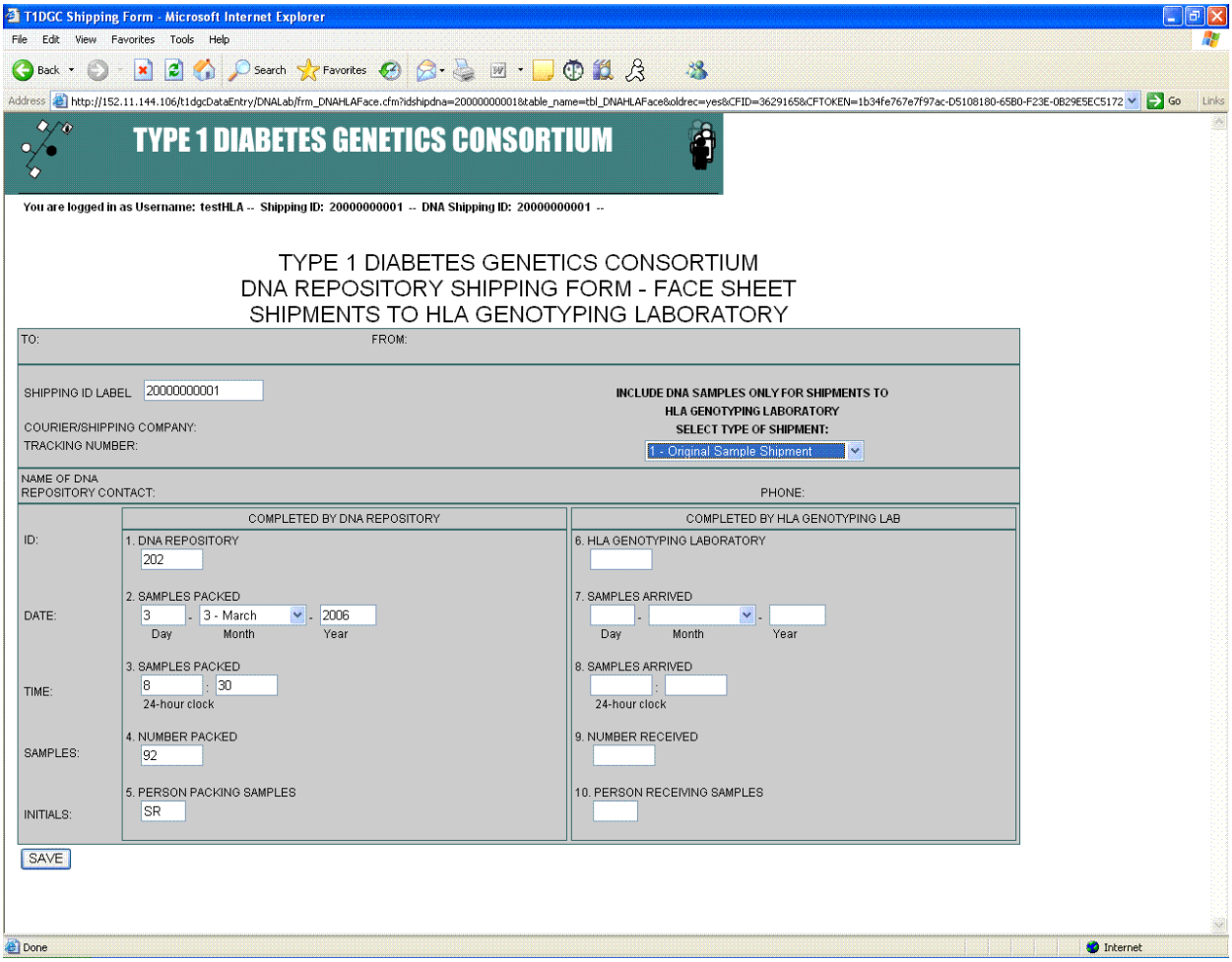


Figure 5. *DNA Shipping Form - Face Sheet.*

b. Enter the right side of the lower portion of the form (titled “Completed by HLA Genotyping Lab”) and press the “Save” button at the bottom of the page.

6. DNA Shipping Form Face Sheet Warnings and Errors

a. Warnings (Orange Dots):

(i) If data entered are out of an “expected” range, the form is redisplayed with an orange dot at the top describing the potential mistake (Figure 6).

(ii) Confirm that the data on the form matches that entered on the web page.

(iii) If the data match, scroll to the bottom and press the “Save with Warnings” button. If the data do not match, correct the discrepant data and press the “Save” button.

(iv) HLA Genotyping Laboratory staff **cannot and should not** correct data on shipping forms that were entered by the DNA Repository staff without consulting the DNA Repository.

b. Errors (Red Dots):

(i) If data entered are out of an “expected” range or the data field is blank and the field is **required**, the form is redisplayed with a red mark at the top describing the potential error (Figure 6).

(ii) Confirm that the data on the form matches that entered on the web page.

(iii) If the data match and are valid, the Coordinating Center should be contacted.

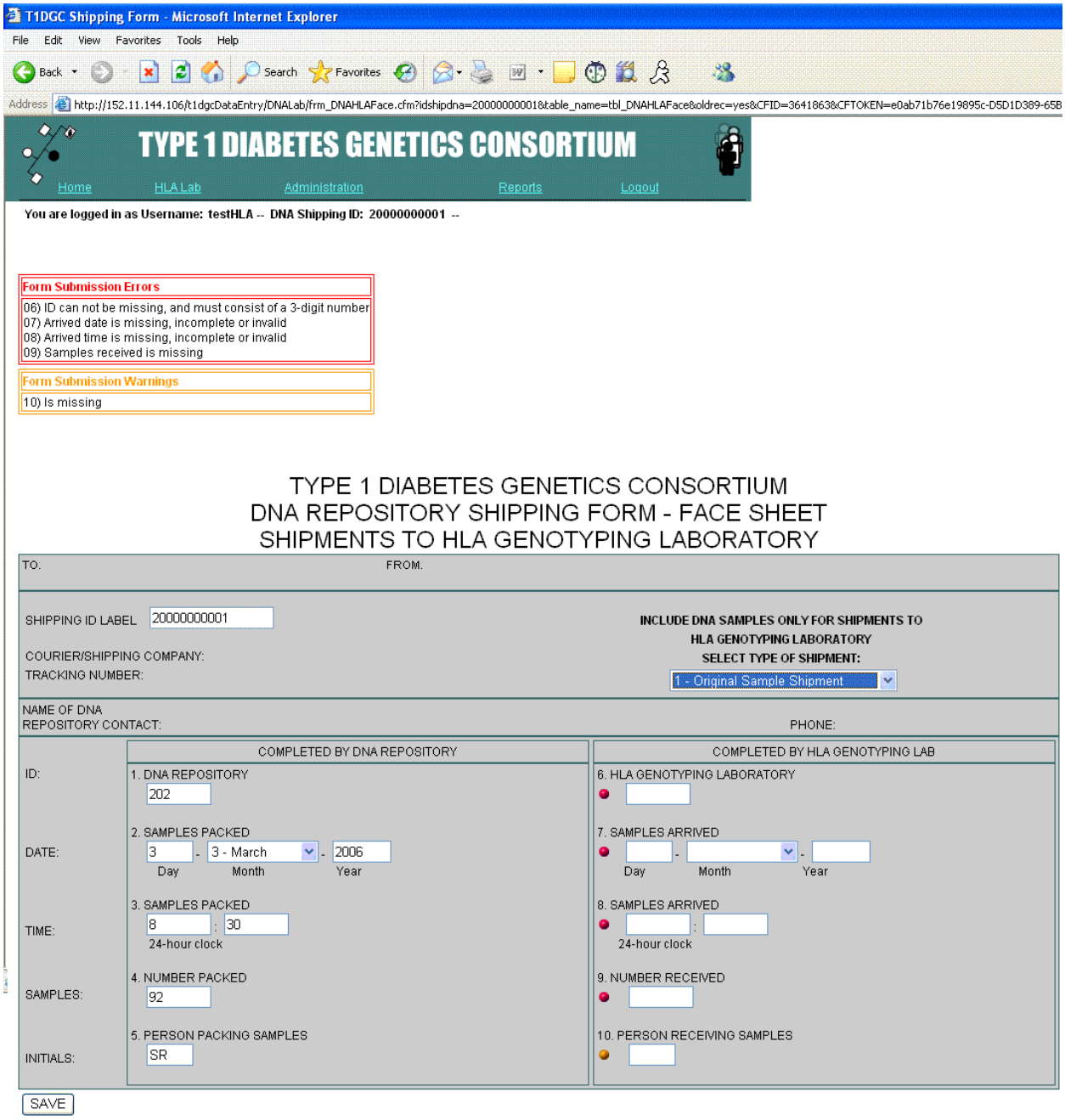


Figure 6. *DNA Shipping Form – Face Sheet* with warnings and errors.

7. *DNA Shipping Form - Contents Sheet*

   a. After a successful save of the *Face Sheet*, the HLA Genotyping Laboratory is redirected back to the Shipping Form Selection Page (Figure 4).

b. The HLA Lab user selects *Contents Sheet* and the *Contents Sheet* is displayed (Figure 7). This should be populated with the data entered at the DNA Repository at the time of shipment. If the *Contents Sheet* is blank, the HLA Lab user should enter the **entire** form and contact the Coordinating Center who will in turn contact the DNA Repository to ensure that this does not occur in future shipments.

c. Enter the data recorded in the column labeled "DNA aliquots received" and mark any comments recorded on the form about the receipt of the DNA aliquots. Press the "Save" button at the top or bottom of the page.

d. The HLA Lab user will be unable to save the Contents Sheet if any field is left blank. (*i.e.,* if an aliquot is not received, the HLA Lab user must enter "0" in the field rather than leaving the field blank.)

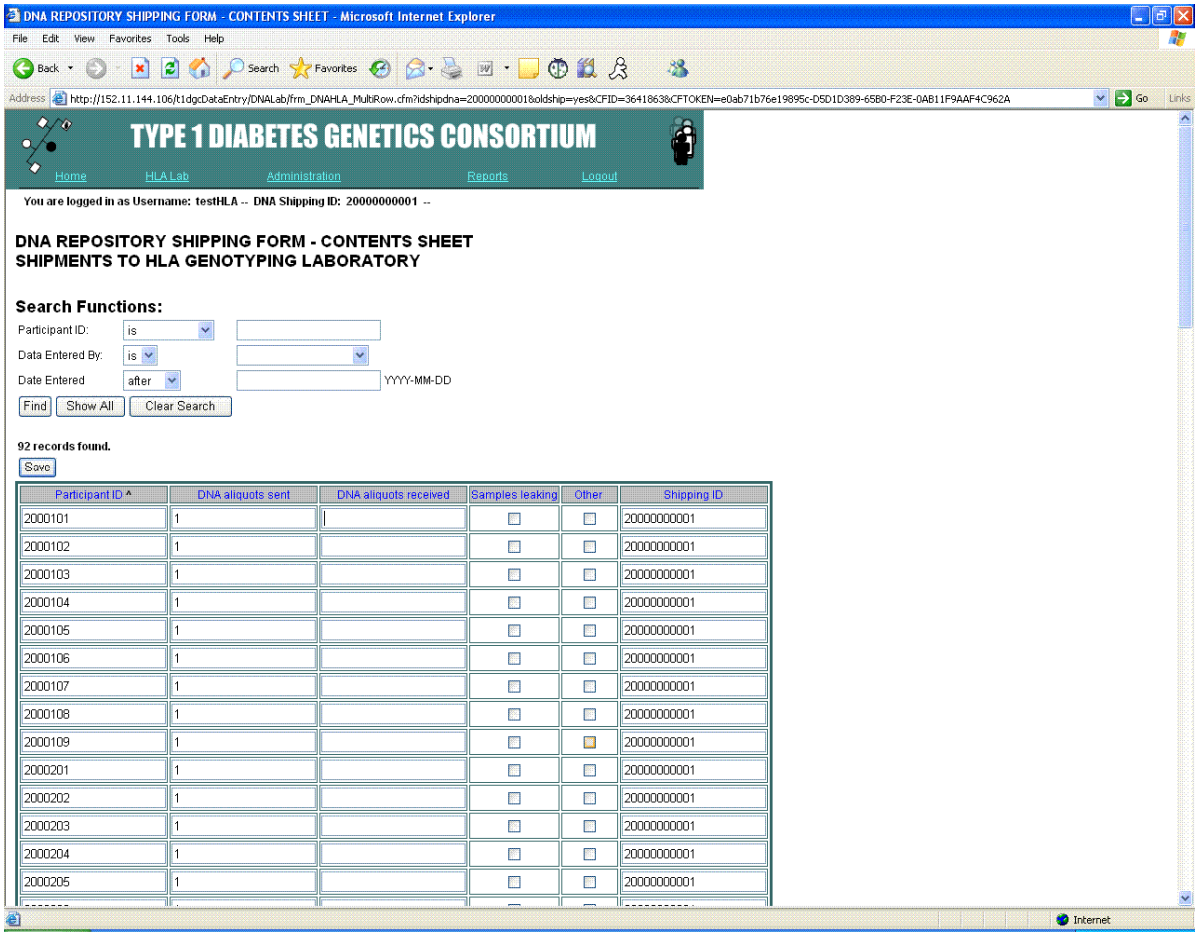


Figure 7. *DNA Shipping Form - Contents Sheet.*

E. Ethnicity Report

1. The Ethnicity Report can be generated for any shipment in the database. This function accesses and compiles the ethnic codes from the participants' T1DGC exam forms in the database. The codes are converted to the corresponding ethnicity and output as text.

2. If data entry of the T1DGC exam forms has not been completed before the DNA shipping form is entered, the HLA Lab user will see the message "The participants forms in this shipment have not been data entered!" on the Ethnicity Report beside the participant ID. Otherwise, the ethnicity code(s) will be displayed for each participant.

3. To access the Ethnicity Report, click on the "Ethnicity Report" link on the HLA Lab System page. A list of DNA shipping IDs will be displayed; the HLA Lab user clicks on the desired shipment (Figure 8).

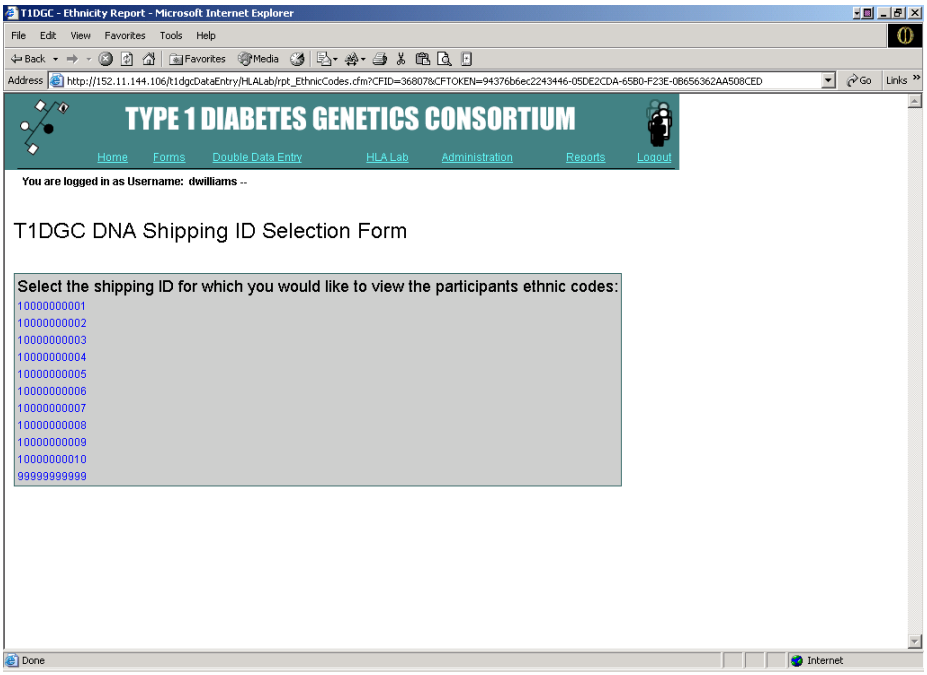


Figure 8. Selection of DNA Shipping Form for viewing participant's ethnic origins.

4. The Ethnicity Report for the specified DNA shipping ID will be displayed (Figure 9).

5. The HLA Lab user can print this report by selecting “Print” from the web browser menu.

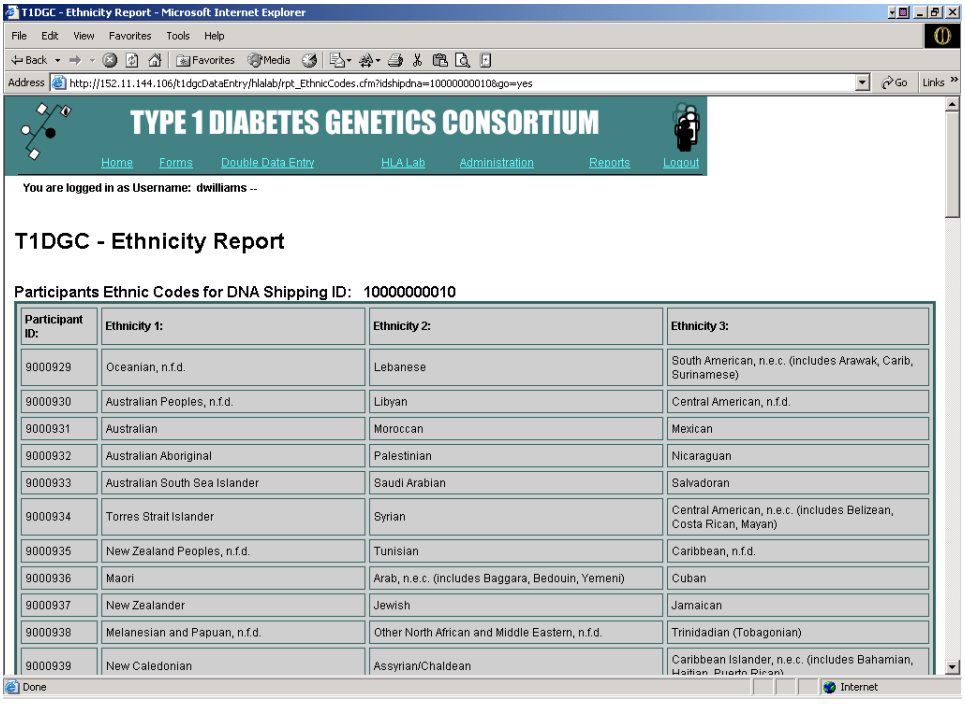


Figure 9. Ethnicity Report.

F. Master Plate Grid

1. When the HLA Lab user accesses the “Master Plate Grid” link, the DNA Shipping ID Selection Form is displayed (Figure 10).

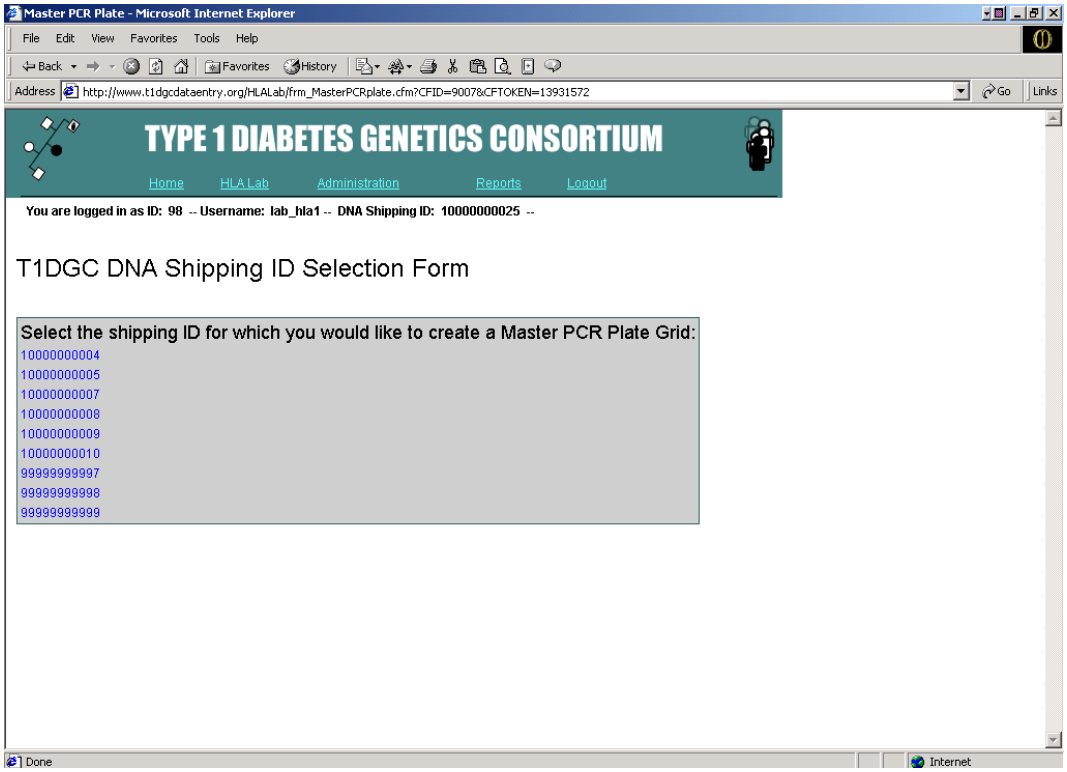


Figure 10. DNA Shipping ID Selection Form.

2. The HLA Lab user must choose the DNA Shipping ID from which to create a Master Plate Grid.

3. Once a shipping ID has been chosen, the Master Plate Grid is displayed and populated with the data from that shipment (Figure 11).
   a. Data are sorted numerically and can be edited at this time. However, there should be very few reasons to use this edit function.
   b. **Once the plate is saved, the HLA Lab user cannot modify the plate.**
   c. If modifications are necessary, the HLA Lab user will need to cancel the Master Plate Grid and start over with a new grid (See Item O).

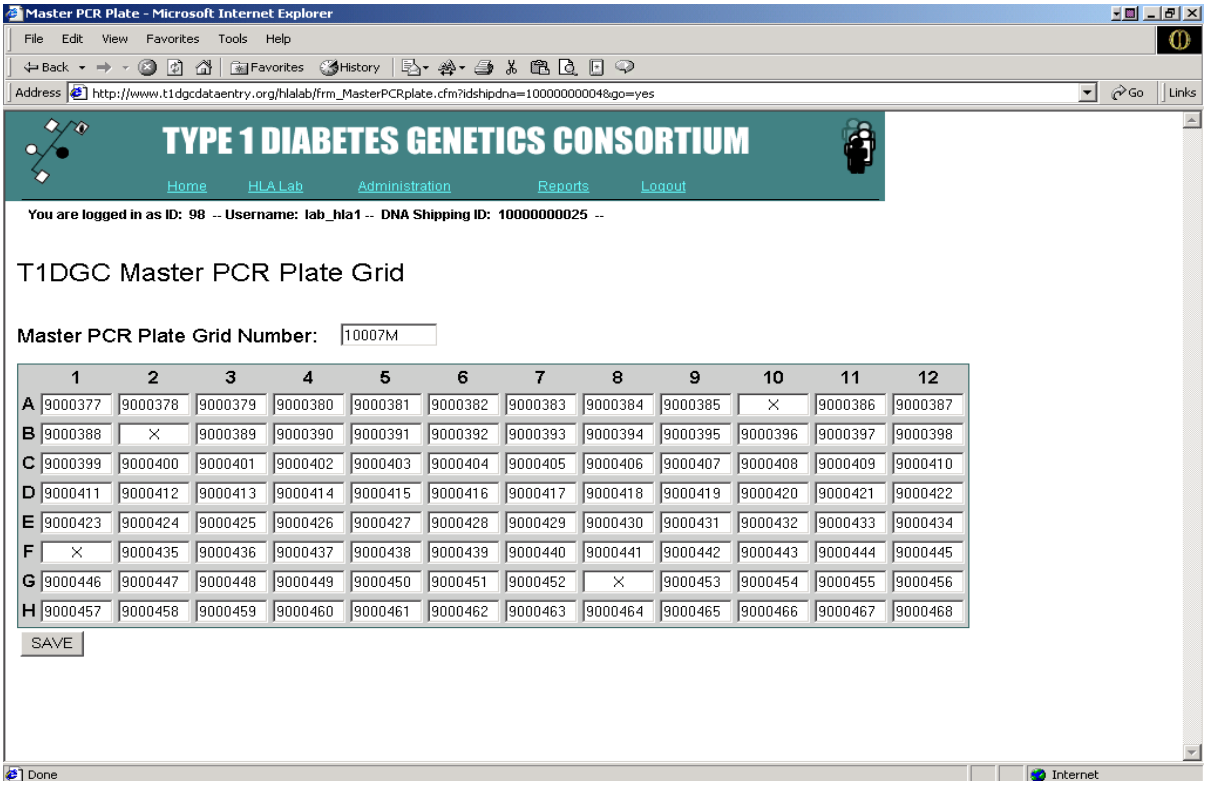


Figure 11. Master Plate Grid Form.

