

# Genomic-based tools for the risk assessment, management, and prevention of type 2 diabetes

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**Abstract:** Type 2 diabetes (T2D) is a common and serious disorder and is a significant risk factor for the development of cardiovascular disease, neuropathy, nephropathy, retinopathy, periodontal disease, and foot ulcers and amputations. The burden of disease associated with T2D has led to an emphasis on early identification of the millions of individuals at high risk so that management and intervention strategies can be effectively implemented before disease progression begins. With increasing knowledge about the genetic basis of T2D, several genomic-based strategies have been tested for their ability to improve risk assessment, management and prevention. Genetic risk scores have been developed with the intent to more accurately identify those at risk for T2D and to potentially improve motivation and adherence to lifestyle modification programs. In addition, evidence is building that oral antihyperglycemic medications are subject to pharmacogenomic variation in a substantial number of patients, suggesting genomics may soon play a role in determining the most effective therapies. T2D is a complex disease that affects individuals differently, and risk prediction and treatment may be challenging for health care providers. Genomic approaches hold promise for their potential to improve risk prediction and tailor management for individual patients and to contribute to better health outcomes for those with T2D.

**Keywords:** diabetes, genomic, risk prediction, management

## Introduction

Type 2 diabetes (T2D) is a complex disease characterized by insulin resistance, impaired insulin secretion, and increased hepatic glucose production. It is a common disorder: more than 29 million people in the US have T2D, and nearly three times that number are at risk of developing the disease.<sup>1</sup> Risk factors for T2D include obesity, physical inactivity, advancing age, hypertension, hyperlipidemia, and a family history of T2D. Dozens of genetic variations have been identified that also increase risk.<sup>2</sup> The progression and severity of T2D in any given individual is dependent on the combination of risk factors, both genetic and nongenetic, that he or she exhibits.<sup>3</sup> Complications of T2D include cardiovascular disease, stroke, neuropathy, nephropathy, retinopathy, periodontal disease, and foot ulcers and amputations.

The serious burden of disease associated with T2D has led to an emphasis on early identification of individuals at high risk so that management and intervention strategies can be effectively implemented before disease progression has begun. Clinical factors such as body mass index (BMI; a measure of overweight and obesity), age, and family history are most often used in predicting T2D risk, and treatment strategies initially tend to be the same for most individuals. However, the complexity underlying individual

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risk, disease progression, and therapeutic response may limit the effectiveness of such standardized risk prediction and therapeutic approaches. Indeed, eight million people in the US are thought to be undiagnosed, and 86 million people in the US exhibit signs of prediabetes (blood glucose levels higher than normal but below diagnostic levels for diabetes).<sup>1</sup> In addition, most people diagnosed with T2D will eventually require more than one pharmacologic treatment to achieve glycemic control.

The identification of genetic variants that increase risk for T2D has led to the hypothesis that risk prediction and treatment could become more precise by including genomic factors in risk assessment, management, and prevention strategies. Tools using genomic information to predict those who are at risk and to tailor pharmacologic and lifestyle modification therapies have been developed and tested, with varying degrees of success and promise. This review briefly summarizes recent advancements in the application of genomics to the clinical care of T2D.

## Genetic risk factors for type 2 diabetes

A very small percentage (1%–2%) of diabetes cases, often misdiagnosed as T2D, are monogenic, resulting from mutations in a single gene. In contrast, dozens of gene variants contribute to increased risk for T2D. Rapidly advancing techniques in DNA sequencing and genetic analysis have led to the identification of more than 65 genetic variations that increase risk for T2D.<sup>4</sup> Many of these variants are thought to affect insulin secretion by impairing the function of beta cells, rather than affecting insulin action in tissues.<sup>5</sup> The majority of identified genetic variations increase T2D risk by approximately 10%–45%;<sup>3</sup> however, individuals carrying homozygous copies of certain risk alleles face much higher risk than do noncarriers. For example, risk for T2D in homozygous carriers of a variant in the gene *TBC1D4* is about ten times higher than that for noncarriers.<sup>6</sup> For comparison, risk factors such as obesity, hypertension, and hyperlipidemia increase risk by approximately two to six times.<sup>7</sup> Table 1 lists the relative risk associated with identified genetic variations, as well as that associated with other common risk factors.

