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# Personalized medicine in diabetes mellitus: current opportunities and future prospects

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## Abstract

Diabetes mellitus affects approximately 382 million individuals worldwide and is a leading cause of morbidity and mortality. Over 40 and nearly 80 genetic loci influencing susceptibility to type 1 and type 2 diabetes, respectively, have been identified. Additionally, there is emerging evidence that some genetic variants help to predict response to treatment. Other variants confer apparent protection from diabetes or its complications and may lead to development of novel treatment approaches. Currently, there is clear clinical utility to genetic testing to find the at least 1% of diabetic individuals who have monogenic diabetes (e.g., maturity onset diabetes of the young and $K^{ATP}$ channel neonatal diabetes). Diagnosing many of these currently underdiagnosed types of diabetes enables personalized treatment, resulting in improved and less invasive glucose control, better prediction of prognosis, and enhanced familial risk assessment. Efforts to enhance the rate of detection, diagnosis, and personalized treatment of individuals with monogenic diabetes should set the stage for effective clinical translation of current genetic, pharmacogenetic, and pharmacogenomic research of more complex forms of diabetes.

### Keywords

monogenic diabetes; type 2 diabetes; pharmacogenetics, gene–environment interaction; pharmacogenomics

## Introduction

Currently, there are 382 million people living with diabetes mellitus around the world, and the total number is predicted to increase by over 50% over the next 20 years. Diabetes mellitus is a spectrum of metabolic disorders characterized by hyperglycemia. Poorly controlled diabetes mellitus can lead to microvascular and macrovascular complications, including kidney failure, blindness, amputation, and cardiovascular disease. Fortunately, medical advances have increased the number of treatment options for diabetes and improved outcomes for many individuals. However, there remains a need to determine the appropriate therapy for each individual, since a significant number of monotherapy treatments fail

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within 3 years and diabetes-related morbidity and mortality continue.[1,2] Additionally, inappropriate therapies can subject patients to increased risk of hypoglycemic events. Personalizing diabetes treatment based on patient genetics can improve patient care by decreasing the number of therapy failures and reducing the complications associated with diabetes mellitus.

Currently, there is little widespread implementation of personalized medicine in diabetes mellitus treatment. Diabetes mellitus encompasses a range of hyperglycemic conditions, which the American Diabetes Association (ADA) divides into four categories. The first category, type 1 diabetes mellitus (T1DM), is classified as an autoimmune disease with progressive β cell destruction, leading to polyuria, polydipsia, weight loss, and hyperglycemia. Individuals with type 1 diabetes eventually become completely reliant on non-endogenous insulin.[3] In the case of true type 1 diabetes, glucose levels must be closely monitored and insulin levels individualized to maintain glucose homeostasis. It could be said that making a proper diagnosis of type 1 diabetes, including obtaining clear evidence of β cell destruction through the presence of auto-islet antibodies, and then prescribing endogenous insulin, represents a form of well-established personalized medicine that will not be discussed further in this review. There is also emerging evidence that oral medications including those used to treat type 2 diabetes may be effective adjunct therapies for individuals with insulin-requiring type 1 diabetes.[4] Thus, some of the findings discussed in this review may ultimately have relevance for type 1 diabetes. Finally, there are some 40 genes implicated in the complex etiology of type 1 diabetes, with currently unknown practical clinical implications.[5]

Most diabetes is classified in the second category, type 2 diabetes mellitus (T2DM), a heterogeneous group of disorders caused by some combination of insulin resistance and impairment of insulin secretion.[6] T2DM has a range of risk factors, etiologies, and clinical presentations. Progress has been made in understanding the genetic etiology of T2DM, with nearly 80 susceptibility loci identified,[7] but the use of molecular testing to customize treatment is not yet possible. Other risk factors (many of which themselves are partially influenced by genetics) include obesity, low activity, and poor diet, sometimes referred to as lifestyle or environmental risk factors. As the knowledge base increases, the ideal implementation would use genetic testing and variant analysis to help clarify the etiology of T2DM, the appropriate therapy for the patient, and, possibly, susceptibility testing for at-risk relatives and members of the general population. Future genetic testing may help to identify which patients with diabetes and prediabetes (elevated glucose not in the diabetic range) may benefit from specific lifestyle interventions and which may need pharmaceutical treatment as an adjunct to a healthy lifestyle. Results of studies examining genetic influences on response to both behavioral and pharmaceutical interventions to prevent, delay, or treat diabetes will be examined in this review.

