SEARCH 4 MOP
Section 10 - Registry and Cohort Visits
Physical Measures, Laboratory Measures, Surveys, and Data Collection Forms
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10. Registry and Cohort Visits

10.1. OVERVIEW

When conducting Registry and/or Cohort visits, study staff and coordinators will use good clinical standard practice.

10.1.1. *Registry Visit Overview (refer to Appendix A for further lab explanation)*

The Registry Visit will be completed for a portion of registered cases diagnosed in 2016. Cases eligible for the IPV will include all cases diagnosed during 2016 with a provider diagnosis of T2D, cases with a provider diagnosis of T1D who are of minority race/ethnicity, and 33% of non-Hispanic white youth with a provider diagnosis of T1D. This sample will include only those NHW T1D registered cases who have a birthday in the 1st 10 days of any month. Registered cases with secondary diabetes will not be eligible for a visit.

Table 10-1 Registry Visit Data Collection

Eligible	Registry Visit Data Collection
Complete visits on the following 2016 cases: ▪ All T2D ▪ All Minority Race or Ethnicity (T1D/T2D) ▪ T1D Non-Hispanic White with birthdates 1-10 of each month	*Initial Participant Survey* (if not completed prior to study visit) *Physical Exam* Height, weight, waist circumference (NHANES and natural waist), blood pressure, acanthosis nigricans *Medication Inventory* Currently prescribed medications *Lab/specimens* Blood and 1st morning urine void Diabetes autoantibodies (GAD65, IA2, ZnT8), HbA_{1c}, Fasting C-peptide, glucose, and lipids Fasting Cystatin C and serum creatinine (for storage) Urine albumin/creatinine *Contact Information* Current contact information *Storage* Fasting serum and plasma, DNA* and urine

*Except the Navajo site

When scheduling participants please note the following:

- Fasting visits (at least 8 hours overnight) are strongly preferred.

- Participants who are pregnant cannot take part in a study visit until 4 months after the end of the pregnancy. When appropriate, ask the participant if she is pregnant prior to scheduling the visit.
- All components of the Registry study visit ideally should be completed on the same day. If that doesn't happen, complete all elements within three months.

What is closing date for entry of core data?

As above, ALL RELEVANT DATA FORMS (IPS, extended core form) may be entered up until the close of the window for each incident year. At a minimum, this includes date of birth, date of diagnosis, sex, race/ethnicity (if known) and diabetes type.

What is the closing date for any 2016 in-person registry visits?

Close of the 2016 window is June 30, 2019. VISITS SHOULD BE COMPLETED AND FORMS ENTERED NO LATER THAN THIS DATE.

10.1.2. *Cohort Visit Overview (refer to Appendix B for further lab details)*

A subset of SEARCH 3 Cohort and SEARCH 3 Registry participants will be invited for a SEARCH 4 in-person visit. The eligible group will include all SEARCH 3 participants with T2D, all minority youth with T1D, and a random sample of NHW youth with T1D. The Coordinating Center (CoC) will provide a list of randomly selected NHW youth with T1D to be invited for participation such that all participants will be 10 years or older, have at least 3 years of time elapsed since their SEARCH 3 visit and have at least 5 years of duration of diabetes at the time of their planned SEARCH 4 IPV. In addition, the SEARCH 4 IPV will include a sample of 450 participants to be identified by the CoC to have cardiac echocardiogram measurements taken. This sample will include 225 T1D and 225 T2D with representation from four clinical sites and have racial/ethnic diversity.

The remainder of SEARCH 3 participants (an estimated ~ 700 participants who are NHW with T1D) will form the survey-only group with no IPV in SEARCH 4. The survey-only option will also be offered to individuals who are eligible but refuse participation in the IPV. The survey-only group will be asked to complete questionnaires by mail, phone or internet.

Table 10-2: Cohort Visit Data Collection

Eligible	Cohort Visit Data Collection
Eligible cases must meet the following criteria (list of eligible participants provided to sites): ▪ All SEARCH 3 (including 2012 IPV) participants with T2D ▪ All SEARCH 3 (including 2012 IPV) minority youth participants with T1D ▪ Random sample of 1400 of the approximately 2000 non-Hispanic white youth with T1D from SEARCH 3 (including 2012 IPV) with the goal of obtaining 700 visits All participants must be: ▪ ≥ 10 years of age ▪ Have at least three years since SEARCH 3 visit ▪ Have at least five years of duration of diabetes	**Lab/specimens**: Blood ▪ Fasting glucose, C-peptide, serum creatinine, Cystatin C, hsCRP, and lipids (total cholesterol, HDL-cholesterol, LDL-cholesterol, triglycerides) ▪ A1c ▪ Fasting IL-6 and AGE (CML) (for storage) ▪ Storage of fasting plasma and serum, DNA* Urine (see table 10-3 for more details) ▪ Urinary albumin and creatinine (first morning void) ▪ Storage of urine
	Physical Exam Height, weight, waist circumference (NHANES and natural waist), BP, acanthosis nigricans
	Michigan Neuropathy Screening Instrument (MNSI) Foot exam and questionnaire
	Questionnaires
	Retinal Photos 2 images of each eye, Field 1 centered on optic nerve and Field 2 centered on macula
	Cardiac Measures (SphygmoCor) Heart Rate Variability (HRV), Pulse Wave Velocity (PWV), Pulse Wave Analysis (PWA)
	Thinking and Attention (Neurocognitive tests) NIH Toolbox
225 T1D and 225 T2D in SC, OH, CO and WA (enrolled sequentially to fill cells)	*Cardiac Echocardiography (Images of the Heart)* LV mass, systolic & diastolic function

*Except Navajo

<u>When scheduling participants please note the following</u>:

- Fasting visits (at least 8 hours fasting overnight) are strongly preferred.
- Participants who are pregnant cannot take part in a study visit until 4 months after the end of the pregnancy. When appropriate, ask the participant if she is pregnant prior to scheduling the visit.
- Data may be collected in one or two visits. All elements should be completed within **three months**.

10.2. PROCEDURES COMMON IN REGISTRY AND COHORT VISITS

10.2.1. *General Information*

Missing Data Collection

There will be instances when one or more components of the in-person visit are not completed. This may occur for a variety of reasons, such as participant or parent refusal, inability of participant to complete interviews or questionnaires due to developmental delay, or lack of participant cooperation. If one or more components of the in-person visit are not completed, it should be noted in the data management section of the website as NOT USED. When a participant refuses or is unable to respond to an individual question within an interview or a questionnaire, the response should be recorded and data-entered as "-9" (or "1800" for unknown dates).

Data Entry of Consent Forms

A consent tracking form will be data entered for each visit participant. This form will contain the layers of consent included in each site specific consent form.

Procedures for Participants Transferring to another SEARCH Site

Participants transferring to another SEARCH site may be seen for a visit at the new site but remain registered at their original site of registration; therefore, the participant's PID remains the same. Participants are not to be un-registered because they are moving or have moved. If the new site mistakenly re-registers the participant, the new site must un-register the participant using "other" as the reason. The new site can conduct data collection on the transfer participant but only the original site can perform the data entry of the forms. The project managers from the respective sites should coordinate the secure transfer of the forms to the original site. Participants should be (re)consented at the site where they complete the visit. Copies of these consents should be sent to the original site for storage in the participants' files. (08/13)

The new site should retain a copy of the forms. The original site will receive any data validation queries at the time of data entry and may need to contact the new site to assist with resolution of the query.

If a SEARCH study participant meets the eligibility criteria as an incident case at one SEARCH center, and then moves to another eligible SEARCH center within his/her incident year, then the site where the participant lived closest to the date of diagnosis is the site that should register this participant.

For participants who transfer, visit scheduling and follow-up will be done at the new site. The original site will notify the new site when a participant is eligible for a visit so they can attempt to schedule a study visit.

Both sites should review medical records since they may exist at either site. Extended Core and the Medical Record Validation worksheet information (if applicable) should be sent to the original site to be data entered.

Lab results, as well as notification of required repeat samples and alert values will be sent from the CBL to the original site.

Refusals

There will be three categories for participant refusals:

1. **Do not contact** - Someone who refuses this visit and all other future contact
2. **Refusal** - Someone who refuses this visit only (either actively or passively) but might be interested in future efforts
3. **Unable to contact** - Someone for whom we have inadequate contact information and are unable to locate or speak with them to determine if they will do the visit.

10.2.2. *Physical Examination*

Note: Physical examinations are only to be conducted on eligible participants **at least 3 years of age**.

Scientific Rationale

Height and weight are the mainstays of anthropometric measures in epidemiological studies and have been used to assess the degree of an individual's obesity or thinness [1,2]. Waist circumference, an index of deep adipose tissue and general obesity has also been found to correlate with fat mass. Since obesity is a known risk factor for the development of type 2 diabetes in adolescents; height, weight, and waist circumference will be recorded for all participants who are three years of age or older. Body mass index will be calculated to assess each participant's obesity or thinness [3,4]. These measures will be used to assess the frequency of obesity or thinness in each type of diabetes. These and other clinical measures will then be used to develop a clinical profile for each type of diabetes that may help clinicians identify the likelihood that a participant has a specific type of diabetes based on clinical criteria.

Equipment and Supplies

- **General**: screened area for privacy with secure place for storing participant valuables with measurements made in a warm, well lighted room
- **Height**: portable or stationary wall stadiometer, wooden block, centimeter measuring rod
- **Weight**: portable electronic scale capable of weighing in kilograms with graduations of at least 0.1 kg., capacity of at least 200 kg

- **Waist Circumference**: non-tension, tape measures (Creative Health Products model BMS-8 [fiberglass] and Rosscraft Anthropometric [flexible steel tape]) with a leading blank zero segment, which measures in centimeters with graduations of at least 0.1 cm, length of at least 150 cm.
- **Blood Pressure**:
  - **Manometer**: Welch Allyn Tycos 767-Series Mobile Aneroid manometer (Modification for a stand to allow table top use is permitted)
  - **Blood pressure cuffs**: 5 sizes: infant, child/adult, adult, large adult, and thigh
  - **Stethoscope:** stethoscope with adult and pediatric double heads, including diaphragm and bell.

Height

Calibration of Equipment

Portable stadiometers will be calibrated annually or according to manufacturer's guidelines. Equipment must meet the following standards for use in this study:

- Stadiometer: adjusted to within 0.1 cm of the measuring rod

Measurement Approach

Height is measured and recorded twice. A third measurement is made only if the second measure differs from the first by ***> 0.5 cm.***

Outer clothing and shoes will be removed. The presence of a non-removable appliance (e.g., cast or brace) will be noted.

Height is measured in centimeters, using a stadiometer. The participant will stand erect with the heels, buttocks, and shoulders tangentially against the measuring device (see Figure 1). The heels will be together with the feet at a 45-degree angle to each other in a comfortable stance. The participant will look straight ahead. The participant will then be told to take and hold a deep breath making himself/herself as tall as possible.

Figure 1. Participant's positioning for height measurement

It is preferable to have participants with tall hairstyles take down their hair so the bar on the Stadiometer (portable Road Rod™ or stationary wall stadiometer) can be used as designed (sliding perpendicular measurement guide onto the top of the head). The Road Rod™ height measurement bar is designed in a way that takes the actual measurement using a pointer that extends above the level of the head by slightly more

than an inch. The placement of the pointer on the measurement device is corrected (by design of the Road Rod™) to result in the correct height.

The observer makes sure that the heels are on the floor and in the correct position. The sliding head projection bar is then brought firmly down on the crown of the head and secured; and the stature is recorded to the nearest tenth of a centimeter (see Figure 2).

Figure 2.
Height measurement

Large participants may find it uncomfortable to stand with their feet too close together or against the wall. To prevent sway, these participants will be instructed to stand with their feet as close together as possible while maintaining a comfortable stance. A wooden block is used to align the feet of larger participants should the size of the buttocks prevent the heels from aligning tangentially against the measuring device.

Documentation

The following is an example of height documentation:

Figure 3. Height documentation

1. Height:

1	2	0	.	2	cm.	1	2	0	.	4	cm.				.		cm.
First						Second						*Third					

*Third measurement required if first two measurement differ by >0.5 cm.

Weight

Calibration of Equipment:

Scales will be calibrated annually or according to manufacturer's guidelines. Equipment must meet the following standards for use in this study:

- Scales: calibrated to within the nearest 0.2 kg using standard weights

Measurement Approach

Weight is measured and recorded twice. A third measurement is made only if the second measure differs from the first by > ***0.3 kg.***

Participants should be encouraged to wear lightweight clothing preferably a top/shirt and bottom/pants, shorts. Outer clothing and shoes will be removed. Participants will be encouraged to empty their bladder and bowels prior to any measurements. The presence of a non-removable appliance (e.g. cast or brace) will be noted.

Body weight is measured in kilograms, using an electronic scale. There are two approved weight scales: SECA model 770 and model 876.

Figure 4. Two approved weight scales

Model 770 Model 876

Note: Manufacturing of model 770 has been discontinued. However, sites that still have model 770 scales that are operational may continue to use them. When replacement of the scale is necessary, sites will purchase SECA model 876.

- The scale is placed on a flat, level and uncarpeted surface.
- Confirm that the scale is balanced (zeroed). Balance if necessary.
- The participant will stand comfortably with arms at the side and looking straight ahead.
- The participant's feet will be parallel, but not touching, and centered on the scale platform; and the weight is recorded to the nearest tenth of a kilogram.
- If 'Error 16' appears on the scale, tap the scale with your foot in order to make the scale balance out.

