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# Ethical Issues of Predictive Genetic Testing for Diabetes

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## Abstract

With the rising number of individuals affected with diabetes and the significant health care costs of treatment, the emphasis on prevention is key to controlling the health burden of this disease. Several genetic and genomic studies have identified genetic variants associated with increased risk to diabetes. As a result, commercial testing is available to predict an individual's genetic risk. Although the clinical benefits of testing have not yet been demonstrated, it is worth considering some of the ethical implications of testing for this common chronic disease. In this article, I discuss several issues that should be considered during the translation of predictive testing for diabetes, including familial implications, improvement of risk communication, implications for behavioral change and health outcomes, the Genetic Information Nondiscrimination Act, direct-to-consumer testing, and appropriate age of testing.

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## Introduction

Type 2 diabetes mellitus (T2DM) is a prevalent, chronic condition associated with extensive morbidity, decreased quality of life, and increased utilization of health services.[1] Approximately 23 million people in the United States are affected with diabetes, and more than twice that number are prediabetic.[2] The annual risk of developing T2DM for the average person living in the United States with normal glucose levels is approximately 0.7% per year.[3]

The polygenic nature of T2DM has been a major challenge to identifying genes involved in the pathogenesis of this disease—knowledge that could give rise to new treatments and tests. However, following the completion of the Human Genome Project and HapMap and the development of high-throughput technologies, scientists are in a much better position to tackle the complex genetic underpinnings of T2DM.[4] The rise of genetic and genomic studies has aligned with the increasing incidence rate of T2DM (**Figure 1**). A number of commercial tests have already been developed that assay a panel of genetic variants in several genes identified from genome-wide association studies of T2DM. Among the best studied of these are two very closely linked single nucleotide polymorphisms (SNPs) in the transcription factor 7-like 2 (*TCF7L2*) gene.[5] More than 20 studies have replicated the association between these two SNPs in *TCF7L2* and increased T2DM risk. The largest pooled analysis reported an overall odds ratio of 1.37 with a single copy of the higher-risk allele at one of the *TCF7L2* SNPs.[6] In comparison, individuals with a positive family history for T2DM are at a 2–6 times increased risk compared to those without a family history.[7–10]

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**Abbreviations:** (ASHG) American Society of Human Genetics, (GINA) Genetic Information Nondiscrimination Act, (SNP) single nucleotide polymorphism, (T2DM) type 2 diabetes mellitus, (*TCF7L2*) transcription factor 7-like 2

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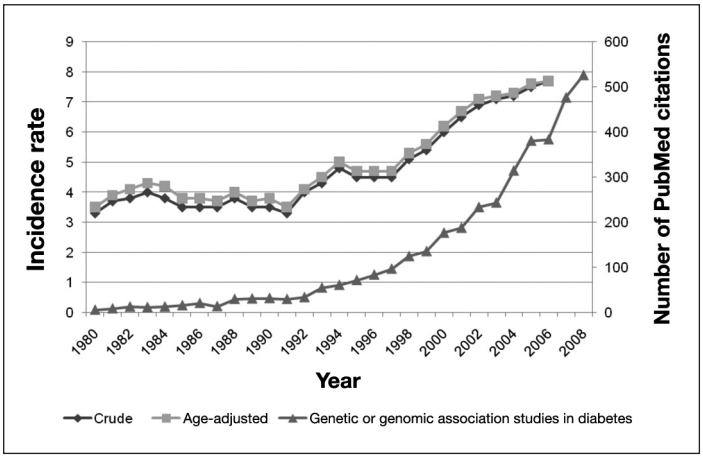


**Figure 1.** U.S. incidence rate of diabetes (1980–2006)[11] and the number of PubMed-cited genetic or genomic association studies on diabetes (1980–2008).