A third category of diabetes encompasses forms with specific known genetic and non-genetic etiologies, including the at least 1% of all diabetes cases which are caused by a defect in a single gene. These varieties of monogenic diabetes are highly penetrant and often have similar clinical presentations to T1DM or T2DM. Monogenic forms of diabetes mellitus are the low-hanging fruit in which genetic testing has already proven the ability to

improve treatment,[8] but they are currently underdiagnosed. Clinical implementations for genetic diagnosis and treatment of monogenic diabetes can provide a template for translating genetic findings of T2DM into clinical practice in the future, and will be discussed in that context. The fourth category of diabetes, gestational diabetes, may have etiology in common with other types of diabetes and represent expression of underlying susceptibility enabled by pregnancy-induced insulin resistance.[9]

There is still a great deal of progress to be made in the field of personalized diabetes mellitus therapy. This review will focus on the current opportunities for implementations of genetically personalized medicine in diabetes mellitus, specifically monogenic diabetes, as well as the state of current research and potential prospects for future implementation in T2DM.

## Monogenic diabetes mellitus: current implementation of personalized medicine

Some forms of monogenic diabetes already present the opportunity for implementation of personalized medicine. The most well-known and well-studied form of monogenic diabetes is maturity-onset diabetes of the young (MODY). There are currently 13 different types of MODY, classified by the dysfunctional gene causing the phenotype. MODY, by its classical definition, presents in lean individuals before the age of 25 and is inherited in an autosomal dominant manner while the patient still has signs of pancreatic β cell function.[10] Epidemiological studies conducted since MODY was initially defined suggest that the original criteria do not capture all cases.[11] It is predicted that MODY makes up 1–2% of diabetes mellitus cases.[12] However, because the presentation contains characteristics of both type 1 (early onset, lean body type) and type 2 (family history of diabetes, maintained pancreatic β cell function), it is often misdiagnosed. Misdiagnosis is especially troubling because the most prevalent types of MODY have specific pharmacogenetic recommendations based on the gene etiology.

MODY3 is the most common form of MODY, comprising 52% of cases in the well-characterized United Kingdom,[12] though prevalence varies by ethnicity and geographic region. It is caused by a mutation in *HNF1A*, which encodes the transcription factor hepatic nuclear factor 1-α (HNF1-α), which promotes transcription of multiple genes related to glucose metabolism, insulin secretion, and insulin production. HNF1-α has 55% amino acid similarity with hepatic nuclear factor 4-α (HNF4-α), which is mutated in MODY1. MODY1 makes up about 10% of MODY cases in the United Kingdom.[12] HNF1-α and HNF4-α have also been shown to interact with each other in an epistatic manner.[13] Diagnosis of MODY1 or MODY3 is important for proper clinical therapy because those patients have been found to be hypersensitive to sulfonylureas.[8,14,15] This hypersensitivity is due to decreased expression of HNF1-α and HNF4-α target genes in the liver, which leads to decreased uptake of sulfonylureas, resulting in sustained increased circulating levels of sulfonylureas.[16] As a result, MODY1 and MODY3 patients need approximately one-tenth of the sulfonylurea dose, although this varies depending on the patient. The high sensitivity to sulfonylureas makes them a first-line treatment for MODY1 and MODY3.[10] Patients with these two types of MODY remain insulin-sensitive, since the genetic etiology causes

dysfunction of pancreatic β cells. It has been demonstrated that genetic diagnosis of MODY1 followed by switching of treatment from insulin to sulfonylureas improved glycemic control as measured by %HbA1c.[8]