The SECA 876 scale measures to the 0.1kg for weights <150kg and to 0.2kg for weights >150kg. The SECA 770 measures all weight ranges to the 0.1kg.

Some scales may be capable of measuring to the nearest 0.05 kg. If weight measurements are taken with scales measuring to the nearest 0.05 kg, ignore the last digit and record the weight to the nearest tenth.

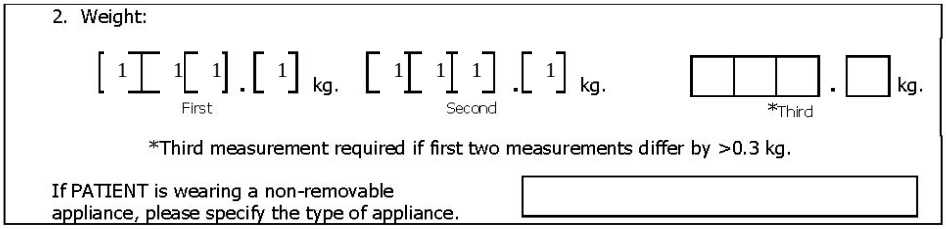
Document two weight measurements. A third measurement should be taken if the first two measurements vary by > 0.3 kg. Note: Scales used for weight measurement must have the capability of weighing to the nearest 0.1 kg for weights <150kg and at least to the 0.2kg for weights >150kg.

The SECA model 876 scale has an Adult-Child Function that allows a child to be weighed while being held by an adult. This feature should be used only when the child is unable to be weighed on the scale alone. If the Adult-Child Function is necessary, the adult is weighed alone first. Then the Adult-Child button is pressed and the adult is re-weighed holding the child. The scale ascertains the difference between the two measurements and this value is recorded as the weight of the child.

Documentation

The following is an example of weight documentation:

Figure 5. Weight documentation



Waist Circumference

Waist circumference is measured using two protocols distinguished by different anatomical landmarks:

a. NHANES (National Health and Nutrition Examination Survey) using the iliac crest and mid-axillary line as identification markers

b. Natural Waist using the mid-point between the lower rib and the iliac crest, or the line at natural side bend.

Measurements are performed using a non-tension tape measure marked in centimeters that includes a leading blank segment. For participants whose waist circumference is equal to or less than 150 cm use the Creative Health Products fiberglass tape; for larger participants use the Rosscraft flexible steel tape.

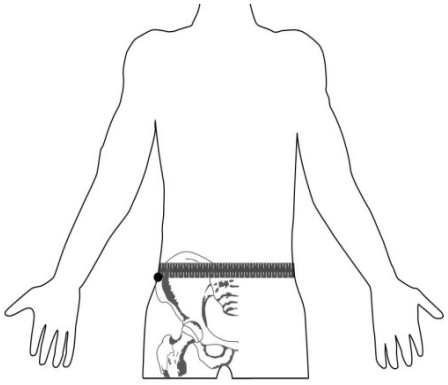
> The fiberglass tape measure required for this protocol is model BMS-8 (Creative Health Products).
>
> The flexible steel tape measure required for this protocol is the Anthropometric tape from Rosscraft.

For both protocols, waist circumference is measured and recorded twice. A third measurement is made only if the second measure differs from the first by ***> 1.0 cm.*** The participant should stand erect with abdomen relaxed, arms at their side, and feet together. Measurements should not be made over clothing. For measurement purposes, shirts will be lifted and pants lowered in order to expose the waist. This should be done in a way that will not change the natural contour of the waist. Clothespins or clips may be used to secure garments away from the waist. It is suggested this measurement be performed using two persons but for some participants, a single person can perform the

measurement using a mirror to assure the horizontal alignment of the tape is maintained. The measurement should be taken at the end of the normal expiration with the tape snug but not compressing the skin.

"NHANES" Protocol for Waist Circumference

Figure 6. NHANES protocol for waist circumference



- Measurer should first stand at participant's right side to palpate the hip area for right iliac crest.
- With a cosmetic pencil mark a horizontal line just above the uppermost lateral border of the ilium. Then cross the line to indicate the line that drops from the middle of the axilla.
- Place measuring tape around the subject in a horizontal plane (parallel to the floor) at the level of the crossed lines on the right iliac crest.
- If, after palpating the hip area, the measurer has difficulty locating the iliac crest, instruct the participant to place his/her hands on both of their hips with the fingers placed anterior, thumbs placed posterior, and palms inferior. Use this area as a landmark and try palpating again.

"Natural Waist" Protocol

- Measurer should face participant.
- Place the measuring tape around the subject in a horizontal plane (parallel to the floor) at the level of the natural waist (midway between the lowest rib margin and the iliac crest in the line that drops from the center of the axilla). If the rib margin cannot be identified, the natural waist can be identified as the point of "natural bend".

Helpful Hint: In some children, it may be difficult to identify the natural waist. If the rib margin cannot be identified, the natural waist can be identified as the point of natural bend. The natural bend can be determined by asking the participant to lean to the side without swaying forward or backward. The point of natural bend can be marked with a blue cosmetic pencil and the measurement made at that level once the participant has returned to the upright position. Be certain that horizontal alignment of the tape is maintained.

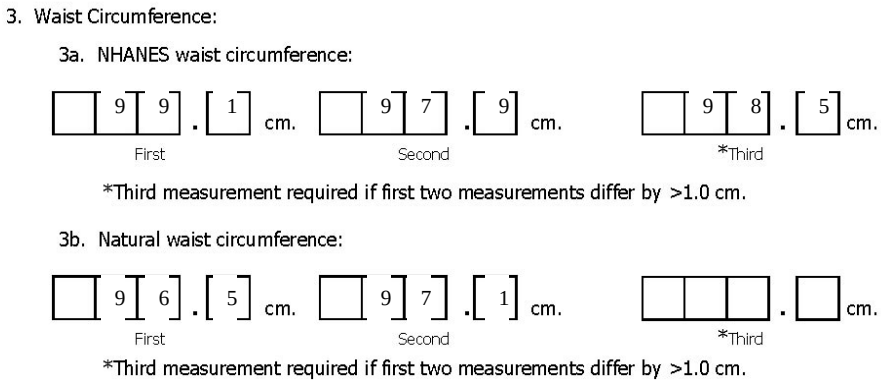
Documentation

Space is provided on the Physical Examination Form for each separate protocol of waist circumference. Two measures for each protocol should be obtained. Caution should be used to be certain the appropriate measurements are placed in the appropriate section. The two protocols are likely to yield different results, and either protocol might have a greater value. Note that neither protocol depends on the location of the umbilicus.

When measuring the waist circumference it is essential that the two protocols be measured separately, i.e., all "NHANES" measurements first, then all "natural waist" measurements.

Note: Within each protocol, a third measurement should be taken if the first two measurements vary by more than 1.0 cm.

Figure 7. Third waist circumference measurement



Blood Pressure

Scientific Rationale

Risk of illness and death is related to changes in blood pressure. Hypertension is associated with cardiovascular disease and is a known complication of diabetes. Hypertension is also associated with the development of other types of complications, such as retinopathy and nephropathy [5]. Therefore, blood pressure will be recorded for all participants age three years or older.

Equipment and Supplies

- **General**: Screened area for privacy with secure place for storing participant valuables with measurements made in a quiet, warm, well-lit room
- **Manometer**: Welch Allyn Tycos 767-Series Mobile Aneroid manometer (Modification for a stand to allow table top use is permitted)

- **Blood pressure cuffs**: 5 sizes: infant, child/adult, adult, large adult, and thigh
- **Stethoscope:** stethoscope with adult and pediatric double heads, including diaphragm and bell.

Calibration of Equipment: The aneroid manometer is calibrated when it is manufactured. However, regular inspection of the blood pressure cuffs, tubing, stethoscope and manometer is necessary to eliminate conditions that could cause the blood pressure to be measured as erroneously high or low. Additionally, a calibration check using the NeTech Digimano 1000 digital pressure-vacuum meter should be performed on the manometer at a minimum of every 6 months or whenever it is transported by car.

These checks should be performed on a daily basis:

a. Check for cracks on the manometer dial face

b. Check that the manometer needle is at 0mmHg when not under pressure

c. Check the cuffs, pressure bulb, manometer and stethoscope tubing for cracks or tears

d. Check the pressure control valve for sticks or leaks

e. Check stethoscope diaphragm for cracks

f. Equipment that is not working properly needs to be repaired or replaced. Never attempt to repair the equipment yourself.

The aneroid sphygmomanometer unit should be checked for accuracy every 6 months or when transported by car. Repair or replacement of the unit is required if the aneroid unit differs from the calibration device by 4 mm Hg or more.

Equipment required for accuracy check:

a. Pressure-vacuum meter (NeTech Digimano 1000)

b. Y-tubing and plastic adaptor (Y- or T-shaped)

c. Adaptor ends (female and male) for connecting Y-tubing to the aneroid unit and the blood pressure cuff tubing

d. Aneroid sphygmomanometer

e. Blood pressure cuff and bulb/valve assembly.

Aneroid Accuracy Check Protocol

(Adapted from the document "Protocol for Assessing the Accuracy of Aneroid Sphygmomanometers" by Carol Nash, RN, BSN and Vincent J. Canzanello, MD, Division of Hypertension and Internal Medicine, Mayo Clinic, Rochester, MN)

a. Disconnect blood pressure cuff from the sphygmomanometer.

b. Connect the long end of the Y-tubing to the coiled tubing of the aneroid unit using the female adaptor end.

c. Connect one short end of the Y-tubing to the Digimano pressure vacuum meter (does not require an adaptor end).

d. Connect the other short end of the Y-tubing to the blood pressure cuff tubing using the male adaptor.

e. Turn on the pressure-vacuum meter.

f. Select "mm Hg" as the type of unit to be measured.

g. Pump up blood pressure cuff until the aneroid unit reads 280 mm Hg. Check to see if the aneroid unit is within ±3 mm Hg of the readout on the pressure-vacuum meter. Record the pressure-vacuum reading on the calibration log under the "280 mm Hg" column.

h. Continue to deflate the cuff in 20 mm Hg increments along the entire range down to zero. Record the pressure-vacuum reading at each 20 mm Hg interval (280, 260, 240, etc.). Variations greater than ±3 mm Hg requires the unit to be removed from service and shipped to the manufacturer for repair or replacement.

i. After complete release of the pressure, make sure the aneroid unit "zeros". If complete "zeroing" does not occur, the aneroid unit should be removed from service and shipped to the manufacturer for repair or replacement.

Annual Certification of the Pressure-Vacuum Meter

The Digimano pressure-vacuum meter should be shipped to the manufacturer annually to be calibrated and certified. The process takes about 3-4 weeks and there is a charge for the service and shipping. A Certificate of Calibration will be returned with the meter.

The Netech DigiMano digital pressure and vacuum meter is Part no. 200-2000IN. This meter can be purchased from the Netech Corporation for ~$345.00. (Vendor information - (Netech Corp. info. 1-800-547-6557 www.netechcorporation.com)

Measurement Approach

Before beginning blood pressure measurements, the participant should be seated quietly for at least five minutes. The blood pressure should be measured following the collection of blood samples; and for the cohort visit, just prior to the SphygmoCor measurements. The right arm should be used for blood pressure measurements. If the participant or parent indicates a reason why these measurements should not be taken on the right arm, the left arm may be used. If there is a problem with both arms, do not take the blood pressure.

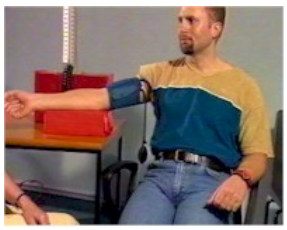
In some sites it may not be feasible to collect blood pressure under these circumstances. This may be due to distance traveled, timing of visit, and anxiety about blood draw. Therefore blood pressure should be taken using the opposite arm in which blood was drawn.

- In the SEARCH study, an aneroid manometer will be used to assess blood pressure.
- The manometer should be placed in a position that can be easily seen by the examiner and at his/her eye-level.

Figure 8.
Aneroid manometer

- The participant will be seated at a table in a relaxed, but not slouched, position with feet flat on the floor, if possible. For tall participants, it may be necessary to support the arm higher than a standard desk or tabletop.
- Place the tall participant's forearm on a pillow, large book or directory to raise the arm to heart level. For small participants, place a cushion or large book on the chair so the **arm is at heart level** when it is resting on the desk or tabletop.

Figure 9.
Arm support for a tall person



- The right arm will be placed on the table, slightly flexed with palm upward. The arm should be positioned so that it is resting on the table at heart level (halfway between the shoulders and the waist). The elbow must not be lower than the lowest rib and must not be raised as high as the shoulder.
- Place a box or large book under the feet if they do not rest flat on the floor. If the participant is unable to sit, do not measure the blood pressure. The participant will be wearing clothing that is non-restrictive: short-sleeve or

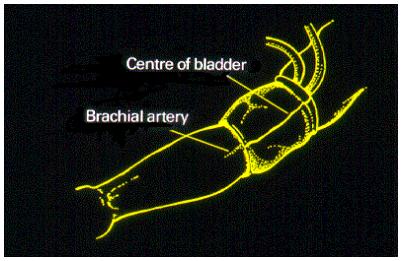
sleeveless top or gown. If they are wearing a top with sleeves, the sleeve should be rolled loosely up to the shoulder.