4. When the Master Plate Grid is set, press the “Save” button at the bottom of the page.

5. Once the Master Plate Grid has been saved, the HLA Lab user is directed to a screen that queries “Please select what you would like to do”, with three options (Figure 12):
   a. **Set up a new Master Plate Grid:** displays the DNA Shipping ID Selection Form (Figure 10);
   b. **Print Out Current Master Plate Grid:** displays the Master Plate Grid Report (which allows the HLA Lab user to print the Master Plate Grid); or
   c. **Return to the HLA Lab Page:** displays the HLA Lab System Menu (Figure 2).

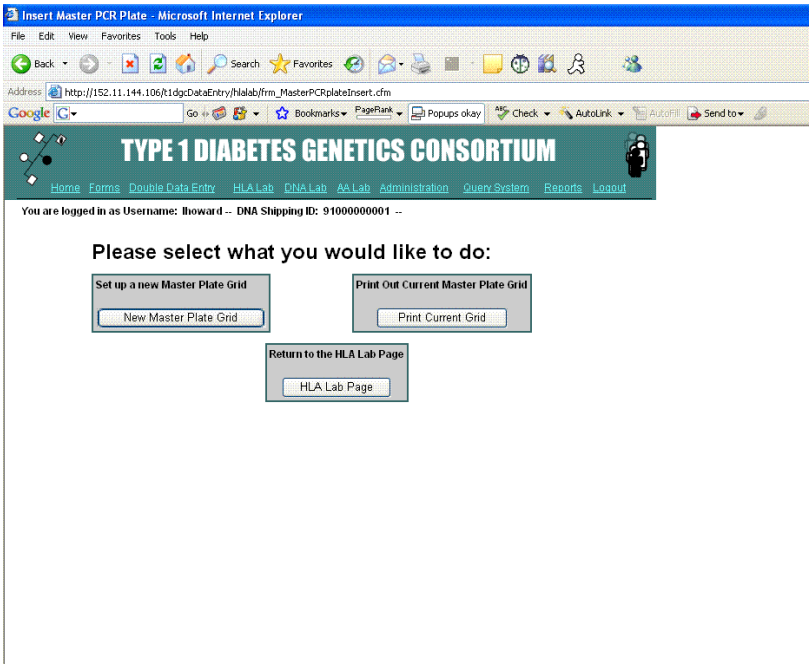


Figure 12. Master Plate Grid Selection Page.

G. Master Plate Grid Report

1. When the HLA Lab user accesses the Master Plate Grid Report, a list of available Master Plate Grids is displayed (Figure 13).

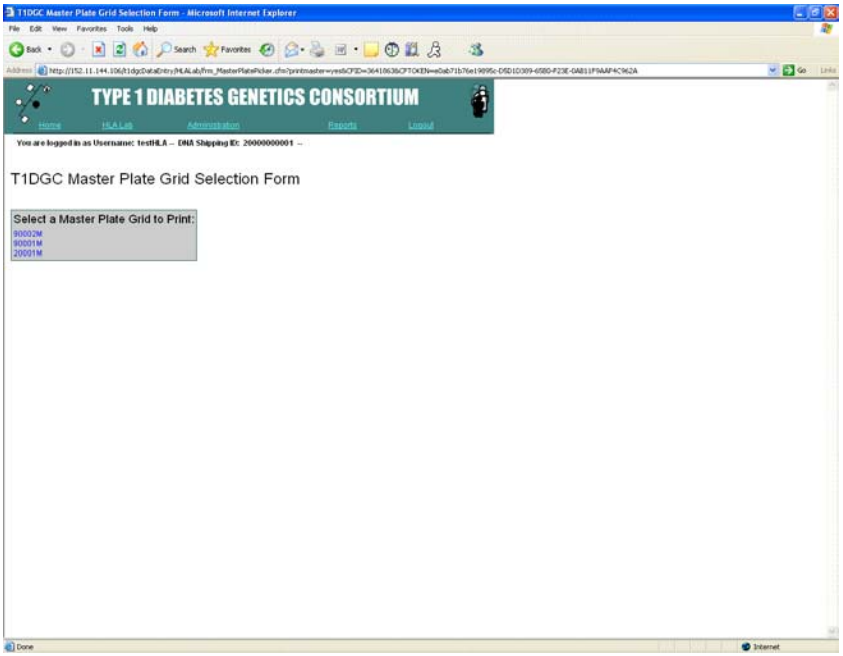


Figure 13. List of Available Master Plate Grids.

2. Click on the Master Plate Grid to be printed. The print dialogue box is displayed over the Master Plate Grid Report (Figure 14).

   a. If the printed page does not fit on one sheet, try printing in Landscape.

   b. Note that if the orientation is changed to landscape, all subsequent pages printed from the browser will print in landscape mode. To change the print orientation back, click “File” and select “Page Setup.”

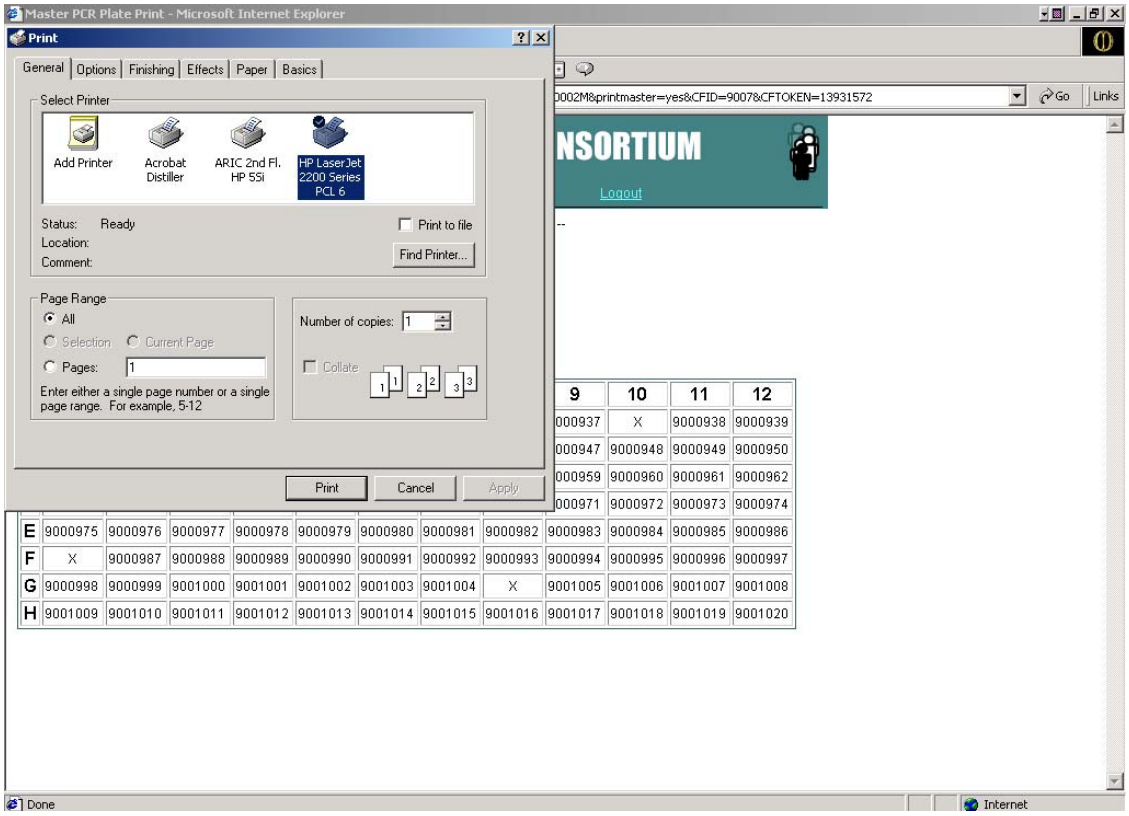


Figure 14. Print Master Plate Grid Form.

H. Sub-typing Plate Grid

1. When the HLA Lab user accesses the Sub-typing Plate Grid, the Master Plate Grid Selection Form is displayed (Figure 15).

2. The HLA Lab user must choose the Master Plate Grid that will be used to create a Sub-typing Plate Grid.

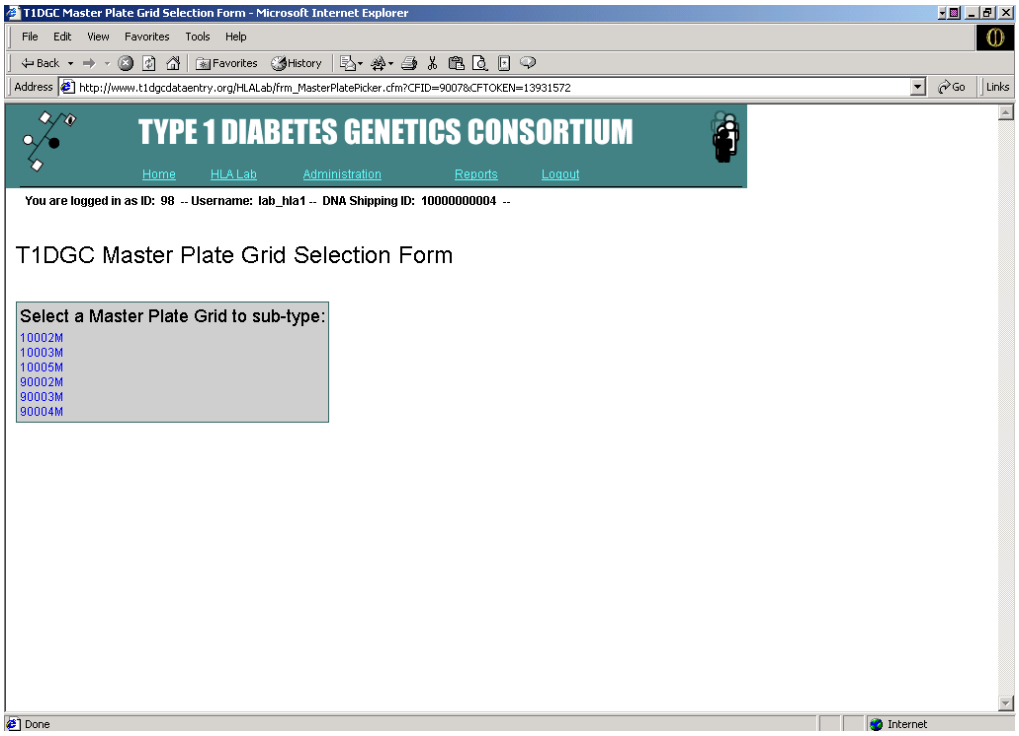


Figure 15. Master Plate Grid Selection Form.

3. Once a Master Plate Grid has been chosen, the Sub-typing Plate Grid Form is displayed and the top portion of the form is populated with the data from that Master Plate Grid (Figure 16).

4. Set the placement criteria.
   a. The Placement Address will default to the next well in chronological order; however, the HLA Lab user can change the placement address to another well if desired.
   b. The "Fill Mode" will default to place the IDs horizontally. The HLA Lab user can choose to place the IDs horizontally or vertically.
   c. Select the "Assay" to be associated with the selected IDs (WLF, WPR, YSTS, VH, GYK or YSTG).

5. Select all of the IDs to sub-type for a particular assay. **ALWAYS select a "Control" at the end of each assay on a Sub-typing Plate Grid.**

6. Press “Place” to place the IDs into the Sub-typing Plate Grid.

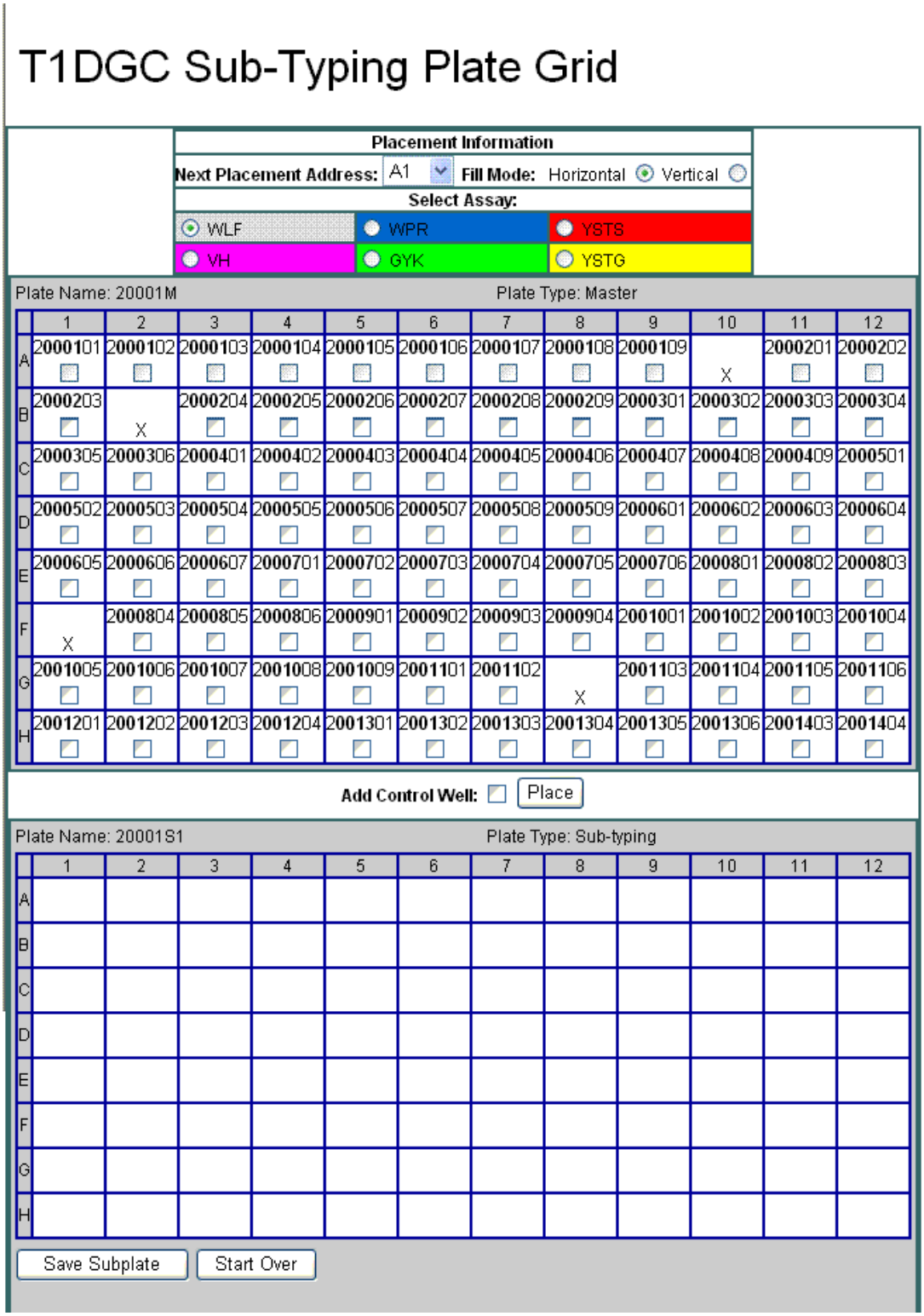


Figure 16. Sub-typing Plate Grid (before Sub-typing Plate Grid filled).

7. When the grid is complete, press the “Save Subplate” button at the bottom of the page (Figure 17). If the HLA Lab user needs to start over, press the “Start Over” button at the bottom of the page to clear the Sub-typing Plate Grid.

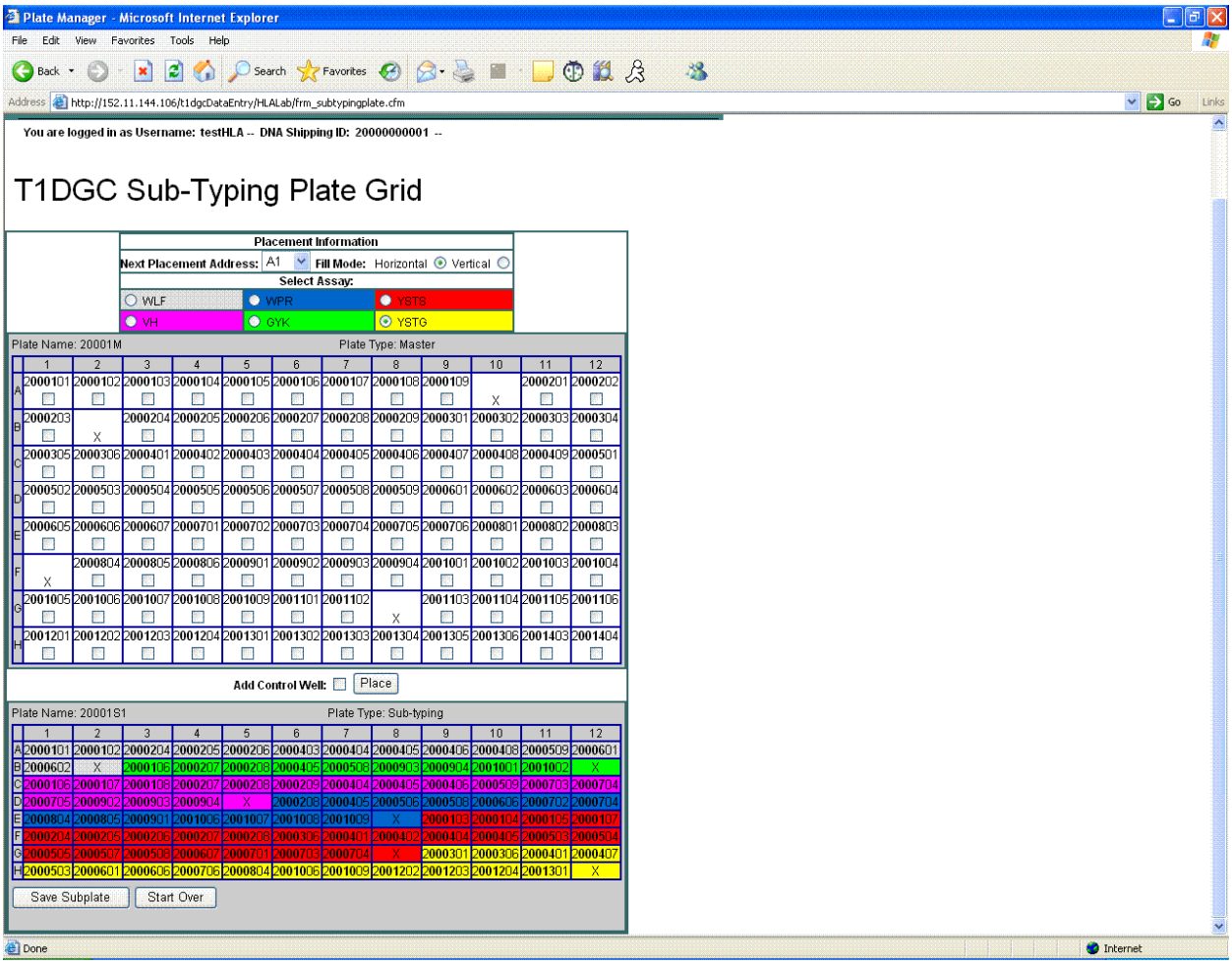


Figure 17. Sub-typing Plate Grid (after Sub-typing Plate Grid filled).

8. The Master Plate Grid Selection Form is displayed with a message stating the Sub-typing Plate Grid has been saved (Figure 18).

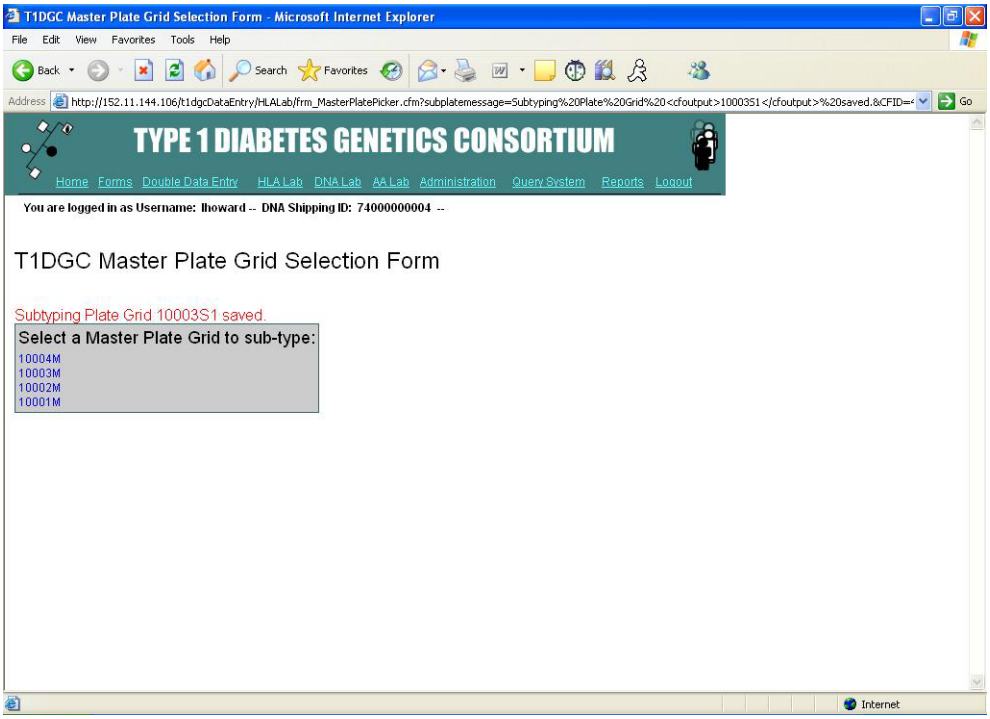


Figure 18. Master Plate Grid Selection Form (after Sub-typing Plate Grid has been saved).

I. Sub-typing Plate Grid Report

1. When the HLA Lab user accesses the Sub-typing Plate Grid Report, a list of available Sub-typing Plate Grids is displayed (Figure 19).