Another common cause of MODY is mutation in *GCK*, which encodes the enzyme glucokinase, causing MODY2.[17] MODY2 makes up 32% of MODY diagnoses in the United Kingdom.[12] The damaging *GCK* mutations cause decreased function in the glucokinase enzyme, which is crucial for pancreatic β cell monitoring of blood glucose levels. As a result, MODY2 patients present with mild hyperglycemia. Interestingly, MODY2 patients generally do not progress to the microvascular and macrovascular complications associated with diabetes mellitus at a rate greater than non-diabetic populations. As a result, MODY2 patients do not need pharmaceutical therapy.[18] However, some evidence has shown that the mild hyperglycemia can lead to insulin resistance,[19] and gestational diabetes mellitus is frequent among *GCK* mutation carriers.[20,21] In particular, the carrier status of *GCK* mutations of the mother and fetus appears important for ideal glycemic control during pregnancy, given that maternal GCK mutations can lead to high birth weight and, conversely, fetal *GCK* mutations can restrict birthweight.[22]

Another type of actionable monogenic diabetes is neonatal diabetes mellitus (NDM). NDM is diagnosed within the first 6 months of life in a transient or permanent form, which can have a number of gene etiologies including, *KCNJ11*, *ABCC8*, *GCK*, *INS*, *ZFP57* and chromosome 6q24 paternal duplication or hypomethylation, as well as several others, such as *EIF2AK3* and *PTF1A*, that cause syndromic forms. NDM is most commonly caused by activating mutations in *KCNJ11* or *ABCC8*, the two genes encoding the subunits that make up the ATP-sensitive potassium channel in pancreatic β cells. These mutations prevent membrane depolarization in response to a decreased ATP:ADP ratio, resulting in decreased insulin secretion.[23] Most patients with these mutations can be treated successfully with high-dose sulfonylureas instead of the insulin that is the default treatment for neonatal diabetes and is more expensive, more invasive, less effective, and places individuals with these mutations at a greater risk for hypoglycemic episodes.[24–26] Sulfonylureas close the same channels that become constitutively open owing to NDM mutations.

These cases demonstrate the value of a proper diagnosis of monogenic forms of diabetes. In the SEARCH for Diabetes in Youth study, it was discovered that 47 study participants (8.0% of those who did not have type 1–related antibodies and had endogenous insulin production as measured by C-peptide) had mutations in one of the three most common MODY genes, although only three of those individuals had a MODY diagnosis before the study.[27] Consequently, 79% of MODY patients were on suboptimal treatment rather than the treatment indicated by their diagnosis. The advent and advances of next-generation sequencing techniques have provided the opportunity for accurate diagnoses of these genetic disorders. Multiple studies have demonstrated the capabilities of different sequencing platforms to accurately detect pathogenic variants.[28,29] Before next-generation sequencing, most monogenic diabetes studies focused on the prevalence and characteristics of MODY1, MODY2, and MODY3. Although this method covers the majority of monogenic diabetes cases, it does not address the prevalence or characteristics of less common forms of monogenic diabetes. Besides MODY and NDM caused by less-common genetic etiologies,

there are also many other syndromic and non-syndromic forms of diabetes with monogenic etiologies.

Identifying individuals who can benefit from genetic testing for monogenic diabetes is challenging, owing to clinical overlap with other types of diabetes, incomplete knowledge of the full phenotypic spectrum of monogenic diabetes, and the lack of a standard accepted screening and diagnostic algorithm. Other challenges to patients receiving an accurate diagnosis are the expense of testing and lack of awareness of many providers. The American Diabetes Association recommends that genetic testing for monogenic diabetes be considered in children in four situations: (1) diabetes diagnosed in the first 6 months of life; (2) strong family history of diabetes without risk factors for type 2 diabetes (obesity, certain ethnicities); (3) mild fasting hyperglycemia (100–150 mg/dl), especially without obesity; and (4) diabetes without autoantibodies, obesity, or insulin resistance.[6] These criteria are not all straightforward to apply in practice and are likely too narrow because, for example, it is possible for monogenic diabetes to coexist with obesity, especially where obesity prevalence is high.