- The examiner will be seated facing and slightly to the participant's right, allowing easy access to the arm. After explaining the procedure to the participant, the examiner will locate the brachial and radial pulse points in the right arm.
- The right arm will always be used unless specific conditions prohibit its use. Use the following guidelines:

  - If the radial pulse is apparent, whether or not the brachial pulse can be felt, proceed with the measurement of the first blood pressure.
  - If the radial pulse cannot be felt in the right arm, use the left arm.
  - If the radial pulse cannot be felt in either arm, the blood pressure should not be measured.

After locating the pulse points, select a cuff size that appears to be appropriate. Check the size before applying the cuff by making sure that the index line falls completely within the range lines. If the cuff is barely large enough, use the next larger size. If none of the cuffs (infant, child, small adult, adult, large adult, and thigh) is the appropriate size, do not measure the blood pressure. The procedure for applying the cuff is as follows:

Figure 10.
Cuff placement



a. Check the index line to determine if it lies completely within the range lines marked on the cuff.
b. Position the cuff at least 1" above the crease of the elbow. Place the artery arrow on the inner part of the cuff directly over the brachial artery.
c. Wrap the cuff smoothly and snugly around the arm. Cuff should be wrapped in a circular manner. No spiral direction of the cuff should be used.
d. Check the fit by placing both thumbs under the cuff and tugging gently. Should the cuff slip or come off, reposition and rewrap the cuff securely.

e. It is possible when using the larger cuffs that the cuff length from shoulder to elbow may be too long. If so, place the stethoscope bell head directly over the brachial pulse point under the cuff.

f. Cuff placement should not be altered once the Maximum Inflation Level (MIL) has been obtained. If the cuff needs to be refitted for any reason, the MIL must be measured again.

To determine the MIL, connect the inflation tubing to the manometer by twisting the two ends of the tubing together. The MIL is then determined as follows:

a. Locate the radial pulse point in the arm to be used.

b. Close the thumb valve. Feel the radial pulse and watch the needle of the aneroid manometer.

c. Inflate the cuff quickly to 60 mm Hg, then inflate in increments of 10 mm until the radial pulse disappears (or until 270 mm is reached), mentally noting the reading of the needle at that point. Continue inflating the cuff for another 30 mm at increments of 10 mm, pausing briefly to make sure the pulse is absent.

d. Rapidly deflate the cuff by opening the thumb valve completely and disconnecting the tubing.

e. Record the pressure required to obliterate pulse.

f. Add 30 mm to the reading at the point the radial pulse disappeared. Record this number as the MIL.

If unable to determine MIL, wait at least 30 seconds and make a second attempt. If still unable to determine the MIL, do not measure the blood pressure. If the radial pulse is still felt to a level of 270 mm Hg or higher (MIL 300 mm Hg), repeat the MIL and if it is 300 mm/ Hg, measure the blood pressure using 300 as the MIL. Record 300 as the systolic blood pressure and the measured 5th phase diastolic reading. Do not remove the cuff after measuring the MIL. If it is necessary to re-adjust the cuff after measuring the MIL, wait at least 30 seconds and repeat the MIL measurement.

Three consecutive blood pressure readings will be obtained using the same arm. Wait at least 30 seconds between readings. Open the thumb valve completely and disconnect the manometer tubing after each reading to reduce the pressure level to zero.

The following procedure will be used in measurement of the blood pressure:

a. Position the stethoscope comfortably in your ears with the earpieces turned forward, toward the nose.

b. Feel the brachial pulse and place the stethoscope diaphragm head directly over the pulse just below the cuff. The diaphragm should be applied with light pressure so that there is no air between the skin and the edge of the diaphragm. If the brachial pulse is too faint to be felt, place the stethoscope diaphragm over the innermost part of the elbow fold crease and proceed. If possible, avoid allowing the cuff, tubing, or stethoscope to touch. The following three situations would be indications for using the bell of the stethoscope: 1) when hard to hear, 2) with very small arms (i.e. babies and toddlers), 3) when the blood pressure cuff is riding low and would be pushing on the edge of the diaphragm.

c. Close the thumb valve. Rapidly and steadily inflate the cuff to the MIL. If you inflate the cuff more than 10 mm Hg above the MIL open the thumb valve, rapidly deflate the cuff and disconnect the tubing. Discontinue this reading and wait 30 seconds before inflating again.

d. When the MIL is reached, open the thumb valve and smoothly deflate the cuff at a constant rate of approximately 2 mm Hg per second (one mark per second).

e. Your eyes should be level with the center of the aneroid manometer dial. Watching the needle, note the reading at the point when pulse sounds first appear. Listen for at least two consecutive beats to eliminate recording a single erroneous sound. Note the reading at the point the first pulse sound appears, not at the second beat. This is the systolic blood pressure reading.

f. Continue deflation at 2 mm Hg per second. Note the reading when the sounds completely disappear. This is the fifth phase diastolic blood pressure reading.

g. Continue steady deflation at 2 mm Hg per second for at least 10 mm Hg below the diastolic reading; then open the thumb valve completely and disconnect the tubing. Let the cuff fully deflate. Wait 30 seconds between measurements.

h. Record the first reading (sounds appear) as the systolic pressure, the second reading (sounds disappear) as the diastolic pressure. Use the nearest even digit. If the needle fell between two digits, record the higher even digit.

i. In many instances in children, pulse sounds normally continue to be heard down to zero pressure. The diastolic reading should be recorded as "000". Assure the participant's parent, if present, that there is no problem.

j. Repeat this procedure for the second and third measurements and record measurements.

k. If unable to obtain 3 blood pressures, record reason on Physical Examination form.

If a measurement is unsatisfactory because of improper technique or instruction, that particular measurement can be repeated if you inflate the cuff on the participant's arm no more than five times, i.e., two MIL attempts plus three blood pressure readings or one MIL and four blood pressure attempts.

If the blood pressure sounds are not heard during the first measurement, review your technique, check stethoscope position, check for loose connections or tubing kinks, and maintain a quiet environment. Relocate the brachial pulse and apply the bell head directly over the pulse point. Take care to wait at least 30 seconds between measurements. Use the following techniques to enhance the sounds:

1. Have the participant raise his/her arm and forearm for at least 60 seconds. Then lower the arm, inflate the cuff, and measure blood pressure immediately; OR

2. Instruct the participant to open and close his/her fist 8 to 10 times. Inflate the cuff and measure blood pressure immediately.

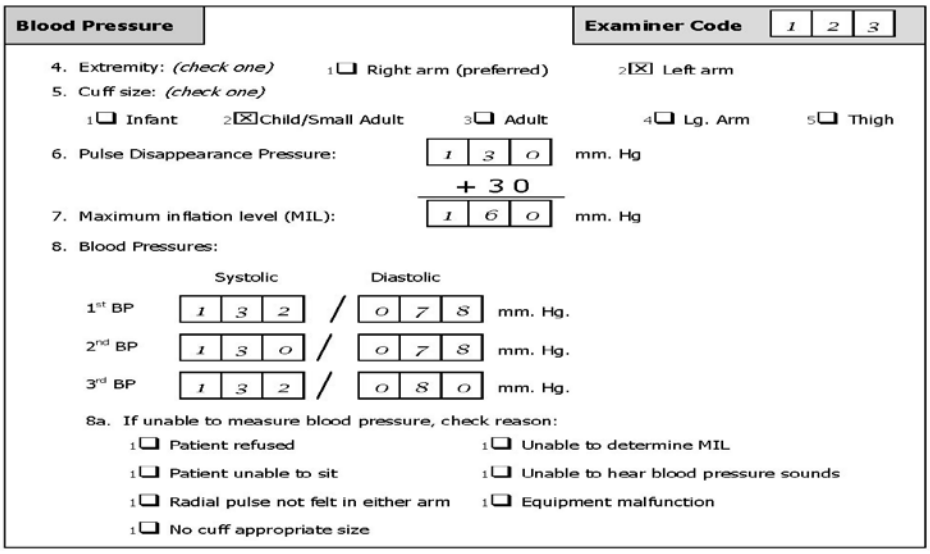
If you still do not hear the blood pressure sounds during the second measurement, repeat above procedure until cuff has been inflated a total of five times.

Documentation

Documentation of the participant's blood pressure includes:

- The arm used to take the reading (right arm is preferred)
- The cuff size (e.g., child, adult, thigh)
- The pressure at which the pulse no longer becomes palpable
- The maximum inflation level (pulse pressure PLUS 30 mm/Hg), and
- **Three** blood pressure readings. *Note: Remember to wait for a minimum of 30 seconds between the first and second measurements and the second and third measurements.*

Figure 11. Blood pressure readings documentation



Alert Values

Individual participant blood pressures will be compared to a table of blood pressure levels at the 95th percentile (per the NHLBI guidelines table), based on the participant's gender, age, and height percentile. If the participant's blood pressure (systolic and/or diastolic) is greater than the 95th percentile, the participant or the parent/legal guardian <18 years of age will be informed that the participant's blood pressure is higher than expected. If the participant is not already being monitored and treated for high blood pressure, study personnel will recommend that they follow-up with their healthcare provider. However, if the BP is greater than the 99th percentile plus 5, the study staff will ask that the participant seek immediate medical attention within the next three days. Staff personnel should provide documentation to the participant the BP value collected and document the BP result and in the participant's research record noting the participant was informed to seek immediate medical attention. (See Appendix C for the 90%ile, 95%ile and 99%ile+5 Blood Pressures by Gender Age Height) (6/12)

Acanthosis Nigricans

Scientific Rationale

Acanthosis nigricans is an eruption of the skin characterized by hyperpigmentation and velvety cutaneous thickening that can occur on any part of the body but characteristically affects the axillae, the posterior portion of the neck, the groin, the antecubital and popliteal surfaces and the umbilicus. Acanthosis nigricans is now recognized as a sign of insulin resistance [6]. Insulin resistance, however, can occur in the absence of acanthosis nigricans [7]. A higher prevalence of acanthosis

nigricans is found in ethnic populations with darker skin than lighter skin [6]. Studies in children and adolescents demonstrated that the neck was most significantly affected and always involved when other areas of the body have acanthosis nigricans [8]. In a field study of children, the anatomical area that proved to be the most reproducible was the neck [9]. Changes in texture must be present to identify acanthosis nigricans [8].

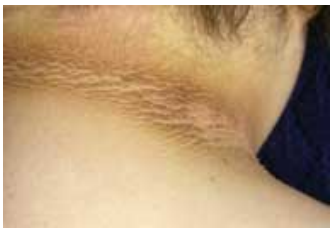


Figure 12. Acanthosis nigricans of neck

Equipment and Supplies

None

Measurement Approach

Acanthosis nigricans will be assessed for all participants by comparing the texture of the forearm with palm facing up and the texture of the nape of the neck. The participant will face the examiner with hands at their side and hands in the supine position. The examiner will face the participant and slowly and gently run their finger down the anterior aspect of the mid-portion of the forearm mid-way between the antecubital fossa and the wrist to assess normal texture (smooth). The participant will then turn around with their back to the examiner. The examiner will inspect the posterior portion of the neck from pinna of the right ear to pinna of the left ear. The examiner will divide this area into four quadrants and slowly and gently run their fingers from superior to inferior in each of the quadrants. The presence of "rough" texture in any quadrant will identify the presence of acanthosis nigricans. The presence of increased pigmentation only does not denote acanthosis nigricans. The presence of acanthosis nigricans will be recorded as **YES, NO, or MAYBE**.

Documentation

The following is an example of Acanthosis Nigricans documentation:

Figure 13. Acanthosis Nigricans documentation

Acanthosis Nigricans		Examiner Code			
9. Is Acanthosis Nigricans: *(check one)*	1❑ Yes	2❑ No	3❑ Maybe		

10.2.3. *Laboratory Measurements*

Overview

This section provides a brief overview of the laboratory procedures to be collected on SEARCH participants. Further information regarding obtaining, handling, and shipping specimens to the SEARCH Central Laboratory (Northwest Lipid Laboratories, Seattle, WA) is provided in Section 11 (Laboratory Manual). Review the summary table of specimen types and maximum allowable blood draw volumes for children in Section 11.

Obtaining laboratory specimens is an important component of the study visit; and obtaining fasting blood samples is considered a study priority.

a) If a participant comes for a study visit and refuses to provide a blood sample, the participant should be asked if they are willing to come back to provide a fasting blood sample within three months of the in-person visit.

b) If a participant comes for a study visit non-fasting, obtain blood and urine samples that do not require fasting (see Section 11) and encourage the participant to re-schedule for a fasting sample within the appropriate time window. If the participant returns for a fasting visit, obtain only those samples not obtained on the previous visit.

c) If a participant is willing to schedule a Registry Visit but notifies staff in advance that they will not give a blood sample, staff should use their discretion in scheduling this visit. If they are fairly certain that the participant/parent will not change their mind and provide a blood sample, then the study visit should not be scheduled and it should be coded as “refused”.

d) When a participant refuses to provide a blood sample, the visit will be counted as a “partial” visit. The physical examination will be performed and all other data collection forms will be completed. For Registry Visits, these participants will not be included in analyses using biochemical type since blood samples are needed for biochemical typing.