The contribution of genetic factors to diabetes risk, onset, and progression is estimated to be as high as 40%, but that number is highly variable from person to person.<sup>8</sup> Research into the genetic factors that increase risk for T2D has reinforced the concept that T2D is a complex disease characterized by a unique combination of genetic variants, clinical risk factors, and behavior in each individual. In patients meeting

**Table 1** Relative risk associated with type 2 diabetes risk factors

Risk factor	Relative risk
Age $\geq 45$ years	5–6 $\times$
Obesity: body mass index $\geq 30$ kg/m <sup>2</sup>	4–5 $\times$
Overweight: body mass index $\geq 25$ , $< 30$ kg/m <sup>2</sup>	2–3 $\times$
Hypertension	2–3 $\times$
Hyperlipidemia	4 $\times$
<b>Family history</b>	
One first-degree relative or two second-degree relatives	2–3 $\times$
Two first-degree relatives, or one first-degree and two second-degree relatives	5–6 $\times$
<b>Genetic variant carrier</b>	
Heterozygous	1.1–1.4 $\times$
Homozygous	Up to 10 $\times$

**Note:** Relative risk estimates of overweight and obesity are compared with those with body mass index  $< 25$  kg/m<sup>2</sup>. Data from.<sup>3,6,7,16</sup>

the diagnostic criteria of T2D, substantial variability may exist in the genetic variants present and in the amount of risk they confer together, pathogenic mechanisms, and clinical features.<sup>3</sup> For example, patients with T2D who are younger and leaner (lower BMI or smaller waist circumference) have a stronger genetic predisposition compared with patients with T2D who are older and overweight or obese.<sup>9–11</sup> Adding complexity to the quantification of genetic contribution to risk is the notion that certain variants confer protection against T2D.<sup>12</sup> This complexity is further heightened when taking into account genetic variations that are separately associated with T2D risk factors such as obesity, hypertension, and hyperlipidemia. Thus, some portion of genetic risk for T2D is captured by measuring those clinical risk factors. Overlap exists between the genetic and other risk factors for T2D, but questions remain as to their additive effects.

## Family history as a risk factor

Family history is an established risk factor for T2D. For individuals with one or more first-degree relatives diagnosed with T2D, risk is estimated to increase by approximately two to six times.<sup>13</sup> Concordance studies in identical and fraternal twins have firmly established the genetic heritability of T2D,<sup>14</sup> but family history has the added capability of revealing both shared genetic factors and environmental factors that families tend to share, such as physical activity and dietary behaviors. Interestingly, the contribution of family history to risk is independent of that conferred by other risk factors.<sup>7,15,16</sup> For example, having one first-degree relative with T2D doubles the risk of having T2D (Table 1), even after adjusting for other risk factors that may be present, such as hypertension, hyperlipidemia, and obesity.<sup>7</sup>

The use of family history as a screening tool to detect undiagnosed diabetes and identify those who may be at increased risk has been evaluated by a number of studies,<sup>15–17</sup> one of which estimated that a risk prediction model including family history would identify 23% more undiagnosed cases of T2D than would one without family history.<sup>17</sup> Accordingly, the most commonly used risk prediction models for T2D include questions about T2D in family members.<sup>15</sup>

## Genomic applications in the risk assessment and prevention of type 2 diabetes

Risk assessment tools for T2D usually include questions about age, sex, ethnicity, hypertension, BMI or weight, family history, and a history of gestational diabetes; some include measurements of biochemical markers such as cholesterol and glucose levels.<sup>18</sup> Continued discovery of genetic variants contributing to increased risk for diabetes has led to the hypothesis that genetic information beyond that revealed by family history could enhance current risk assessment tools and improve T2D diagnosis and risk stratification.

### Genetic risk scores

Although T2D risk assessment tools based on clinical risk factors typically are quite accurate, genetic tests, both alone and in combination with clinical risk factors, have been evaluated for their ability to improve the accuracy of T2D risk prediction.<sup>18,19</sup> A number of studies have been undertaken to evaluate the ability of genetic tests to predict the development of T2D. These tests usually are designed to detect several of the genetic variants associated with T2D and include an algorithm that quantifies risk by scoring the number and type of risk alleles present and returning a “genetic risk score” (GRS). A high GRS indicates a high number of risk alleles, and therefore a high risk for T2D. Studies have shown that some GRSs can stratify patients into risk categories and accurately predict those who will develop T2D.<sup>9,20–23</sup> In a study of participants enrolled in the Diabetes Prevention Program, a high GRS was associated with increased risk of progression to diabetes and a lower probability of regressing to normal glucose regulation,<sup>20</sup> and in adolescents enrolled in the Bogalusa Heart Study, a GRS significantly predicted the development of T2D in adulthood.<sup>22</sup> Further, an association between a GRS and cardiovascular disease in patients with T2D was observed even after adjusting for other risk factors, suggesting potential utility for GRSs in predicting health outcomes.<sup>24</sup>