Multiple diagnostic algorithms have been proposed to accurately predict the presence of monogenic diabetes.[30–32] Two centers with extensive experience in the diagnosis and treatment of monogenic diabetes provide criteria for consideration of a monogenic diabetes diagnosis on their websites: the University of Exeter Medical School (diabetesgenes.org, which includes a link to the current International Society of Pediatric and Adolescent Diabetes (ISPAD) guidelines, which are cited by the ADA and are more extensive), and the University of Chicago Kovler Diabetes Center (http://monogenicdiabetes.uchicago.edu/). One of the authors of this paper (TIP), with colleagues, published a review and a suggested algorithm for utilizing genetic family history session to detect potential cases of monogenic diabetes.[33]

Genetic testing for monogenic diabetes should be performed using a Clinical Laboratory Improvement Amendments (CLIA)-certified laboratory to assure proper regulations and quality control metrics are observed. There are multiple testing centers available in the online databases available at Genetests (www.genetests.org) and the Genetic Testing Registry (http://www.ncbi.nlm.nih.gov/gtr/). Upon receipt of genetic results, the requesting physician should ensure proper result interpretation by consulting with experts in the field of monogenic diabetes.[34] The most well-established treatment changes that can result from a genetic diagnosis are high-dose sulfonylureas rather than insulin for *KCNJ11*/*ABCC8*-related diabetes (usually neonatal),[26] low-dose sulfonylureas rather than insulin (especially at early stages) for MODY1 (*HNF4A*) and MODY3 (*HNF1A*), and no treatment for MODY2 (*GCK*).[34] An exciting new progression in testing for diabetes is the incorporation of next-generation sequencing. Next-generation sequencing allows multiple genes to be sequenced in a single assay in a cost-effective manner and should provide more information about a broader range of gene etiologies of monogenic diabetes. This will hopefully provide insights into clinical indications for other forms of monogenic diabetes.

The University of Maryland Center for Diabetes and Endocrinology is implementing a Personalized Diabetes Medicine Program (PDMP) comprising a simple screening process

followed by next-generation sequencing using a multi-gene panel to find and diagnose patients with monogenic diabetes, an effort led by one of the authors of this paper (TIP) and being evaluated and disseminated as part of the National Human Genome Research Institute (NHGRI)-funded Implementing Genomics in Practice (IGNITE) Network (ignite-genomics.org). Patients referred by providers or screening positive on the questionnaire with one of the following profiles are selected for further evaluation: (1) diabetes diagnosed at < 1 year of age; (2) diagnosed with T1DM and having a parent or child with T1DM; (3) diagnosed with T2DM at <30 years old; (4) diagnosed with T2DM at < 45 years of age and two or more first- or second-degree relatives diagnosed at < 50 years of age, or (5) presence of diabetes plus an extrapancreatic feature that may be indicative of a syndrome. Further evaluation using a combination of laboratory testing (C-peptide and IA-2 antibodies[35,36]) and family and medical history elicited by a genetic counselor is used to determine eligibility for testing using a 40-gene next-generation sequencing panel. Variants detected by the sequencing panel are confirmed clinically, and a report is generated and incorporated into the electronic medical record. Guidance is provided to clinicians regarding treatment implications, and participants are encouraged to share results and opportunities to be counseled and tested with at-risk family members. [33]

## Pharmacogenetics of oral T2DM medications

Individuals with type 2 diabetes make up by far the greatest proportion of the population with diabetes mellitus. The first-line medication for T2DM is metformin, a biguanide medication that functions by decreasing gluconeogenesis in the liver. Secondary oral medications include sulfonylureas, meglitinides, thiazolidinediones, glucose-like peptide-1 (GLP-1) analogs, and dipeptidyl peptidase-4 (DPP4) inhibitors.[37] Each of these medication classes has a different mechanism of action and different molecular interactions, and consequently, different genetic variants that affect function. Studies of the genetic variants that can alter response to oral diabetes medications have generally shown modest effects, some of which are contradictory. Regardless, these studies represent findings that could provide information about future pharmacogenetic recommendations for oral T2DM medications. The etiology-specific treatment recommendations for monogenic diabetes provide a current model of genetic diagnosis to pharmacological treatment that can be used for future implementation of pharmacogenetic findings into clinical recommendations. However, before any of these genetic associations can be implemented into clinical practice, further studies need to be performed to analyze the effectiveness of a priori genetic testing on the patient outcomes.