Blood Collection Process

Instructions for completing the Blood Collection Process can be found in Section 11 of the MOP, Laboratory Procedures. The Specimen Collection Form outlined below address blood collection (questions 9-13).

Urine Collection Process

Table 10-3: Cohort Visit Urine Collection

Types of urine collections performed	First morning void A repeat sample will be obtained if the first sample is rejected due to positive dipstick for blood, leukocytes, nitrites, or turbidity; or if the albumin/creatinine ratio is ≥ 0.03 mg/mg.
Window for urine collections	First morning void: the morning of the in-person visit or on another morning within three months following the in-person visit.
Screening for transient proteinuria	Questions at the time of the in-person visit and performing the "dipstick" test at the laboratory will markedly reduce the risk of identifying transient proteinuria.
Measurements performed on the first morning void collection by the laboratory in Seattle	Albumin concentration (mg/dl) Creatinine concentration (mg/dl) Calculation: albumin/creatinine ratio in mg of albumin per mg creatinine
Storage of urines samples	First morning void: five 2 ml aliquots and 2 pellets
Serum Creatinine	Serum creatinine will be measured by the laboratory and GFR calculated by the Coordinating Center using the CKDEPI formula for ≥ 18 yrs of age and the new Schwartz's equation for < 18 yrs. The estimated GFR is considered a "research value" and will not be reported to the clinical sites.

The goal is to collect and process urine samples for analyses that will provide the opportunity now and in the future to assess the effect of diabetes on the kidney and other bodily functions in SEARCH 4 participants.

Window for Urine Collections

If the participant does not provide a first morning void at the time of the in-person research visit, the clinical center will attempt to obtain a first morning void within three months of the in-person visit. A three-month window was chosen to allow a comparison between concomitant blood glucose control (hemoglobin A1c).

A repeat first morning void urine sample may be requested to confirm an abnormal result or in the presence of blood, leukocytes, nitrites, or turbidity in the first sample. The repeat sample should be collected as close in time to the visit as possible, and not to exceed 3 months following the visit.

A repeat first morning void urine can be picked up by or delivered to the study staff directly, or a urine collection kit can be mailed to the participant allowing the individual to collect the sample at home and mail it directly to the CBL via overnight shipping. The urine kit will include the following items:

- collection instructions
- urine cup
- 10ml transfer tube
- cleansing wipes
- biohazard bag
- cold pack
- Styrofoam mailer
- Fed Ex shipping label for the CBL.

Shipping fees will be incurred by the clinic site. Strong efforts should be made by clinic staff to recollect a first morning void urine sample before the team determines that it cannot be obtained.

Screening of urine sample: prevention of detection of transient proteinuria

Transient proteinuria is a normal occurrence and does not reflect pathology. Having procedures in place to limit the detection of transient proteinuria will reduce the false positive rate.

Common causes of transient proteinuria include fever, rigorous exercise, a urinary tract infection, and contamination of the urine sample from menstrual flow. To limit the likelihood of identifying transient proteinuria in the first morning void, SEARCH will employ the following questions and the laboratory personnel in Seattle will perform the Dipstick test and assess all urine samples for turbidity.

A positive answer to any one of the questions (1-8 on the Specimen Collection form) will result in the clinical site not sending the first morning urine sample collected on the day of the in-person visit, but collecting another first morning urine sample within three months of the in-person visit.

Specimen Collection Form

The Specimen Collection Form provides information regarding the visit type and participant's status at the time laboratory specimens were obtained. This form should not be confused with shipping and specimen forms provided by the SEARCH Central Biochemistry Laboratory (CBL). Data from the Specimen Collection Form will be

entered into the SEARCH data entry system; information will remain within this system unless the CBL makes requests for information.

Prior to obtaining laboratory specimens, verify and document that a consent form has been signed for the appropriate specimens, including sample storage and DNA sample collection.

1. Have you had DKA in the last 4 weeks that resulted in hospitalization of had to be treated by IV fluids?
2. Have you had a severe low blood sugar in the past 24 hours that required you to get help (glucagon injection, called 911, went to an emergency room or urgent care center)?
3. Have you had a fever greater than 100 degrees in the past 24 hours?
4. In the past month, have you been told by a doctor that you have a urinary tract infection?
5. Are you currently pregnant? *In some cases, the participant may be uncertain about pregnancy e.g., if their period is late and the possibility exists they are pregnant or they are simply uncertain. Therefore, an option exists for checking* ***"Yes," "No,"*** *or "****Unsure."*** *If the participant responds 'yes' -* ***do not collect a blood or urine specimens at this time and do not complete this form.*** *If the participant is unsure of their pregnancy status -* ***collect blood or urine specimens at this time. Staff should inform the participant if she later finds out that she is pregnant to please let the staff know, and the samples will not be analyzed.***
6. Were you menstruating when you did your 1st morning void urine collection? *If the participant responds 'yes,' do not send the 1st void urine and reschedule.*

If blood collection is indicated, complete the remainder of the questions.

7. Asks for insulin taken within the previous **4** hours. This does NOT include basal insulin per insulin pump.

   Mark "yes" or "no." If yes, indicate each insulin dose taken by checking the appropriate box. If the 2nd or 3rd box is checked, write in the time of the last dose taken. If no, go to question 9.

8. Asks for other diabetes medications taken within the previous **8** hours.

   Mark "yes" or "no." If yes, ask which medication and mark by the appropriate list on the form; then answer question 9a.

   If any diabetes medicine taken does not appear on the list of insulins or oral diabetes medications, write in the name of the medication in the next section, as well as the time of the last dose taken.

NOTE: If an unacceptable insulin or oral medication was taken, proceed with the blood draw and try to schedule a fasting re-draw visit.

8a. If a re-draw visit is necessary, did the participant agree (yes or no)?

9. Ask study staff to document if the participant had anything to eat or drink within the past **8 hours**.

9a. If "**Yes**" is selected, ask the participant what they had to eat or drink. Describe what they had to eat or drink and continue to question 10b.

9b. If participant consumed a non-allowable food or drink, record most recent time.

9c. If a re-draw visit is necessary, did the participant agree (yes or no)?

While it is optimal to have the participant in a complete fasting state, it may be impossible to achieve in all circumstances. Therefore, interviewers are requested to determine exactly what types of foods and beverages were consumed in the 8 hours prior to the visit to assess that a threshold of 5 gm of carbohydrates is not exceeded. If the participant consumed a diet beverage, one stick of gum, less than 2 Life Saver candies, 2 Chiclets or 2 Tic Tacs, the laboratory samples can be drawn without requiring a return visit. It is important for the interviewer to prompt the participant to determine the type and estimated amount of foods and beverages consumed, placing that information in the 'notes' section provided.

Note: If the participant consumed more than the allowable 5 gm of carbohydrates within 8 hours of the visit, obtain blood and urine specimens that do NOT require fasting. Attempt to re-schedule the participant for a fasting visit within a 3 month period. If the participant returns for a fasting visit, obtain only those samples not obtained on the previous visit.

Likewise, if only partial samples are collected for any other reason (i.e., difficult draw, etc.) a redraw visit should be scheduled within 3 months. At the redraw visit, obtain only those samples not obtained at previous SEARCH 4 visit.

10. Asks for a glucose meter reading. This test is to be completed after all blood specimen(s) have been collected. Study personnel can use a drop of blood from the blood collection device to apply to the glucose meter strip. This decreases the number of punctures the participant must endure. Example: After drawing blood specimens, the phlebotomist places a drop of blood onto the glucose meter strip and performs a glucose meter check of the participant's blood glucose.

- Enter the glucose meter result. Be certain to begin entry with the far right box.

Figure 14. Glucose meter reading

11. Glucose meter reading: ☐☐☐ *(May use drop from blood collected with venipuncture samples)*

If glucose is > 300 mg./dl., perform urinary ketone check and record in 11a.

11. Asks for any symptoms the participant may have. Check all that apply.
12. Asks for additional comments. If yes, write comments in box.
13. Asks for the identification number/code of the person that obtained the specimen. (Each SEARCH staff person is assigned a 3-digit code number.)
14. Asks for the date the specimen(s) was obtained. As in previous examples, use **2** digits for month and date and **4** digits for year.
15. Asks for the time the specimen was obtained. Please remember to check if the specimen was obtained in the morning (AM) or afternoon/evening (PM).

    A positive dipstick or turbidity test will result in the laboratory discarding the sample and reporting this action to the clinical center. A repeat first morning void collection will also be requested to confirm an abnormal result. The clinical center will attempt to recollect and process a second sample to replace the original sample within three months of the in-person visit. A urine kit can be mailed to the participant to facilitate the collection and the sample would be shipped via overnight express directly to the CBL.

    Tests performed by the Northwest Lipids Laboratory:

    a. Dipstick for leukocytes: If the reading is “small, moderate, or large” the sample will be discarded.
    b. Dipstick for blood: if the blood reading is “moderate or large” the sample will be discarded. “Small” will not be reported or rejected.
    c. Dipstick for nitrites: if the reading is positive the sample will be discarded.
    d. Assessment of turbidity: the laboratory personnel will visually inspect all urine samples. Any sample that is considered “turbid” will be assessed by the laboratory personnel. If the laboratory personnel are not able to read 12 point font through the urine sample, the sample will be declared turbid and will be discarded.

    A repeat first morning urine collection will be necessary if:

    - the first morning urine samples cannot be tested accurately due to presence of leukocytes, nitrites or blood;
    - urine albumin:creatinine ratio ≥ 0.03 mg/mg.

If the first morning void is positive for both leukocytes and nitrites, the participant may be at risk of having a urinary tract infection. When this occurs, the clinical site will notify the participant and/or provider regarding a possible urinary tract infection (UTI) according to local guidelines. If a UTI is confirmed, the recollection should be postponed until the infection has cleared.

Limitations of the screening Process for Transient Proteinuria

SEARCH recognizes that the screening process established by SEARCH will not identify all causes of transient proteinuria. For example, rigorous exercise and recent sexual activity may result in an increase in the amount of albumin measured in the urine. However, due to the inability to identify a standardized question that will effectively screen subjects to eliminate those who have participated in rigorous exercise, and the sensitive nature of information collected regarding sexual activity, SEARCH has chosen to not address these issues, which may result in the identification of some false positive tests for proteinuria.

Tests that will be performed on urine samples by the laboratory:

1. Albumin concentration (mg/dl)
2. Creatinine concentration (mg/dl)
3. Calculation: Albumin/creatinine ratio in mg of albumin per mg creatinine.

Storage of Urine samples

The clinical center will send the CBL the first morning void urine in a 10 ml transfer tube for the laboratory to process, prepare and store five 2 ml aliquots.

Post-phlebotomy Participant Instructions

- Instruct the Participant to check their blood glucose level (if this has not already been done) and take medication if indicated.
- Provide the Participant with SphygmoCor snack (cohort visit) or breakfast/snack (registry visit).

Note: Follow site-specific guidelines for medication adjustment. Contact the PI or site-designated pediatric endocrinologist if further assistance is needed.

Specimen Shipment - Fresh and Frozen

Instructions for completing the Fresh and Frozen Specimen Shipment Form can be found in Section 11 of the MOP, Laboratory Procedures.

Laboratory Result Reporting

Laboratory Reports

Laboratory reports will be distributed to designated center personnel via electronic mail (in the form of PDF files). Laboratory reports have been designed to accommodate both Cohort and Registry Visits.

Each PDF file consists of 2 pages:

- Page 1 of the report is labeled "Provider Report" and provides information including PID, participant results and corresponding reference ranges. Comments regarding specimen collection or shipping may be included if appropriate. This is the page printed and mailed to their health care providers. GAD, IA2 and C-Peptide results are displayed for the Registry visit and this report notifies the provided or urine rejection.

  Figure 15. Example of laboratory comments

  Example:

  Laboratory Comments
  1-01-12345 - Poor centrifugation resulting in non-defined gel barrier - sample unusable, new sample required.

  Note: These comments should be carefully reviewed with corrective measures taken.

- Page 2 of the report is labeled "Participant Report" and duplicates page 1, eliminating details on specimen and shipping issues. This is the page printed and mailed to participants.

Study staff will notify participants they are at risk of having a Urinary Tract Infection (UTI) if the first morning void is positive for BOTH leukocytes and nitrites. Additionally, the individual sites can determine the method by which the results will be conveyed to the participant and providers.

Laboratory Report Schedules

Table 10-4 provides the types of reports mentioned above, their associated distribution times, and content. Distribution times are based on normal circumstances. If reports are not received within a reasonable period of time, center personnel should contact the SEARCH Laboratory.

Table 10-4 Laboratory Report Distribution

Report	Report Distribution	Report Contents
Registry	Within 6 weeks of specimen receipt	HbA1c, fasting lipids, glucose, C-peptide, and urine albumin and creatinine
Cohort	Within 6 weeks of specimen receipt	HbA1c, fasting lipids, glucose, C-peptide, and urine albumin and creatinine

The only laboratory test determined to have an alert value is triglycerides. ***Laboratory personnel will report triglyceride levels ≥ 1000 via electronic mail and facsimile as soon as possible after the test is completed.***

The laboratory will also report urine samples that were rejected, as well as those that have an albumin/creatinine ratio ≥ 0.03 mg/mg. These will be reported via e-mail notification in "real time."