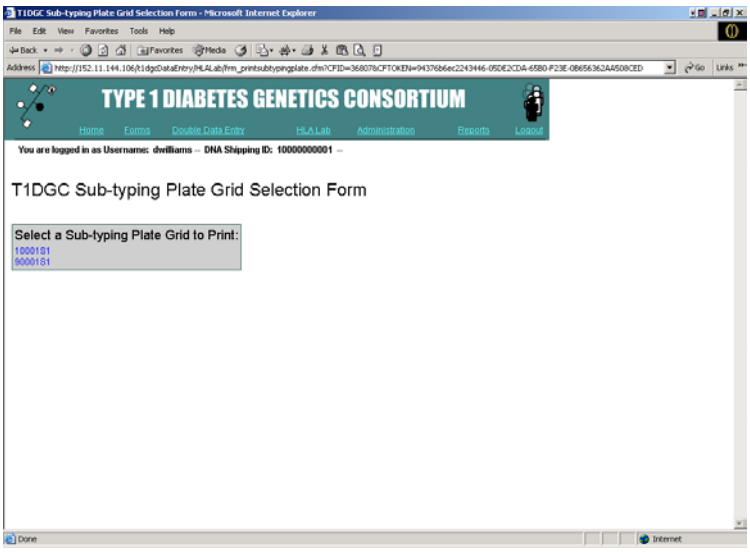


Figure 19. List of Sub-typing Plate Grids available to print.

2. Click on the Sub-typing Plate Grid to be printed. The print dialogue box is displayed over the Sub-typing Plate Grid Report (Figure 20).

   a. If the printed page does not fit on one sheet, try printing in Landscape.

   b. Note that if the orientation is changed to landscape, all subsequent pages printed from the browser will print in landscape mode. To change the print orientation back, click “File” and select “Page Setup.”

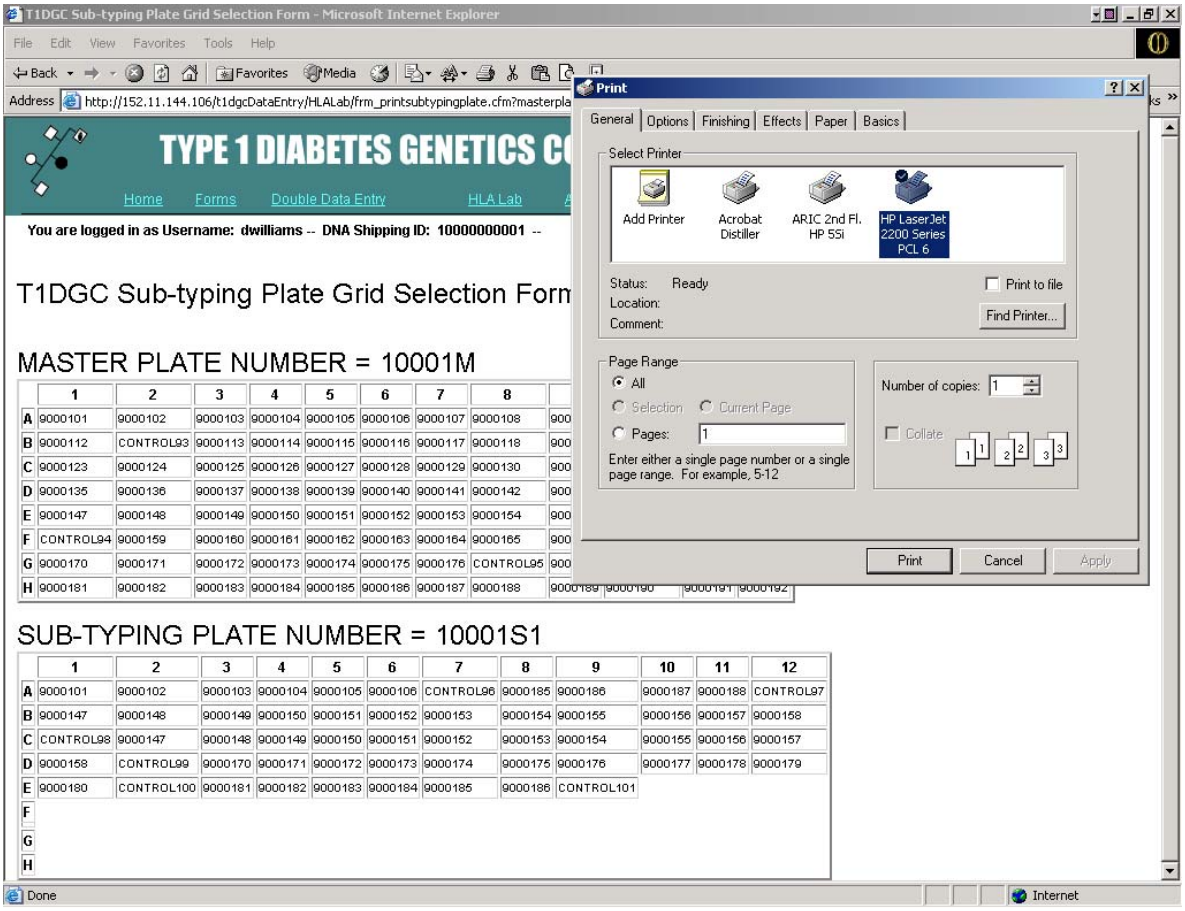


Figure 20. Sub-typing Plate Grid Report .

J. Sub-typing Plate Grid Details Report

1. When the HLA Lab user accesses the Sub-typing Plate Grid Details Report, a list of available Master Plate Grids is displayed (Figure 21).

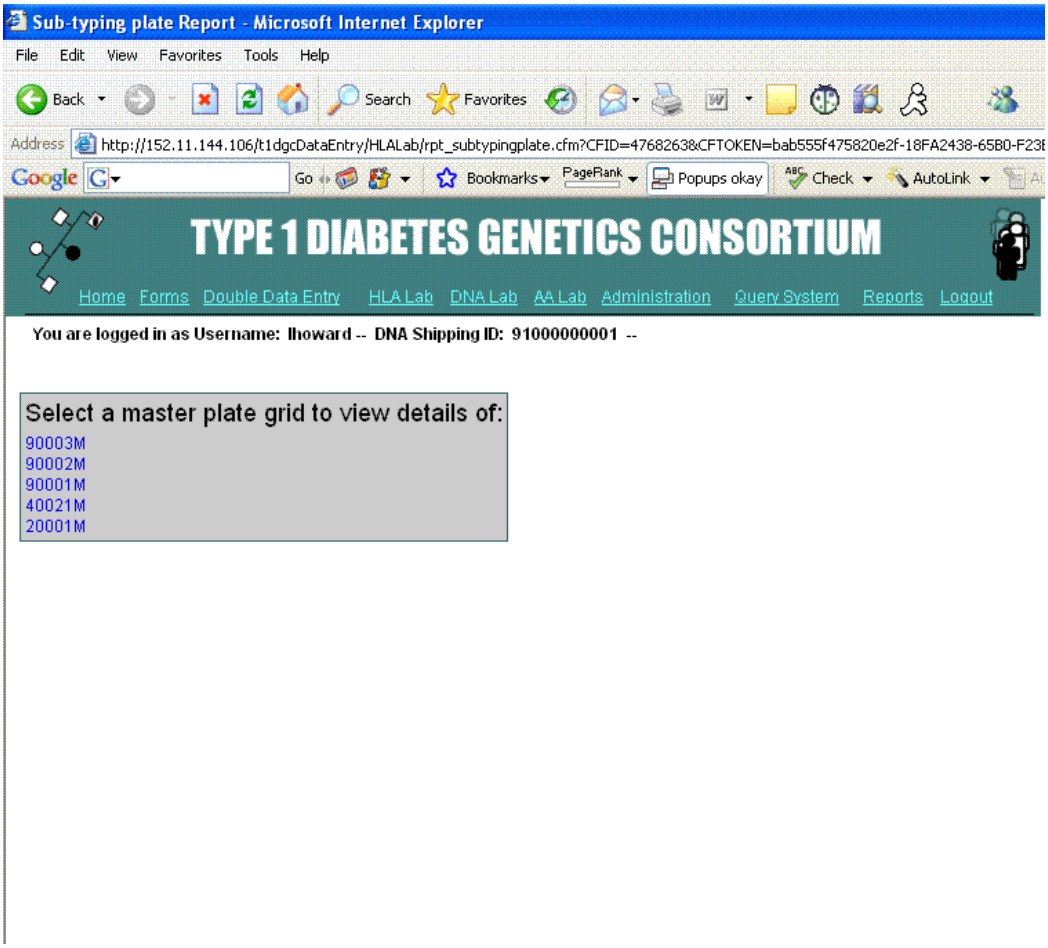


Figure 21. List of Master Plate Grids available to view.

2. To obtain the detailed list of assays and IDs for a Sub-typing Plate Grid, the HLA Lab user must choose the Master Plate Grid ID corresponding to that Sub-typing Plate Grid.

3. Once a Master Plate Grid has been chosen, the Sub-typing Plate Grid Details Report is displayed (Figure 22).

4. Select “Print” from the web browser menu to print this report.

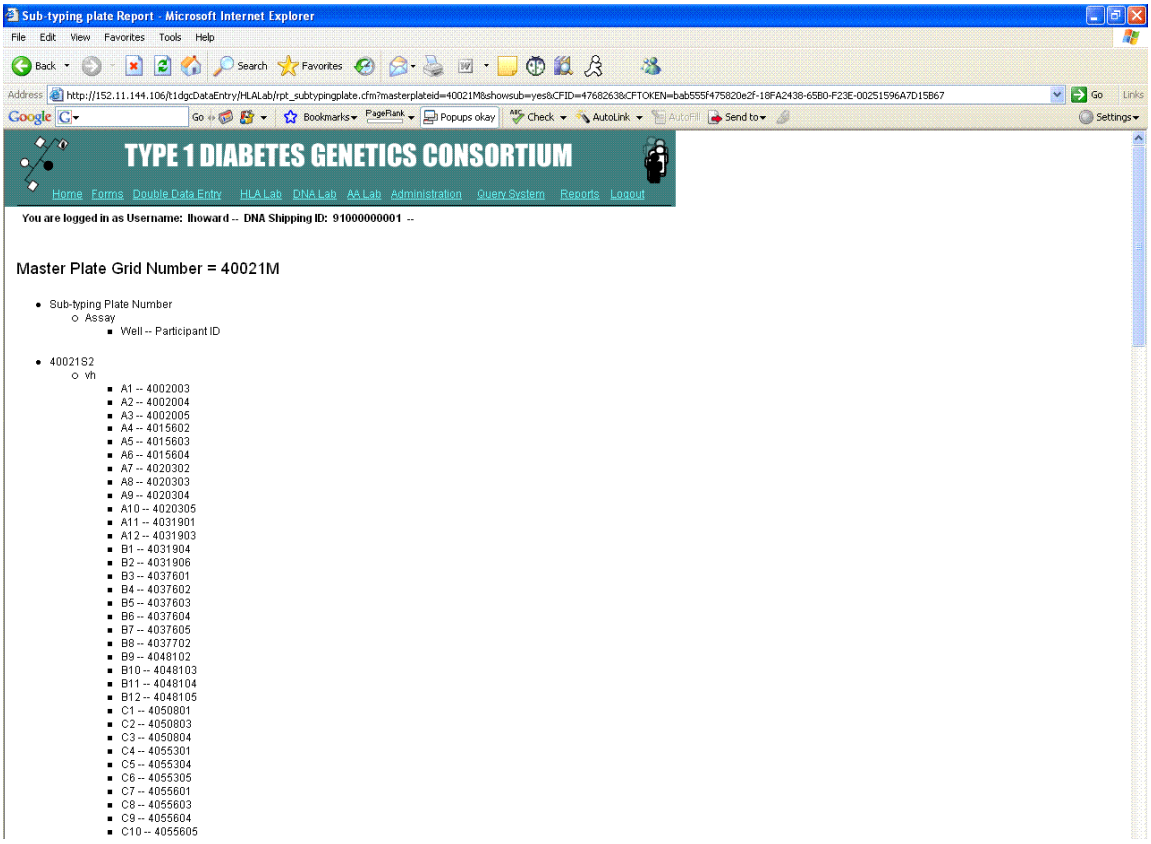


Figure 22. Sub-typing Plate Grid Details Report.

K. Sub-typing to Master Grid Report

1. When the HLA Lab user accesses the Sub-typing to Master Grid Report, a list of available Sub-typing Plate Grids is displayed (Figure 23).

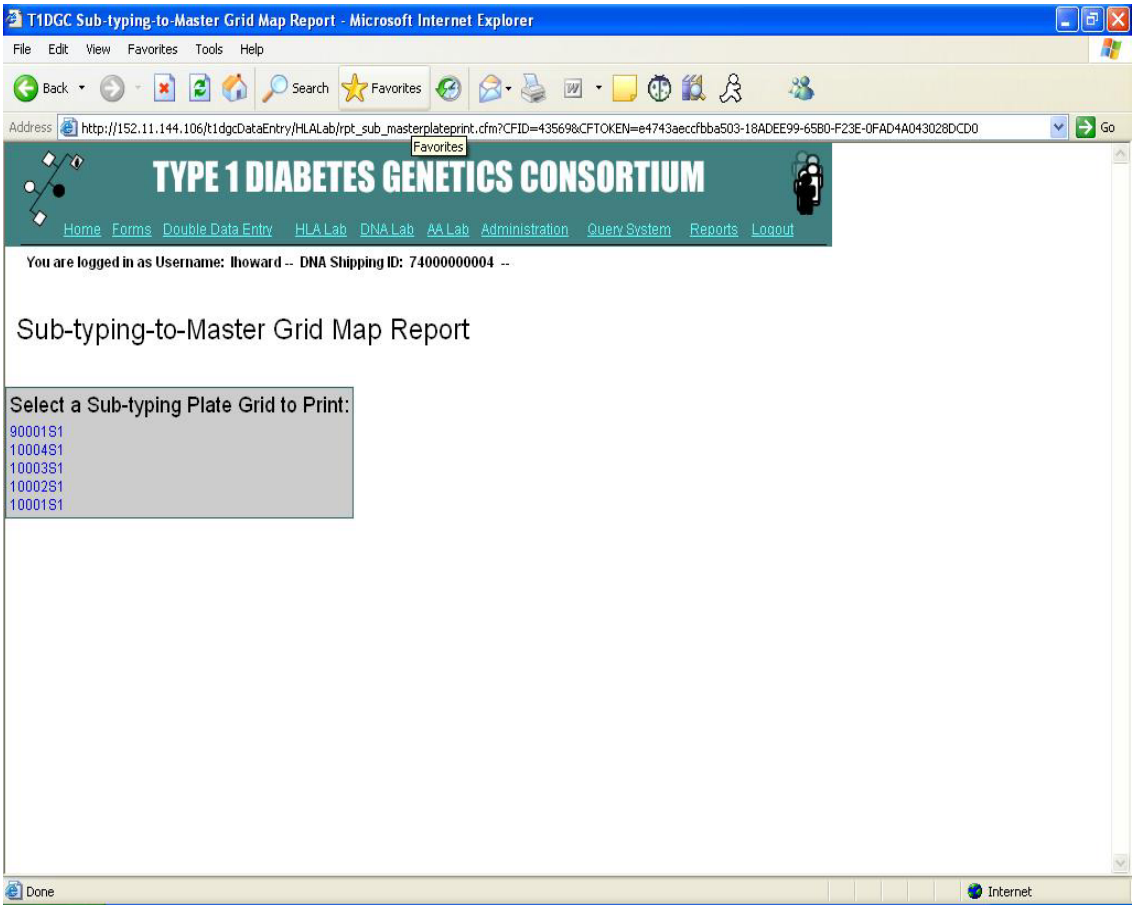


Figure 23. List of Sub-typing Plate Grids available to print.

2. Click on the Sub-typing Plate Grid to be printed. The print dialogue box is displayed over the Sub-typing to Master Grid Report (Figure 24).

   a. If the printed page does not fit on one sheet, try printing in Landscape.

   b. Note that if the orientation is changed to landscape, all subsequent pages printed from the browser will print in landscape mode. To change the print orientation back, click “File” and select “Page Setup.”

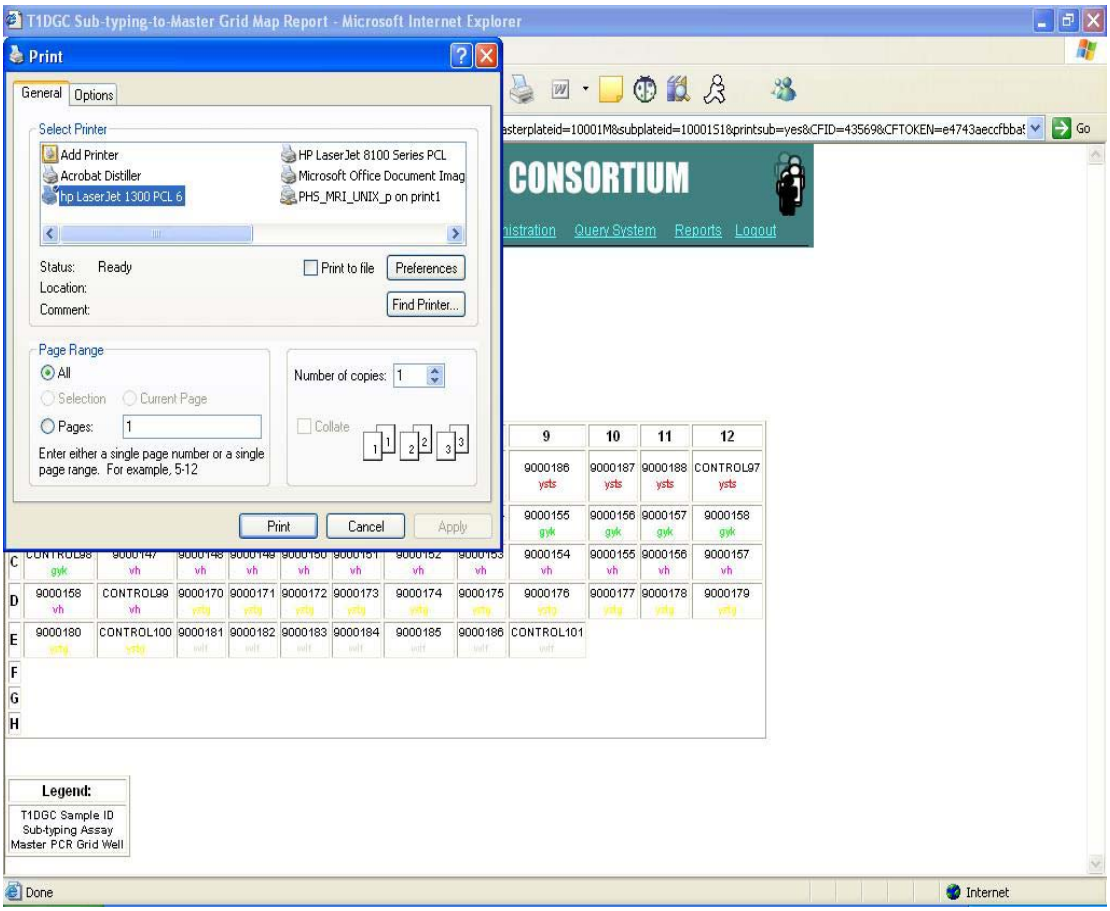


Figure 24. Sub-typing to Master Grid Report.

L. Redo Plate Grid

1. When the HLA Lab user accesses the Redo Plate Grid, the HLA Master Plate Grid Selection Form is displayed. The HLA Lab user must choose the Master Plate Grid that will be used to create a Redo Plate Grid. By selecting the Master Plate Grid, the HLA Lab user will be able to select IDs on the chosen Master Plate Grid (Figure 25).

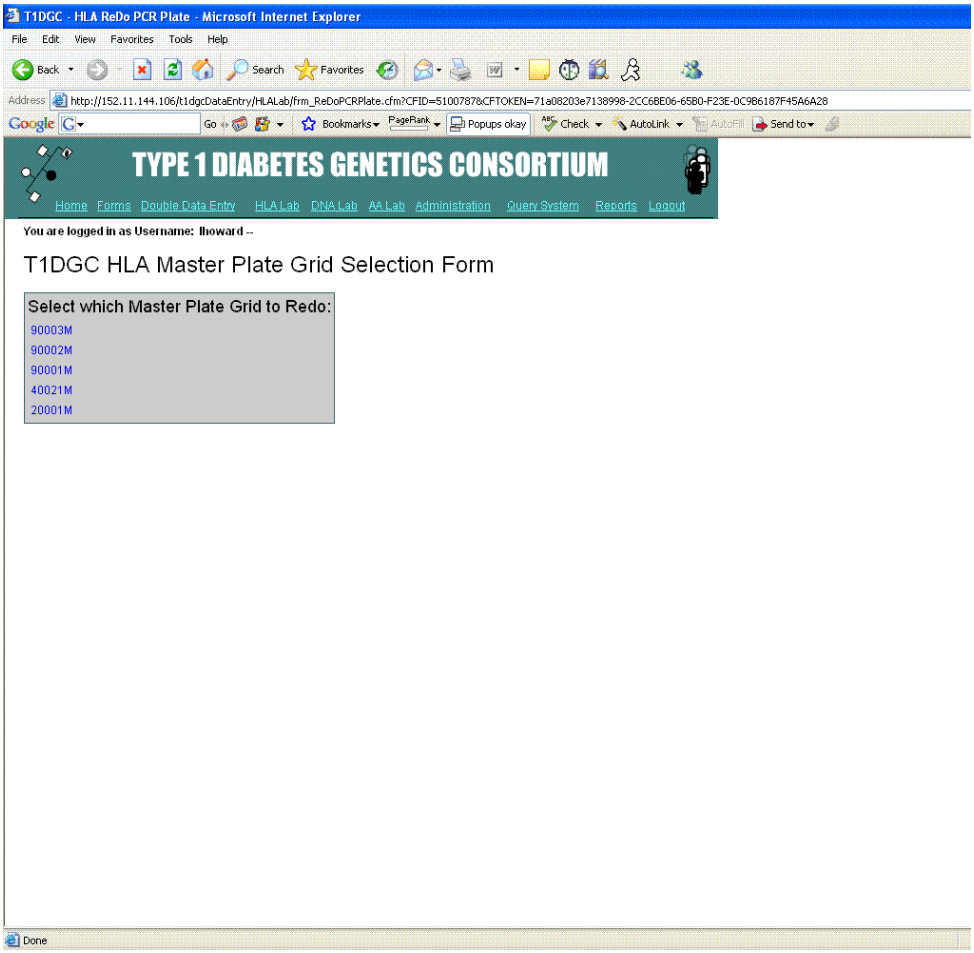


Figure 25. HLA Master Plate Grid Selection Form.