Despite the ability of the GRS to stratify risk and predict progression to T2D and to potentially predict cardiovascular disease, its clinical use beyond that of phenotypic-based risk prediction models is questionable. When considered along with other phenotypic markers such as blood glucose level and BMI, the GRS appears to provide very limited or no added value to prediction of T2D risk or progression.<sup>21,22,25–30</sup> Potentially promising results have been shown in subpopulations, however. In patients younger than 50 years, a GRS modestly improved risk classification even after accounting for other clinical risk factors.<sup>9,10,21</sup> Similarly, a GRS provides slightly more accurate risk prediction in individuals with a lower BMI, suggesting that assessing genetic variants, which are constant in an individual from conception, may have more clinical utility before the emergence of clinical risk factors that are acquired over time.<sup>29</sup> Conversely, a GRS slightly improved risk prediction beyond clinical risk factors in patients who are obese or who have a family history of T2D, possibly because it provided a mechanism by which to distinguish the magnitude of risk conferred by known genetic variants otherwise masked by the more prominent risk factors of obesity and family history.<sup>25</sup> However, these studies have been small, and others have not come to the same conclusions.<sup>22,25</sup> Several trials examining the potential of GRSs to improve risk prediction and prevention are currently ongoing and may provide refined information on which subpopulations would benefit from use of a GRS.

### Genetic risk scores and patient motivation

A potential of genome-based medicine is to motivate individuals to make personalized lifestyle changes that lessen their disease risk.<sup>31,32</sup> Patients report a high level of interest in genetic testing for chronic diseases such as T2D.<sup>8,33–37</sup> Genetic information carries special significance for patients because it is “scientific,” “certain,” and “durable,” which are qualities that patients may not attribute to family history and environmental risk factors.<sup>8,38–40</sup> Several studies have examined whether the provision of a T2D GRS affects motivation to make lifestyle changes. In patients at high risk for T2D based on phenotypic risk factors, those receiving a hypothetical high GRS report higher motivation to adopt healthier behaviors than those receiving a low GRS.<sup>8,37,40,41</sup> In patients with T2D, a majority report that a high GRS would lead to better medication adherence.<sup>39</sup> However, behavior change in response to genetic risk appears to be dependent on patients’ baseline motivation levels. Among individuals at increased T2D risk according to phenotypic risk factors

such as hypertension and glucose levels, those who are highly motivated report that a hypothetical high GRS would result in further inspiration and that a low GRS would not detract from their behavioral modification goals.<sup>8</sup> However, those who are less motivated report that they are more likely to use a hypothetical low GRS to justify their decision not to actively pursue lifestyle modifications.<sup>8</sup> For T2D, these results suggest that the disclosure of genetic test results should include explanations of how genetic risk can be affected by lifestyle and behavior. Studies that continue to reveal the characteristics of those patients who will derive motivation from genetic test results, along with methods of structuring the disclosure of genetic test results to optimize motivational potential, will be valuable.

## Genetic counseling and risk communication

Risk can be communicated to patients in many ways, and using terms that patients understand is important for their perception of personal risk and for promoting positive health outcomes.<sup>42</sup> Genetic counseling sessions typically involve in-depth conversations about risk and guidance about what different risk levels mean for the patient's health and the health of family members.<sup>43</sup> It has been suggested that genetic risk counseling as an accompaniment to a GRS can improve prevention efforts and better motivate patients to make lifestyle modifications. A recent study demonstrated that patients were better able to understand the results of a GRS delivered during an in-person genetic counseling session compared with results delivered online with no involvement of a genetic counselor.<sup>44</sup> In another study, receipt of a GRS followed by a structured genetic counseling session resulted in high-risk patients reporting that they were more motivated than were low-risk patients to participate in a 12 week lifestyle modification program.<sup>45</sup> However, actual attendance in the lifestyle modification program was not altered, and weight loss was not significantly different among those who received the GRS and genetic counseling compared with those who did not.<sup>45,46</sup> Short-term results from a different trial have shown small changes in dietary intake and weight loss among participants who received a GRS and genetic risk counseling compared with those who did not; longer-term results have not yet been reported.<sup>47</sup> Other trials examining different genetic counseling and health coaching approaches to effectively communicate risk with GRSs are currently underway.<sup>48–50</sup>