Common Participant Forms

A. Contact Information

In order to maintain contact and update participants about SEARCH, the Contact Information Form is completed at least annually. Information that is captured includes participant's name, Social Security Number, parent/guardians' names, mailing and email addresses, phone numbers, alternate contacts, and permission to contact at work. There are participant and parent versions.

B. Consent Tracking

The Consent Tracking Form is a means of communicating with the CoC. The form confirms the data elements the participants have consented to use as a part of the SEARCH study. The online form has been made into a hard copy that can be put into the visit packet for the study staff use only and can be used as a prompt for the study staff when entering the data.

C. Unanticipated Occurrence/Event Reporting

Instructions for completing the Unanticipated Occurrence form can be found in Section 17.7 of the MOP (Patient Safety, Alert Values and Event Reporting and Monitoring).

10.3. PROCEDURES SPECIFIC TO REGISTRY VISITS

Table 5. Registry Participant Study Forms

(eligible)	Adult Participant	Participant < 18 years	
		Child	Parent
IPS	X		X
Contact Information form	X		X
Medication Inventory (interview style)	X		X
Physical Exam (≥ 3 yrs. of age)	X	X	
Specimen Collection	X	X	

Registry Study Staff Forms
Consent Tracking
Extended Core
Specimen Collection Form
Specimen Shipment - Fresh
Specimen Shipment - Frozen
Unanticipated Occurrence
Unregistration

10.3.1. *Registry Visit Questionnaires*

A. IPS (refer to Section 9 of the MOP for specific details)

If the IPS was not completed prior to the visit, it may be completed during the visit. Refer to Section 9 for specific guidance on completion of the IPS.

B. Medication Inventory (Interview)

The medication inventory form was designed to record all insulin and other prescription medications taken by participants and whether medications were used in the last 2 days.

Question 1: Asks *are you taking prescribed medications, and, if yes, what prescribed medication(s) are you taking?*

Check all insulins and other diabetes medications and write the names of the other prescribed medications currently being taken.

Question 2: A*sks that of the medications listed for question 1, which of those have been taken in the past 2 days.* Check yes or no

- If Other Insulin is checked, write in medication name.
- If other injectable medication was used, check box and write name of medication.

At the bottom of the form there is a place to write in other medication being taken including diabetes medications not listed.

Check yes or no if the medication has been taken in the past 2 days.

10.3.2. *Secondary Diabetes Identified During or After an In-person Visit*

Participants identified as having a diagnosis of Other Specific Type of Diabetes during or after an in-person visit will complete the in-person visit including blood and urine specimens. The blood and urine specimens will be processed per protocol procedures. The results of the tests will be transmitted to the participants per study protocol. However, the only data that will be used in the analysis will be the presence/absence of diabetes in the ascertainment year, gender, ethnicity, date of diagnosis, and date of birth. This information will be used to meet one of SEARCH's primary goals describing the prevalence and general characteristics of this type of diabetes (see Appendix D).

10.4. PROCEDURES SPECIFIC TO COHORT VISIT

The S4 cohort visit is completed for participants who are at least 10 years old, and who appear on the cohort visit eligibility list for either an in-person visit or S4 cohort surveys-only collection. Some data collection elements are to be completed at home prior to the visit and other elements are completed at the time of the in-person visit. Please refer to the list below for details.

Data collection to be completed at home prior to the in-person visit:

The expected time to complete these elements is 75 minutes.

1. First morning urine void
2. On-line S4 cohort survey

See the table below for data collection to be completed at the in-person visit.

Table 6. S4 cohort visit data collection

(eligible)	Adult Participant	Participant < 18 years	
		Child	Parent
Informed consent form, including permission for data storage	X	X	X
Fasting blood draw and specimen collection forms	X	X	
CESD questionnaire	X	X	
Food Frequency Questionnaire (FFQ)	X	X	
Tanner stage questionnaire (until stage 5 is achieved)	X	X	
Contact information form	X	X	X
S4 cohort survey form (ONLY if not completed on-line prior to the visit)	X	X	X
Physical exam (BP, height, weight, waist circumference, acanthosis and Physical Exam form	X	X	
MNSI (foot exam and questionnaire)	X	X	
Neurocognitive testing including the Neurocognitive form	X	X	
SphygmoCor testing including the SphygmoCor form	X	X	
Retinal photography including the Eye Vision form	X	X	
Echocardiogram (if applicable)	X	X	
Unanticipated occurrence form (if applicable)	X	X	

The expected time to complete these elements is 3 hours.

Suggested sequence of visit procedures

Because we are unsure how food intake may affect the SphygmoCor testing, it is our goal to minimize the effects of food. In order to be consistent, all participants should be given a standardized snack (Nutri-Grain bar) after the collection of the fasting blood samples and before the SphygmoCor testing. Participants should take insulin with this snack according to their usual regimen. After the snack has been consumed, study staff will measure the participant's blood pressure (per SEARCH protocol). Immediately following the blood pressure measurements, SphygmoCor testing will begin. The outline below suggests the preferred order of procedures. To allow sites flexibility to address unique issues related to the implementation of the cohort visit, some of the measures can be performed in any order and it is permissible to collect the data at two (2) separate visits. If the data collection visits are split, the time period between them should be minimized as much as possible and should not exceed 3 months.

A. Single visit

1. Obtain informed consent; review outline of the visit
2. Study staff accepts the first morning urine sample collected earlier that day
3. Fasting blood draw
4. Standardized snack/ insulin
5. Cardiac measures
    a. Blood pressure
    b. SphygmoCor and corresponding form
6. All other measures (in any order)
    a. Physical examination (height, weight, waist, acanthosis nigricans)
    b. MNSI exam and questionnaire
    c. Neurocognitive testing
    d. Retinal photos
    e. CESD, FFQ, and Tanner stage questionnaires
    f. S4 cohort survey and contact update form (if not previously completed on-line)
    g. Echocardiogram (for a subset of 500 cohort-eligible participants)

B. If two visits are required

Move any of the measures listed in number 7 above to another visit

a. Interval between these 2 visits should be < 3 months
b. If interval > 3 months, measure blood pressure and hemoglobin A1c at both visits

<u>Standardized snack</u>

1. The standard snack will be a Nutri-Grain bar and water. Nutri-Grain bars consist of the following macronutrients:
    a. CHO = 24-26 gms.
    b. Fat = 3-4 gms.
    c. Protein = 2 gms.
2. If the participant is allergic to the contents of the Nutri-Grain bar, has celiac disease, or refuses the standard snack for any other reason, the following are *alternatives to the standard snack* - **listed in order of preference:**

a. Glutino gluten-free breakfast bar

b. Pre-plan with the participant to bring a snack to the visit that has an equivalent amount of CHO and fat

c. Perform SphygmoCor fasting for at least 8 hours overnight without eating the standardized snack. If the participant eats/drinks something else, record what the participant ate (type and amount of food) on the SphygmoCor form. (This would include the treatment of any low blood glucose level.)

3. Sites may provide a meal or an additional snack upon completion of the SphygmoCor or during/after the study visit (optional), as long as this is provided after the SphygmoCor.

10.4.1. *Cohort Visit Procedures*

A. Central Laboratory

Instructions for collecting blood and urine samples can be found in Section 11 (Central Laboratory) of the MOP.

B. Physical Measures

Instructions for collecting height, weight, waist, blood pressure, and acanthosis nigricans can be found in Section 10.2 of the MOP.

C. Retinopathy

Instructions for collecting Retinal Photos can be found in Section 12 (Retinopathy) of the MOP.

D. SphygmoCor

Instructions for collecting SphygmoCor measures can be found in Section 13 (SphygmoCor) of the MOP.

E. Michigan Neuropathy Screening Instrument (MNSI)

Instructions for collecting MNSI measures can be found in Section 14 (MNSI) of the MOP.

F. Echocardiogram

Instructions for collecting echocardiogram measures can be found in Section 15 (Echocardiogram) of the MOP. Only trained cardiac sonographers will perform echocardiogram measures.

10.4.2. *Cohort Visit Questionnaires*

A. S4 Cohort Survey

The S4 cohort survey is designed as a self-administered form to be completed on-line or on paper if on-line completion is not possible. The S4 cohort surveys combine a number of previous cohort surveys into one survey. The CoC will provide secure log-in information (de-identified user name and password) to allow access to the website and forms. Validation checks will be embedded in the forms to prompt skip patterns and advancement to the next module, as well as to notify participants of percentage of completion and/or if there are missing fields. All participants eligible for the cohort in-person visit will be asked to complete the S4 cohort surveys. These may be completed prior to or during the visit.

Note: There may be instances where adult participants may need to communicate with his/her parent/guardian to complete the survey. This is most likely to occur with questions related to health insurance. Participants are reminded that they can ask others for input at the start of the survey, but SEARCH staff may want to reinforce this when providing instructions/introduction to the forms. All self-administered forms should reviewed for completeness once submitted.

The S4 cohort surveys will include the data elements in the table below.

Table 7. S4 Cohort Survey Data Elements

	Adult pt.	Parent	14 - 17 pt.	10 - 13 pt.
Contact information	X	X	X	X
Insulin use & meds	X	X	X	partial
Glucose monitoring	X	X	X	no
Self-care	X	X	X	X
Acute complications	X	X	partial	partial
Medical history	X	X	no	no
Reproductive health	X	X	no	no
Health insurance	X	partial	X	partial
Health care costs	X	X	no	no
Transition to adult care	X	X	X	no
Health care providers	X	X	no	no
Diabetes care	X	X	partial	no
Provider ratings	X	X	partial	partial
Family medical history	X	X	no	no

	Adult pt.	Parent	14 - 17 pt.	10 - 13 pt.
Household	X	partial	partial	partial
Food security	X	X	partial	partial
Immigration	X	X	no	no
Physical activity	X	no	X	X
Substance use	X	no	X	X
Diabetes eating problems	X	no	X	X
Low blood sugar	X	X	X	X
PedsQL	X	X	X	X
Diabetes quality of life	X	X	X	X
Discrimination	X	no	X	X

The following questionnaires will be collected at the in-person visit.

B. Depressed mood - CES-D Form

Scientific Rationale

Depression among adolescents is an important cause of morbidity. Almost one in five teens will become depressed sometime in adolescence.[10] Poorer health status can be associated with depression and depression affects functioning on multiple levels. Thus, for diabetes, depression represents an important co-morbidity, which can impact on adherence to treatment regimens and progression of disease. For Type 2 diabetes, it is unclear if depression represents a risk factor for diabetes, as well. If depression is associated with incidence and persistence of obesity, it could indirectly impact on development of diabetes.

Measurement Approach

Since diagnostic interviewing is time and labor intensive, most studies measure depressive symptoms. No one scale adequately measures depressive symptoms among children, adolescents, and young adults. The Centers for Epidemiologic Study - Depression Scale (CES-D) has been widely used among adolescents.[11]

The CES-D gives flexibility with regard to analytic strategy by working as both a continuous and a dichotomous measure. It can be used as a continuous measure of depressive symptoms or scores can be dichotomized at cut points that maximize the sensitivity and specificity for predicting major depressive disorder (MDD).[11,12] The cut points for predicting MDD differ for teens and adults. It is well received by subjects and easy to complete.

- The depression questions are directed toward the participant.
- Data for the CES-D will be collected by self-report.
- The cover sheet provides information to the participant about:
  - Why the form is being used (to determine how they felt or behaved during the past week)
  - What the response selections will be (rarely, some of the time, occasionally, or most of the time), and
  - If there is potential for the participant to require treatment, their information will be shared with their Parent/Legal Guardian.

Response Selections

The following categories are presented as response selections for the CESD:

> Response categories are:
> **0=Rarely** or none of the time (less than once per week)
> **1=Some** or a little of the time (1-2 days per week)
> **2=Occasionally** or a moderate amount of the time (3-4 days per week)
> **3=Most** or all of the time (5-7 days per week)
> However on questions # the scale is reversed.

Participant Scoring and Action Values

Participant scores are determined by adding the values of all 20 responses. **Action values are: ≥ 24 for subjects < 18 yrs. of age (both males and females) and ≥ 16 for subjects 18 yrs. of age or older.** A scoring grid provided at each site will allow rapid scoring of the CES-D to determine if an Action Value has been reached. A laminated 'overlay' of the CES-D is provided that will align with the participant's response to each question. The overlay has the appropriate score for each question placed under each the response set. Using an erasable marker, place the score for a particular response in the unshaded box on the right of the answer set. When all response values have been entered, subtotal each column and place column totals at the bottom right corner of the overlay. Add the column subtotals to get the total.

C. Eye Vision

The Eye Vision form asks if the participant has an optometrist or ophthalmologist that he/she sees. If the participant sees an optometrist or ophthalmologist, the name, phone number, and mailing address are recorded on the form. The form also

captures if laser treatment or injections due to diabetic retinopathy have been administered. In the For Study Use Only box, staff should record if there were any difficulties in obtaining the retinal images. If there were difficulties, the main reason for the difficulty should be checked (camera, participant, operator, or other).