### Metformin

Metformin is the first-line medication for T2DM because of its safety profile as an insulin-sensitizing agent. However, it has a high variability of efficacy between patients, and it often needs to be supplemented with secondary agents. Metformin's mechanism of action has not been well defined, and therefore its target molecules have not been analyzed for important pharmacogenetic variants. However, a large-scale genome-wide association study (GWAS) discovered that single nucleotide polymorphism (SNP) rs11212617 near the *ATM* locus was associated with reduction in HbA1c in response to metformin.[38] *ATM* encodes the ataxia-

telangiectasia mutated gene, a member of the phosphatidylinositol 3-kinase family important for cell cycle control and DNA repair. In a meta-analysis replication of this study, the association was confirmed, although one of the three cohorts showed no association.[39] Finally, the Diabetes Prevention Program (DPP) found that there was no association between rs11212617 and progression from impaired glucose tolerance to diabetes.[40] This SNP needs further confirmation and exploration for validation and future studies into metformin's mechanism of action.

On the other hand, metformin's transport between cell types has been well characterized. Metformin is actively transported between tissues, but it is not metabolized before excretion. It is absorbed into the intestinal epithelium through the plasma membrane monoamine transporter (PMAT encoded by *SLC29A4*) and the organic cation transporter 3 (OCT3 encoded by *SLC22A3*). Organic cation transporter 1 (OCT1) transports the metformin through the basolateral membrane of the epithelium to the bloodstream, and OCT1 is also responsible for uptake into hepatocytes. Metformin is transported from the bloodstream into the renal epithelium through organic cation transporter 2 (OCT2 encoded by *SLC22A2*). From there, metformin is excreted into the urine through the multidrug and toxin extrusion proteins 1 and 2 (MATE1 and MATE2 encoded by *SLC47A1* and *SLC47A2*).[41] These transporters have provided targets for genetic analysis.

The OCT1 gene (*SLC22A1*) has multiple genetic variants that are associated with decreased efficacy of metformin. The variants R61C (rs12208357), G401S (rs34130495), G456R (rs34059508), and 420del (rs72552763) have all been shown to decrease the effectiveness of metformin, as well as to increase renal clearance, in multiple studies.[42–45] However, another study discovered no effects due to the R61C and 420del variants.[45] The DPP discovered another *SLC22A1* polymorphism (rs683369 encoding L160F) that affected metformin efficacy. The major allele of this variant was associated with a 31% risk reduction in diabetes incidence in metformin-treated participants, but not in those treated with placebo.[46] Variants in *SLC47A1* have demonstrated an enhancing effect of metformin treatment. Two variants, rs2289669 and rs8065082, in linkage disequilibrium with each other, were separately found to produce these effects. An association between rs2289669 and decreased level of HbA1c in metformin users was initially observed in a pilot study.[47] In another finding by the DPP, rs8065082 was associated with decreased incidence of T2DM in the metformin arm but not the placebo arm, validating the study by Becker *et al*.[46] With further validation, these genetic variants associated with metformin response could be used to predict the efficacy of metformin treatment in patients before they take the drug.

## Sulfonylureas

Sulfonylureas are insulin secretagogues that act by binding the SUR1 subunit (encoded by *ABCC8*) to close the ATP-sensitive potassium inward-rectifying channel, causing membrane depolarization followed by calcium influx and insulin secretion. The other subunit of the $K^{ATP}$ channel is Kir6.2 (encoded by *KCNJ11*), which is located within close proximity to *ABCC8* on chromosome 11.[48] High-dose sulfonylureas are used to treat NDM caused by activating mutations in *ABCC8* and *KCNJ11 (*and low-dose sulfonylureas are the first-line treatment for MODY1 and MODY3). Studies of polymorphisms of these genes have

discovered a common haplotype of E23K in *KCNJ11* and S1369A in *ABCC8*, which is associated with T2DM.[49] This haplotype has been shown to be less sensitive to sulfonylurea inhibition through patch-clamp analysis.[50] Separately, both the E23K and S1369A polymorphisms have disputed associations with T2DM and sulfonylurea efficacy.[51,52] Other genes have also been associated with response to sulfonylureas. *TCF7L2*, the gene with the strongest association with T2DM, encodes transcription factor Tcf-4, which plays a role in cell proliferation through the Wnt signaling pathway. The GoDARTs study found that TT individuals at rs12255372 of *TCF7L2* were less likely to respond to sulfonylurea therapy than their GG counterparts.[53] Likewise, carriers of the common rs1801278 variant in insulin receptor substrate-1 (IRS-1) have an increased rate of secondary failure to sulfonylureas in addition to the general increased risk of T2DM associated with the polymorphism.[54] These genetic variations could affect the pharmacological regimens for individuals known to be carriers.