Genetic counseling for those with a family history of T2D has shown promising potential. In a trial of healthy adults who have more than one first-degree relative with T2D,

a brief genetic counseling session that included discussion of the seriousness of T2D, risk factors for T2D, benefits of lifestyle modification in those genetically predisposed, and guidance on specific lifestyle modifications resulted in a significantly higher sense of control over diabetes onset compared with those who did not receive counseling.<sup>51</sup> It remains to be seen whether the improved sense of control will lead to lifestyle modifications that decrease T2D risk and onset.

## Genomic applications in the management of type 2 diabetes

Although much attention and focus have been devoted to methods for identifying those at risk for T2D and preventing its onset, strategies for optimally managing those patients who have been diagnosed with T2D or identified as at risk are important as well, as complications from T2D can result in significant morbidity. Lifestyle modification consisting of a healthful diet and increase in physical activity, with the goal of reducing body weight, often in the context of a formal program led by a counselor or instructor, is recommended for nearly everyone diagnosed with T2D or at risk of developing it.<sup>52</sup> In addition, pharmacologic therapy is usually initiated in those with or at risk for T2D.<sup>52</sup> However, neither lifestyle modification nor pharmacologic therapy is effective in every patient.<sup>53–56</sup> Advances in the understanding of the genetic control of T2D are contributing to the development of management options that may be individually tailored on the basis of the patient's genotype, and may be potentially more successful.

## Pharmacogenomics of T2D therapeutics

Pharmacologic treatment of T2D is intended to lower blood glucose concentrations and maintain nearly normal hemoglobin A1c levels without inducing hypoglycemia.<sup>57</sup> Several classes of oral drugs are available to achieve such goals. The preferred first-line agent is usually metformin, a biguanide that decreases hepatic glucose production, intestinal absorption, and to a lesser extent, glucose uptake into peripheral tissues.<sup>57</sup> Second-line agents of choice tend to be sulfonylureas (eg, glipizide, glyburide) and meglitinides (eg, repaglinide, nateglinide), which directly increase insulin secretion; GLP-1 (glucagon-like peptide-1) receptor agonists such as exenatide; DPP-4 (dipeptidyl peptidase-4) inhibitors (eg, alogliptin, linagliptin); and the alpha glucosidase inhibitor acarbose.<sup>57</sup> Thiazolidinediones (eg, pioglitazone, rosiglitazone) also are available but are not commonly used because of uncertainty about their cardiovascular risk.<sup>57</sup> Most patients with T2D eventually require combination therapy, including the use of insulin products.<sup>58,59</sup>



Patient response to oral antihyperglycemia drugs can be variable and challenging to predict. No single drug exists that optimally lowers blood glucose levels in all patients,<sup>53</sup> and nearly 40% of patients do not reach desired hemoglobin A1c levels while being treated.<sup>54</sup> The variable and incomplete response to T2D drugs is thought to be partially the result of genetic variations that affect the metabolism of, and response to, the drug.<sup>60</sup> In some cases, genetic variations may result in increased effectiveness. Patients who carry variants in the gene encoding cytochrome P450 2C9 have decreased sulfonylurea clearance; in response to some sulfonylureas including glipizide, glimepiride, glyburide, and tolbutamide, larger decreases in blood glucose levels and higher 12-hour insulin secretion are observed in variant carriers compared with in patients carrying the most common allele.<sup>58,61–65</sup> In addition, carriers of certain variants in *PPAR $\gamma$* , which regulates fatty acid storage and glucose metabolism, show greater decreases in blood glucose and hemoglobin A1c levels in response to rosiglitazone and pioglitazone than do noncarriers.<sup>59,66,67</sup> Conversely, genetic variants may alter the effectiveness of a medication. For example, a small study showed that carriers of variants that reduce hepatic uptake of metformin show decreased glucose-lowering response to metformin compared with noncarriers, suggesting metformin may not be as effective in variant carriers as in noncarriers.<sup>59,68</sup> Other studies have not replicated that finding but have shown differences in the pharmacokinetics of metformin with several gene variants.<sup>69–71</sup> Another potential effect of genetic variants is adverse events. For example, carriers of variants that result in glucose 6-phosphate dehydrogenase (G6PD) deficiency are at risk for hemolytic anemia when taking certain sulfonylureas. Accordingly, the labels of glipizide, glyburide, and chlorpropamide note that prescribers should consider a nonsulfonylurea in G6PD-deficient patients.<sup>72–74</sup> For the most part, studies on the pharmacogenomics of antihyperglycemic agents have been small, and their results have not yet translated into changes in clinical practice. Nonetheless, they demonstrate the concept that significant variability in patient response to T2D therapeutic agents is a result of genetic variation and reinforce the complexity of choosing the most effective therapies for individual patients.