D. Food Frequency Questionnaire

Overview

Many dietary factors may be important in the development of risk factors for atherosclerosis in persons with type 2 diabetes, either as a function of energy balance or through metabolic pathways that are independent of obesity. Specific nutrients of interest include total caloric intake, dietary fats (total fat and specific fatty acids), and carbohydrates. In addition, there is increasing recognition of the potential health effects of whole foods, food groups, and other dimensions of dietary patterns. Despite the widely recognized importance of diet in the management of diabetes, no study to date has systematically documented usual dietary intake in a large, diverse sample of youth with diabetes. The potential role of dietary intake in development of risk factors for cardiovascular disease (particularly dyslipidemia) has recently been extensively reviewed and will not be repeated here [18]. This technical review provided the basis for the recently published Evidence-Based Nutrition Principles and Recommendations for the Treatment and Prevention of Diabetes and Related Complications [11].

Research Questions relate to risk factors for chronic complications and to processes of care, as follows:

Dietary intake in relation to risk factors for macrovascular complications

- What is the association of carbohydrate intake on plasma triglyceride concentration among youth with diabetes?
    - Does this differ according to dietary intake of fiber or whole grain foods?
    - Does this differ according to current level of obesity, or according to change in BMI from the time of diagnosis?
- What is the association of fat intake (total fat and saturated fat) on plasma LDL concentration among youth with diabetes?
- What is the association of total fat intake with current level of obesity? What is the association of fat intake with BMI change from the time of diagnosis?

Dietary intake in relation to processes of care

- How does the reported nutritional content of the diet (specifically percent calories from macronutrients) compare to current ADA recommendations for

nutrition in individuals with diabetes? Does this vary according to other aspects of diabetes self-management (e.g., frequency of HbA1c testing, SBGM).

Methodology

The diet assessment questionnaire is a staff assisted, self-administered survey of the dietary habits of SEARCH participants, limited to participants age 10 years and older. The SEARCH dietary assessment is designed to facilitate analysis of specific nutrients and whole foods, as well as overall dietary patterns. The diet assessment will be used at the Cohort Study Visit. It is modified from the Kids' Food Questionnaire, developed by Gladys Block and validated in children as young as 8 years old, including African American youth living in a low-income neighborhood. Modifications include addition of selected foods likely to be important to nutrient intake in the ethnically and regionally diverse SEARCH population, as well as consideration of the age range of SEARCH. The original Kids' Food Questionnaire included about 75 food lines; the SEARCH form includes about 85 food lines. These additions were based primarily on foods identified for inclusion for the NIH/NIDDK-funded Diabetes Prevention Program that has similar diversity (albeit an adult population). Other modifications include a small number of questions designed to more fully understand whether the period of recall (one week) reflects "usual" intake for the individual, use of dietary supplements and use of low-fat products.

Instructions for Administration of the Diet Interview

The goal of the Food Questionnaire is to obtain information about **usual** dietary practices of the participants, and to do so consistently at all clinical centers. Note that the form is called the "Food Questionnaire" rather than the "Diet Questionnaire" or "Nutrition Questionnaire". This is to minimize bias related to reporting of intake that is considered desirable rather than focusing on food actually eaten. Ideally, for a hypothetical participant, the same results would be obtained no matter who is administering the questionnaire, how it is administered (self or interviewer), when it is administered, or where it is administered. However, in any multi-center study, differences in the administration of a questionnaire will exist among staff and interviewers, among centers and over time. These differences can seriously bias results of statistical analyses. Thus, standardization of the administration of the Food Questionnaires is critical to the data quality. The DAC has established certification guidelines (see Training and Certification) and will maintain listings of certified staff and interviewers.

The mode of administration of the SEARCH diet assessment will be **staff-assisted self-administration**. "Staff assisted" refers to the process of providing instruction to the participant, rather than simply handing a blank form to the participant. It is important to provide the participant with instructions for completing the form and answer any questions that may be asked (see below for guidelines). If, due to participant circumstances (such as literacy or vision impairment), the form must be completed as an interview, this is acceptable (see instructions for interview administration, below).

Instructions for the participants to complete the form on their own

A simple, clear introduction is extremely important to obtaining valid information from the questionnaire. Instructions are included throughout the form. Do not overwhelm the participant with too much detail! **Keep it simple.**

Do Not Give The Form To The Participant And Try To Read It To Them At The Same Time. Generally, This Is A Poor Interview Style Because Participants Cannot Read And Pay Attention To You At The Same Time

- Present the form to the participant and let them know that you will take a few minutes to explain how to fill out the form.
- Read the information on page 2. Be sure to write in your name so that the participant is comfortable going to you by name to ask questions. If the form goes home, be sure to provide a stamped envelope for them to use to return the form. Write down the date the form is due (one week from giving out the form), and be sure you make this clear to the participant.
- Important Note: It is up to the SEARCH staff and participant to determine if the form is to be completed by the participant while they are in the clinic, or whether the participant will take the form home, complete it there, and return it by mail (or in person). However, from our experience, it is much better to have the form completed in clinic if possible. This allows easy access to study staff should any questions arise, and ensures that the form is returned in a timely manner, with minimal staff effort in follow-up. This also allows for the form edit to be done quickly and any omissions or clarifications to be obtained with the participant still present in clinic.
- Encourage the participant to be careful to mark the appropriate bubble and to fill in the bubbles completely using a #2 pencil. Use the first three short questions (top of page 3) to demonstrate filling in the bubbles correctly.
- Continue reading instructions on page 3.

- When you say (on page 3), "…sometimes using the pictures at the back of the form," go over portion size responses located as the last page of the form. These are self-explanatory. Indicate that for each food, the participant will be asked how much they ate. When the form tells them to use the pictures, this is what they turn to for pictures of different amounts of food, either on plates or in bowls. When the participant is working on the form, they can pull out this page of pictures and keep it beside the rest of the booklet (just be careful not to lose the picture page if they are working at home). This approach is designed intentionally to provide only limited information about portion size. Be careful to avoid bogging down in detail here!
- Turn to page 4 of the form.
- To help participants feel oriented to the form, tell them the items are grouped by type of food.
- Remind participants to think of foods eaten at home and away from home. Remind them to include both meals and snacks.
- Emphasize completeness and that no line should remain blank. The participant should check "no" rather than simply skip foods he or she rarely or never eats.
- Inform participants that if they don't eat a particular food, they may leave the serving size blank.
- Point out open-ended section (on page 16), to record anything else eaten every day or almost every day.
- Point out the few additional questions at the end.
- Point out the space to let us know anything else they would like us to know about their usual dietary practices.
- Note that the last page is for clinic use only.
- Ask if there are any questions. Give the form to the participants and let them know they may call anytime if questions arise.

Tracking Self-Administered Forms

Encourage the prompt return of the questionnaire. If more than one week has passed, and the form has not been returned, attempt to follow-up with the participant and make arrangements for the return of the form.

If you suspect that the participant is unlikely, unwilling or unable to complete the form, you may collect the data over the phone (see instructions for interviewing, below).

Notes on General Interviewing Style and Cultural Sensitivity

The skill and consistency of the interviewers will strongly influence the quality of the dietary data. Please review the general interviewing techniques provided at the beginning of the SEARCH MOP. In particular, remember to establish a non-judgmental atmosphere. You are not here to evaluate dietary intake. You are here to facilitate accurate reporting of dietary behaviors by the participant, and to accurately record the participants' responses.

SEARCH has a major advantage because of the diverse population included across the clinical centers. The nutrition interview includes a wide variety of foods that are likely to contribute substantially to nutrient intake within the various subgroups of ethnicity and geographic region included in the study. *Keep in mind: the only important foods to consider in this dietary assessment are those that contribute substantially to overall usual nutrient intake.* Foods that are important from a cultural perspective but which are eaten only infrequently (e.g., special holiday foods) generally do not contribute substantially to usual nutrient intake. Therefore, such foods have not been included in the interview.

It is necessary to achieve a balance between cultural sensitivity, sensitivity to the individual, and standardization. For the purpose of standardization, each diet interviewer must include (by saying out loud) the complete listing of all foods when interviewing study participants. For purposes of sensitivity to individual dietary choices and to culture, the diet interviewer needs to listen carefully to the participant, and can spending relatively more time on foods consumed more frequently and less time on foods rarely consumed. For example, if the participant is unfamiliar with a particular food, it is unlikely to be an important source of nutrients. Minimize time on these items.

However, DO NOT ASSUME that you can anticipate what a particular individual may eat. In today's cities, ethnic foods are easily available to all. Therefore, interviewers need to:

- Be familiar with all foods on the FFQ form.
- Be familiar with the foods common in your community.
- Be aware of possible language barriers.
- Be aware of cultural and/or personal differences in communication style.
- Note that if a participant reports a food and you do not know what the food is, ask the participant to describe it, including major ingredients and cooking method. Do not assume that the DAC will know what it is! Write the information down so that we can determine how to code the food.

- Be aware of language differences among participants. Have a bilingual conversation as needed.
- Be aware that some foods may only be known in the original language (e.g., frijoles for beans).
- Be aware of literacy level and level of understanding when interviewing participants. The interview scores at about the 8th grade level (lower for instructions only). However, this assumes English as a first language.

Specific Instructions for Conducting the Diet Interview

Introduction of the Interview

Use the text on the form as a general guide to briefly introduce the form.

NOTE: The exact wording on the form is for the benefit of the participants who will complete this as a self-administered form. Adjust the language as appropriate for interviewer-administration. For example, instead of "tell us how often…," say, "I will ask you how often…"

General Questions

General questions such as meal and snack frequency are designed to help orient the participants' thoughts to the topic of what he/she ate last week. They are also used to understand aspects of dietary behaviors.

Meal and Snack Frequency

If the participant gives a range, take the midpoint and confirm with the participant. For example, for a response of "2 to 4," the interviewer would ask, "Would you say 3 is a good average?" For a response like 2-3, ask, "Is it more often 2 or more often 3 snacks a day?" If the participant insists on 2.5, code it as 3 (i.e., round up). If meal or snack frequency is very different for days they work vs. days off, ask about "most" days.

Frequency of School Lunch (or Breakfast)

This generally refers to cafeteria-style service. It does not include taking breakfast or lunch from home.

Restaurant Frequency

This includes fast foods, "take-out", and home delivery of whole meals, including pizza if this constitutes a meal.

Body of Interview: Food Frequency

Note, during an interview process or if the participant has questions relating to a particular food, first ask if the participant ate a particular food at all. Show

the participant the cue card for frequency (1/week….up to every day) and review all responses. Keep this cue card out and easily available.

Body of Interview: Portion Size

Simply note that for each type of food, you will be asking about how much the participant ate. See Instructions for Self-Administered Forms, regarding portion size.

> **NOTE**: *Do Not* get bogged down in excessive detail -- we are not expecting exact reporting of portion sizes. We simply want the participant to tell us the general ballpark of their typical portion size for each line item. The approaches to portion size are explained above.

Food List

There are headings throughout the form to identify the type of foods to be queried. The first section is "Breakfast Foods". Let the participant know the name of the section to help him/her orient their thinking. For example, say, "First, we'll go over fruits and juices."

For each line item, in general, you should read all items on the list. There are some items that will almost never apply to certain centers or to certain participants. It is sometimes appropriate to use some judgment here, but remember that consistent use of the interview across centers is vitally important. As an example, if a person says that she is a vegetarian, you should still confirm in the food list section that she does not eat any type of beef, then any type of pork, then any type of chicken, etc. You would not need to mention each type of beef within the roast beef line item. Inclusion of all line items is necessary to avoid missing the particular food choices that may enable us to discern relatively small but potentially important differences in nutrient intake between individuals. **The key thing to remember is not to assume too much.**

Most items in the meat, fish and poultry section are main dish items. While you can check to make sure that the total number of main dishes makes some sense, remember that many people do have eating habits that may seem unusual to you. Probe further if you hear something that seems highly unlikely, but don't try to get answers based on your expectations of food habits.

Beverages

IMPORTANT: When you review the response set for beverages and you are using cue cards, be sure to remove the old set from sight and point to the new set of answers to avoid confusion. Be sure that the frequency of milk as a beverage does not include milk used on cereal or in coffee or tea.

If a participant thinks of additional information during the interview related to a food item you have already coded, go ahead and go back to that item while the participant is thinking of it and modify the answer as needed.

Food Preparation

Tell the participant that you will now ask a few more questions about their diet. Review responses (never eat the food, seldom or never, sometimes, often or always). For the questions about type of fat used, the scanner will accept either one or two answers. If the participant only uses one type of fat, if at all, fill in only one bubble. If the participant uses more than two types of fat, record only the two that he uses most frequently.

Additional Foods (page 16)

Ask the participant if there are any other foods that they eat every day or almost every day. These should be foods that have not been reported previously! Give the participant a moment to think before moving on. For any foods reported at this time that are included elsewhere on the form, incorporate them into the main body of the questionnaire as appropriate, including frequency and portion size. Record any additional foods on page 16. Be sure items are legible and the frequency is complete. For mixed dishes, be sure main ingredients and preparation method is obvious or noted. The DAC will code these items.

Comment Section

Sometimes a participant will tell you something about his/her diet that is important to him/her but which is not appropriate for inclusion on the interview form. For example, a participant may note that she/he doesn't like vegetables. You can note these things in the comment section so that the participant knows you are listening to him/her and are ready to move on. These comments generally require no further review. (See Section below on editing.)