Unlike single-gene testing for Mendelian disorders that produce a relatively certain prediction of disease, genomic testing for complex diseases like T2DM will generate disease *risk* information. Some of the ethical issues of genome risk profiling or predispositional testing overlap with single-gene testing used primarily for diagnosis, although additional issues related to predispositional testing include challenges of communicating risk information (particularly low risks), uncertainty of disease risk and psychosocial impact of "at-risk" status, and ensuring patient comprehension. Of substantial importance is that individuals are informed about these and other issues when they are deciding if the test is appropriate for them. Although written informed consent may not be warranted, a discussion with a physician or other professional such as a genetic counselor can serve to educate and encourage careful consideration of the benefits and risks of testing as well as alternatives to testing. This article presents an overview of several issues that should be considered as genome risk profiling for T2DM becomes integrated into clinical care.

## Familial Implications

As with any type of genetic testing, it is important to consider the impact of testing on family members. Predisposition testing for T2DM and other chronic diseases raises familial implications on two levels. The implication of test results for biological family members raises the issue of whether and how to discuss the results with other family members.[12] Tested individuals may be reluctant to share the results due to fear it will disrupt relationships, be hesitant of having to contact estranged and distant family members, and feel guilt.[13–16] Those who opt to share the results with family members may have difficulty accurately communicating the results[17,18] or minimize the seriousness of the finding.[19] Although a positive test result could be inferred from changes in lifestyle and preventive medical procedures, individuals undergoing testing should ascertain the wishes of other family members prior to discussing their test results.[20] Furthermore, as many individuals choose to undergo genetic testing for the sake of their children, they will need to understand when and how best to discuss the results with their children.[21,22] Family members who decide to learn of their relative's results must also decide how they'll act upon them (e.g., getting themselves tested), if at all.

Second, given that environment can substantially influence risk for T2DM and other complex diseases, a positive result of one individual can affect the lifestyle of the entire family. For example, adoption of healthy eating habits may be better achieved if the entire family is involved in promoting healthy living.[23–26] Special treatment of a child found to be at increased genetic risk may lead to feelings of ostracism, stigmatization, and inferiority.

A related issue of the familial implications of genetic testing is the duty of physicians to disclose genetic test results to family members when their patient chooses not to do so. Studies have identified a subset of patients who declined to inform at-risk family members of their genetic test result.[27,28] In these situations, physicians may feel somewhat obligated to contact family members, although the practice is not common.[28] A handful of legal decisions have ruled that, under circumstances where a disease may be prevented, a physician has an obligation to warn relatives at risk.[29,30] Experts recommend physicians should encourage their patients to share test results with at-risk family members during the pretest and posttest counseling sessions.[31,32] The American Society of Human Genetics (ASHG) recommends that "the legal and ethical norm of patient confidentiality should be respected" and that the harms of nondisclosure must be weighed against breaching patient confidentiality.[33] It is unlikely that knowledge of the genetic risk of T2DM would satisfy the four ASHG criteria for disclosure, particularly the criterion of imminent harm.[33]

## Risk Communication

Communicating and understanding risk or probabilities has been an ongoing challenge for health professionals and patients, respectively. Misunderstanding genetic risks may lead to psychosocial harms or familial

implications and significantly impact life decisions (e.g., family planning).[34–37] Unfamiliarity with genetic concepts and terminology as well as preconceived perceptions of personal and familial risk may pose barriers to understanding genetic test results.[36] For instance, individuals with a family history of heart disease did not always perceive themselves at increased risk since they felt "different" in crucial ways from affected relatives.[38] While there appears to be a tendency to overestimate risk for inherited cancers,[39] some studies have found individuals who test positive *underestimate* their risk.[40] Furthermore, some individuals may interpret their risk as an absolute prediction of disease (fatalism), which may affect their likelihood to engage in preventive steps due to reduced perception of personal controllability to reduce disease risk.[41–43] However, this does not appear to be a typical response,[44] and often individuals will undergo genetic testing in order to *gain* a sense of control.[45,46]

To maximize patient understanding, a combination of numeric, verbal, and pictorial approaches may be warranted to effectively communicate genetic risk.[47] The personal meaning of a test result is further framed by the ethnic and cultural environments of the individual and community.[48–52] Small to moderate risks revealed by testing can also pose a challenge to communication. Some patients may struggle with the concept of being "at risk" for a disease.[53] The concept of a singular, static general population ignores the fact that societies are highly diverse with different experiential influences and attitudes that can change over time.[51,54–56] Therefore, health professionals will need to be sensitive to these additional factors that may influence patient understanding and application of risk information.

