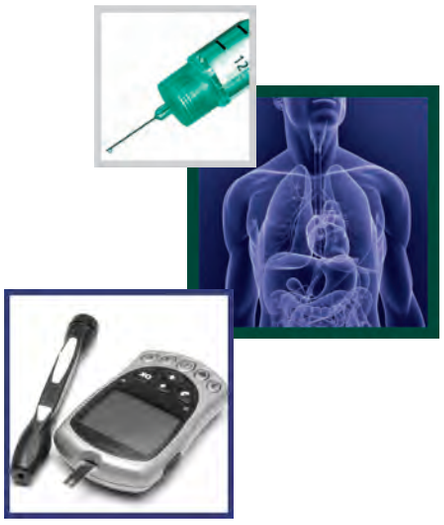
REVIEW

Genomic science: what are the implications for personalized diabetes care?



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Practice Points

- Personalized medicine uses patient-specific molecular biomarkers, as well as more traditional testing, to individualize preventive, diagnostic and treatment strategies for patient care.
- Monogenic forms of diabetes are found in less than 5% of diabetic patients and patients are often misdiagnosed as having Type 1 or 2 diabetes.
- Genetic testing for maturity-onset diabetes of youth (MODY) should be performed in diabetes patients with autosomal dominant inheritance, onset at less than 25 years of age and β-cell dysfunction typically in the absence of insulin resistance or obesity.
- Glucose-lowering medications are rarely needed in patients with MODY2 except during pregnancy.
- Patients with MODY1, MODY3 and permanent neonatal diabetes with *KCNJ11* and *ABCC8* mutations can be switched from insulin to sulfonylureas without worsening of hyperglycemia.
- Currently identified genetic variants associated with Type 1 and 2 diabetes, and diabetes complications only modestly add to risk assessment models; therefore, genetic risk assessment for diabetes and its complications is not currently recommended in clinical practice.
- Variants in *CYP2C9*, *KCNJ11*, *ABCC8* and *TCF7L2*, and *SLC22A1*, *SLC22A2* and *SLC47A1* are associated with interindividual variability in response to sulfonylureas and metformin, respectively.
- While personalized medicine holds great promise, many challenges exist that need to be addressed before this approach becomes standard of care in diabetes management.

SUMMARY Developments in personalized medicine are adding to the clinician's armamentarium and will allow for more individualized care for diabetes patients. The discovery of mutations causing many forms of monogenic diabetes now allows for the design of patient/mutation-specific targeted interventions. While many genetic loci are associated with Type 1 and 2 diabetes, and diabetes complications, these variants only modestly add to risk; therefore, genetic risk assessment for diabetes and its complications is not currently recommended in clinical practice. Genetic variants are also associated with drug metabolism,

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efficacy and side effects. Clinical studies are required to determine if genotype information improves day-to-day clinical management of diabetes and our overall approach to clinical practice. While the development of personalized medicine is promising for the future, a number of challenges remain that will need to be overcome before personalized medicine becomes standard of care in Type 1 and 2 diabetes management.

With the rapid improvement in technology, extensive data, including genomic, proteomic and metabolomic information, may soon be available for individual patients. Through the implementation of personalized medicine, these data have the potential to revolutionize the practice of medicine. Personalized medicine involves using patient-specific molecular biomarkers derived from these tests, as well as more traditional testing to individualize preventive, diagnostic and treatment strategies rather than using general population guidelines to direct patient care. This transformation in the practice of medicine promises to produce improvements in patient care and patient outcomes, as well as lower healthcare costs by limiting preventive care, diagnostic testing and treatment to those known to be effective in patients with specific genomic, proteomic and metabolomic profiles.

Diabetes

While the practice of personalized medicine in the field of diabetes is still in its infancy, early indications demonstrate areas of clear and potential benefit [1]. Diabetes is a heterogenous disorder made up of a number of subtypes, including the more common polygenic forms of diabetes, such as Type 1 diabetes (T1DM) and Type 2 diabetes (T2DM), and the less common monogenic forms such as maturity-onset diabetes of youth (MODY) and neonatal diabetes. Given the heterogeneity of diabetes, it is not surprising that one strategy does not work for all patients. The purpose of this article is to review the current and future role of personalized medicine in the care of the diabetic patient.