2. The system will display the selected Master Plate Grid and the blank Redo Plate Grid below (Figure 26).

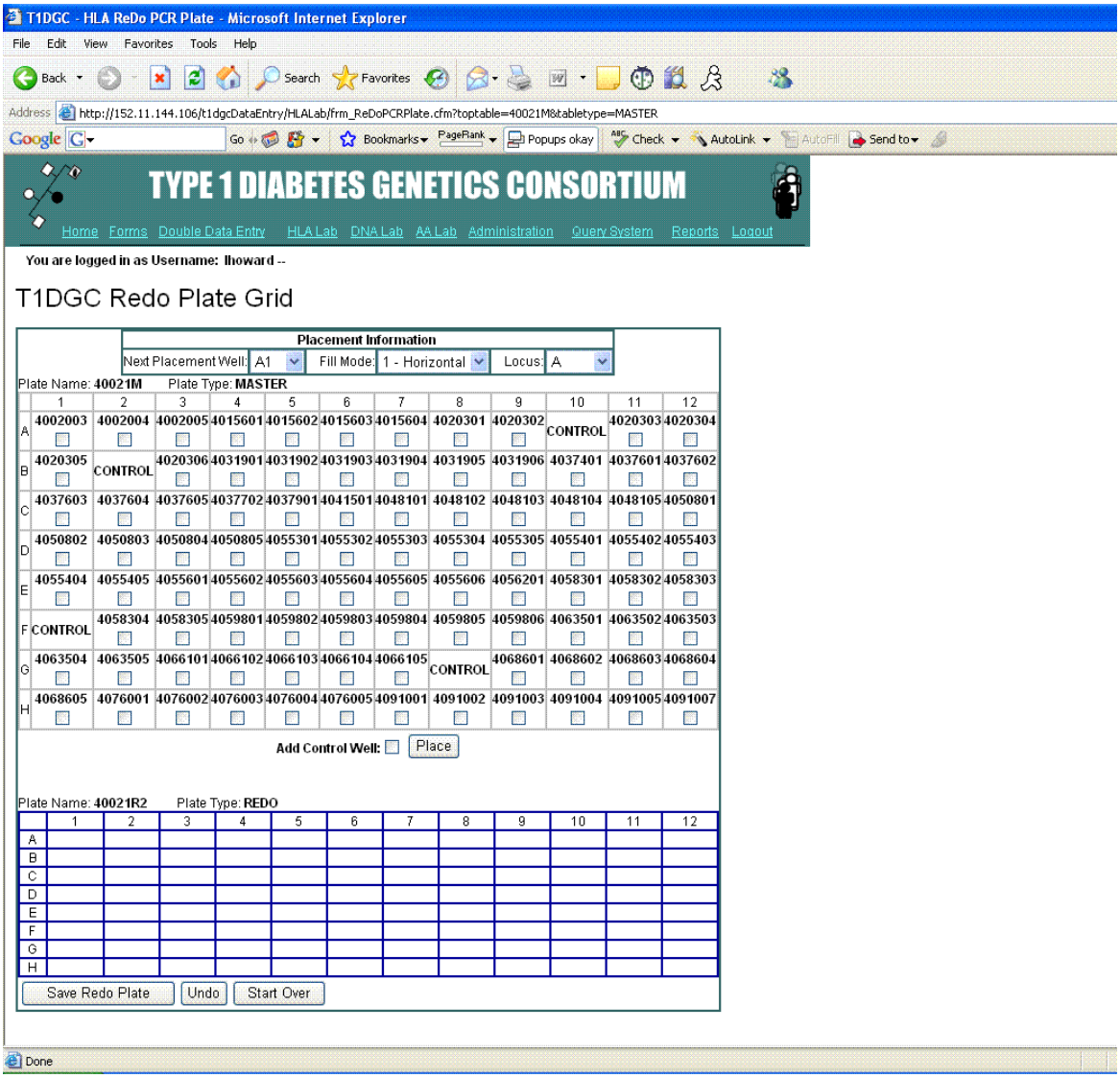


Figure 26. Redo Plate Grid (before Redo Plate Grid filled).

3. Set the placement criteria.

   a. The Placement Address will default to the next well in chronological order; however, the HLA Lab user can change the placement address to another well if desired.

   b. The “Fill Mode” will default to place the IDs horizontally. The HLA Lab user can choose to place the IDs horizontally or vertically.

   c. Set the “Locus” to be associated with the selected IDs.

4. Select all of the IDs to redo for a particular locus. **ALWAYS check the "Add Control Well" box at the end of each assay on a Redo Plate Grid**.

5. Press "Place" to place the IDs into the Redo Plate Grid.

6. When the grid is complete, press the "Save Redo Plate" button at the bottom of the page (Figure 27).

7. The HLA Master Plate Grid Selection Form is displayed with a message stating the Redo Plate Grid has been saved (Figure 28).

8. If the HLA Lab user selects the information after placing the IDs, the HLA Lab user can click "Undo" and clear the **last** stack of IDs that were added to the Redo Plate Grid. (NOTE: Only the last group of IDs placed can be removed. If group 1 is placed and then group 2 is placed, group 2 can be undone, but group 1 cannot be undone.)

9. If the HLA Lab user needs to start over, press the "Start Over" button at the bottom of the page to clear the Redo Plate Grid.

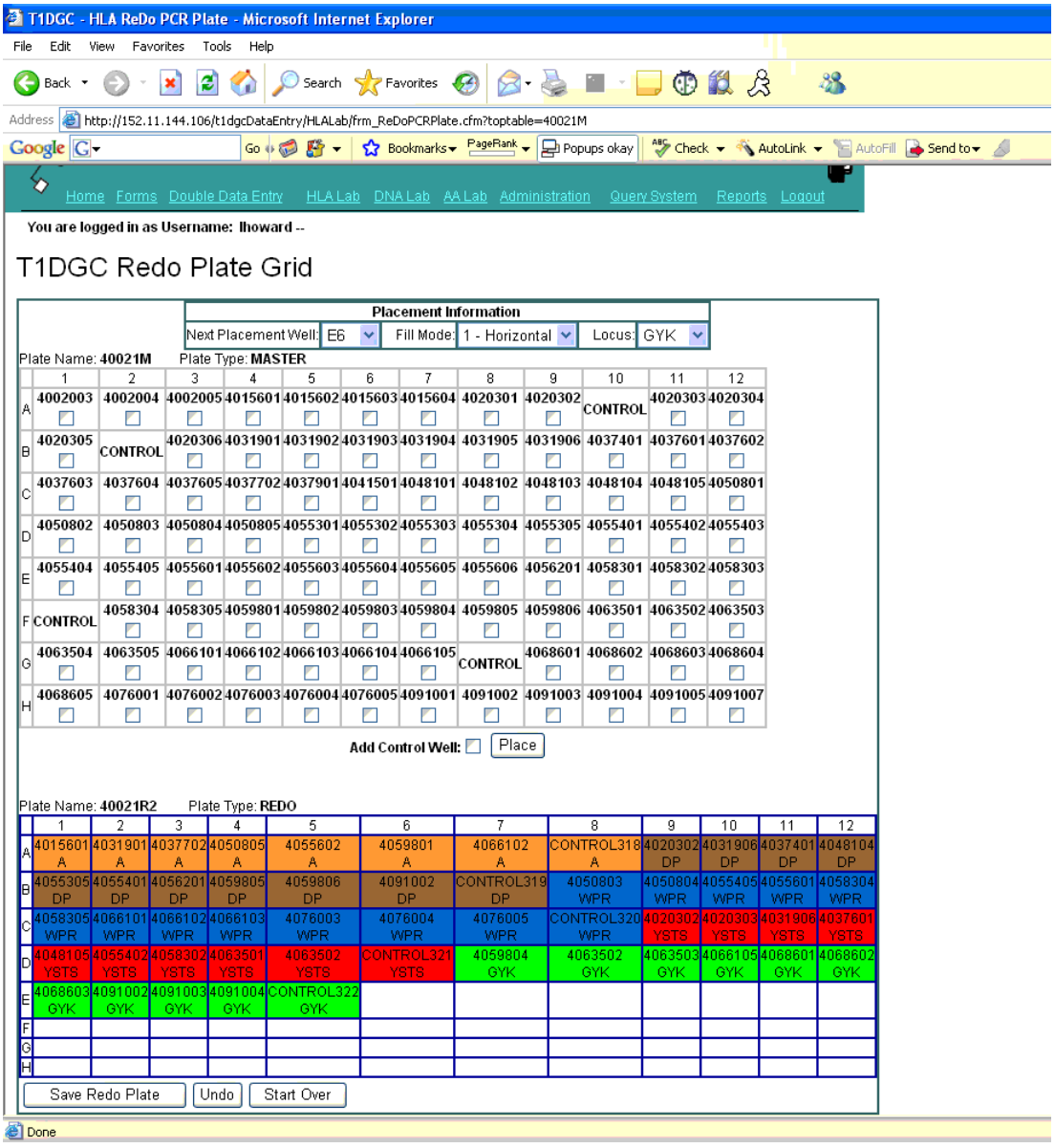


Figure 27. Redo Plate Grid (after Redo Plate Grid filled).

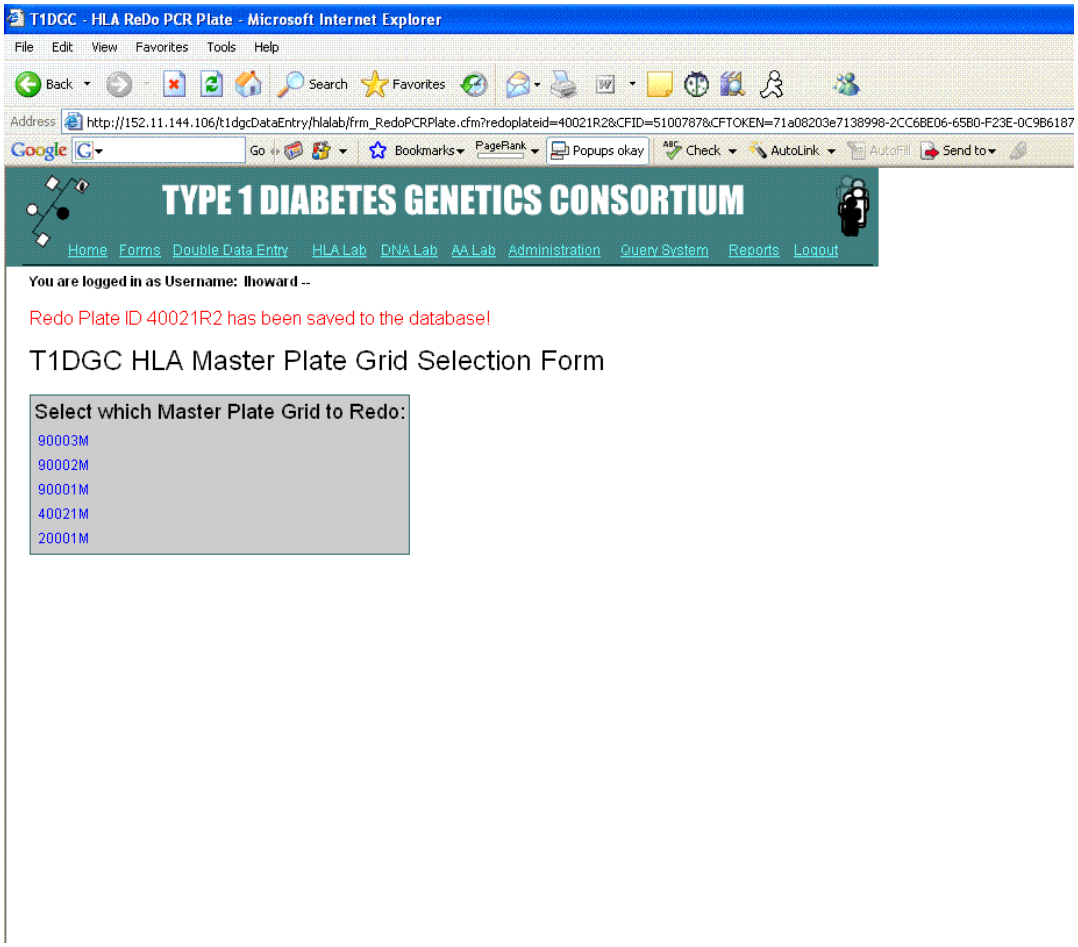


Figure 28. HLA Master Plate Grid Selection Form (after Redo Plate Grid has been saved).

M. Redo Plate Grid Report

1. When the HLA Lab user accesses the Redo Plate Grid Report, a list of available Redo Plate Grids is displayed (Figure 29).

2. Click on the Redo Plate Grid to be printed. The print dialogue box is displayed over the Redo Plate Grid Report (Figure 30). The Redo Plate Grid Report displays all Master Plate Grids, along with the Redo Plate Grid.
   a. If the printed page does not fit on one sheet, try printing in Landscape.
   b. Note that if the orientation is changed to landscape, all subsequent pages printed from the browser will print in landscape mode. To change the print orientation back, click “File” and select “Page Setup.”

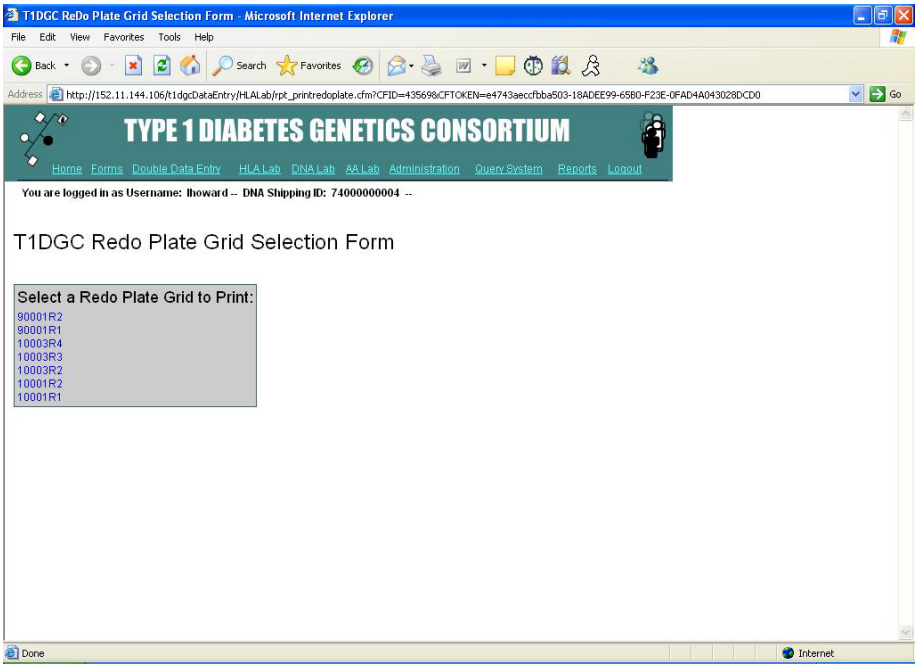


Figure 29. List of Redo Plate Grids available to print.

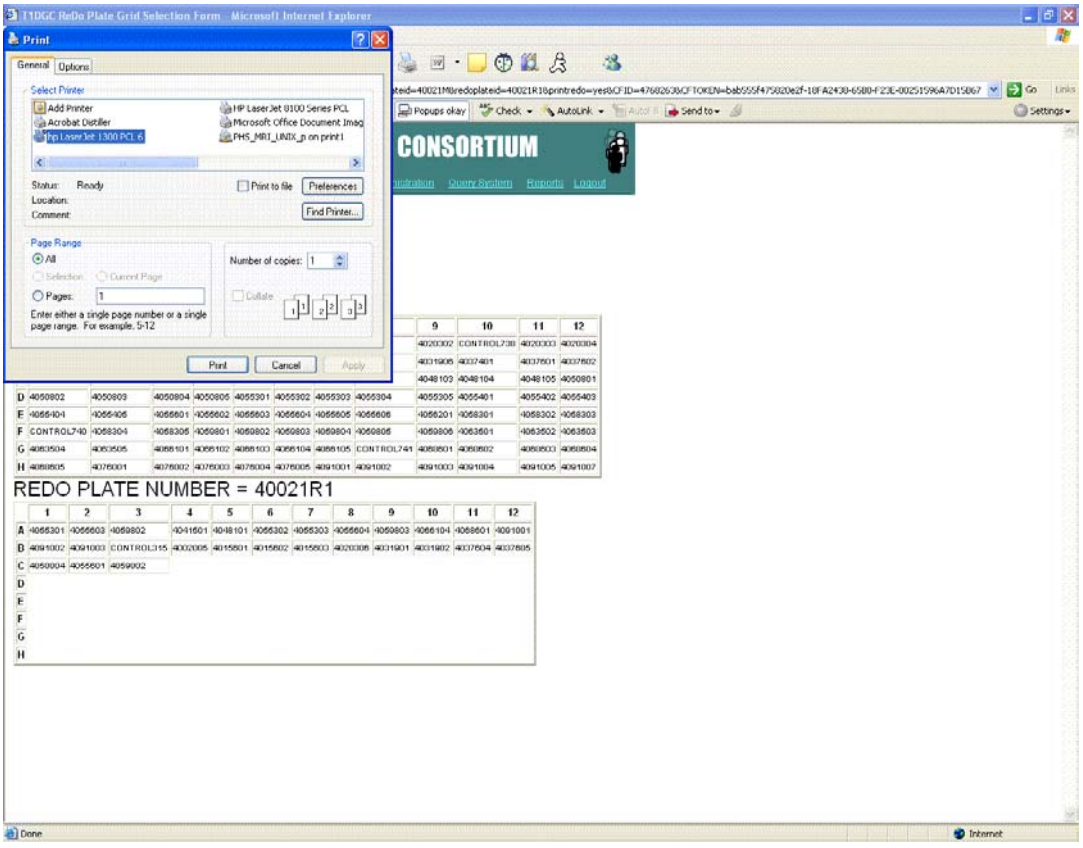


Figure 30. Redo Plate Grid Report.

N. Redo-to-Master Plate Grid Report

1. When the HLA Lab user accesses the Redo-to-Master Plate Grid Report, a list of available Redo Plate Grids is displayed (Figure 31).

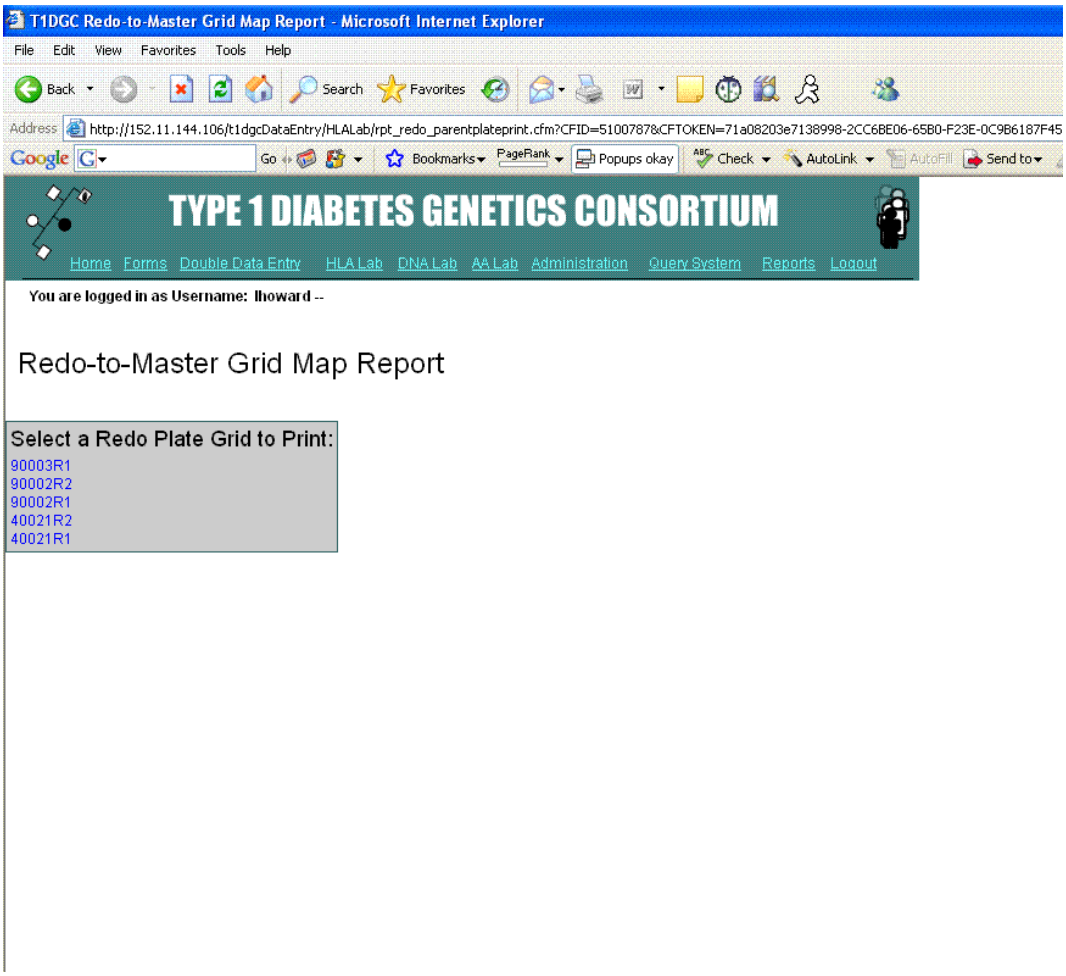


Figure 31. List of Redo Plate Grids available to print.

2. Click on the Redo Plate Grid to be printed. The print dialogue box is displayed over the Redo-to-Master Plate Grid Report (Figure 32). The Redo-to-Master Plate Grid Report lists the participant ID followed by the locus followed by the well that contains the participant ID on the Master Plate Grid in each well of the Redo Plate Grid.

   a. If the printed page does not fit on one sheet, try printing in Landscape.

b. Note that if the orientation is changed to landscape, all subsequent pages printed from the browser will print in landscape mode. To change the print orientation back, click “File” and select “Page Setup.”

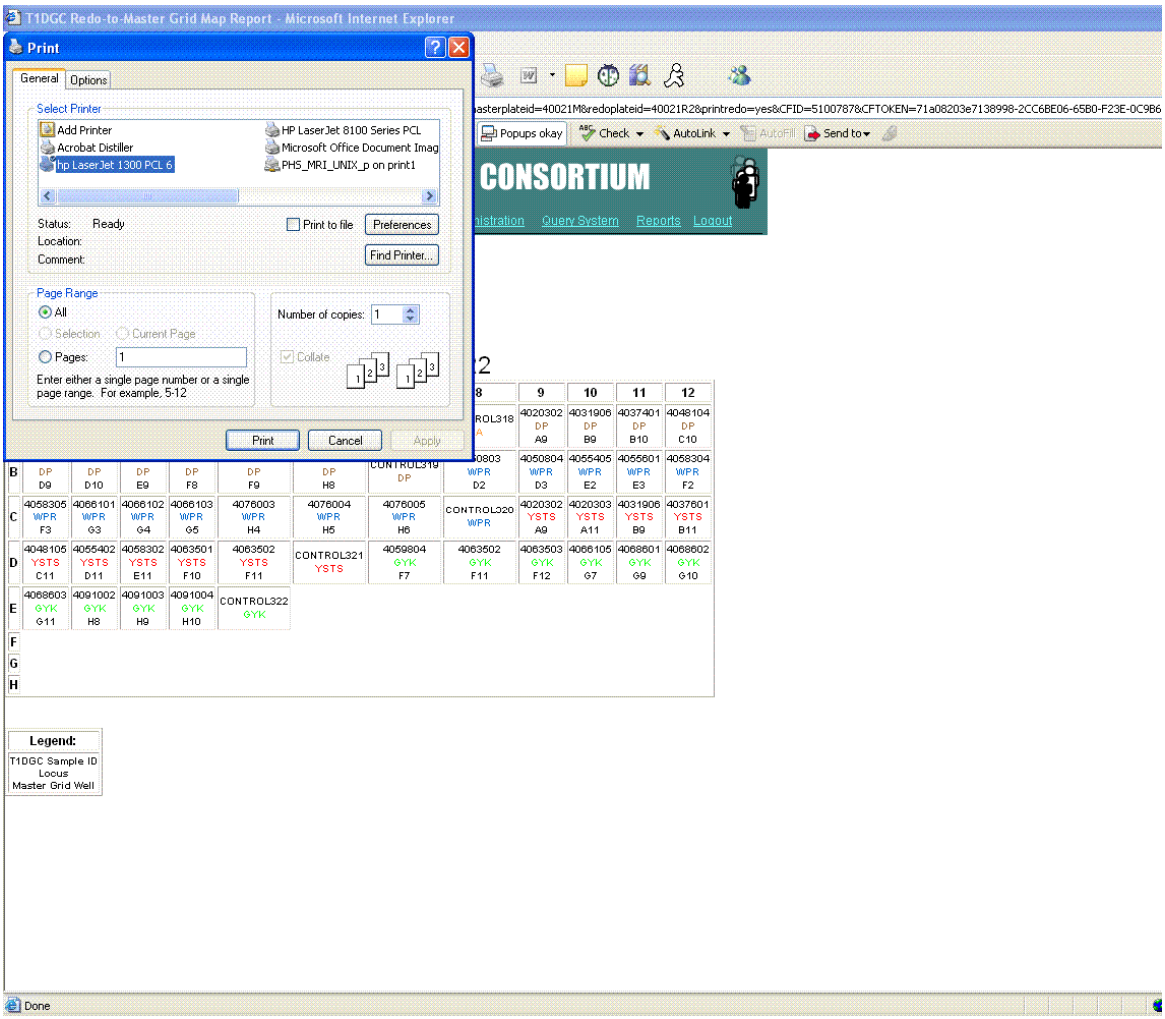


Figure 32. Redo-to-Master Grid Report.