## Implications for Behavioral Change and Improved Health Outcomes

The clinical utility of T2DM risk information to prevent disease or reduce disease severity will depend on the likelihood of individuals to modify behaviors. The Diabetes Prevention Program demonstrated that an intensive program of lifestyle change (healthy eating and daily exercise) or initiation of metformin can delay diabetes onset.[57] Lifestyle changes and treatment with metformin have been shown to reduce the risk of progression of prediabetes back to baseline in individuals with an increased genetic risk, suggesting that preventive interventions in genetically at-risk individuals may prevent or delay T2DM onset.[58] However, data on the impact of genetic information for positive behavior have been conflicting, suggesting that such information may not serve as a strong motivator for behavior change.[59] For example, genetic testing was not found to motivate smoking cessation[60] but has been found to increase regular cancer screenings[43,61–64] and other positive health behaviors regardless of efficacy[65] in high-risk individuals. The relationship between family history, genetic testing, and behavioral change has also been shown to be ambiguous.[66,67]

The determination of whether knowledge of perceived health risk motivates individuals to adopt risk-reducing behaviors is a complex process involving both cognitive and emotional responses.[68–71] The motivation for behavior change has been linked to an individual's underlying perception of disease risk and disease-related worry.[70,72,73] Individuals with a higher perception of risk prior to testing have been shown to have greater intention to modify their behavior to reduce risk.[7,74] Beliefs in genetic fatalism may influence perceptions of personal controllability and ability to take action against a gene threat.[42] However, this does not appear to be a typical response,[44] and often, individuals will undergo genetic testing in order to gain a sense of control.[45,46] In addition, information-seeking behavior has been linked with health behavior with respect to establishing knowledge and as part of the coping mechanism.[75,76] Individuals who do not seek health information are less likely to take preventive actions.[77,78] Clinical studies are urgently needed to assess likelihood of behavior change based on genetic risk information compared to standard clinical risk factors, including family history.

## Discrimination

Genetic discrimination has been a long-standing concern regarding the use of genetic tests and participation in genetic research.[79–81] Although only a few cases of employment or health insurance discrimination have been documented,[79] empirical evidence suggests the occurrence may be more widespread.[82,83]

In 2008, the Genetic Information Nondiscrimination Act (GINA) was signed into law,[84,85] 13 years after the first federal bill was introduced to prohibit discrimination by health insurers or employers. Health insurers (group, individual, and Medicare issuers) are prohibited from adjusting premiums or contribution amounts, requesting or requiring an individual or a family member of an individual to undergo a genetic test, obtaining and using genetic test results in making a determination regarding payment, or requesting, requiring, or purchasing genetic information for underwriting purposes.

With some exceptions, employers are prohibited from using genetic information to discriminate against applicants or employees based on their genetic information (hiring, firing, or any personnel decisions), to "limit, segregate, or classify" employees on this basis, and to "request, require, or purchase genetic information with respect to an employee or a family member of an employee." Regulations will be developed by the appropriate federal agencies for implementation in 2009. As a majority of states have legislation prohibiting genetic discrimination by employers and health insurers, the new federal law will not preempt state laws with broader protections but rather will establish a minimum level of protection for all.

While GINA provides comprehensive protections against employment and health insurance discrimination, the law does not prohibit use of genetic information by long-term care, disability, and life insurers.[86] Given the range of complications and high mortality (seventh leading cause of death[2]) of T2DM, individuals at risk for T2DM or other chronic diseases may consider purchasing or increasing their coverage provided by these groups.[87] In addition, the health insurance protections do not apply to members of the U.S. military or individuals who receive their health care through the Department of Veterans Affairs or Indian Health Service. Patients considering genetic testing should be informed of state and federal protections and be advised of noncovered groups.