Monogenic diabetes

Monogenic forms of diabetes are found in less than 5% of diabetic patients and are primarily disorders of β-cells and insulin secretion [2,3]. These disorders provide the best example of how a personalized medicine approach can guide diagnosis and treatment in diabetes patients. The most common subtypes of monogenic diabetes are MODY and neonatal diabetes. Patients with monogenic diabetes are often misdiagnosed as having T1DM or T2DM, leading to misguided treatment decisions [4]. MODY is characterized by autosomal dominant inheritance, onset at less than 25 years of age and β-cell dysfunction, typically in the absence of insulin resistance or obesity **(Table 1)** [2,5]. To date, eight genes have been identified as causing MODY: *HNF4*α (MODY1), *GCK* (MODY2), *HNF1*α (MODY3), *IPF1* (MODY4), *HNF1*β (MODY5), *NEUROD1* (MODY6), *KLF11* (MODY7), and *CEL* (MODY8) [2,5], although not all believe that *NEUROD1* and *KLF11* meet all of the criteria to be included under the MODY subcategorization. Neonatal diabetes is usually diagnosed before 6 months of age and can be either transient neonatal diabetes (TNDM) or permanent neonatal diabetes (PNDM) [6]. TNDM represents 50–60% of cases of neonatal diabetes. Depending on the study, 50–75% of TNDM cases have a mutation on chromosome 6q24 near the *PLAGL1* and *HYMAI* genes [3,7]. Another 10% of TNDM cases are attributable to mutations in the *KCNJ11* gene that codes for Kir6.2, while 13% are attributable to mutations in the *ABCC8* gene that codes for Sur1 [7]. Kir6.2 is part of a potassium channel in the insulin secretion pathway. Sur1 regulates the opening and closing of the Kir6.2 channel. Mutations in either of these proteins can block closure of the channel, which, in turn, decreases insulin secretion (TNDM or PNDM), or leave the channel closed, which results in unregulated insulin secretion (hypoglycemic hyperinsulinemia of infancy). Approximately 50% of patients with PNDM have mutations in the *KCNJ11* gene. The next most common mutations causing PNDM are found in the insulin and *ABCC8* genes [8]. Homozygous mutations in *IPF-1* and *GCK*, genes that cause MODY in their heterozygous form, also account for a small percentage of neonatal diabetes. In 25–40% of cases, the causative genes for neonatal diabetes have yet to be identified [8].

Since specific gene mutations are known to cause MODY and neonatal diabetes, a personalized medicine approach utilizing commercially available molecular genetic testing can be used to ascertain the specific gene mutation causing diabetes in an individual patient. With this

Table 1. Maturity-onset diabetes of youth.

MODY	Gene	Function	MODY cases (%)	Phenotype	Ref.
MODY1	*HFN4α*	Transcription factor	30–70	Onset in adolescence or early adulthood Progressive defect of insulin secretion Sensitive to sulfonylureas	[2,5]
MODY2	*GCK*	Glycolytic enzyme	30–70	Mild hyperglycemia beginning at birth Often do not require glucose-lowering medication except during pregnancy	[2,5]
MODY3	*HFN1α*	Transcription factor	5–10	Onset in adolescence or early adulthood Progressive defect of insulin secretion Sensitive to sulfonylureas	[2,5]
MODY4	*IPF1*	Transcription factor	Very rare	Adult onset Progressive defect of insulin secretion Pancreatic agenesis in homozygotes	[2,5]
MODY5	*HFN1β*	Transcription factor	5–10	Renal cysts and diabetes	[2,5]
MODY6†	*NEUROD1*	Transcription factor	Very rare	Early adulthood Obesity Progressive β-cell failure	[66]
MODY7†	*KLF11*	Transcription factor	Extremely rare	Diagnosed in adulthood Progressive β-cell failure	[67]
MODY8	*CEL*	Lipolytic enzyme	Extremely rare	Exocrine and endocrine pancreatic deficiencies	[68]

†There is debate as to whether *NEUROD1* and *KLF11* should be included as MODY genes.
MODY: Maturity-onset diabetes of youth.