O. Cancel Plate Grid

1. The “Cancel Plate Grid” link should only be used **only on rare occasions**.

2. When the HLA Lab user accesses this link, a drop down box displays the type of Plate Grid to cancel (Figure 33).

   a. To view all the Master Plate Grids available, click “Master Plate Grid”.

b. To view all the Sub-typing Plate Grids available, click “Sub-typing Plate Grid”.

c. To view all the Redo Plate Grids available, click “Redo Plate Grid”.

d. To view all available Plate Grids, click “All Plates”.

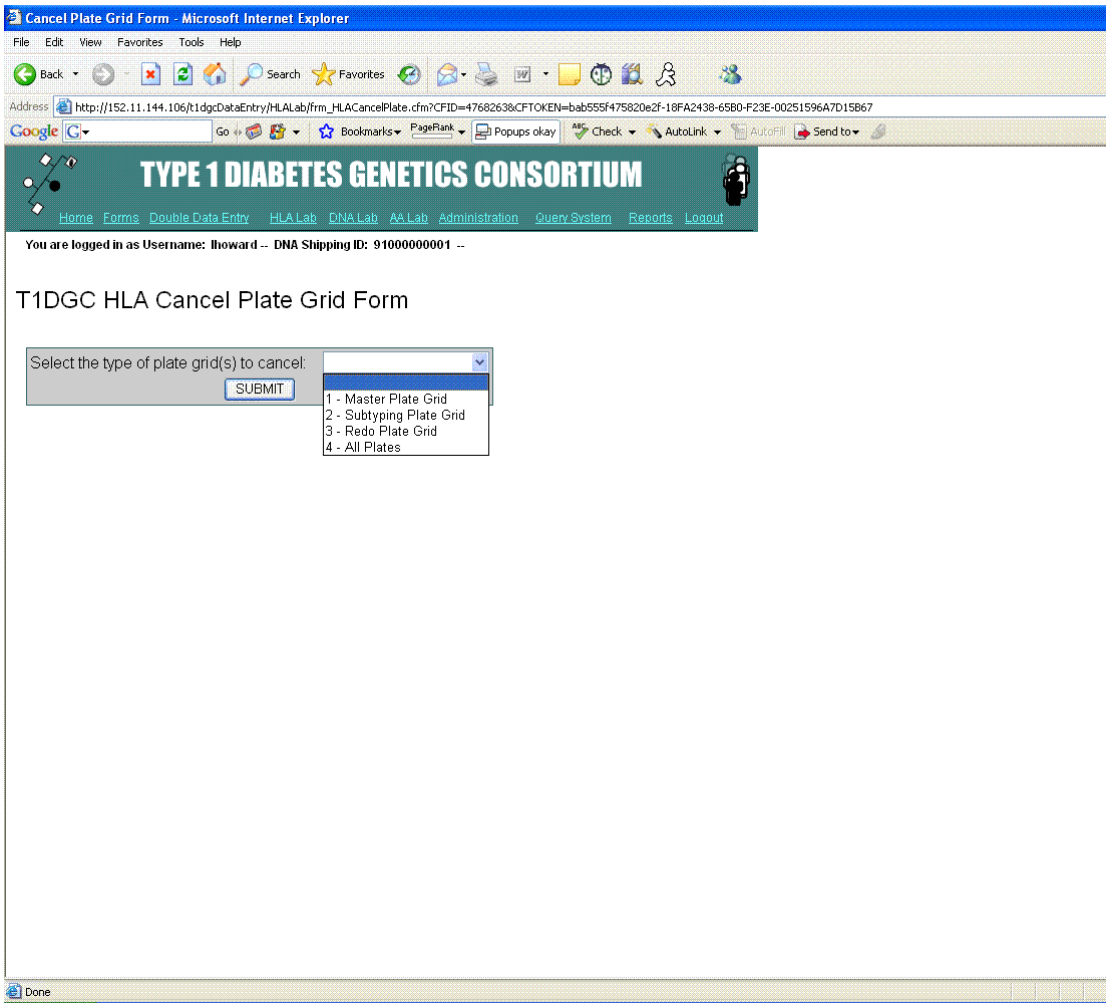


Figure 33. Cancel Plate Grid Form.

3. Once the HLA Lab user has selected a plate type, a list of plates that can be cancelled is displayed (Figure 34).

a. If the HLA Lab user wants to cancel a Master Plate Grid that has Sub-typing Plate Grids associated with it, first cancel the Sub-typing Plate Grids associated with the Master Plate Grid to be cancelled.

b. An asterisk (*) will appear beside any Plate Grids that have an associated Redo Plate Grid. If a Master Plate Grid has a Redo Plate Grid associated with it, the Redo Plate Grid must be cancelled before the Master Plate Grid can be cancelled.

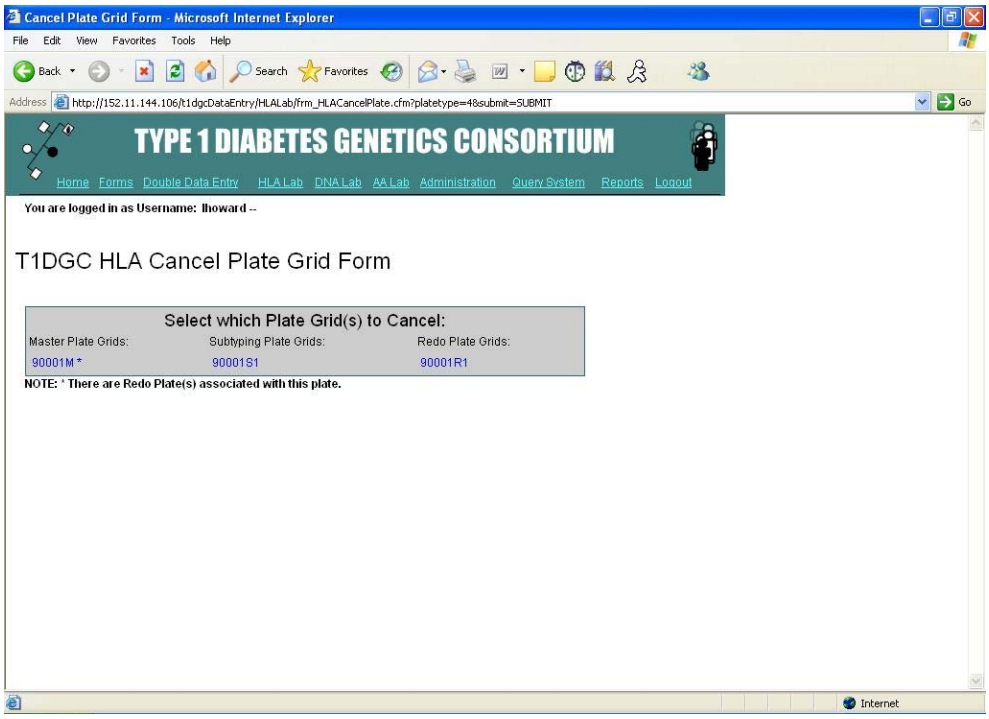


Figure 34. Cancel Plate Grid Form selection.

4. Click on the Plate Grid to be cancelled.

5. The HLA Lab user will confirm the selection (Figure 35). If “yes” is clicked, the Plate Grid will be permanently cancelled and the IDs associated with that shipment will be available to create a new Plate Grid.

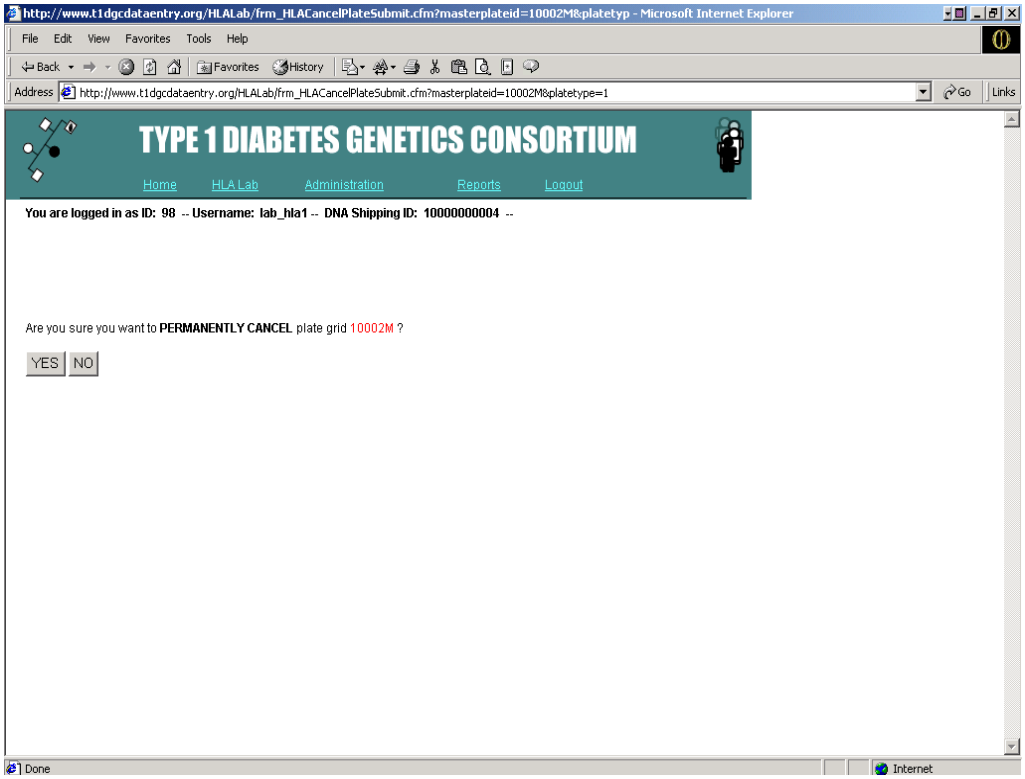


Figure 35. Cancel Plate Grid Form confirmation.

P. HLA Sample File Download

1. The Sample File Download Form is used to download the text files **used in StripScan.**

2. When the HLA Lab user accesses this link, a drop down box displays the type of Plate Grid to download (Figure 36).
   a. To view all the Master Plate Grids available, click “Master Plate Grids”.
   b. To view all the Sub-typing Plate Grids available, click “Sub-typing Plate Grids”.
   c. To view all the Redo Plate Grids available, click “Redo Plate Grids”.
   d. To view all of the Plate Grids available, click “All Plates”.

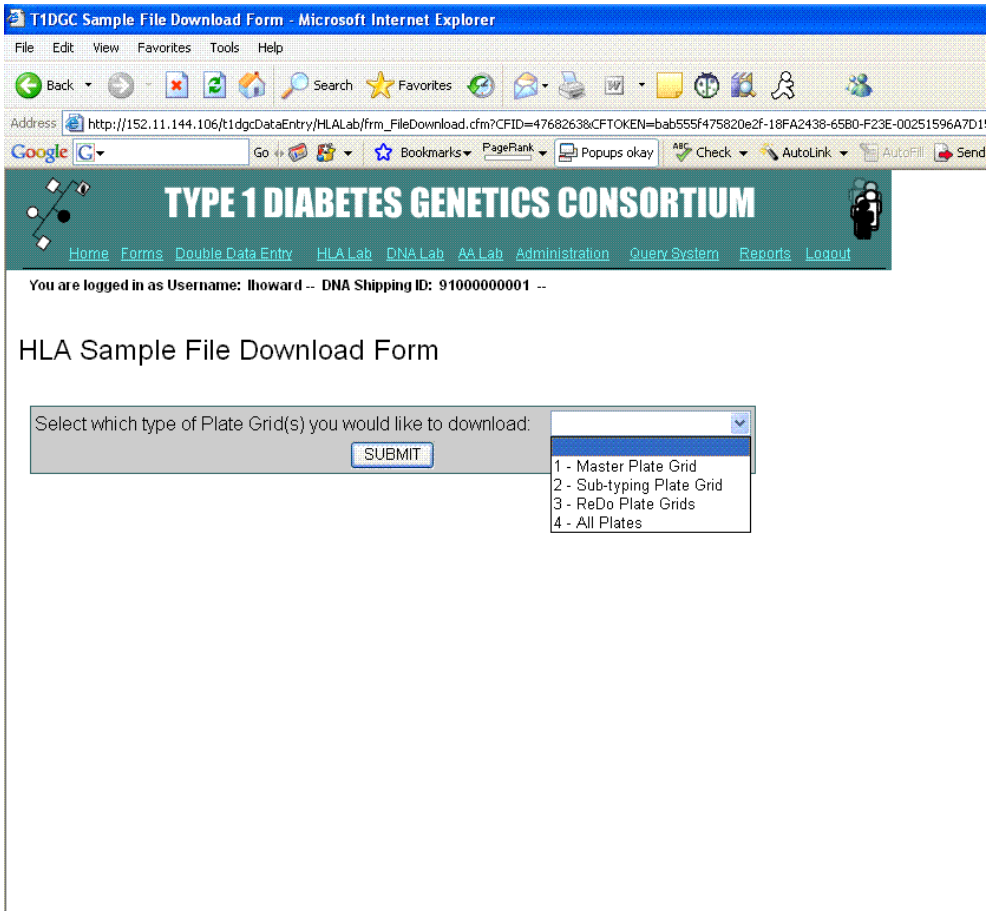


Figure 36. Sample File Download Form.

3. Once a plate type is selected, a list of files that can be downloaded is displayed (Figure 37).

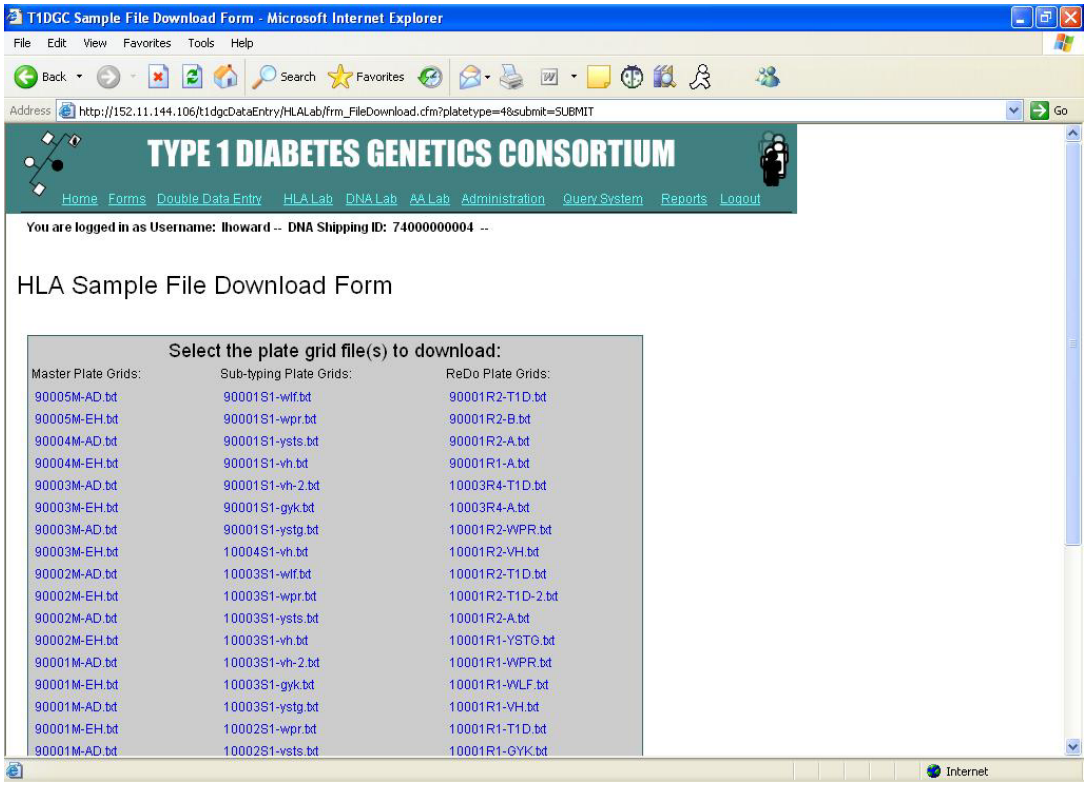


Figure 37. Sample File Download Form Selection.

4. Click on the link to be downloaded.

5. The HLA Lab user will be asked what to do with the file. Select “Save this file to disk”, choose a location to which to save the file, and press “Save” (Figure 38). The file should always be saved to the file directory downloaded when StripScan was downloaded.

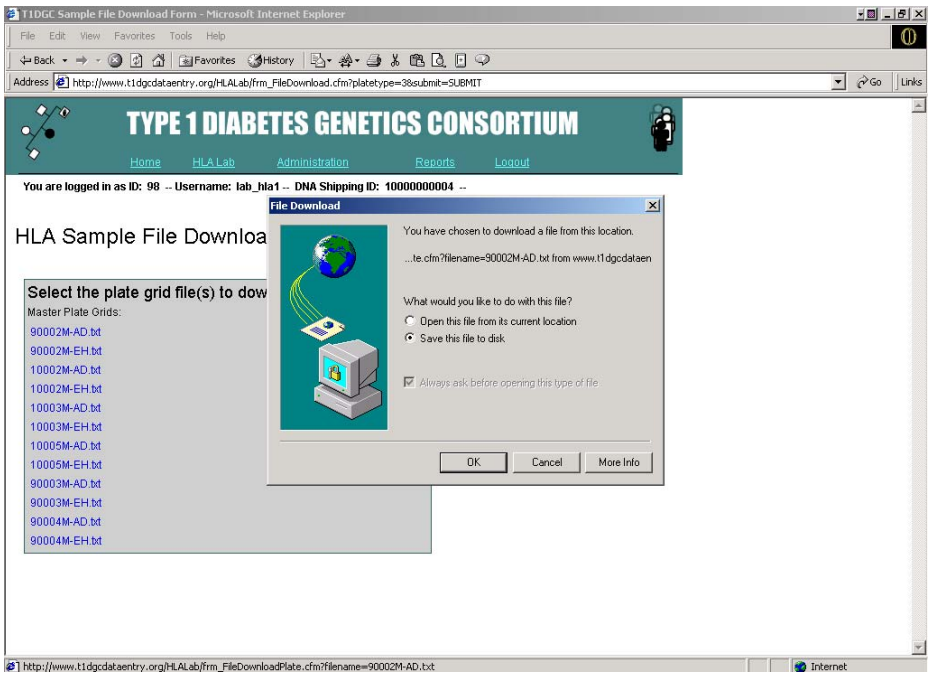


Figure 38. Sample File Download Form Confirmation.

7. **Prior to saving any of the HLA files, use StripScan to create a directory structure and save these files into the folders created by the StripScan software.**

   a. If sample files have been downloaded properly and are up-to-date, StripScan will manage Plate Grid names and identifiers, with the exception of re-dos.

   b. StripScan permits editing Plate Grid name and sample identifiers, but this should not be used, with the exception of re-dos.

   c. StripScan will create a file folder for each loci (A, B, C, DP, DQ, T1D) and the DRB1 subtypes (GYK, WLF, WPR, VH, YSTS, and YSTG).

   d. Store sample import files corresponding to Master Plate Grids and Sub-typing Plate Grids for <plate number>. These files are used for importing Plate Grid T1DGC sample identifiers into StripScan; the file extension is ".txt".

   e. For a full Master Plate Grid (i.e., 92 samples and 4 negative controls), there will be 2 StripScan import files: upper (AD) and lower (EH). This is due to the BeeBlot capacity of 48 samples which necessitates the

"splitting" of plates into separate BeeBlot runs for the upper (rows A through D) and lower (rows E through H) halves. For example, a full Master Plate Grid (Plate Number: 40005M) would have 2 import files named 40005M-AD.txt and 40005M-EH.txt.

f. Sub-typing assay file names include the Sub-typing Plate Grid number and the specific assay name. For example, a sub-typing file for YSTS could be named 40005S1-YSTS.txt.

g. There may be more than one Sub-typing Plate Grid for a given Master Plate Grid. In this event, the files could be named 40005S1-YSTS.txt, 40005S1-VH.txt, 40005S1-GYK.txt, and 40005S2-YSTG. This would indicate that the first three sub-typing assays were on the first Sub-typing Plate Grid and the fourth assay was on a second Sub-typing Plate Grid.

h. It may not be necessary to perform all 6 sub-typing assays for the samples on the Master Plate Grid. Try to contain a sub-type assay to one Plate Grid; that is, try not to split assays across Sub-typing Plate Grids.

i. In the rare event that more than 48 samples on a Master Plate Grid require a specific sub-type assay (e.g., YSTS), split the assay across two BeeBlot runs. There will be two StripScan files for the same assay. For example, these files would be named as 40005S1-YSTS.txt and 40005S1-2.txt.

Q. HLA File Upload

1. The HLA File Upload is used to upload the **xml file from SCORE.**

2. When the HLA Lab user accesses this link, a page is displayed with a form on the left side of the screen and list on the right side of the screen (Figure 39).

3. The files listed on the right are files previously uploaded by the HLA Lab user's network. Note that files are named in the SCORE program as <Batch_LabID_YYYYMMDD>.

