
Genetic Services Policy Project

Type 2 Diabetes and Genetic Technology: A Policy Brief

What is type 2 diabetes (T2D)?

- T2D is a progressive endocrine disorder characterized by abnormal secretion or action of insulin, which leads to elevated blood glucose (high blood sugar).
- Elevated blood glucose results in damage to multiple organ systems over time.
- A pre-diabetes phase, with abnormal glucose tolerance or insulin response, typically precedes the development of T2D.

Who is affected by T2D?

- T2D has reached epidemic proportions in the U.S. and is increasing around the globe.
- As of 2005, 20.8 million people in the U.S. (7 percent of the population) have diabetes, including an estimated 6.2 million who have not yet been diagnosed. (NIDDK)
- Over 20 percent of the population older than 60 has diabetes.
- Prevalence is increasing in children and adolescents, particularly in association with obesity.
- Women with gestational diabetes during pregnancy are at increased risk.
- The disease is more prevalent in certain racial and ethnic groups, including Hispanics, African Americans, Native Americans, and Southeast Asians.

What is known about the genetic and non-genetic causes of T2D?

- T2D is a multi-factorial disorder, with both genetic and environmental components.
- T2D risk is increased in people with a family history of the disorder. Rare cases of early onset T2D, known as Maturity Onset Diabetes of the Young (MODY), are associated with single gene mutations. Most cases of T2D, however, are believed to be related to multiple genes, each with a relatively modest effect, acting in concert with environmental influences.
- Obesity is a major risk factor, but not all individuals with diabetes are obese and not all people with obesity develop diabetes.
- Research into the genetic causes of T2D has been an area of intense interest over the past 20 years. Though many different genes have been implicated, replication of findings has proven challenging. New techniques, such as whole genome analysis and the availability of large population-based DNA banks, have accelerated progress in this area.
- In March 2006, deCODE Genetics, a biotech company from Iceland using samples from their national population-based DNA bank, announced the discovery of a gene on chromosome 10 with a strong association to diabetes.
 - Specific variants in the transcription factor 7-like 2 (TCF7L2) gene increased risk of diabetes by approximately 1.45 times in heterozygote and 2.41 times in homozygotes with a population attributable risk of 21 percent.
 - An estimated 7 percent of the general population is homozygous for high risk variant.

- Gene-disease association studies for TCF7L2 have subsequently been replicated in multiple studies and populations.
- Mutations in TCF7L2 are associated with impaired insulin secretion and increased hepatic glucose production. (Lyssenko, et al. 2007)
- Since the discovery of TCF7L2, researchers have identified a number of additional genes with connections to diabetes. None have demonstrated the same degree of risk as the TCF7L2 variants. (Sladek, et al. 2007) (Steinthorsdottir, et al. 2007) (Florez, Jablonski, et al., 2007)

What are clinical features of T2D?

- Individuals in the pre-diabetes and early stages of T2D may be asymptomatic or may have a variety of non-specific symptoms, including increased thirst, frequent urination, hunger, fatigue, weight loss, irritability, and blurred vision.
- Rarely the disease may present acutely with diabetic coma, a life-threatening condition.
- Complications of T2D are associated with end-organ damage and include heart disease, stroke, blindness, kidney disease, peripheral neuropathy, and amputations.
- Diabetes was ranked as the sixth leading cause of death in 2002, primarily due to complications.

What are the psychosocial impacts of T2D?

- Adequate management of T2D and/or prevention of T2D in pre-diabetics requires significant behavioral change that may be frustrating for patients and health care providers.
- Depression is a common problem in T2D and may precede development of the disease. Diabetic individuals with untreated depression have poorer glucose control, increased risk of complications, and higher health care costs.
- The psychosocial and behavioral impacts of knowing one's genetic risk for T2D is not known.

Who provides care for T2D and in what setting?

- Multiple providers are involved in the care of individuals with or at risk for T2D including primary care providers (internal medicine, family medicine), endocrinology specialists, other specialists who manage complications (e.g., cardiology, ophthalmology, nephrology, surgery, rehabilitation), nutritionists, diabetes educators, nurses, social workers.
- Academic institutions and community medical centers may offer diabetes specialty clinics which provide coordinated, comprehensive care.
- Geneticists and genetic counselors are typically not involved in the care of individuals with diabetes, other than those who have a monogenic form of the disease (e.g., Maturity Onset Diabetes of the Young). Currently, one web-based "virtual" genetics clinic, DNA Direct, offers the deCODE T2™ test directly to the public. Physicians may also order the test from deCode Genetics, Inc. in Iceland.

What are standard treatments and therapies for T2D?