Checking/Editing the Completed Form (whether interview or self-administered)

When the questionnaire is returned (or the interview is complete) spend a few minutes (usually two to five minutes) checking over the questionnaire. Ideally, you will do this while the study participant is still there. If the questionnaire is returned by mail, check the form as soon as possible in case clarification is needed. Do not mail the form to the DAC unit until editing is complete**. The goal is to identify obvious omissions or errors, NOT to judge the quality of the participant's diet.**

- Make sure the information in the "For Clinic Use Only" is complete and correct.
- Check for omissions - skipped foods, missing information.
- If there is an occasional missing line within the list of foods, you do not need to contact the participant. If three or more items in a row are missing, contact the participant to complete the items.
- If any other question has been skipped, contact the participant.
- Check for extremely unlikely frequencies, such as "every day" for an entire page of main dishes. Contact the participant to confirm such responses, and, if needed, provide a comment in the "For Clinic Use Only" box (see below).
- If other foods are reported in the open-ended question, be sure these are described (e.g., a recognizable name of food, or if a mixed dish, the main ingredients and cooking method).
- Complete the For Clinic Use Only review flags. These include:
  - "DAC review needed for coding". Mark this as "yes" if something has been written in on page 16.
  - "Comment" (yes / no). Mark this as "yes" if there is other information regarding reported foods or questionable reliability of the form that may impact on data quality. Briefly describe your question or comment. If you are unsure, feel free to contact the DAC directly (contact information above) and we will respond very quickly to your inquiry.

E. Michigan Neuropathy Screening Instrument (MNSI)

(See Section 14 of the MOP for specific details)

Overview

The Michigan Neuropathy Screening Instrument is used to assess the presence of peripheral diabetic neuropathy and is conducted at the cohort visit. The MNSI consists of two parts: Part A is a brief questionnaire about symptoms of peripheral neuropathy, and Part B includes a physical examination of the feet.

Part A: Neuropathic History Questionnaire

The MNSI questionnaire is designed to be a self-administered form and consists of 15 questions asking about the presence or absence of peripheral neuropathy symptoms in the participant's legs or feet. The allowed response to this series of questions is YES or NO only. The participant should place an X in the box that best describes the feeling in his/her legs and feet.

Upon review of the form, staff should pay special attention to the answers to questions 7 and 13 as these are sometimes inadvertently marked NO since the absence of symptoms for the other questions on the form is indicated with a NO answer. If the answer to question 7 or 13 is marked NO, please repeat the question to the participant as it is written to ensure that they answered in the way they intended. If they still answer NO, then leave the answer. However, if they indicate that they should have answered YES, correct the answer by putting one line through the unintended answer and place an X in the correct box. Initial and date the change on the form.

Part B: Physical Assessment

Part B of the MNSI form is the data collection sheet for the physical examination of both feet that includes the following components: 1) foot inspection, 2) ankle reflexes, 3) vibration sensation, and 4) monofilament testing for touch sensation.

Each of the five questions on the form allows for recording of the findings for the right foot and left foot and answers may vary based on the measure and the foot tested.

Question 1 concerns the appearance of the foot. If no abnormalities are observed upon inspection of the foot, question 1a should be marked YES. However, if abnormalities are observed, then question 1a should be marked NO and question 1b should be completed by marking all the abnormalities from the listing that were evident. Specific abnormalities listed are Deformities; Dry skin, callous; Infection; Fissure; and Other.

A description and examples of each abnormality follow:

- Deformities (hallux valgus or bunion, claw foot, Charcot foot, hammer toe);
- Dry skin, callous (thick, flaky, leathery skin often localized over a pressure point, not evenly distributed). Common dry skin that looks like it could be resolved by an application of skin lotion should not be marked as an abnormality here;
- Infection (Athlete's Foot as evidenced by red, flaky, macerated skin between and around the toes or other infection marked by pus and irritated skin);
- Fissure (deep split in the skin);
- Other (specify).

If "Other" is marked, the examiner should write in the abnormality on the line provided. Possible observances that might be classified as "Other" are toenail fungus, amputation, and fracture.

Question 2 concerns the presence or absence of ulceration and is answered by marking the correct box (Absent or Present) for each foot. Superficial scrapes and cuts of the skin that are healing properly should not be considered ulceration. To warrant a positive response for ulceration, there should be evidence of a skin penetration that is often roundish and well-demarcated for which the participant can give no clear reason. They are sometimes painless and often occur over a pressure point or bony prominence at the heel, toe or metatarsal heads.

Question 3 records the findings of the ankle reflex test at the Achilles tendon and is answered by marking either Present, Present/Reinforcement (if the Jendrassic Maneuver was necessary to elicit the reflex), or Absent for each foot.

Question 4 records the results of the vibration perception tuning fork test of each foot. The answer is recorded by marking either Present, Reduced or Absent. A response of Present indicates that after the participant signaled that no more vibration of the tuning fork was felt, the tester could sense the vibration at the DIP of the index finger for only $\leq$10 seconds. A response of Reduced indicates that the vibration of the tuning fork at the DIP of the index finger was felt by the tester for >10 seconds, and a response of Absent indicates that the participant was unable to sense any vibration sensation of the tuning fork at the DIP of the great toe.

Question 5 records the number of monofilament applications detected at the dorsum of the great toe between the toe nail and the DIP joint. The answer is recorded by marking either Present, Reduced or Absent. A response of **present** indicates that the participant accurately detected >8 monofilament touches at the great toe. A response of **reduced** indicates the participant accurately detected 1-7 touches and a

response of **absent** indicates the participant could not identify when the monofilament was being applied to the great toe.

Part C: MNSI Quality Control

A repeat MNSI examination (only the examination part of the test will be repeated) will be performed on approximately 5% of subjects at each site, by a separate examiner on the same day as the primary test. A random sample weighted towards younger participants with earlier estimated visit dates were selected for QC component.

The primary examiner (determined by the site) will perform the examination and record the results in the usual manner and enter the results into the SEARCH on-line data entry program. The second examiner must not be present and must not see the results that the primary examiner has recorded.

The secondary examiner will perform the examination, record the results on a paper form, and place the results into a sealed envelope. This exam and recording is done outside the presence of the primary examiner. The primary and secondary examiner should not discuss their results until the primary test data has been entered and secondary test data has been entered. The CoC can then compare the QC and primary data for agreement. Sites will receive feedback regarding inter-examiner agreement. The CoC will to provide regular updates of primary/secondary tests to the University of Michigan. Disparities noted between examinations will be addressed with sites by Cathy Martin at the University of Michigan.

The subject identification on second form will need to indicate that the test is a quality control test - Write “QC” after the subject ID number. Also, both primary and secondary testers should be recorded.

F. SphygmoCor Form (see section 13 of the MOP for specific details)

Instructions for completing the SphygmoCor can be found in Section 13 of the MOP (SphygmoCor). On the SEARCH SphygmoCor form, staff ask if caffeine, nicotine, and decongestants/asthma medications have been used on the morning of the SphygmoCor test. If a participant answers yes, record on the form what has been used. Continue with the test even if the participant has had caffeine, nicotine, decongestants, or asthma medication. Other information that is completed includes what the participant ate (if anything) prior to the test, the condition of the exam room (hot or cold), what measurements were obtained, all or partial measurements for Heart Rate Variability, Pulse Wave Velocity, and Pulse Wave Analysis for femoral, radial, and foot. There is also a space on the form for recording if the participant has been selected for a SphygmoCor QC measurement.

G. Tanner Stage Forms (Age 10 to 17 or until Stage 5 is reached)

Overview

Onset of puberty is associated with changes in insulin sensitivity and other metabolic and endocrine processes. Puberty is also associated with changes in social interactions and self-esteem. The Tanner Stage self-assessment of physical body changes will allow assessment of onset of puberty. Temporal sequence of puberty onset will help establish the relationship of puberty with insulin resistance and self-esteem, psycho-social factors, and/or depressive symptoms.

Administration of Form

The Tanner Stage Form is a self-administered form. **Different forms are supplied for males and females**.

Females

The participant should be given the form and informed to mark the box by each picture that most closely resembles their upper and lower body appearance. The participant should be given privacy while filling out this form.

Males

The participant should be given the form and informed to mark the box by the picture that most closely resembles their lower body appearance. The participant should be given privacy while filling out this form.

H. Echocardiogram

See Section 15 for Details

I. Neurocognitive Testing

See Section 16 for Details

REFERENCE LIST

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APPENDIX A - REGISTRY LAB EXPLANATION

Diabetes antibodies - SEARCH measures 3 diabetes antibodies: GAD65, ZnT8 and IA2. Type 1 Diabetes occurs when the immune system destroys the insulin-producing cells of the pancreas. The diabetes antibodies are evidence of this process. The presence or absence of diabetes antibodies helps us to determine whether the individual has Type 1 Diabetes. Approximately 90% of people with Type 1 Diabetes have at least one of these antibodies present at the time of diagnosis.

C-peptide - measures how much insulin the pancreas is producing. The C-peptide level helps us to determine whether the individual has Type 1 Diabetes or Type 2 Diabetes. People with Type 1 Diabetes usually have low levels of C-peptide, while individuals with Type 2 Diabetes often have higher levels of c-peptide. C-peptide levels need to be measured while fasting because the results are affected by the amounts and types of food we eat.

Glucose - measures the sugar level in the blood. Glucose levels in the blood are usually higher in people with diabetes. SEARCH is measuring glucose levels to aid us in the interpretation of the c-peptide level.

Hemoglobin A1c - is a measure of the average blood sugar level over the past 3 months. Lower Hemoglobin A1c levels indicate "good" control, while higher levels indicate less control. SEARCH is measuring Hemoglobin A1c because higher levels may indicate that the individual is at increased risk for diabetes complications that affect the heart, eyes, kidneys, and nerves.

Lipid profile - measures the fat levels in the blood. It includes total cholesterol, triglycerides, LDL (the "bad" cholesterol), and HDL (the "good" cholesterol). It is best to have lower levels of total cholesterol, triglycerides, and LDL; and higher levels of HDL. SEARCH is measuring the lipid profile because high fat levels in the blood may indicate that the individual is at increased risk for diabetes complications related to the heart, such as a heart attack. Lipid profiles are most accurate when measured while fasting.

Urine albumin and creatinine - measures how much protein is being lost through the kidneys. SEARCH is measuring the protein level in the urine because high levels of protein may indicate that the individual is at increased risk for diabetes complications related to the kidney.

APPENDIX B - COHORT LAB EXPLANATION

Glucose - measures the sugar level in the blood. Glucose levels in the blood are usually higher in people with diabetes. SEARCH is measuring glucose levels to aid us in the interpretation of the c-peptide level.

Hemoglobin A1c - is a measure of the average blood sugar level over the past 3 months. Lower Hemoglobin A1c levels indicate "good" control, while higher levels indicate less control. SEARCH is measuring Hemoglobin A1c because higher levels may indicate that the individual is at increased risk for diabetes complications that affect the heart, eyes, kidneys, and nerves.

Lipid profile - measures the fat levels in the blood. It includes total cholesterol, triglycerides, LDL (the "bad" cholesterol), and HDL (the "good" cholesterol). It is best to have lower levels of total cholesterol, triglycerides, and LDL; and higher levels of HDL. SEARCH is measuring the lipid profile because high fat levels in the blood may indicate that the individual is at increased risk for diabetes complications related to the heart, such as a heart attack. Lipid profiles are most accurate when measured while fasting.

C-peptide - measures how much insulin the pancreas is producing. The C-peptide level helps us to determine whether the individual has Type 1 Diabetes or Type 2 Diabetes. People with Type 1 Diabetes usually have low levels of C-peptide, while individuals with Type 2 Diabetes often have higher levels of c-peptide. C-peptide levels need to be measured while fasting because the results are affected by the amounts and types of food we eat.

Urine Albumin and Creatinine - Urine albumin and creatinine measures how much protein is being lost through the kidneys. SEARCH is measuring the protein level in the urine because high levels of protein may indicate that the individual is at increased risk for diabetes complications related to the kidney.