In addition to the effects of genetic variants on target genes, variation in the enzymes responsible for sulfonylurea metabolism also affect drug efficacy. *CYP2C9* is the major metabolizer of the drug class. Two polymorphisms, *CYP2C9*2* (I359L) and *CYP2C9*3* (R114C) are associated with increased serum sulfonylurea levels.[55] There is a risk of hypoglycemia in carriers of the *CYP2C9*3* polymorphism, although studies have also shown that carriers have an increased capability to reach target HbA1c levels.[56] By having knowledge of *CYP2C9* polymorphisms, it may be possible to preemptively adjust sulfonylurea dosage to avoid hypoglycemic events while still maintaining the effectiveness of the medication.

## Meglitinides

Meglitinides are another class of insulin secretagogues that also act by inhibiting the $K^{ATP}$ channel to induce depolarization and insulin secretion. However, these medications act in a much shorter timeframe than sulfonylureas and consequently confer less risk of hypoglycemia. Meglitinides are rapidly metabolized by the liver.[57] The transporter SLCO1B1 is responsible for uptake into the liver, and the c.521T>C polymorphism has been shown to decrease the rate of metabolism of meglitinides, but the altered pharmacokinetics have little physiological effect on glucose levels.[58,59] Another gene, *KCNQ1*, contains intronic variant rs2237892 associated with repaglinide response. The individuals carrying a TT phenotype showed improved HOMA-IR and 2-hour glucose response to 48-week repaglinide therapy, although this effect was lost when accounting for age, gender, and body mass index.[60] Meglitinide metabolism differs between repaglinide (by CYP2C8 and CYP3A4) and nateglinide (by CYP2C9). Although genetic variants in these metabolizing enzymes may alter pharmacokinetics of the medications, it does not appear to have major effects on the glucose levels of patients.[61,62]

## Thiazolidinediones

Thiazolidinediones (TZDs) are PPAR (peroxisome proliferator–activating receptor) activators that act by improving insulin sensitivity and decreasing hyperglycemia by decreasing circulating free fatty acids. Troglitazone was withdrawn from the market due to hepatotoxicity, but pioglitazone and rosiglitazone are still available.[63] However, these

medications have associated drug-specific increased risks of fluid retention, heart failure, or bladder cancer,[64,65] indicating they should be prescribed with caution and careful examination of the risk/benefit ratio. Individual genotype information may be of great benefit for this examination, and genetic variants that predispose individuals to these side effects have already been discovered. The rs296766 T allele of *AQP2* (aquaporin 2) and the rs12904216 G allele of *SLC12A1* (sodium/potassium/chloride transporter) are both associated with edema in patients taking rosiglitazone.[66] Regarding the efficacy of TZDs, the well-studied P12A variant in PPAR-γ has been associated with decreased fasting blood glucose and decreased HbA1c in response to rosiglitazone.[67] Additionally, carriers of the A allele of rs6467136 in *PAX4* showed improved response to rosiglitazone.[68] This is significant because *PAX4* has been associated with T2D through GWAS, and mutations in the gene can cause MODY type 9. These are also studies indicating that the *3 variant of *CYP2C8*, the major metabolizer of TZDs, has decreased insulin response, but these studies have generally been underpowered.[69]

### GLP-1 analogs/DPP4 inhibitors

The newest class of oral antidiabetic medications act through the incretin signaling pathway. These medications include GLP-1 analogs that act as incretin mimetics and DPP4 inhibitors that stop the degradation of endogenous GLP-1 and gastric inhibitory peptide (GIP). Promoting incretin signaling induces insulin secretion, inhibits glucagon secretion, reduces gastric emptying, and decreases appetite.[70] Because these medications have been approved for less than 10 years, there have been relatively few studies on the pharmacogenetics of incretin mimetics. However, a study in non-diabetic individuals found that SNP rs7202877 regulates expression of the *CTRB1* and *CTRB2* genes for chymotrypsin, an important regulator of the incretin pathway.[71] There is still a great need for further exploration of pharmacogenetics of these new medications.

