**Studies to Treat Or Prevent Pediatric Type 2 Diabetes**

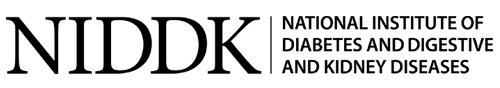
**TODAY Study Group Genetics Protocol**



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# Introduction and Objective

The TODAY study group has prepared a protocol with the primary objective of collecting blood and phenotypic information to be used to explore relationships between candidate genes and type 2 diabetes (T2D), as well as obesity, insulin resistance, and cardiovascular complications of insulin resistance. Participation in the genetics study includes a blood draw for analysis of diabetes type and DNA extraction, as well as collection of basic family and medical history. Appropriate informed consent and assent are obtained from all participants to extract DNA and send blood, genetic material, and medical history to the Central Repository of the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) of the National Institutes of Health (NIH). The data are kept indefinitely by the Central Repository. The NIDDK will issue requests for proposals (RFP) throughout the scientific community for research that may help in the development of new diagnostic tests, new treatments, and new ways to prevent diabetes and other related comorbidities.

The genetics study is the second protocol being conducted under the auspices of the TODAY study group. The study group has established the infrastructure needed to conduct the research and is well positioned to recruit the unique sample of adolescents and youth diagnosed with T2D. The TODAY study group is composed of investigators associated with the fifteen clinical centers (Baylor College of Medicine, Case Western Reserve University, Childrens Hospital Los Angeles, Children’s Hospital of Philadelphia, Children’s Hospital of Pittsburgh, Columbia University, Joslin Diabetes Center, Massachusetts General Hospital, Saint Louis University, State University of New York Upstate Medical University, University of Colorado Health Sciences Center, University of Oklahoma Health Sciences Center, University of Texas Health Sciences Center at San Antonio, Washington University in St Louis, and Yale University), the NIDDK project office, the coordinating center (George Washington University Biostatistics Center), the study chair, and other experts from central cores and reading centers. An additional ten clinical centers were brought on to recruit participants for the TODAY Genetics Study (Kansas City Children’s Mercy Hospital, Connecticut Clinical Medical Center Children’s Hospital, Children’s Hospital Central California, University of California San Diego, Texas Tech University, University of Arkansas, Vanderbilt University, Emory University, Indiana University, and the University of Florida).

This protocol is written by the TODAY study group with guidance from the TODAY Genetics Advisory Committee. The protocol is approved by the TODAY Steering Committee, TODAY Data Safety Monitoring Board, and the Institutional Review Boards (IRB) of each participating clinical center prior to the initiation of recruitment.

# Background and Significance

## Type 2 Diabetes

T2D has dramatically increased throughout the world in many ethnic groups and among people with diverse social and economic backgrounds. Over the last decade, the increase in the number of children and youth with T2D has been labeled an “epidemic” [ADA 2000]. Before the 1990s, it was rare for most pediatric centers to have patients with T2D. By 1994, T2D patients represented up to 16% of new cases of diabetes in children in urban areas [Pinhas-Hamiel et al. 1996], and by 1999, depending on geographic location, the range of percent of new cases due to T2D was between 8-45% and disproportionately represented in minority populations [Dabelea et al. 1999; Rosenbloom et al. 1999].

T2D in children and youth, as in adults, is due to the combination of insulin resistance and relative β-cell failure. It appears that there are a host of genetic and environmental risk factors for insulin resistance and limited β-cell reserve. The epidemic of pediatric T2D is coincident with the rise in the number of children who are overweight or at risk for overweight and with a decrease in the physical activity pattern of youth [Dietz 1998; Goran et al. 1995; Troiano and Flegal 1998; Kimm et al. 2000]. There has been a strong association between T2D and the onset of puberty, a positive family history of T2D, and elements of the metabolic syndrome such as acanthosis nigricans and polycystic ovarian syndrome (PCOS) [Arslanian 2000; Arslanian and Kalhan 1994].

The TODAY study represents one of the first large-scale studies to investigate the pathophysiology, treatment, and complications of type 2 diabetes and associated disorders in children and youth. The long-term complications and costs associated with T2D make such studies imperative. Since the long-term microvascular and cardiovascular complications relate to duration of diabetes and to control of glycemia, it could be hypothesized that the increasing number of children and youth diagnosed with T2D could dramatically add to the economic burden of this disease over the ensuing decades. Between 1997 and 2002, the estimated cost of diabetes with regard to direct medical cost increased from $44 billion to $92 billion, and the total cost increased from $98 billion to $132 billion [ADA 2003]. The vast majority of monies are spent on the long-term complications of this disorder [ADA 2002].