4. The form on the left is used to upload new files.

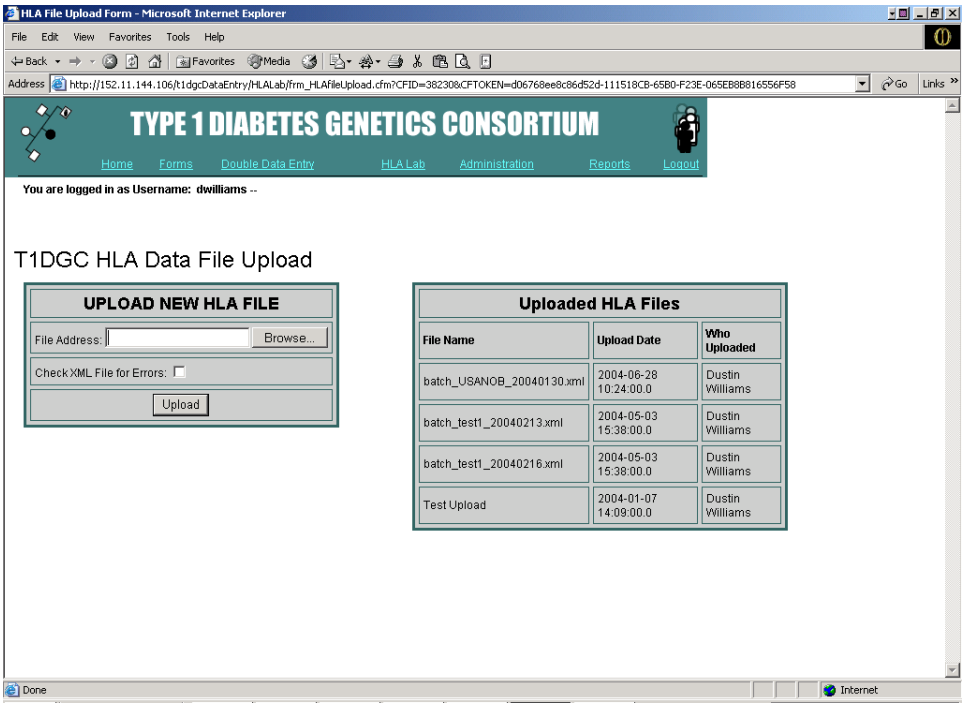


Figure 39. File Upload Form.

a. To upload a file, click “Browse” to locate the file on the computer. Click “Open” or double click on the file to submit the file address.

b. To check the xml file (generated by SCORE) for errors before a final upload, click the box next to “Check XML File for Errors:” and press the Upload Button (Figure 40). **When a file is checked for errors, it does not save to the database.**

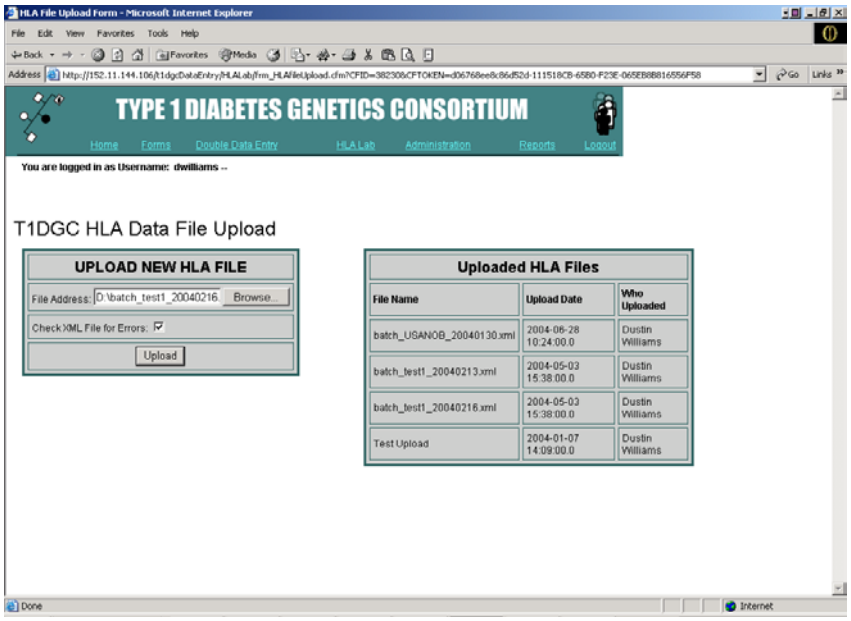


Figure 40. Xml file check to identify mistakes prior to final upload.

c. If there are any errors, a list will be displayed with a description (Figure 41).

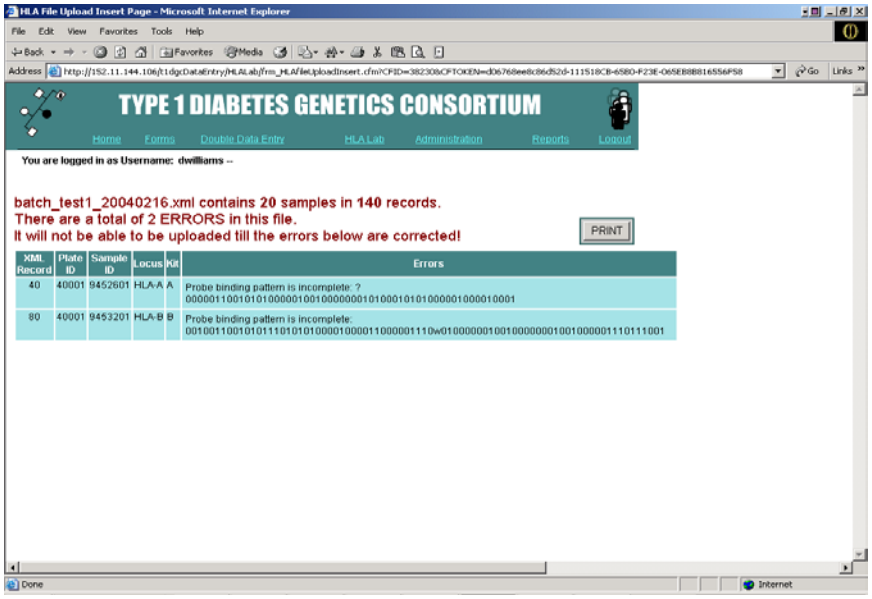


Figure 41. Xml file check lists the mistakes and errors in the file.

d. Click the “Print” button to print the error report in the file (Figure 42).

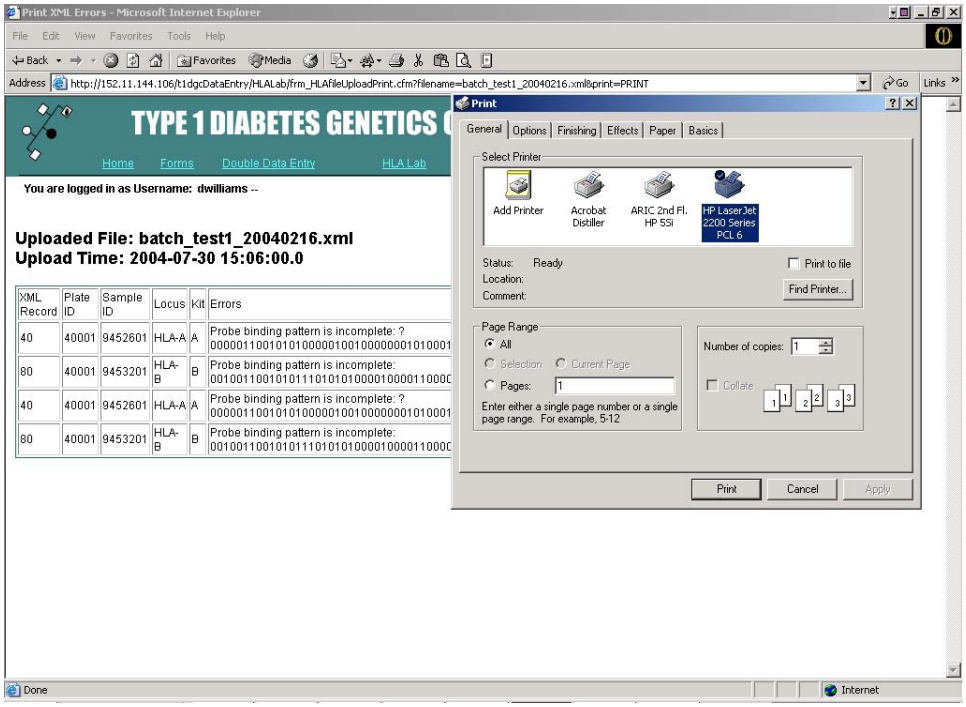


Figure 42. Print the list of errors from the xml file.

e. When the HLA Lab user is satisfied with the file and ready to upload the information to the Coordinating Center, enter the file name and **do not** mark "Check xml file for errors." If there are no errors, the file will upload and appear on the uploaded file list (on the right hand side of the screen) as the last uploaded file (Figure 43). If there are errors, the file will not upload and will not appear on the uploaded file list. The HLA Lab user will receive the error report indicating the errors remaining in the file (Figure 41).

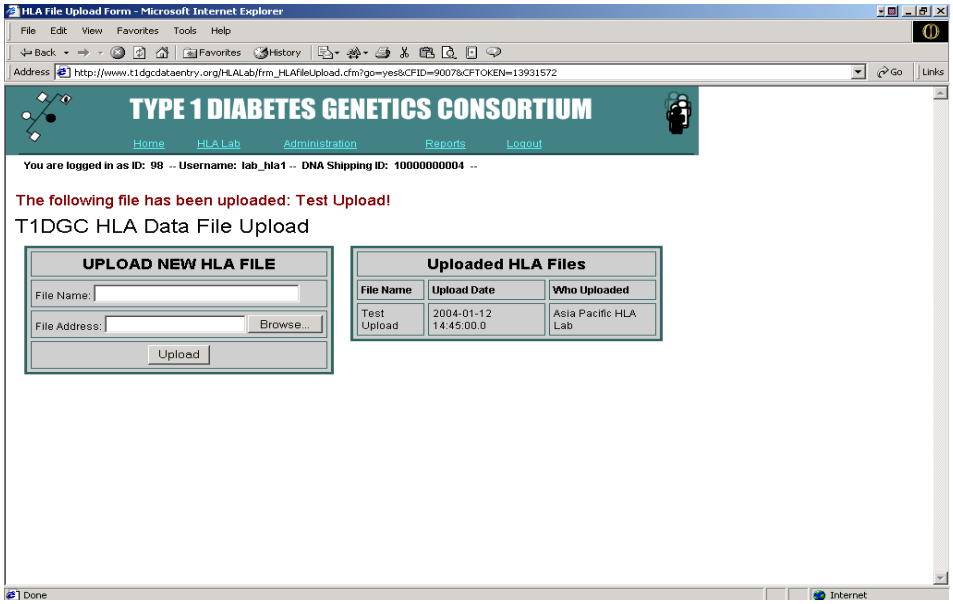


Figure 43. File Upload Form Confirmation.

R. Probe Binding Report

The probe binding report is a downloadable file, a comma separated value formatted file easily imported into Microsoft Excel. This is a cumulative file containing the probe binding and pixel value results for each assay. Results are identified by plate, well, participant ID, locus, and kit name.

The HLA Lab user will be asked what to do with this file. Select “Save this file to disk”, choose a location to which to save the file, and press “Save” (Figure 44).

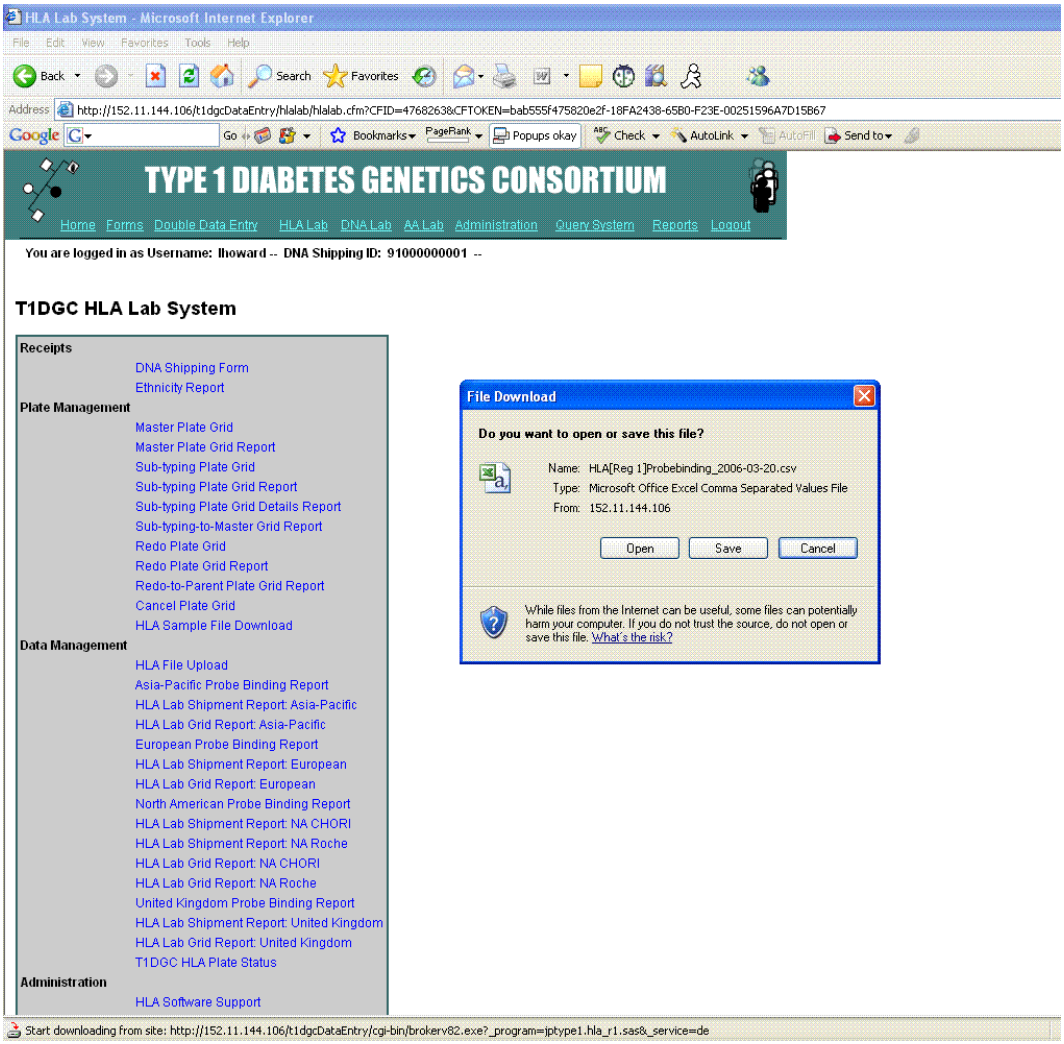
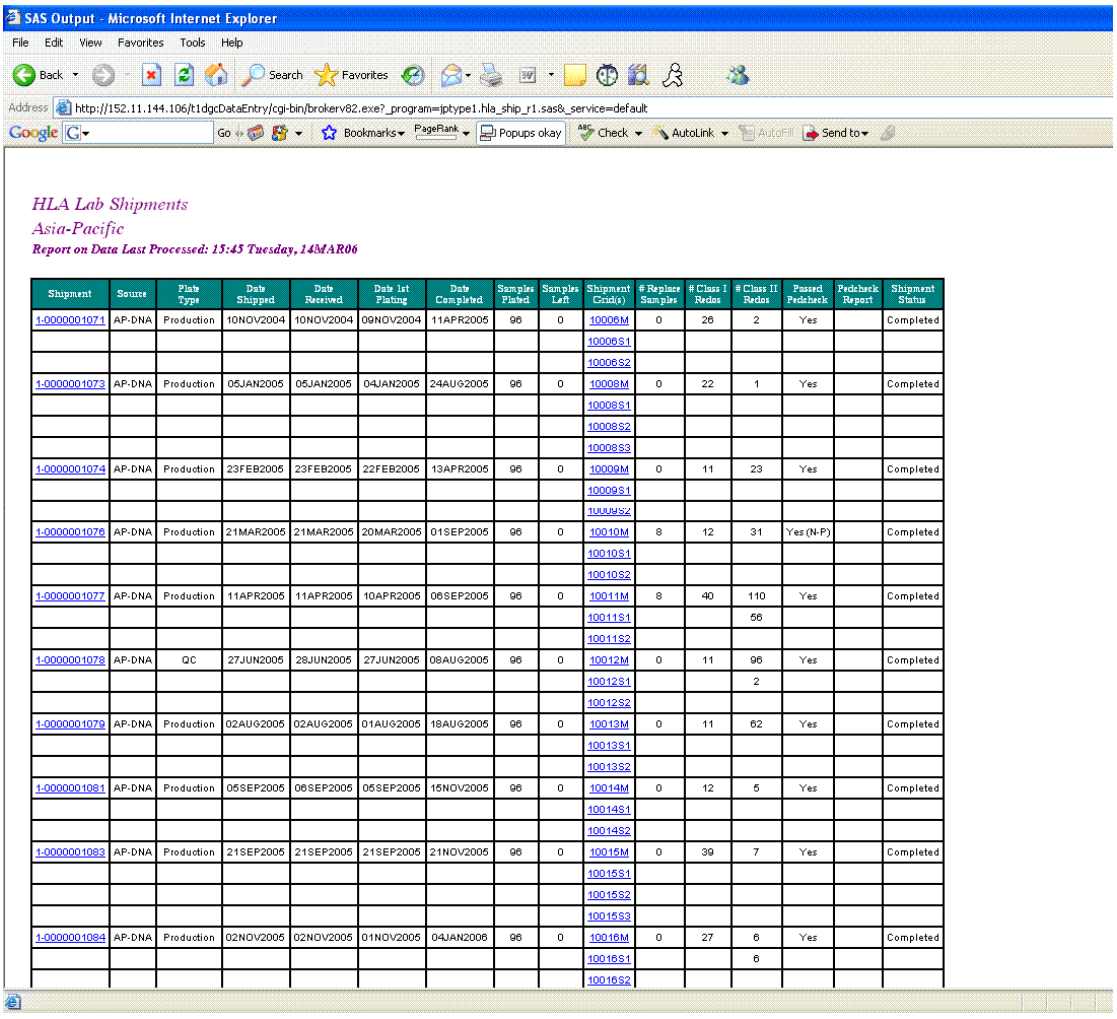


Figure 44. Saving Probe Binding Report to the HLA Lab user's hard drive.

S. HLA Lab Shipment Report

This dynamic report incorporates comprehensive information about each shpping ID, including plates associated with the shipping ID, date received, date completed, number of redos, status of plates, status of Pedcheck and links to associated sub-typing and master plate grids, as well as the Shipping Form (Figure 45). The report can be printed by selecting "Print" from the web browser menu.

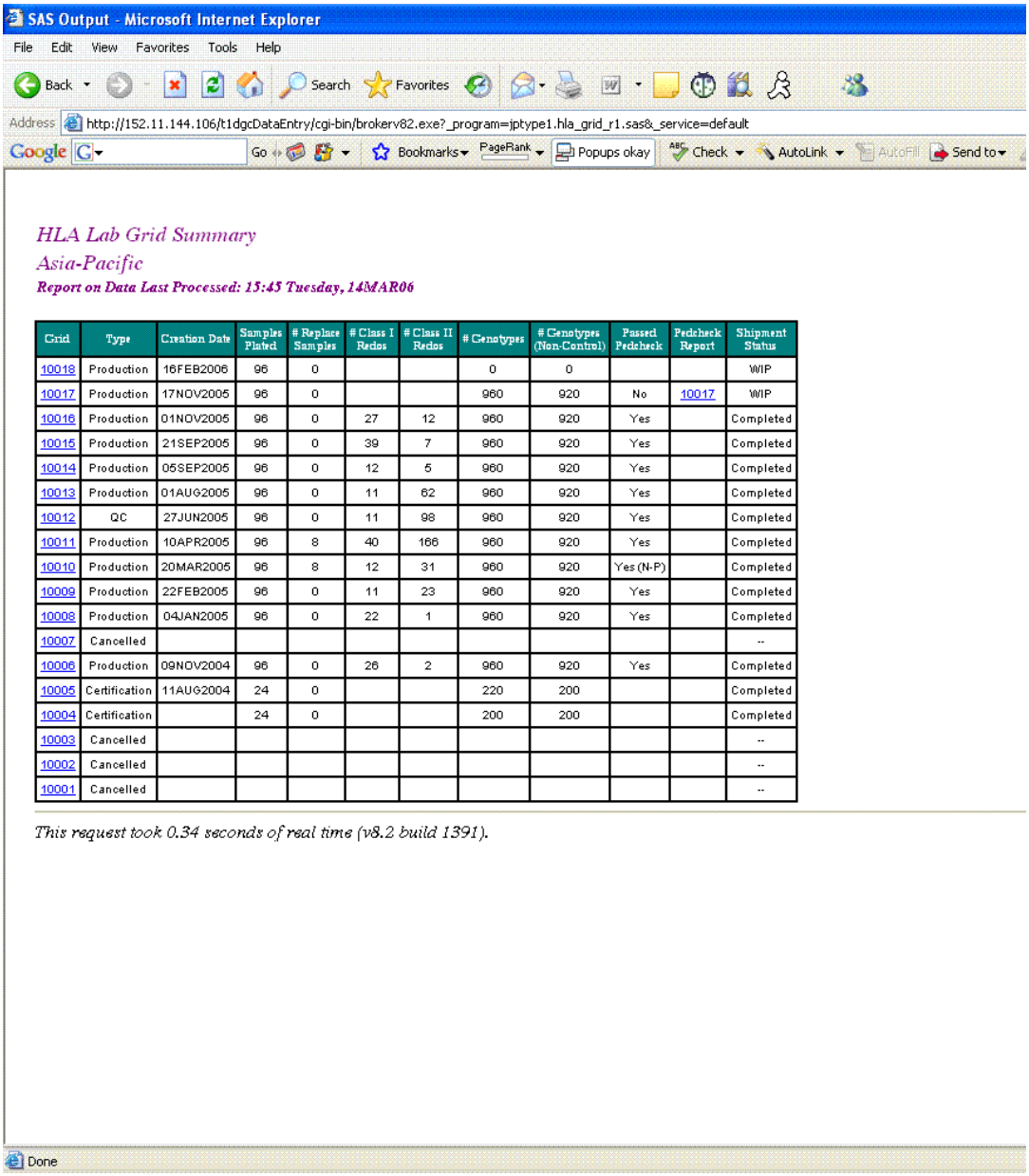


Shipment	Source	Plate Type	Date Shipped	Date Received	Date 1st Plating	Date Completed	Samples Plated	Samples Left	Shipment Grid(s)	# Replace Samples	# Class I Redos	# Class II Redos	Passed Pedcheck	Pedcheck Report	Shipment Status
1-0000001071	AP-DNA	Production	10NOV2004	10NOV2004	09NOV2004	11APR2005	96	0	10006M	0	26	2	Yes		Completed
									10006S1						
									10006S2						
1-0000001073	AP-DNA	Production	05JAN2005	05JAN2005	04JAN2005	24AUG2005	96	0	10008M	0	22	1	Yes		Completed
									10008S1						
									10008S2						
									10008S3						
1-0000001074	AP-DNA	Production	23FEB2005	23FEB2005	22FEB2005	13APR2005	96	0	10009M	0	11	23	Yes		Completed
									10009S1						
									10009S2						
1-0000001076	AP-DNA	Production	21MAR2005	21MAR2005	20MAR2005	01SEP2005	96	0	10010M	8	12	31	Yes (N-P)		Completed
									10010S1						
									10010S2						
1-0000001077	AP-DNA	Production	11APR2005	11APR2005	10APR2005	06SEP2005	96	0	10011M	8	40	110	Yes		Completed
									10011S1			56			
									10011S2						
1-0000001078	AP-DNA	QC	27JUN2005	28JUN2005	27JUN2005	08AUG2005	96	0	10012M	0	11	96	Yes		Completed
									10012S1			2			
									10012S2						
1-0000001079	AP-DNA	Production	02AUG2005	02AUG2005	01AUG2005	18AUG2005	96	0	10013M	0	11	62	Yes		Completed
									10013S1						
									10013S2						
1-0000001081	AP-DNA	Production	05SEP2005	06SEP2005	05SEP2005	15NOV2005	96	0	10014M	0	12	5	Yes		Completed
									10014S1						
									10014S2						
1-0000001083	AP-DNA	Production	21SEP2005	21SEP2005	21SEP2005	21NOV2005	96	0	10015M	0	39	7	Yes		Completed
									10015S1						
									10015S2						
									10015S3						
1-0000001084	AP-DNA	Production	02NOV2005	02NOV2005	01NOV2005	04JAN2006	96	0	10016M	0	27	6	Yes		Completed
									10016S1			6			
									10016S2						

Figure 45. HLA Lab Shipment Report.

T. HLA Lab Grid Report

This dynamic report incorporates comprehensive information about each plate including date the plate was created, number of samples, number of replacement samples, number of redos, number of genotypes, information from PedCheck, and status of each plate (Figure 46). The HLA Lab user is able to click on any Master Plate ID and receive the same information about any sub-typing plates associated with the Master Plate (Figure 47). Both of these reports can be printed by selecting “Print” from the web browser menu.