- Maintaining tight control of blood glucose is important for preventing long-term complications.
- Key components of diabetes treatment include:
 - Weight management

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- Diabetic diet
- Physical activity
- Medication: oral hypoglycemics, insulin
- The Diabetes Prevention Program trials demonstrated that T2D can be prevented or delayed by lifestyle intervention (weight management, diet, and physical activity) or treatment with metformin in pre-diabetics.
- Researchers and biotechnology companies are particularly interested in developing molecular test and treatment combinations.

What are the costs associated with T2D?

Total direct and indirect costs of diabetes were \$132 billion in 2002. (NIDDK)

What is the role of genetic services in T2D?

- Family history assessment
 - Family history of diabetes may be identified during routine health care visits, though the extent to which this information is used in management or screening decisions is not clear.
 - The American Diabetes Association recommends screening for T2D in the following groups:
 - Every three years in individuals over age 45, particularly with BMI > 25 kg/m²
 - More frequently and at a younger age in individuals with a family history of diabetes in first- and second-degree relatives, high risk racial/ethnic groups, or the presence of other risk factors, particularly hypertension or hyperlipidemia.
 - Several risk assessment tools, such as the ADA diabetes risk score, are available to assess an individual's risk of T2D. Family history is a key component of these tools.
 - For those at higher risk or with symptoms of diabetes, the recommended screening and diagnostic test is a fasting plasma glucose (FPG).
 - Prediabetes=FPG 110-126
 - Diabetes=FPG >126
- Genetic testing
 - To date, genetic testing has not played a significant role in diabetes care or management other than in association with early onset T2D and in research settings.
 - In April 2007, deCODE Genetics, Inc. launched the deCODE T2™ test, a genetic test for the highest risk variant of the TCF7L2 gene.
 - A test is positive if it shows two copies (homozygous) for the high-risk gene variant.
 - The company's stated rationale for the test is that knowing one's genetic risk will motivate people to change their behavior and may suggest lifestyle or medication intervention in individuals with pre-diabetes.
 - The test has not been studied in clinical trials and is not subject to FDA regulation.

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- The test is available through a web-based retail genetics service (DNA Direct, Inc) or it may be ordered directly from deCODE Genetics in Iceland.
 - Test costs \$300
- Evidence suggests that a panel of genes may be more useful in predicting diabetes risk than a single gene test, though there are no clinically validated or commercially available genetic test panels at the current time. (Weedon, et al. 2006)
- Several online genetics companies (e.g., geneOB) offer non-specific genetic tests for diabetes risk of uncertain benefit.
- There are currently no clinical guidelines or professional statements related to the use of genetic tests for diabetes.

Are genetic services for T2D cost-effective?

- There have been no cost-effectiveness studies, nor clinical utility studies, for the deCODE T2™ genetic test.
- There have also been no cost-effectiveness studies of targeted screening for diabetes based on family history. Diabetes screening is cost-effective in individuals with cardiovascular risk factors (hypertension and hyperlipidemia), particularly in the 55-75 age group. (Cooksey, et al. 2006)

Who uses genetic services for T2D? Where are the gaps?

- Currently, there are only a few anecdotes related to use of the genetic tests for T2D. The actual number of tests performed since the new test was launched is not available. DNA Direct is conducting a non-scientific survey to gauge interest in the test. A new multi-partner study, the Multiplex Initiative, funded by the National Human Genome Research Institute, the National Cancer Institute, and the National Institutes of Health, is exploring the interest of healthy young adults in a number of genetic susceptibility tests, including one for T2D. A follow-up survey of those consenting to receive the test will gauge behavior change attributable to the testing.

Who are the major stakeholders?

- Consumers
 - High risk groups/disparities
- Advocates
 - American Diabetes Association
- Health care providers/professional associations
- Academic/research institutions
- Biotech/pharmaceutical industry
 - deCODE Genetics, Inc.
- Retail genetics
 - DNA Direct
- Government/public health
 - Centers for Disease Control and Prevention
 - State-based Diabetes Prevention and Control Programs

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- Health Resources and Services Administration
 - Health Disparities Diabetes Collaboratives
- National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), National Institutes of Health

What genetic service delivery or policy issues does this case highlight?

- Clinical issues
 - Implementation and utilization of diabetes screening programs, including family history risk assessment
 - Clinical utility/cost effectiveness of genetic tests for T2D predisposition
- Public health issues
 - Role of family history and genetic testing in population-based T2D prevention programs
- Public and private payer issues
 - Coverage of screening and prevention services
 - Diabetes Screening and Medicaid Savings Act 2007- in committee
- Legal/regulatory issues
 - FDA oversight of genetic testing
 - Regulation of direct-to-consumer marketing of genetic tests
- Biotech/pharmaceutical issues
 - Developing genetic test and medication combinations
 - Genetic risk panels
- Research issues
 - Outcomes associated with genetic testing for genetic predisposition

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News Articles

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Gene Sherpas: Personalized Medicine and You. (<http://thegenesherpa.blogspot.com>) by Steve Murphy, MD

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