## Genetics of T2D in Humans

Susceptibility to T2D is strongly inherited as evidenced by the > 80% concordance rates in monozygotic twins [Barnett et al. 1981; Lo et al. 1991; Kahn et al. 1996; Medici et al. 1999], familial aggregation, and ethnic predispositions [Jun et al. 1999]. Heritability of subphenotypes related to T2D, e.g., insulin resistance and β-cell function, is even higher [Permutt et al. 2005]. Environmental factors also clearly play an important role [Permutt et al. 2005; Florez et al. 2003]. Several genes for relatively rare monogenic forms of diabetes such as MODY, syndromic (Wolfram syndrome), lipoatrophic, and mitochondrial-inherited diabetes have been identified [Khanim et al. 2001]. However, the underlying genetic basis for the more common and genetically complex T2D, accounting for > 95% of patients, has remained elusive. The identification of susceptibility genes is made difficult by the polygenic nature of the phenotype [Cox et al. 1992], its reflection of convergent, distinct metabolic processes producing identical phenotypes (phenocopies), and the potent gene-gene and gene-environment (e.g., obesity) interactions that characterize the disease. Clear genetic influences on the “endophenotypes” of β-cell mass/function and insulin resistance described above have been shown, and vary among ethnic groups [Pimenta et al. 1995; Gelding et al. 1995; Knowler et al. 1993; Hanley et al. 2003]. It is becoming clear that despite some notable successes (e.g., PPARG, CAPN10, TCF7L2, CDKAL1), the number of genes conveying diabetes risk is large and may vary by race/environment. In addition, the mechanism(s) by which alleles of genes such as PPARG, TCF7L2, etc. result in susceptibility to diabetes remain unknown [Permutt et al. 2005; Owen and McCarthy 2007].

T2D is a complex genetic disorder, and those diagnosed young help contribute to our understanding due to the strong likelihood that they represent a population enriched for susceptibility genes.

# Recruitment and Screening

Recruitment is conducted within a ‘catchment’ area that includes (a) the patient pools of the 25 clinical centers and (b) collaborating clinics and physicians who either refer subjects to a TODAY site or obtain IRB approval to conduct the protocol at their own locale. In the case of patient referrals, study staff may not directly approach a patient for recruitment until that patient has been informed of the study by his/her physician who has ascertained that the patient is willing to discuss participation with study representatives.

The TODAY sites were chosen partially based on the ethnic/racial composition of their patients with T2D. It is estimated that the ethnic/racial distribution of enrolled participants in both protocols will be 34% African American, 34% Hispanic (largely Mexican American), 2% Native American, 23% non-Hispanic White, and 7% other (largely Asian American).

Recruitment is expected to last through February 2015. There are no site-specific sample size goals, and the overall target sample size is 2500 participants.

## Informed Consent and Assent

Participants provide informed consent (parents for a minor child or patient ≥ 18) and informed assent (minor child):

* to collect 27 mL of blood,
* to provide family and medical history by self report,
* to send the blood for extraction of DNA to the NIDDK Central Repository,
* to send blood for measurement of glucose, C-peptide, and autoantibody analysis to a central blood laboratory,
* for the study to inform the primary care provider if pancreatic autoimmunity is detected, and
* to send data collected by questionnaire and laboratory analysis to a coordinating center for processing prior to being sent to the NIDDK Central Repository.

The participant agrees that the information will be retained indefinitely at the Central Repository and made available as appropriate to the scientific community for the development of new diagnostic tests and new treatments for diabetes and other related diseases.

The informed consent/assent process is designed to meet the ethical obligations to the patient. It is an interactive, conversational process, providing information in verbal and written form, with the ultimate goal of maximum understanding of the purposes of the TODAY genetics study, its risks and benefits, the rights of the patient, and the responsibility of the investigators to the patient.

## Eligibility Criteria

Inclusion:

1. Diabetes by one of the following criteria:
2. For patients diagnosed prior to January 1, 2010
3. Laboratory determination of fasting glucose ≥ 126 mg/dL, or random glucose ≥ 200 mg/dL, or two-hour OGTT glucose ≥ 200 mg/dL documented and confirmed in medical record.
4. *Or* Laboratory determination of HbA1c ≥ 7%.
5. For patients diagnosed after January 1, 2010
6. Same as 1.a.i. above.
7. *Or* Laboratory determination of HbA1c ≥ 6.5%.
8. For asymptomatic patients diagnosed with diabetes with a normal fasting glucose but an elevated two-hour glucose during an OGTT, the HbA1c must be ≥ 6%.
9. BMI ≥ 85th percentile documented at time of diagnosis.
10. Age < 18 at time of diagnosis.
11. Signed informed consent and assent forms as appropriate.

*Exclusion:*

1. Genetic syndrome or disorder known to affect glucose tolerance other than diabetes.
2. Patient on medication known to affect glucose tolerance, insulin sensitivity or secretion within 60 days of the time of diagnosis. If diagnosis is confirmed after the patient has been off the medication for 60 days, the patient may be included. Exclusionary medications include but are not limited to
   1. inhaled steroids at dose above 1000 mcg daily fluticasone equivalent,
   2. oral glucocorticoids,
   3. antirejection or chemotherapy agents (e.g., tacrolimus, Lasparaginase),
   4. atypical antipsychotics.
3. Blood relative of a TODAY participant or another TODAY Genetics participant.