Grid	Type	Creation Date	Samples Plated	# Replace Samples	# Class I Redos	# Class II Redos	# Genotypes	# Genotypes (Non-Control)	Passed Pedcheck	Pedcheck Report	Shipment Status
10018	Production	16FEB2006	96	0			0	0			WIP
10017	Production	17NOV2005	96	0			960	920	No	10017	WIP
10016	Production	01NOV2005	96	0	27	12	960	920	Yes		Completed
10015	Production	21SEP2005	96	0	39	7	960	920	Yes		Completed
10014	Production	05SEP2005	96	0	12	5	960	920	Yes		Completed
10013	Production	01AUG2005	96	0	11	62	960	920	Yes		Completed
10012	QC	27JUN2005	96	0	11	98	960	920	Yes		Completed
10011	Production	10APR2005	96	8	40	166	960	920	Yes		Completed
10010	Production	20MAR2005	96	8	12	31	960	920	Yes (N-P)		Completed
10009	Production	22FEB2005	96	0	11	23	960	920	Yes		Completed
10008	Production	04JAN2005	96	0	22	1	960	920	Yes		Completed
10007	Cancelled										--
10006	Production	09NOV2004	96	0	26	2	960	920	Yes		Completed
10005	Certification	11AUG2004	24	0			220	200			Completed
10004	Certification		24	0			200	200			Completed
10003	Cancelled										--
10002	Cancelled										--
10001	Cancelled										--

Figure 46. HLA Lab Grid Report.

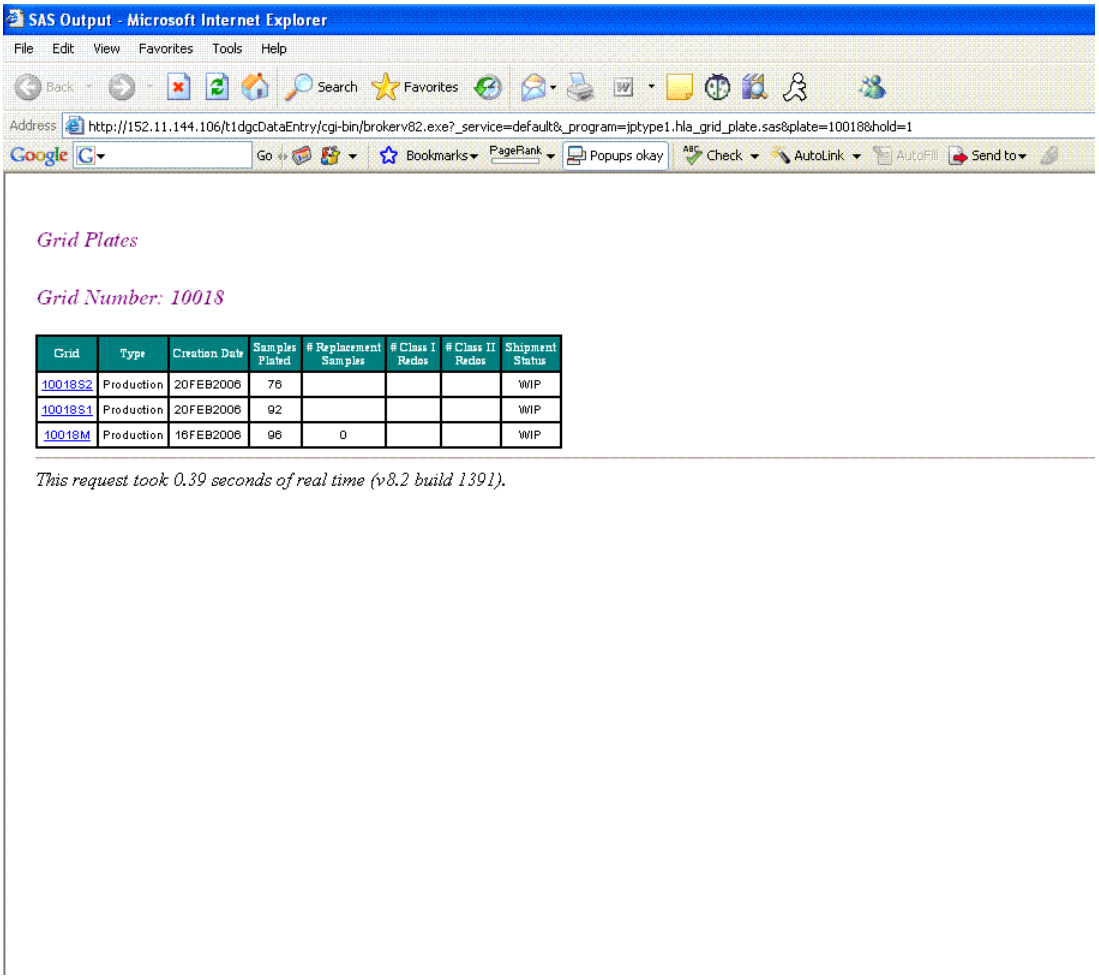


Figure 47. HLA Lab Grid Plates.

U. T1DGC HLA Plate Status

This dynamic report summarizes all plates logged into the HLA Lab system. The status of each plate is reported: the completion status and the number of genotype results for participants per assay (Figure 48). In addition, the total number of logged plates is tallied for those plates completed or in process. The report can be printed by selecting “Print” from the web browser menu.

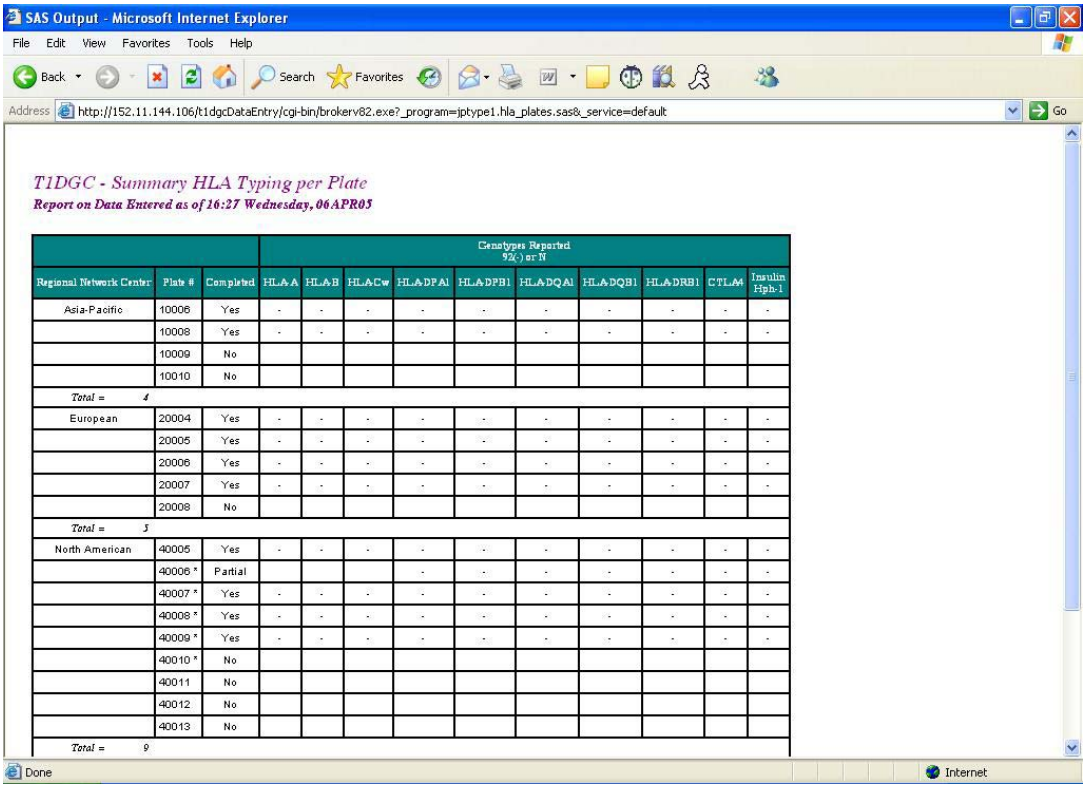


Figure 48. HLA Plate Status Report.

V. HLA Software Support

1. Click on this link to list the SCORE and StripScan files available to be downloaded (Figure 49). (NOTE: HLA Genotyping Laboratories can only download files from this page; specific users have rights to upload files.)

2. To download the current version of SCORE or StripScan, click on the program to be downloaded (Figure 50).

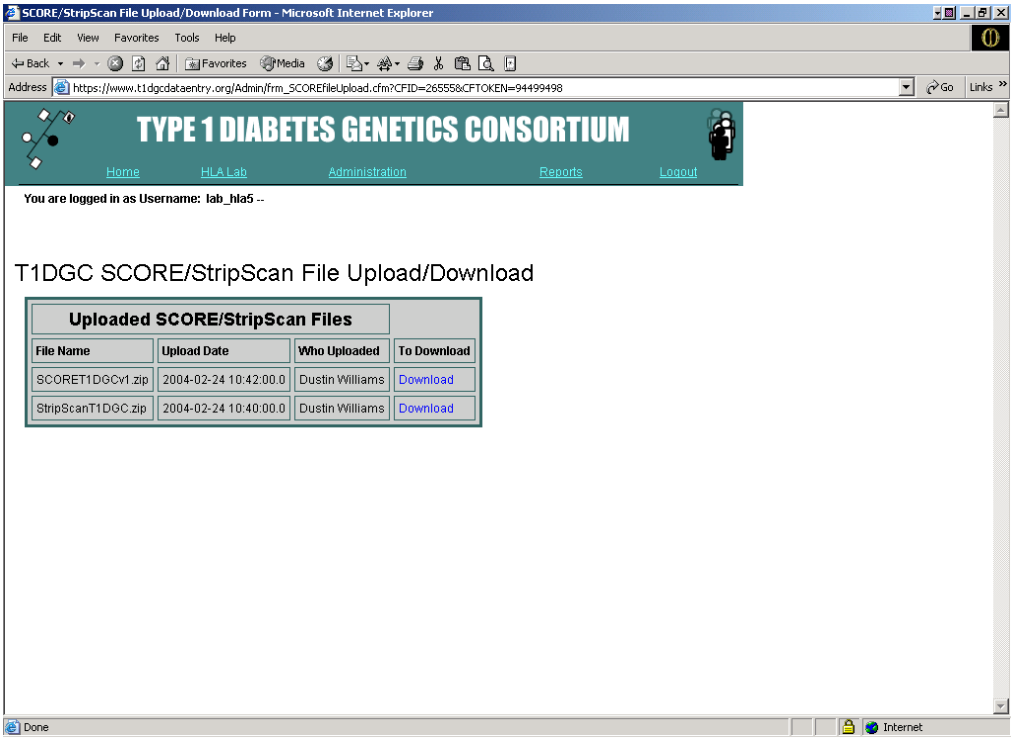


Figure 49. SCORE and StripScan Files Available for Download.

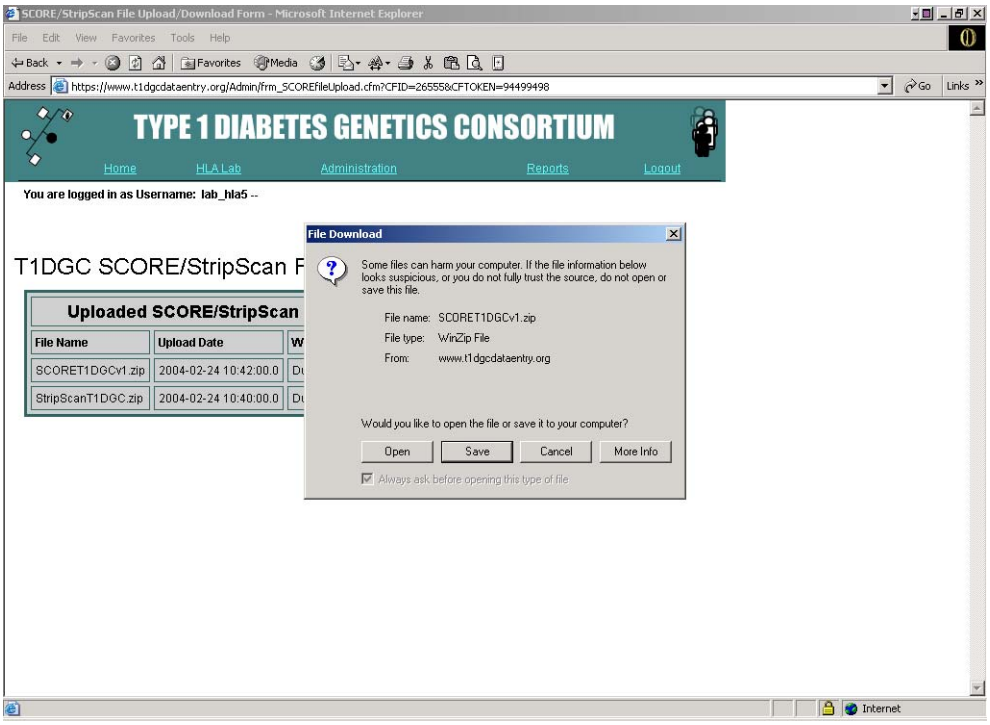


Figure 50. Confirmation that HLA Lab user wants to download program.

3. Save the zip file to a specific location (Figure 51). Double click the file to unzip it and then double click the .exe file and follow the instructions.

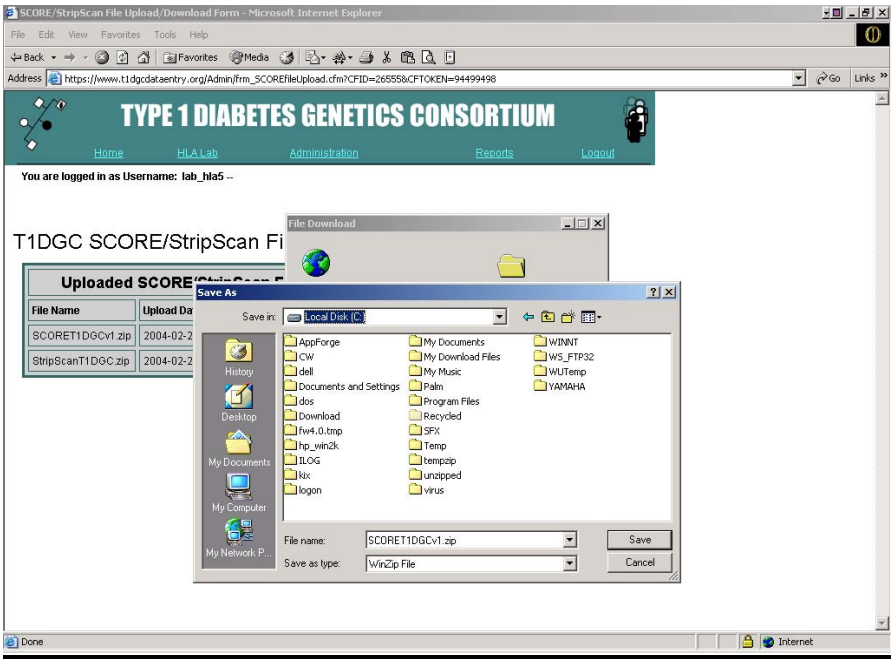


Figure 51. Confirmation of where to save SCORE or StripScan to HLA Lab user's computer.

4. Once the file has been downloaded to the HLA Lab user's computer, confirmation that the file has been downloaded will be received (Figure 52).

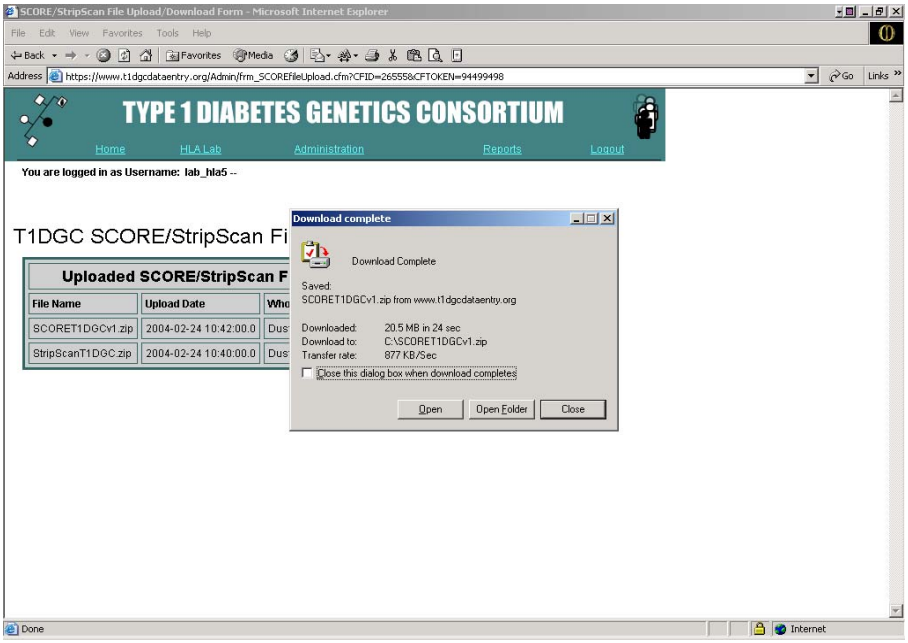


Figure 52. Confirmation that download for SCORE and StripScan is complete.

W. Request for Replacement

1. When the HLA Lab user accesses the Request for Replacement, the Request for Replacement Form is displayed (Figure 53).

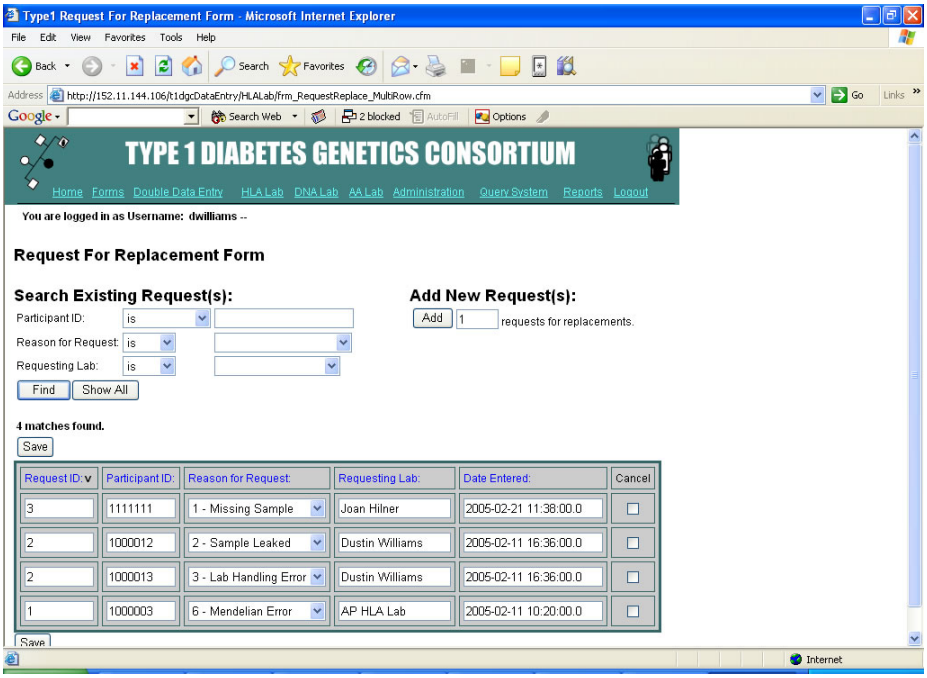


Figure 53. List of Previously Requested Replacement Samples.

2. Requesting a Replacement Sample

a. The HLA Lab user enters the number of requests needed and clicks the "Add" button.

b. Entry fields for the number of requests for replacement samples entered will be displayed (Figure 54).

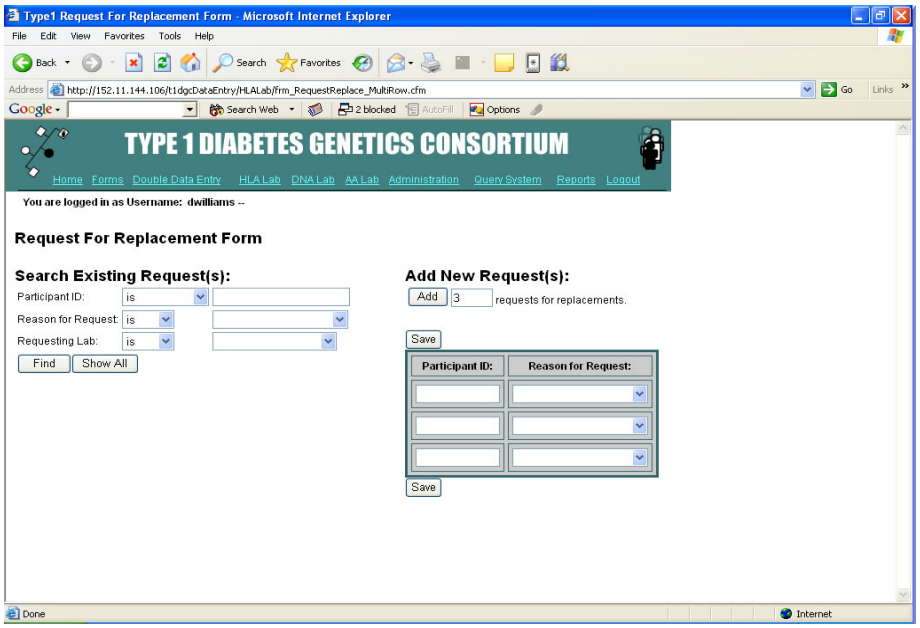


Figure 54. Request a Replacement Sample (not completed).

c. Scan the participant ID and enter the reason for the request(s) for all rows and press the "Save" button (Figure 55).

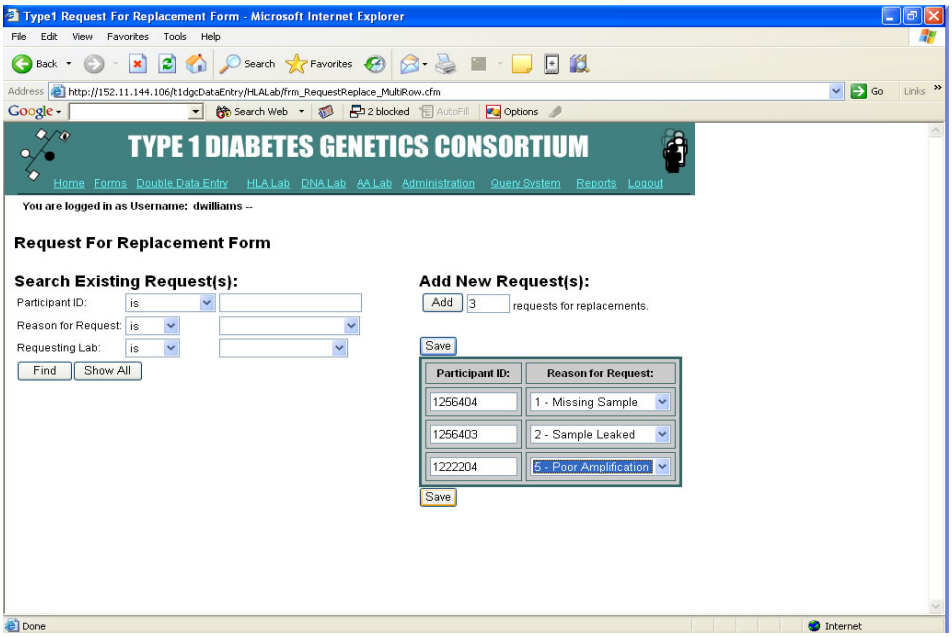


Figure 55. Request a Replacement Sample (completed).

d. Once the "Save" button has been pressed a confirmation is displayed (Figure 56). An e-mail requesting a replacement sample is sent to the DNA Repository and copied to Joan Hilner, Joe Mychaleckyj, and the requesting HLA Genotyping Laboratory (Figure 57).