information, a patient-specific treatment plan can be designed that addresses the best treatment options, the likelihood of progression of the disease and the development of diabetes-related complications, and recommendations for genetic counseling. For example, *GCK*, the gene causing MODY2, is considered to be the glucose sensor of the β-cell and phosphorylation of glucose by glucokinase is the rate-limiting step for insulin secretion [5]. Mutations in *GCK* lead to decreased glucokinase affinity for and phosphorylation of glucose with a shift to a higher glucose threshold for insulin secretion. Patients with MODY2 tend to have modest levels of hyperglycemia that does not progress with age (mean fasting glucose: 128 ± 22 mg/dl; range: 77–297 mg/dl; HbA1c: 6–7%), since once glucose levels reach the higher threshold required for affinity to glucokinase, insulin secretion occurs [9,10]. As a result, diabetes complications are uncommon in MODY2 [5]. Identifying patients with glucokinase mutations impacts their care, since unlike patients with T1DM and T2DM, glucose lowering medication is rarely needed except during pregnancy. Spyer *et al.* demonstrated that knowing both the mother's and baby's *GCK* genotype may be relevant to prenatal care [11]. Non-MODY2 offspring born to MODY2 mothers are heavier than MODY2 offspring born to MODY2 mothers (3.9 ± 0.6 vs 3.2 ± 0.8 kg; $p < 0.001$) and are more likely to have macrosomia (39 vs 7%; $p = 0.001$) [11]. While *in utero* GCK genotyping of babies with MODY2 mothers is not routinely performed, genotyping should be considered when excess fetal growth occurs as knowing the baby's GCK genotype can provide valuable information for tailoring maternal diabetes treatment, which, in turn, may improve fetal outcomes. In the case of the mother with MODY2 and the baby without MODY2, treatment with insulin should be instituted to decrease the risk of macrosomia and obstetric complications. However, when both mother and offspring have *GCK* mutations, insulin treatment is generally not necessary [12].

Unlike MODY2, MODY1 and MODY3 patients have progressive β-cell failure resulting in increasing hyperglycemia and the need for glucose-lowering medication [13]. Because of the younger age at diagnosis and absence of metabolic syndrome, many MODY1 and MODY3 patients are inappropriately diagnosed with T1DM and started on insulin therapy [14]. However, patients with MODY1 and MODY3 are highly responsive to sulfonylureas [15–17]. Therefore, once patients with MODY1 and

MODY3 are correctly diagnosed, they can be successfully transferred from insulin to sulfonylurea therapy without deterioration in glycemic control [18]. Differences in pathogenesis, prognosis and treatment of MODY highlight the importance of personalized medicine in diabetes care and strongly support genetic testing in appropriate individuals. Current recommendations for genetic screening for MODY can be found at the 'Diabetes Genes' website [101].

In children with neonatal diabetes, knowing the specific mutation helps in establishing if a child has TNDM or PNDM. Children with TNDM are treated in the short term with insulin with the expectation that diabetes will resolve by 18 months [19]. These children require continued monitoring as diabetes often recurs during adolescence. Two of the genes associated with PNDM, *KCNJ11* and *ABCC8*, code for proteins targeted by the sulfonylurea class of diabetes medications. In 85–90% of patients with variants in one of these genes, treatment can be switched from insulin to sulfonylureas with blood sugars remaining well controlled [20,21].

Prediction & prevention of diabetes

Since T1DM and T2DM are complex disorders with many genes of varying penetrance and environment factors contributing to disease risk, predicting who will acquire either type of diabetes is much more complicated than predicting who will inherit a monogenic form of diabetes. As a result, predictive models that include primarily genetic factors are not as precise as predicting monogenic diseases.