## Participant Compensation and Reimbursement

Study participants are reimbursed for costs related to getting to the study visit provided that supporting documentation is supplied to a study staff member (receipts from cabs, metro, parking, bus, etc.). This includes parking costs, bus fare, or alternatively, participants may receive bus passes or taxi service to attend visits. Finally, participants are compensated $25 for the blood draw and data collection.

# Data Collection and Processing

Data are collected at a single point per participant. A blood sample (27 mL in four tubes) is drawn and the following data collected:

1. DNA extraction
2. serum glucose
3. C-peptide
4. pancreatic autoimmunity antibodies
5. family and medical history by self-report
   * gender, age at diagnosis, current age, race/ethnicity
   * self and family history of diabetes and treatment
   * components of metabolic syndrome
   * diabetes vascular complications
   * incidence of diabetic ketoacidosis (DKA)

Blood is sent directly to the Central Repository for DNA extraction. Blood is also sent to the central blood laboratory for analysis of glucose, C-peptide, and autoantibodies; those values are transferred to the coordinating center. Self-report data are sent to the coordinating center from the clinical centers, joined with the central blood laboratory values, and forwarded to the Central Repository.

Based on current screening in TODAY, it is anticipated that 10-12% of the sample could yield positive antibodies. Such findings will be reported back to the participant’s primary care provider (see section on Risks, Monitoring, and Risk Management below).

# Confidentiality of Study Data

The study complies with HIPAA guidelines regarding confidentiality of patient data.

All data are labeled with a study ID, including forms and specimens. All data transferred to the coordinating center for accumulation in the central database identify the patient only with the study ID. The coordinating center does not receive any personal identifiers.

Each clinical center maintains a file on each patient that includes personal identifiers, linking name and contact information to the study ID. These data are not entered into the study data management system or into any file accessible by the coordinating center. Patient files are kept in secure locations and the clinical center is responsible for taking every other reasonable measure (those set by the state, the site, and the study) to ensure and maintain record confidentiality and patient privacy.

At the end of the study, at some point after data collection ends and all data and specimens have been sent to the NIDDK Central Repository, the link between the subject and the Repository will be destroyed. After that point, it will not be possible to withdraw from the study and the samples will be retained indefinitely at the Repository.

Training sessions cover confidentiality principles and procedures.

# Sample Size and Analysis

Based upon the recommendations of the TODAY Genetics Advisory Committee, the target sample size is 2500 subjects. The committee has determined that this sample size provides a realistic opportunity to find candidate genes for T2D in this cohort.

Study design and analysis are based upon a candidate gene strategy. Specific objectives and methods of analysis will be proposed by investigators applying to the NIDDK to use the data from the Central Repository.

# Safety and Monitoring

## Data Safety Monitoring Board (DSMB)

The TODAY Data Safety Monitoring Board consists of appropriately qualified independent experts appointed by NIDDK. The purpose of the board is to assure independent review as to whether study patients are exposed to unreasonable risk because of study participation, and to monitor study progress and integrity. The board receives and reviews reports on a regular basis.

The genetics study involves no intervention, no follow-up, and only minimal risk (blood draw). The DSMB mainly reviews that the protocol is being followed and recruitment and data collection are proceeding as designed.

## Risks, Monitoring, and Risk Management

Risks associated with blood draw include discomfort, bleeding, and bruising at the site on entry. There is a very rare chance of fainting or infection. Blood draw and follow-up procedures are conducted according to standard clinical practice. Side effects from blood draw are not reported as adverse events. No serious adverse events are anticipated.

Subjects who are found to have positive islet autoantibodies may benefit from having their primary care providers (PCP) receive this information because it may help guide the doctor in clinical decision making regarding therapy. The clinical center principal investigator will send a letter (see template wording below) to the patient’s PCP making them aware of study findings. If there is no PCP, the patient will be referred to an appropriate diabetes program for follow-up.

**Template Follow-up Letter to Primary Care Provider**

Dear Doctor \_\_\_\_\_\_\_\_,

Your patient, \_\_\_\_\_\_\_\_, recently provided a blood specimen as a participant in a study of the genetics of type 2 diabetes, sponsored by the National Institutes of Health. Although he/she was felt to have type 2 diabetes based on clinical features, screening studies revealed positive pancreatic beta-cell antibodies indicative of pancreatic autoimmunity. These findings may have clinical implications of which you should be aware.

Although your patient may have characteristics typical of patients with type 2 diabetes (such as obesity, positive family history, and acanthosis nigricans), patients with positive antibodies tend to have higher blood glucose levels (and hemoglobin A1C values), are less likely to respond to oral medications, and are more likely to need insulin for adequate glycemic control compared to antibody negative patients. In addition, children and adolescents with antibody-positive diabetes may benefit from being followed by a pediatric endocrinologist. We strongly recommend confirmatory testing and a consultation or referral with a pediatric endocrinologist, if not previously arranged.

If you have any questions or concerns regarding this information, please contact our office at \_\_\_\_\_\_\_\_\_.

Sincerely,

\_\_\_\_\_\_\_\_\_\_, MD

Principal Investigator, Type 2 Diabetes Genetics Study

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