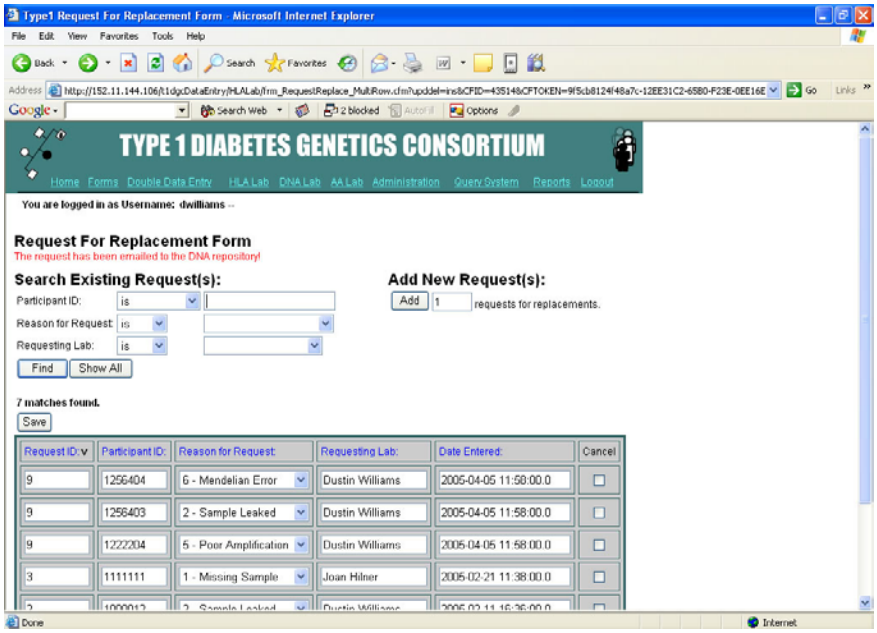


Figure 56. Confirmation of request for replacement sample.

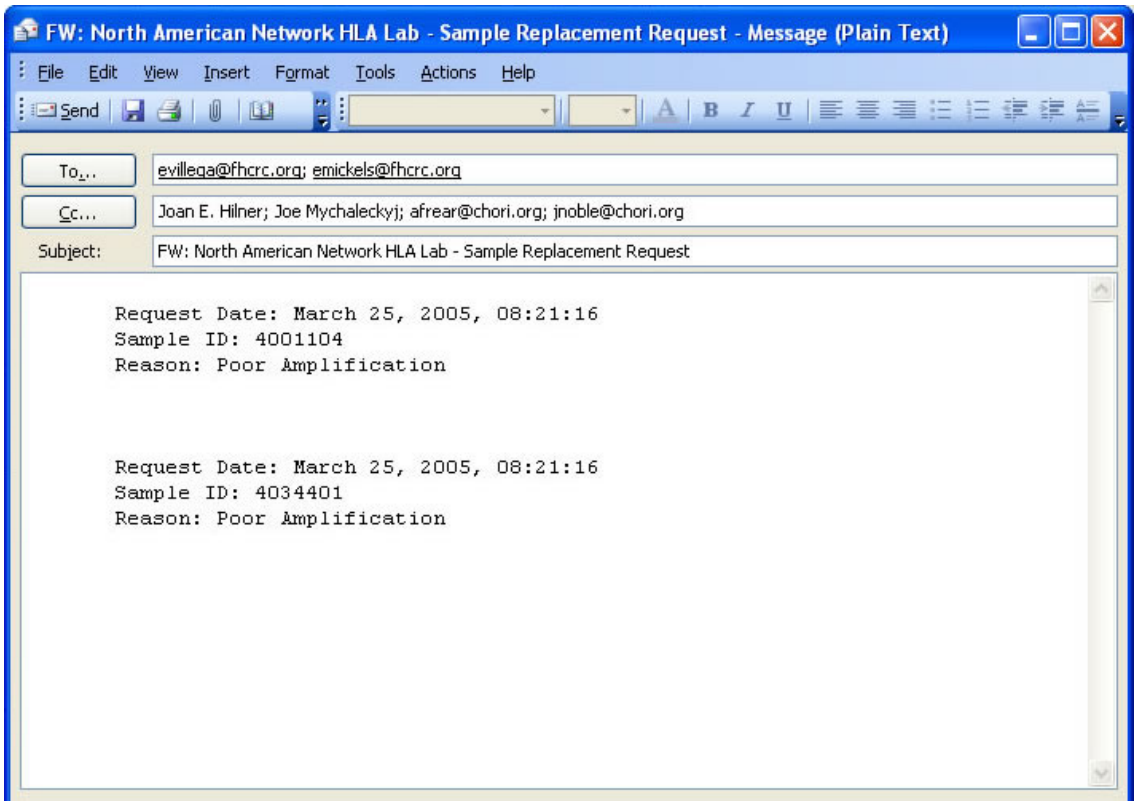


Figure 57. E-mail sent to the DNA Repository requesting a replacement sample.

3. Updating the Request for Replacement Sample.

   a. Once a request has been made, the HLA Lab user can only modify the reason the request has been made.

   b. Left click in the reason(s) to be updated and change the information in the list of previous requests and press the “Save” button (Figure 58).

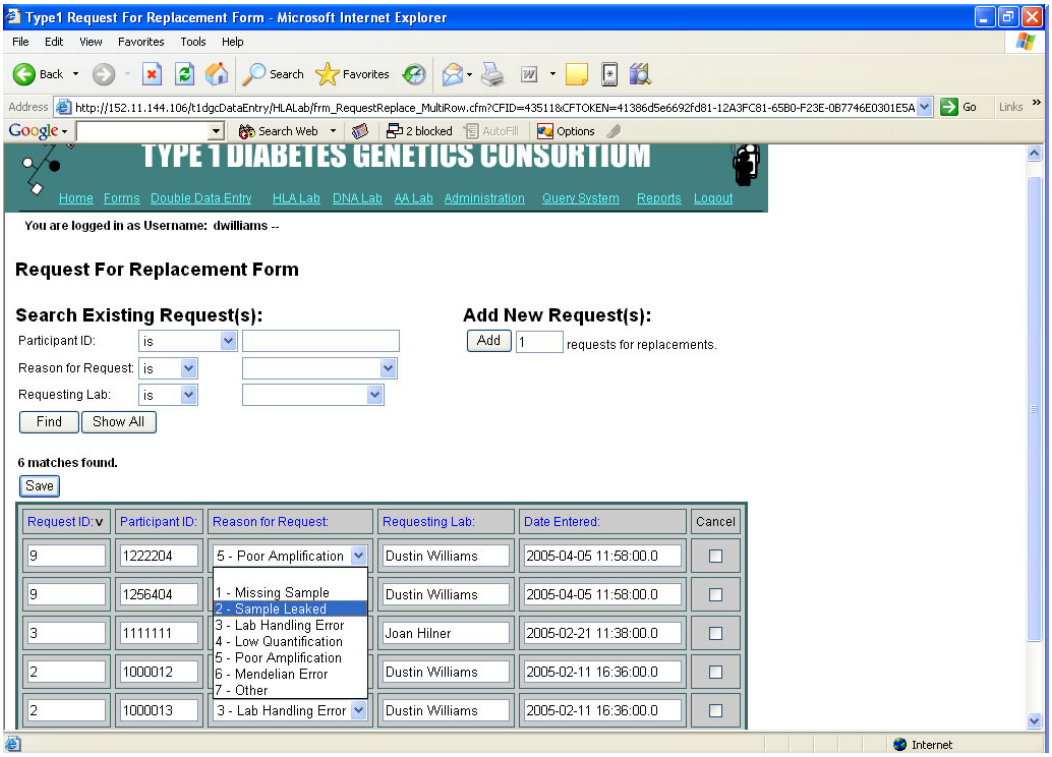


Figure 58. Change the Reason for Requesting a Replacement Sample.

c. Once the “Save” button has been pressed a confirmation is displayed (Figure 59). An e-mail indicating an updated reason for requesting a sample is sent to Joan Hilner and Joe Mychaleckyj and copied to the requesting HLA Genotyping Laboratory (Figure 60).

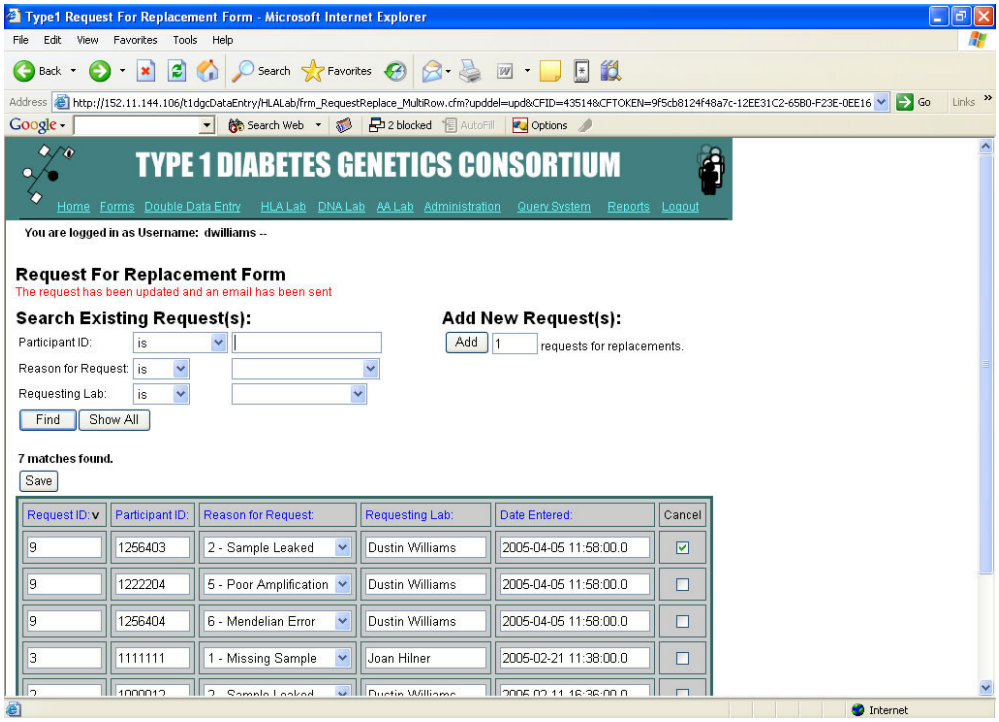


Figure 59. Confirmation of Updating Reason for Request.

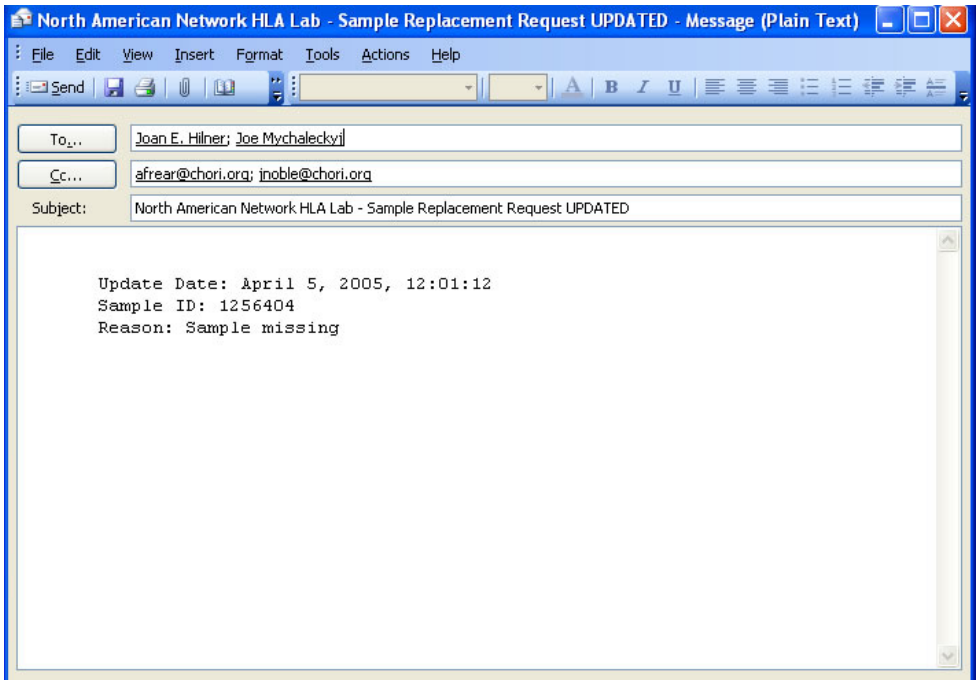


Figure 60. E-mail sent to Coordinating Center explaining update to Request for Replacement.

4. Canceling a Request for Replacement Sample

a. If a request needs to be cancelled, select the checkbox next to the sample ID to be cancelled from the list of previously entered requests and press the “Save” button (Figure 61).

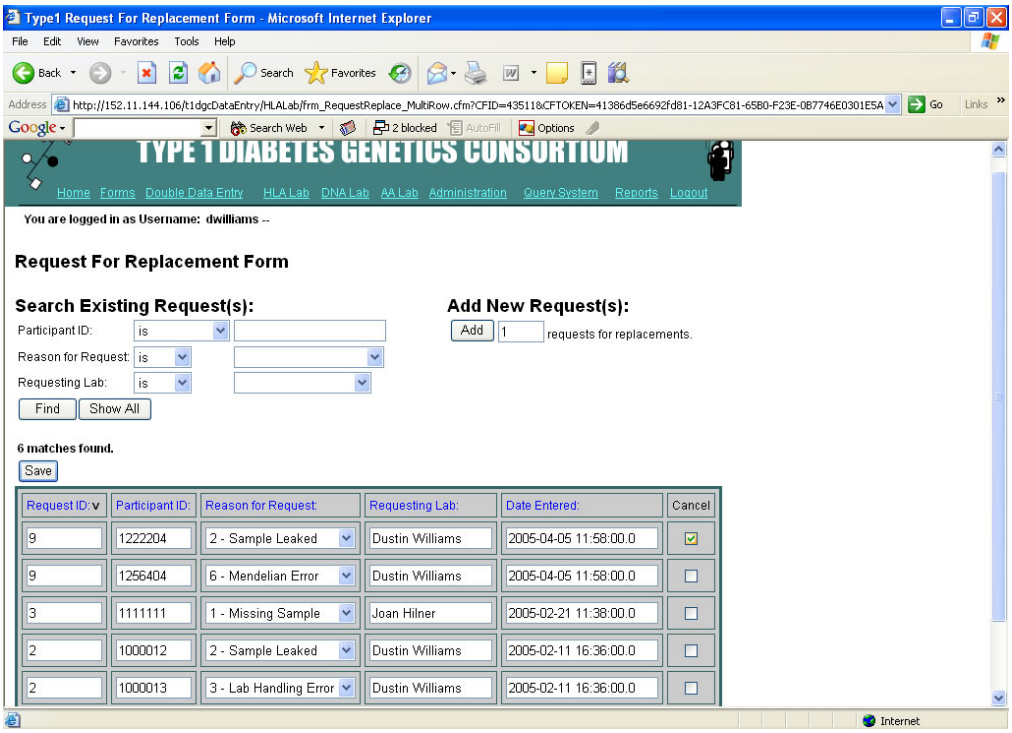


Figure 61. Canceling a Request for Replacement Sample.

b. Once the “Save” button has been pressed a confirmation is displayed (Figure 62). An e-mail canceling the request for the sample is sent to the DNA Repository and copied to Joan Hilner, Joe Mychaleckyj, and the requesting HLA Genotyping Laboratory (Figure 63).

c. If the DNA Repository has already sent the sample, the DNA Repository will “reply to all” on the e-mail stating that the sample has already been sent.

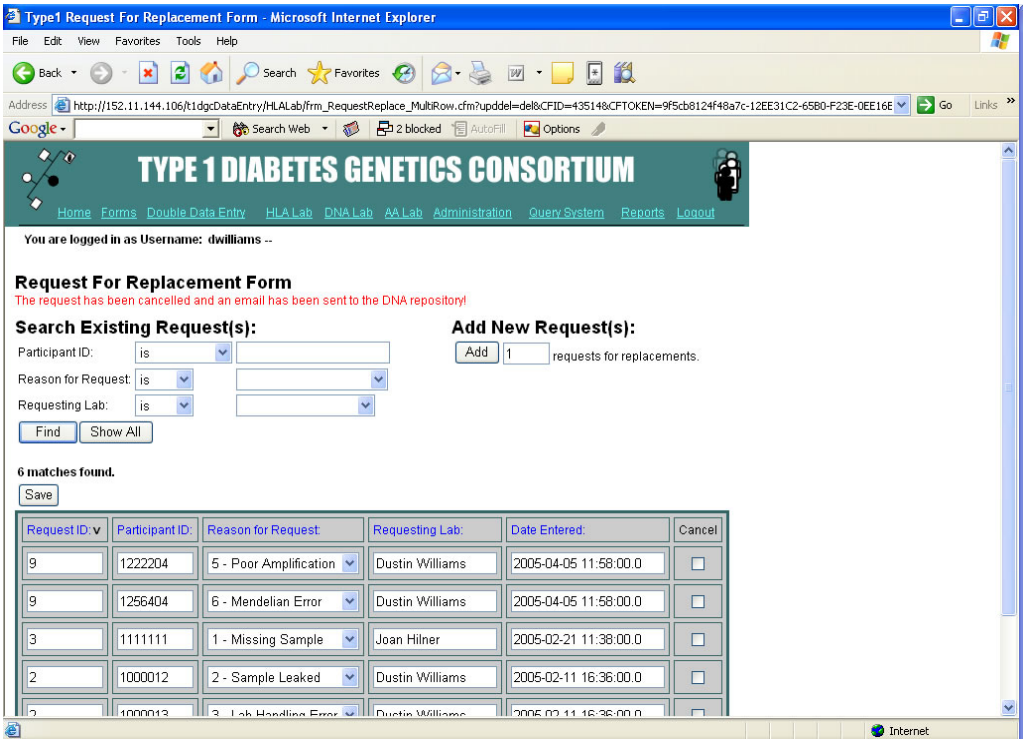


Figure 62. Confirmation of Canceling a Request for Replacement.

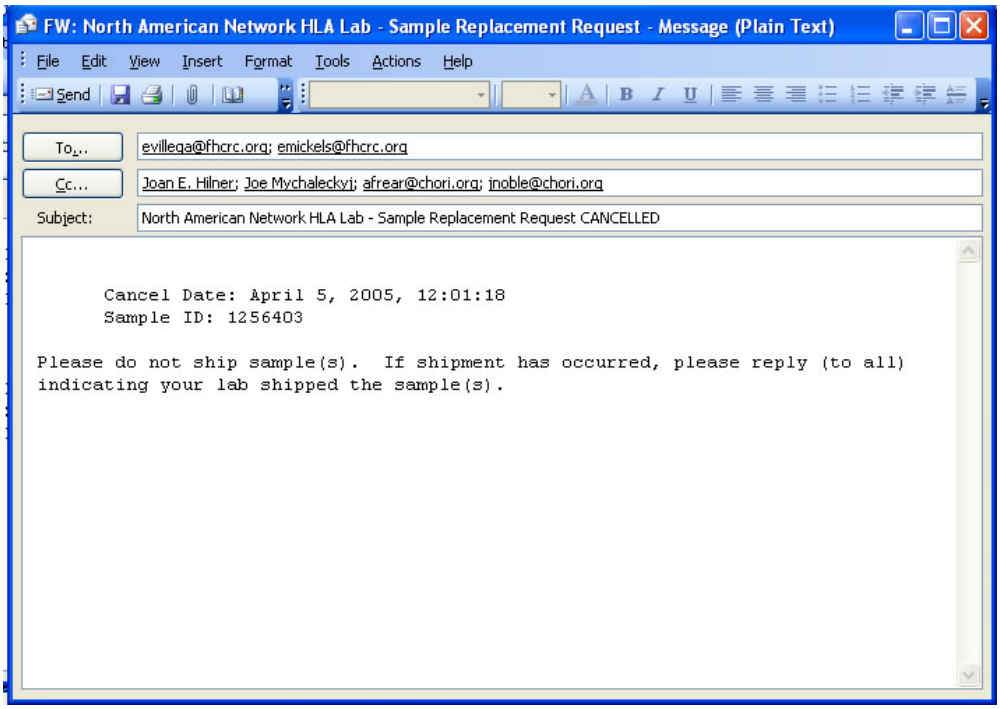


Figure 63. E-mail sent to DNA Repository canceling a request for replacement sample.

5. Searching within the Request for Replacement Form.

To search for an existing participant ID in the system, the HLA Lab user enters specific search criteria and clicks “Find”. The HLA Lab user can search by: (1) participant ID; (2) reason for request; or (3) the requesting lab.

If searching by participant ID, the HLA Lab user enters the participant ID and selects one of the following options: “is”, “is not”, “greater than” or “smaller than”. If searching by reason for request or requesting lab, the HLA Lab user selects a reason or lab from the drop down ment and selects “is” or “is not”. The HLA Lab user can view all participant IDs where a replacement sample has been requested by clicking “Show All”.

The HLA Lab user can also sort all requests by clicking on “Request ID,” “ Participant ID,” “Reason for Request,” “Requesting Lab,” or “Date Entered.” The system defaults and sorts the requests by “Request ID.”

x. Logout

1. HLA Lab users should “Logout” when not using the system.
2. The system will automatically log out a HLA Lab user when there has been one hour of inactivity.

APPENDIX A
LIST OF DNA REPOSITORIES
TYPE 1 DIABETES GENETICS CONSORTIUM

Name	Network	Address
Brian Tait, PhD	Asia-Pacific	Victorian Transplantation and Immunogenetics Services 2nd Floor Rotary Cone Marrow Research Building C/O Royal Melbourne Hospital Grattan Street Parkville 3052 Victoria, Australia Phone: 61 3 9341 6305 Fax: 61 3 9348 1278 E-mail: bdtait@arcbs.redcross.org.au
Bernhard O. Boehm, MD	European	Division of Endocrinology and Diabetes Ulm University Rober-Koch-Str. 8 D-89070 Ulm/Donau, Germany Phone: 49 731 500 24304 Fax: 49 731 500 23 938 E-mail: Bernhard.boehm@medizin.uni-ulm.de
Eric Mickelson, BS	North American	Human Immunogenetics Program Fred Hutchinson Cancer Research Center Room D2-100 P. O. Box 19024 Seattle, WA 98109 Phone: 206-667-4922 Fax: 206-667-6969 E-mail: emickels@fhcrc.org
John Hansen, MD	North American	Fred Hutchinson Cancer Research Center 1100 Fairview Avenue, N, D4-100 Seattle, WA 98109 Phone: 206-667-5111 Fax: 206-667-5255 E-mail: jhansen@fhcrc.org
Sarah Nutland, BSc, Certificate of Education	United Kingdom	JDRF/WT Diabetes & Inflammation Laboratory Cambridge Institute for Medical Research University of Cambridge Wellcome Trust/MRC Building Addenbrooke's Hospital Cambridge, CB2 2XY Phone: 44(0) 1223 762105 Fax: 44(0) 1223 762102 E-mail: sarah.nutland@cimr.cam.ac.uk