Type 1 diabetes

For T1DM, genetic, antibody and metabolic tests are available to estimate disease risk; however, these are primarily used in the research setting in first-degree relatives of T1DM patients owing to their overall low positive predictive value in the general population [22,23]. Family history and HLA are the strongest predictors of T1DM, with HLA accounting for 30–50% of genetic risk [24]. Those with HLA haplotypes DR3-DQA1*0501-DQB1*0201 and DR4-DQA1*0301-DQB1*0302 are at highest risk for developing T1DM. By contrast, those with HLA genotype DRB1*1501-DQA1*0102-DQB1*0602, DRB1*1401-DQA1*0101-DQB1*0503 and DRB1*0701-DQA1*0201-DQB1*0303 are at the lowest risk [22,24,25]. The specific HLA type may also predict the age and rapidity of diabetes onset [22,24–26]. Candidate gene and genome-wide association studies have identified over 50 loci that associate with T1DM [102]. With the exception of HLA, these loci have a modest effect on diabetes risk (odds ratio <1.2) [27]. Not all children with a genetic predisposition to T1DM will develop the disease. An environmental exposure is necessary to initiate β-cell autoimmunity. Many factors have been considered as triggers for the autoimmune response, including viral infections and nutritional factors [22]. Research to confirm the environmental factors has been inconclusive; therefore, until this element is clarified, T1DM prediction models will not include this important component. After the environmental exposure, autoimmune destruction of β-cells commences and antibodies to islet cell antigens, including insulin, GAD65, IA-2 and Znt8, mark this process [22]. With each additional antibody, the likelihood of developing T1DM increases [28,29]. Metabolic tests, such as the oral glucose tolerance test and acute insulin response to glucose, have also been utilized in combination with HLA and antibody testing to help T1DM predictive models [30–32]. Patients with a family history of T1DM, an at-risk HLA genotype, multiple antibodies and low acute insulin response to glucose have more than a 50% chance of developing T1DM. While the specificity of a model including all of these factors improves risk assessment, once the tests display abnormal results the autoimmune destruction has progressed and β-cell damage may not be reversible. With genetic and other 'omics' data, the expectation is for these data to lead to a more comprehensive understanding of T1DM pathophysiology. In a personalized medicine paradigm, this understanding could ultimately produce better risk assessment tools and a means to identify those in need of preventive treatment. Ideally, using this type of approach, an individual patient's specific defective pathway could be precisely targeted and treated, thereby, theoretically avoiding autoimmune destruction of β-cells and T1DM. While the tools described above have improved our predictions for the occurrence of T1DM, until a proven preventative treatment is developed, the threshold for performing these tests will be fairly high outside of the research setting.

Type 2 diabetes

Through candidate gene and genome-wide association studies, over 40 genes/loci have been associated with increased risk of T2DM [33]. The gene variant with the strongest effect

is rs7903146, located in intron 3 of the *TCF7L2* gene. Having one copy of the minor allele for this single nucleotide polymorphism (SNP) increases the risk of T2DM by 1.45-fold and having two copies increases the risk by 2.41-fold [34]. Since the impact of the *TCF7L2* SNP and other SNPs on diabetes risk is small (odds ratio: 1.1–1.4), a genotype risk score based on an individual's number of diabetes risk alleles has been utilized to attempt to improve disease prediction [35]. While some studies demonstrate improved risk prediction [36], other studies using this methodology find that predictions are only slightly better than those based on the presence or absence of nongenetic risk factors alone [37]. To add to the complexity of using genotype to predict T2DM, models do not account for gene–gene or gene–environment interactions. While both interactions are acknowledged as important, little research has focused on how to integrate them into the personalized medicine paradigm.

Medication management

The focus of pharmacogenetics and pharmacogenomics is to define the impact of genetic variation on responses to medications. By using a pharmacogenetics approach, drug therapy can be selected based on its predicted efficacy, pharmacokinetics, pharmacodynamics and side-effect profile in a specific individual. Therefore, this approach has the potential to reduce the large number of treatment failures, and the time and costs associated with failure. As the pathophysiology of diabetes is established, another objective of pharmacogenetic research will be to determine if drugs targeting specific molecular defects can be designed to prevent, cure or improve the treatment of the disease.