## Genomic predictors of effective intervention strategies

Almost all patients diagnosed with and at risk for T2D are encouraged to engage in lifestyle modification that includes improvements in diet and increases in physical activity, with the goal of reducing weight and other risk factors such

as hypertension and hyperlipidemia. Although lifestyle modification programs are quite successful when taken as a whole, certain approaches appear to be more successful in some patients than in others.<sup>55,56</sup> Exploration into the genetic factors that might explain which lifestyle modification behaviors are most likely to reduce T2D risk factors for each patient has been undertaken. For example, in patients with T2D who carry a homozygous *TCF7L2* variant, blood glucose and lipid levels were lower and stroke risk was attenuated with strict adherence to the Mediterranean diet compared with strict adherence to a low-fat diet.<sup>75</sup> The two diets were equally effective in noncarriers of the *TCF7L2* variant.<sup>75</sup> Similarly, in diabetic carriers of certain genetic variants affecting lipid levels, high-density lipoprotein cholesterol levels were increased more after an intensive lifestyle intervention that included caloric restriction and physical activity compared with an intervention that included only diabetes education; noncarriers of the variants did not show such differences in high-density lipoprotein levels in response to either intervention.<sup>76</sup> In a third trial, patients with prediabetes carrying certain variants associated with obesity showed differences in weight loss and weight regain in response to both metformin and lifestyle interventions compared with noncarriers.<sup>77</sup> These examples suggest that patient response to lifestyle modification may be partly controlled by the variants they carry and that interventions may be most effective when tailored to individuals according to their genotype. An additional important point demonstrated by these examples is that genetic risk often can be attenuated by effective interventions.<sup>20,78</sup>

## Conclusion and future directions

Genetic factors play a substantial role in the risk, onset, severity, and downstream complications of T2D. Overall, current knowledge about the contribution of genomic factors to T2D reinforces the concept that T2D is a complex disease that can be different in every person and that risk prediction and treatment are exceptionally challenging for health professionals. Evidence thus far shows variable clinical utility of GRSs, although certain subpopulations may benefit from their use in the near future, and forthcoming research may improve their utility. In addition, important information is being revealed about the genetic basis for differential therapeutic responses to oral antihyperglycemic drugs and to intervention strategies. Although clinical practice guidelines employing genomic approaches to T2D management and prevention do not yet exist, health professionals should be aware that pharmacogenomic factors may result in varying

responses to pharmacologic therapy and that the degree of success of weight reduction through lifestyle modification may be partially dependent on genetic factors.

Genomic analysis in clinical care is rapidly advancing, especially with the use of next-generation sequencing technologies and whole-genome sequencing.<sup>79</sup> A small number of studies have employed whole-genome sequencing in healthy patients as a mechanism to identify risk for future disease onset, and two studies have demonstrated the capability of predicting risk for T2D and other chronic diseases.<sup>80,81</sup> Although the routine clinical use of whole-genome sequencing in patients who appear healthy and asymptomatic is not likely to occur for several years, the studies nonetheless demonstrate the power of the technology and potential future uses. In addition, epigenetic mechanisms such as methylation and histone modification, which often arise as a result of environmental exposures, have recently been examined for their involvement in T2D pathogenesis. Although direct evidence establishing a causal relationship between epigenetic modification and risk for T2D is not yet available, observational and animal studies have suggested that epigenetic alterations in gene expression may play a role. When and if a causal relationship is established, it may be possible to use epigenetic modifications as biomarkers to predict those who may be at increased risk.<sup>82,83</sup> Considering the significantly variable nature of T2D, both in the genetic and environmental risk factors and in the clinical presentation, the most immediate use of genetic information is likely to be in the characterization of individual cases of T2D, with the goal of improving each patient's outcomes, motivation for long-term lifestyle modification, and therapeutic response.

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