## Direct-to-Consumer Testing

Several companies offer genetic testing for a range of diseases directly to consumers without the need to obtain physician authorization. At least three companies (23andMe, Inc., deCodeMe, and Navigenics) currently provide whole genome profiling services from 10 to more than 100 diseases and traits. While direct-to-consumer testing may increase awareness of genetic testing in general and increase accessibility and convenience of testing,[88–90] the lack of involvement of a health professional may increase the potential for inappropriate testing and misinterpretation and misapplication of results.[91,92] Furthermore, consumers may experience confusion, anxiety, and possible discrimination/stigmatization, depending on the confidentiality of results.[91,93–95]

Each of these companies includes T2DM in their panel of diseases or offers stand-alone testing (deCode). However, each company tests for a different combination of genes (**Table 1**). The characteristics of test performance with respect to analytical and clinical validity (including predictive value) and clinical utility are difficult for health professionals, let alone the public, to discern and make an informed decision about the "best" test for them.

**Table 1.**
**Comparison of Genes/Variants Tested between Three Companies Providing Direct-to-Consumer Marketing Testing for Type 2 Diabetes Mellitus as a Stand-Alone Service or Part of a Genomic Risk Profile (as of Feb 2009)**

| Company | Genes/variants tested |
|---|---|
| 23andMe, Inc.[a] | *TCF7L2*, *PPARG*, *KCNJ11*, *IGF2BP2*, *HHEX*, *CDKAL1*, *SLC30A8*, *WFS1*, and *CDKN2A/B* |
| DeCode[b] | *TCF7L2*, *PPARG*, *CDKAL1*, and *CDKN2A* |
| Navigenics | *TCF7L2*, *LOC441171*, *PPARG*, *CDKAL1*, *FTO*, *CDKN2A/B*, *KCNJ11*, *IGF2BP2*, *HHEX*, *WFS1*, Chr. 11.41871942 |

[a] http://www.23andme.com (Demo)
[b] http://www.decodediagnostics.com/T2.php

Although some companies provide access to genetic counseling services by phone, the online communication of genomic risk information introduces a new means for individuals to learn of their testing results. Both genotype and risk information are included in the test report along with information about the disease, the role of genes and environment in disease risk, and links to additional resources, including the scientific literature as well as general health information. Consumers of these services may seek assistance from their health practitioner to interpret and apply the results to reduce their risk of disease.

## Appropriate Age of Testing

Many professional groups strongly discourage genetic testing for children unless immediate clinical benefit can be gained.[96–99] Based on these guidelines, predictive testing for T2DM would likely be discouraged and testing delayed until adulthood. Potential harms include the risk of stigmatization, discrimination, and other adverse psychosocial impacts. However, several commercial genetic laboratories permit testing of children,[100] providing an alternative option for parents interested in learning of their child's risks. Despite the absence of immediate clinical benefit in the prevention of T2DM, children may benefit by reducing their risk for a range of diseases from simple modifications to their lifestyle such as healthy eating and regular exercise and thereby

maintain a healthy weight at a young age. Physicians should discuss the risks and benefits of testing children for T2DM with the entire family and, when possible, obtain the assent of the child.

## Conclusion

As new predictive genetic tests for common, complex diseases such as T2DM are developed and commercialized, it will be critical to the safe and appropriate use of these new applications to consider the potential ethical implications they raise and steps to prevent or ameliorate harms. Although risk-based genetic testing for common diseases raise similar ethical issues to more traditional genetic testing for rare diseases, new challenges are raised due to the type of information revealed and access to tests. With thoughtful deliberation with health professionals, patients and families, test developers and laboratories, insurers and other stakeholders, these issues can be addressed to ensure the safe and appropriate use of these promising new clinical applications.

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