Many of the genes impacting drug efficacy are related to their absorption, distribution, metabolism (activation/inactivation) and excretion. CYP2C9 is the major enzyme responsible for metabolism of sulfonylurea medications. Multiple *CYP2C9* alleles exist, some of which impact the half life of the drugs. In individuals carrying the CYP2C9*3/*3 genotype, sulfonylurea clearance is 20% of those carrying the CYP2C9*1/*1 genotype with heterozygotes (CYP2C9*1/*3) being intermediate between the two groups [38]. Data on whether these differences in drug clearance impact clinical care are lacking. Future studies will be required to determine if utilizing *CYP2C9* genotype in prescribing sulfonylureas will be effective [38]. Several other gene variants that are also associated with increased diabetes risk have been implicated in sulfonylurea efficacy. Sur1 and Kir6.2 proteins are therapeutic targets of sulfonylurea medications. Variants in both proteins have been associated with interindividual variability in sulfonylurea response, as well as secondary sulfonylurea failure [39,40]. Variants in *TCF7L2*, possibly through their effects on GLP-1 [41], are associated with a reduced lowering of HbA1c in patients taking sulfonylurea medications **(Table 2)** [42,43].

As with other drugs, the glycemic response to metformin is variable, with some people having a marked response and others demonstrating little benefit. At least three drug transporters, OCT1 encoded by *SLC22A1*, OCT2 encoded by *SLC22A2* and MATE1 encoded by *SLC47A1,* participate in the distribution and excretion of metformin and have been shown to cause variation in drug response [44–46]. OCT1 is expressed in the membrane of hepatocytes and is responsible for the uptake of metformin into hepatocytes. Genetic variants decreasing OCT1 activity are associated with lower hepatic levels of metformin, as well as a reduced lowering of HbA1c [45,47]. OCT2 is expressed in the membrane of the renal epithelial cells, and transports metformin into these cells [48,49]. Genetic variants decreasing OCT2 activity are associated with impaired renal excretion of metformin and higher metformin blood levels [50,51]. MATE1 carries metformin out of hepatocytes into bile and out of renal epithelium into urine. Decreased MATE1 activity leads to increased plasma and hepatocyte metformin levels, which leads to lower HbA1c levels possibly by a greater inhibition of hepatic gluconeogenesis [52,53]. Therefore, polymorphisms in *SLC22A1*, *SLC22A2* and *SLC47A1* play an important role in therapeutic response to metformin. What has yet to be determined is how to integrate these findings into clinical care.

Complications

Strategies to delay the development and progression of long-term microvascular and macrovascular complications of diabetes involve intensive glycemic management, as well as aggressive therapy for hypertension and hyperlipidemia. However, some patients, despite excellent glucose, blood pressure and lipid control, develop complications while others with poor glucose, blood pressure and lipid control, never develop complications.

Table 2. Effects of polymorphisms on metabolism and efficacy of diabetes medication.

Variant	Effect	Ref.
Sulfonylurea		
*CYP2C9*3*	Higher sulfonylurea levels, greater decrease in fasting glucose levels and more likely to achieve HbA1c <7% in CYP2C9*3 carriers	[69,70]
ABCC8 S1369A	1369A carriers had greater decreases in fasting plasma glucose and HbA1c	[39]
TCF7L2 rs7903146 (C>T), rs12255372 (G>T)	Higher treatment failure (HbA1c <7%) in TT homozygotes of either SNP	[43,71]
Repaglinide		
*CYP2C8*1/*3*	Lower repaglinide mean AUC and peak plasma concentration with CYP2C8*1/*3 genotype	[72]
SLCO1B1 521T>C	Higher repaglinide AUC with *SLCO1B1* 521CC than *SLCO1B1* 521TC and TT genotype	[73]
KCNJ11 E23K	Carriers of K23 allele had greater decrease in HbA1c	[74]
Nateglinide		
CYP2C9	Reduced nateglinide clearance in CYP2C9*3 carriers	[75]
SLCO1B1 521T>C	Higher maximum concentration and AUC in *SLCO1B1* 521CC individuals compared with *SLCO1B1* 521TC individuals	[76]
Metformin		
OCT1 R61C, G401S, M420del, G465R	Higher AUC, maximum plasma concentration and decreased glucose-lowering response to metformin in reduced function allele variants	[45]
OCT2 808G>T	Higher mean renal clearance in 808T carriers	[77]
MATE1 rs2289669 G>A	Greater reduction in HbA1c with each rs2289669 A allele	[52]
MATE1 rs2289669 G>A, *OCT1* rs622342 A>C	Interaction between *MATE1* rs2289669 and *OCT1* with greater decrease in HbA1C levels with each additional *OCT1* rs622342 A allele and *MATE1* rs2289669 A allele	[78]
ATM rs112112617 A>C	A allele associated with improved glycemic response	[79]
Pioglitazone		
PPARγ Pro12Ala	Ala12 allele associated with greater decrease in HbA1c and fasting glucose plasma levels in some studies	[80]

AUC: Area under curve; SNP: Single nucleotide polymorphism.