### SLC30A8 *and zinc supplementation*

An intriguing potential opportunity for translation of T2DM association data to pharmacogenetic applications is the SNP rs13266634 (R325W) in zinc transporter-8 (encoded by *SLC30A8*). The zinc transporter was first associated with T1DM as an autoimmunity antigen. Through candidate assays, it was discovered to also confer risk for T2DM, which has since been verified through multiple studies.[72] Other studies have found that rs13266634 may confer its risk through gene–environment interactions with decreased serum levels of trans-β-carotene.[73] However, a recent clinical trial has shown that individuals carrying the variant could improve insulin response to glucose with daily zinc supplementation for as little as 14 days.[74] Interestingly, loss-of-function variants in *SLC30A8* have protective effects from T2DM.[75] Overall, *SLC30A8* represents an appealing, albeit complex, target for pharmacogenetic-directed therapy to reduce risk from disease-associated variants.

## Opportunities for Pharmacogenomics

Besides the pharmacogenetic studies determining how drug function is affected by genetic variants, a complex disease like T2DM presents the opportunity to utilize

pharmacogenomics for development of novel pharmacologic therapies. In particular, rare genetic variants can provide information about the protective or disease state physiology. The discovery that nonsense mutations in *SLC30A8* are protective against T2DM is an example of a pharmacogenomic finding that could be utilized for pharmaceutical development.[75] By targeting *SLC30A8* for downregulation therapeutically, it could confer the T2DM-protective effects of nonsense variants. *APOC3* nonsense variant R19X is another example of a genetic variant that could lead to future diabetes treatment methods. The nonsense variant decreases circulating levels of APOC3, leading to decreased levels of serum triglycerides and protection from coronary disease.[76,77] As a result, *APOC3* has become a target for pharmaceutical inhibition in order to prevent hypertriglyceridemia. Since hypertriglyceridemia is common complication of diabetes and a risk factor for coronary heart disease, this could a rewarding direction for diabetes drug development.[78] These are just a couple examples of how pharmacogenomics can be important for developing diabetes pharmacotherapeutics.

The studies presented here represent the beginning phase of personalized diabetes treatment. In contrast to the current opportunity for personalized medicine in treatment of monogenic diabetes, the field of personalized diabetes therapeutics for T2DM still needs to mature greatly before clinical implementation is possible. Currently observed pharmacogenetic associations are promising but require expansion made possible by falling costs of large-scale genotyping and sequencing and replication in well-designed clinical trials. Meanwhile, expanding implementation of the available opportunities for clinical implementation in monogenic diabetes will provide a model for future implementation of personalized T2DM medicine.

## Genetic interaction with lifestyle factors

Gene–environment interaction is the interplay of genetic factors and non-genetic factors to influence a phenotypic outcome. The pharmaceutical interventions discussed previously are an example of a non-genetic factor in such an interaction, but another important issue in the field of diabetes mellitus is the relationship between diabetes-associated genetic variants and lifestyle. Alteration of lifestyle through diet and exercise change is the first preventive measure against diabetes onset.[37] Some are able to stop the progression toward diabetes, while others progress despite changing their lifestyle. It would be a powerful tool to determine if genetic risk variants maintain their associations despite environmental changes and which ones have altered risk associations due to non-genetic factors. Similarly, gene–environment interaction studies could be used to determine the most effective type of lifestyle change based on an individual’s profile of genetic risk variants. Some studies have already begun to perform these analyses, as they examined at-risk individuals in their progression toward T2DM.

One of the leading studies for measuring gene–environment interactions is the DPP. This large multicenter trial studied whether lifestyle modification or metformin therapy was able to prevent progression to T2DM in individuals with risk factors for the disease. One of the primary discoveries determined that the environment altered the association with T2DM of the rs12255372 and rs7903146 SNPs in strong linkage disequilibrium in the *TCF7L2* locus.