APPENDIX C - 90TH, 95TH AND 99TH +5 PERCENTILE BLOOD PRESSURES BY GENDER, AGE AND HEIGHT

			Pre Hypertension		High Blood Pressure		Seek Immediate Attention	
Gender	Age	Height	90th %ile	90th %ile	95th %ile	95th %ile	99th %ile+5	99th %ile+5
	(Years)	(Cm)	Systolic B/P	Diastolic B/P	Systolic B/P	Diastolic B/P	Systolic B/P	Diastolic B/P
Female	3	88	100	61	104	65	116	78
Female	3	89	100	62	104	66	116	78
Female	3	91	102	62	105	66	118	79
Female	3	94	103	63	107	67	119	79
Female	3	97	104	64	108	68	120	80
Female	3	99	106	64	109	68	121	81
Female	3	100	106	65	110	69	122	81
Female	4	94	101	64	105	68	117	81
Female	4	95	102	64	106	68	118	81
Female	4	98	103	65	107	69	119	81
Female	4	100	104	66	108	70	120	82
Female	4	103.5	106	67	110	71	122	83
Female	4	106	107	67	111	70	123	84
Female	4	108	108	68	112	71	124	84
Female	5	100	103	66	107	70	119	83
Female	5	102	103	67	107	71	119	83
Female	5	105	105	67	108	71	121	84
Female	5	107	106	68	110	72	122	84
Female	5	111	107	69	111	73	123	85
Female	5	114	109	69	112	73	125	86
Female	5	116	109	70	113	74	125	86
Female	6	106	104	68	108	72	120	85
Female	6	108	105	68	109	72	121	85
Female	6	111	106	69	110	73	122	85
Female	6	115	108	70	111	74	124	86
Female	6	118	109	70	113	74	125	87
Female	6	121.5	110	71	114	75	126	88
Female	6	124	111	72	115	76	127	88

Female	7	113	106	69	110	73	122	86
Female	7	115	107	70	111	74	123	86
Female	7	118	108	70	112	74	124	87
Female	7	121	109	71	113	75	125	87
Female	7	125	111	72	115	76	127	88
Female	7	129	112	72	116	76	128	89
Female	7	131	113	73	116	77	129	89
Female	8	118	108	71	112	75	124	87
Female	8	120	109	71	112	75	125	87
Female	8	124	110	71	114	75	126	88
Female	8	127	111	72	115	76	127	88
Female	8	132	113	73	116	77	128	89
Female	8	135	114	74	118	78	130	90
Female	8	135	114	74	118	78	130	91
Female	9	123	110	72	114	76	126	88
Female	9	125	110	72	114	76	126	88
Female	9	129	112	72	115	76	128	89
Female	9	133	113	73	117	77	129	89
Female	9	137	114	74	118	78	130	90
Female	9	141	116	75	119	79	132	91
Female	9	143	116	75	120	79	132	92
Female	10	127	112	73	116	77	128	89
Female	10	130	112	73	116	77	128	89
Female	10	133.5	114	73	117	77	130	90
Female	10	138	115	74	119	78	131	91
Female	10	143	116	75	120	79	132	91
Female	10	147	118	76	121	80	134	92
Female	10	150	118	76	122	80	134	93
Female	11	131	114	74	118	78	130	90
Female	11	135	114	74	118	78	130	90
Female	11	139	116	74	119	78	131	91
Female	11	144	117	75	121	79	133	92
Female	11	149	118	76	122	80	134	92
Female	11	153	119	77	123	81	135	93
Female	11	157	120	77	124	81	136	94

Female	12	138	116	75	119	79	132	91
Female	12	142	116	75	120	79	132	91
Female	12	146	117	75	121	79	133	92
Female	12	151	119	76	123	80	135	93
Female	12	156	120	77	124	81	136	93
Female	12	160	121	78	125	82	137	94
Female	12	164	122	78	126	82	138	95
Female	13	145	117	76	121	80	133	92
Female	13	148	118	76	122	80	134	92
Female	13	152	119	76	123	80	135	93
Female	13	157	121	77	124	81	137	94
Female	13	162	122	78	126	82	138	94
Female	13	166	123	79	127	83	139	95
Female	13	169	124	79	128	83	140	96
Female	14	149	119	77	123	81	135	93
Female	14	152	120	77	123	81	136	93
Female	14	156	121	77	125	81	137	94
Female	14	160	122	78	126	82	138	95
Female	14	165	124	79	127	83	140	95
Female	14	169	125	80	129	84	141	96
Female	14	172	125	80	129	84	141	97
Female	15	151	120	78	124	82	136	94
Female	15	154.5	121	78	125	82	137	94
Female	15	158.5	122	78	126	83	138	95
Female	15	162	123	79	127	83	139	96
Female	15	166	125	80	129	85	141	96
Female	15	170	126	81	130	85	142	97
Female	15	173	127	81	131	86	143	98
Female	16	152	121	78	125	82	137	95
Female	16	154	122	78	126	82	138	95
Female	16	158	123	79	127	83	139	95
Female	16	164	124	80	128	84	140	96
Female	16	167	126	81	130	85	142	97
Female	16	171	127	81	131	85	143	98
Female	16	174	128	82	132	86	144	98

Female	17	152	122	78	125	82	138	95
Female	17	155	122	79	126	83	138	95
Female	17	159	123	79	127	83	139	96
Female	17	163	125	80	129	84	141	96
Female	17	167	126	81	130	85	142	97
Female	17	171	127	81	131	85	143	98
Female	17	174	128	82	132	86	144	98
Female	>18				140	90	180	110

			Pre Hypertension		High Blood Pressure		Seek Immediate Attention	
Gender	Age	Height	90th %ile	90th %ile	95th %ile	95th %ile	99th %ile+5	99th %ile+5
	(Years)	(Cm)	Systolic B/P	Diastolic B/P	Systolic B/P	Diastolic B/P	Systolic B/P	Diastolic B/P
Male	3	89	100	59	104	63	116	76
Male	3	90	101	59	105	63	117	76
Male	3	93	103	60	107	64	119	77
Male	3	95	105	61	109	65	121	78
Male	3	97.5	107	62	110	66	123	79
Male	3	100	108	63	112	67	124	80
Male	3	102	109	63	113	67	125	80
Male	4	96	102	62	106	66	118	79
Male	4	97	103	63	107	67	119	80
Male	4	100	105	64	109	68	121	81
Male	4	103	107	65	111	69	123	82
Male	4	106	109	66	112	70	125	83
Male	4	108	110	66	114	71	126	83
Male	4	110	111	67	115	71	127	84
Male	5	102	104	65	108	69	120	82
Male	5	104	105	66	109	70	121	83
Male	5	107	106	67	110	71	123	84
Male	5	110	108	68	112	72	125	85
Male	5	113	110	69	114	73	126	86
Male	5	115	111	69	115	74	128	86
Male	5	117	112	70	116	74	128	87

Male	6	108	105	68	109	72	121	82
Male	6	110	106	68	110	72	122	83
Male	6	112.5	108	69	112	73	123	84
Male	6	116	110	70	114	74	125	85
Male	6	119	111	71	115	75	126	86
Male	6	122	113	72	117	76	128	86
Male	6	123	113	72	117	76	128	87
Male	7	113	106	70	110	74	122	87
Male	7	115	107	70	111	74	123	87
Male	7	118	109	71	113	75	125	88
Male	7	122	111	72	115	76	127	89
Male	7	125	113	73	117	77	129	90
Male	7	128	114	74	118	78	130	91
Male	7	130	115	74	119	78	131	91
Male	8	118	107	71	111	75	124	88
Male	8	120	109	72	112	76	125	89
Male	8	123	110	72	114	77	127	90
Male	8	127	112	73	116	78	128	91
Male	8	130	114	74	118	79	130	92
Male	8	133	115	75	119	79	132	92
Male	8	135	116	76	120	80	132	93
Male	9	123	109	72	113	76	125	89
Male	9	125	110	73	114	77	126	90
Male	9	128	112	74	116	78	128	91
Male	9	132	114	75	118	79	130	92
Male	9	136	115	76	119	80	132	93
Male	9	139	117	76	121	81	133	93
Male	9	141.5	118	77	121	81	134	94
Male	10	128	111	73	115	77	127	90
Male	10	130	112	73	115	78	128	91
Male	10	133	114	74	117	79	130	91
Male	10	137	115	75	119	80	132	93
Male	10	141	117	76	121	81	133	93
Male	10	145	119	77	122	81	135	94
Male	10	147	119	78	123	82	135	95

Male	11	132	113	74	117	78	129	91
Male	11	135	114	74	118	78	130	91
Male	11	138	115	75	119	79	132	92
Male	11	143	117	76	121	80	134	93
Male	11	147	119	77	123	81	135	94
Male	11	152	120	78	124	82	137	95
Male	11	154.5	121	78	125	82	137	95
Male	12	137	115	74	119	78	131	91
Male	12	140	116	75	120	79	132	92
Male	12	144	118	75	122	80	134	93
Male	12	149	120	76	123	81	136	94
Male	12	154	121	77	125	82	138	95
Male	12	159	123	78	127	82	139	95
Male	12	162	123	79	127	83	140	96
Male	13	142.5	117	75	121	79	133	92
Male	13	145	118	75	122	70	135	92
Male	13	150	120	76	124	80	136	93
Male	13	156	122	77	126	81	138	94
Male	13	161	124	78	128	82	140	95
Male	13	166	125	79	129	83	141	96
Male	13	169	126	79	130	83	142	96
Male	14	148	120	75	124	80	136	92
Male	14	151	121	76	125	80	137	93
Male	14	156	123	77	127	81	139	94
Male	14	163	125	78	128	82	141	95
Male	14	168	126	79	130	83	143	96
Male	14	173	128	79	132	84	144	97
Male	14	176	128	80	132	84	145	97
Male	15	155	122	76	126	81	139	93
Male	15	158	124	77	127	81	140	94
Male	15	163	125	78	129	82	141	95
Male	15	169	127	79	131	83	143	96
Male	15	174	129	80	133	84	145	97
Male	15	178.5	130	80	134	85	147	98
Male	15	181.5	131	81	135	85	147	98

Male	16	161	125	78	129	82	141	95
Male	16	163.5	126	78	130	83	142	95
Male	16	168	128	79	132	83	144	96
Male	16	173	130	80	134	84	146	97
Male	16	178	131	81	135	85	148	98
Male	16	182	133	82	137	86	149	99
Male	16	185	134	82	137	87	150	99
Male	17	165	127	80	131	84	144	97
Male	17	167.5	128	80	132	85	145	98
Male	17	172	130	81	134	86	146	98
Male	17	176	132	82	136	87	148	99
Male	17	180	134	83	138	87	150	100
Male	17	184	135	84	139	88	151	101
Male	17	187	136	84	140	89	152	102
Male	>18				140	80	180	110

APPENDIX D - SECONDARY DIABETES IDENTIFIED DURING OR AFTER AN IN-PERSON VISIT

NOT Valid
No Diabetes Diagnosed
Glucose Intol.:
Glucose Intol.: Fasting - Normal/High Insulin
Glucose Intol.: Fasting - Low Insulin
Glucose Intol.: Fasting - Insulin Unknown
Glucose Intol.: Post Prandial - Normal/High Insulin
Glucose Intol.: Post Prandial - Low Insulin
Glucose Intol.: Post Prandial - Insulin Unknown
Glucose Intol.: Fasting & Post-Prandial - Norm/High
Glucose Intol.: Fasting & Post-Prandial - Low Ins.
Glucose Intol.: Fasting & Post-Prand. - Ins Unknown
Glucose Intol.: Unknown
Insulin Resistance
Stress Hyperglycemia
Gestational diabetes mellitus (GDM)

Valid
Fully Eligible - for In-Person Visit
Type 1 Diabetes:
Type 1 Diabetes: Immune mediated
Type 1 Diabetes: Idiopathic
Type 1 Diabetes: Unknown
Type 2 Diabetes
Unclassified
Genetic Defect B-cell:
Genetic Defect B-cell: Chrom. 12, HNF-1a(MODY3)
Genetic Defect B-cell: Chrom. 20, HNF-4a(MODY1)
Genetic Defect B-cell: Chrom. 7 glucokinase(MODY2)
Genetic Defect B-cell: Mitochondrial DNA
Genetic Defect B-cell: Others

Secondary - complete IPS only
Dis. Exocrine Pancreas:
Dis. Exocrine Pancreas: Cystic Fibrosis
Dis. Exocrine Pancreas: Neoplasia
Dis. Exocrine Pancreas: Fibrocalcul Pancreatopathy
Dis. Exocrine Pancreas: Hemochromatosis
Dis. Exocrine Pancreas: Pancreatitis
Dis. Exocrine Pancreas: Trauma/Pancreatectomy
Dis. Exocrine Pancreas: Others
Drug or chemical induced:
Drug or chemical induced: Glucocorticoids
Drug or chemical induced: B-adrenergic agonists
Drug or chemical induced: Diazoxide
Drug or chemical induced: Dilantin
Drug or chemical induced: Nicotinic Acid
Drug or chemical induced: Pentamidine
Drug or chemical induced: Thiazides
Drug or chemical induced: Thyroid Hormone
Drug or chemical induced: Vacor
Drug or chemical induced: a-interferon
Drug or chemical induced: Others
Endocrinopathies:
Endocrinopathies: Acromegaly
Endocrinopathies: Aldosteronoma
Endocrinopathies: Cushing's syndrome
Endocrinopathies: Glucagonoma
Endocrinopathies: Hyperthyroidism
Endocrinopathies: Pheochromocytoma
Endocrinopathies: Somatostatinoma
Endocrinopathies: Others
Genetic Defect Ins. action:
Genetic Defect Ins. action: Lephrechaunism
Genetic Defect Ins. action: Lipoatrophic diabetes
Genetic Defect Ins. action: Rabson-Mendenhall syn.

Genetic Defect Ins. action: Type A ins. resist.
Genetic Defect Ins. action: Others
Infections:
Infections: Congenital rubella
Infections: Cytomegalovirous
Infections: Others
Other genetic syn.:
Other genetic syn.: Down's syndrome
Other genetic syn.: Friedreich's ataxia
Other genetic syn.: Huntington's chorea
Other genetic syn.: Klinefelter's syndrome
Other genetic syn.: Laurence-Moon-Biedl syn.
Other genetic syn.: Myotonic dystrophy
Other genetic syn.: Porphyria
Other genetic syn.: Prader-Willi syndrome
Other genetic syn.: Turner's syndrome
Other genetic syn.: Wolfram's syndrome
Other genetic syn.: Others
Uncommon Immune Types:
Uncommon Immune Types: "Stiff-man" syndromes
Uncommon Immune Types: Anti-ins receptor antibody
Uncommon Immune Types: Others
Neonatal