These outcomes highlight the need to be able to distinguish which individuals would benefit most from concentrated interventions to prevent complications, as well as individuals where aggressive interventions are not warranted.

Based on familial clustering of complications and other studies, genetic susceptibility probably plays a role in this heterogeneity [54,55]. Through candidate gene and genome-wide association studies, important steps have been made towards the discovery of genetic markers that may ultimately be useful predictors of complications and responses to therapy [54]. Substantial data suggests that the renin–angiotensin system plays a key role in the occurrence of diabetic nephropathy. In the majority of populations, an insertion(I)/deletion(D) polymorphism of the *ACE* gene influences the clinical course of diabetic nephropathy [56,57]. The II genotype is protective against development and progression of diabetic nephropathy compared with those with the DI and DD genotypes. The difference in clinical course may be due to variation in ACE levels. Subjects carrying one or two copies of the D allele have increased systemic and renal ACE levels compared with those who are homozygous for the I allele [58]. ACE inhibitors are particularly effective in preventing and slowing progression of renal disease in diabetes patients with the II genotype [59]. However, the DD genotype is associated with a better response to angiotensin II receptor blockers [57]. Therefore, the ACE I/D polymorphism is not only helpful in classifying patients as at risk for diabetic nephropathy, but also in choosing the most appropriate renoprotective renin–angiotensin system blockade for treatment.

The challenge

While personalized medicine holds great promise, many challenges exist that need to be addressed before this approach becomes standard of care in diabetes [60–63]. One of the most critical steps will be advancement and innovation in computational and bioinformatics capabilities in order to harness the massive amount of data produced by 'omic' studies and translate these data into useful information for the medical community. Progress in these areas, as well as in technology (e.g., whole-genome sequencing), should lead to a more complete understanding of the functional significance of genes, the large segments of intergenic DNA, gene–gene and gene–environment interactions, and the molecular pathways leading to diabetes. Other gaps that need to be filled to maximize the benefits of personalized medicine for all individuals include identifying structural variants and private or rare variants with large effects, and collecting data on minorities and other ethnic groups who are often not included in large-scale genomic studies. Concerns have also been raised as to the role of large-scale genotyping in predicting a disease in which the current list of susceptibility genes account for only 10% of T2DM risk [61,64], and in which adding genetic data to models using traditional diabetes risk factors does little to improve predicting diabetes for an individual. A more comprehensive picture of the workings of DNA should also help determine if this missing heritability is the result of yet to be identified genetic variability, over estimation of heritability due to genetic interactions or other, as yet, undiscovered factors [65].

New social and ethical issues also arise as an ever increasing amount of data are collected on individuals. Concerns range from how privacy will be maintained and what constitutes privacy, who owns the data (patient and provider, among others) and who has the authority to destroy the data, to the role of direct-to-consumer marketing of genetic tests, many of which have unproven clinical validity and utility, limited oversight from the US FDA and other regulatory bodies, and lack a healthcare provider to interpret results and put the results in an appropriate context for an individual patient [63]. US Congress has tried to address concerns related to genetic discrimination by passing the Genetic Information Nondiscrimination Act in 2008 [60]. The law prohibits genetic discrimination by health insurers and employers. How effective the law will be with the transition to personalized medicine and widespread whole-genome sequencing remains to be seen.

Conclusion & future perspective

Personalized medicine, in general and also for care of the diabetic patient, is still at an early stage with much work ahead to fully realize its potential. For diabetes, personalized medicine success stories can be found in its application to diagnosis and management of patients with MODY1, 2 and 3, and neonatal diabetes. For T1DM and T2DM, advancements in the translation of data from genomics and other 'omic' research into clinically relevant tools for prediction, prevention and treatment of diabetes will be necessary in order for the practice of personalized medicine to become standard of care outside of the research setting.

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