It was shown that the risk alleles conferred a stronger effect in the placebo group than in either the metformin-treated group or the lifestyle-intervention group.[79] This provided evidence that the genetic predisposition for T2DM could effectively be decreased through either type of therapy, particularly lifestyle changes. Additionally, the DPP observed nominally differential improvement of β cell function due to troglitazone therapy or lifestyle changes based on the presence of the protective rs10811661 SNP in the *CDKN2A/B* locus.[80] The DPP study is unique in that it provided large enough sample sizes to have the power to detect gene–environment interactions in a prospective study that incorporated lifestyle intervention.

The Finnish Diabetes Prevention Study (DPS), although not as large as the DPP, was also able to determine interactions between genetics and environment in progression toward T2DM. They showed that lower levels of moderate-to-vigorous physical activity in individuals homozygous for common SNPs in *SLC2A2* (rs5393, rs5394, or rs5404) or *ABCC8* (rs3758947) were 2.6–3.7 times more likely to progress from impaired glucose tolerance to T2DM. The DPS also discovered complex interplay of the *ADRA2B* polymorphism 12Glu9. They found that carriers of the 12Glu polymorphism had decreased risk of T2DM in response to increased leisure-time physical activity. However, homozygous 9Glu9 individuals had greater risk reduction due to dietary changes.[81] These interesting and intricate results illustrate the complexity of gene–environment interactions.

Gene–environment interactions hold a great deal of promise for explaining more of the heritability of diabetes mellitus. However, strong studies focusing on this topic have not been aggressively pursued. This is likely due to the fact that most studies would be underpowered because of the stratification of sample size by addition of another variable and multiple hypothesis–testing correction. On top of the difficulty of attaining sufficient power, it is also extremely difficult to validate findings through replication in different cohorts because of the difficulty of recreating the same gene–environment interaction. Finally, confounders and bias are widespread in attempts to collect large populations with measured environmental contact, which can create false-positive results. Despite these challenges, the field is moving forward with techniques such as joint meta-analysis, selective sampling, and nested case-cohort studies. These topics are further explored in excellent review articles.[82,83]

## Future prospective

Well-characterized forms of monogenic diabetes already present underutilized opportunities for personalized medicine. A complex disease such as T2DM presents challenges in implementation of personalized medicine. There is a growing knowledge base regarding the role of genetic variation in T2DM etiology and treatment response; however, the complexity of this disease (itself in reality a group of diseases), the number of treatment options, and the limited number of clinical trials providing adequate design and power to detect and replicate pharmacogenetic associations are obstacles to overcome. Ever-decreasing prices of genetic sequencing and the growing number of large diabetes research consortia such as Go-T2D, T2D-GENES, and DIAGRAM and emerging comparative effectiveness trials such as the Glycemia Reduction Approaches in Diabetes (GRADE) Study (https://

portal.bsc.gwu.edu/web/grade) are expected to provide the necessary data. Once a scientific evidence base is gathered for pharmacogenetic markers, implementation studies will be needed to determine the most effective way to realistically incorporate testing into medical care in the context of complex healthcare systems. These unfolding opportunities, in addition to current implementation of genetic testing for monogenic diabetes, provide a promising outlook of the future of personalized medicine in diabetes.

## Conclusions

The incidence and prevalence of the diabetes mellitus epidemic around the world are currently at all-time highs. Despite medical advances, many people still suffer high rates of complications. Through pharmacogenetics, it is possible to usher personalized medicine into the field of diabetes. Certain types of monogenic diabetes already present an excellent opportunity to practice personalized medicine. Proper genetic diagnosis and appropriate pharmacological treatment of these patients often prevent unnecessary insulin therapy, simplify and increase efficacy of treatment, and create opportunities for prediction and personalized treatment of diabetes in family members. Current epidemiological studies are also pushing forward the field of pharmacogenetics of more genetically complex forms of T2DM. Although more work needs to be performed, there are already promising examples, such as zinc supplementation for rs13266634 risk allele carriers in *SLC30A8*. Pharmacogenomic discoveries, like the *SLC30A8* and *APOC3* loss-of-function mutations, are providing physiological models that can be mimicked in the drug discovery process. Finally, the emerging field of gene–environment interactions will progress to provide information about how individuals can tailor their environment to either complement or subvert their genetic predispositions. Many of these exciting developments in the field of personalized medicine for diabetes will likely translate into clinical practices to individualize therapy that will improve the patient experience and public health.

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