DIAGNOSIS AND CLINICAL MANAGEMENT OF MONOGENIC DIABETES

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ABSTRACT

Monogenic forms of diabetes are responsible for 1-3% of all young-onset diabetes. The multiple genes involved can cause one or both of the main phenotypes- congenital (neonatal) diabetes or MODY (maturity-onset diabetes of the young). The timely and accurate genetic diagnosis of monogenic diabetes provides an opportunity to target therapy to the underlying gene cause, refine management, and identify affected and at-risk relatives. As there is clinical overlap of monogenic diabetes with type 1 and type 2 diabetes, presenting clinical and laboratory features warrant careful attention to aid in diabetes classification and to identify those individuals who warrant genetic testing. These include those negative for islet cell autoantibodies with persistent c-peptide, suggesting a diagnosis other than type 1 diabetes. While obesity does not preclude monogenic diabetes, certainly individuals lacking obesity and other features of metabolic disease should be referred for diagnostic genetic testing. Understanding who and how to refer for genetic testing and how to interpret test results is key to precision medicine in diabetes. The most common forms of monogenic diabetes have specific therapies and management strategies that can optimize glycemic control and minimize complications resulting in improved health outcomes for affected individuals.

INTRODUCTION

The most common forms of diabetes- type one (T1DM) and type two (T2DM)- are polygenic disorders. There are many identified genes, wherein certain variants cause a genetic predisposition to the development of diabetes. However, they are insufficient to cause disease without additional contributing environmental factors. In contrast, monogenic forms of diabetes are due to highly penetrant variants in single genes or chromosomal abnormalities that are sufficient by themselves to cause diabetes. Phenotypic overlap between monogenic diabetes and polygenic forms means that clinicians must thoughtfully consider diabetes classification in each patient, at diagnosis and thereafter, and order genetic testing to confirm clinically suspected monogenic diabetes.

This chapter will focus on understanding the following important clinical factors for pediatric and adult patients:

- Why test?
- How to test and interpret results.
- Who to test?
- How to treat and manage specific subtypes of monogenic diabetes.

WHY SHOULD YOU DO GENETIC TESTING FOR MONOGENIC DIABETES?

There are two main clinical phenotypes of monogenic diabetes- neonatal diabetes (also called congenital diabetes) and MODY (Maturity-Onset Diabetes of the Young). Neonatal diabetes has a prevalence of 1:90,000 – 1:250,000 and MODY accounts for 1-3% of diabetes diagnosed under 30 years of age (~0.4% of all diabetes) (1-3). Both of these broad phenotypes include syndromic diabetes and there is overlap of causative genes- with MODY, by definition representing autosomal dominant diabetes and neonatal diabetes being caused by a number of overlapping 'MODY genes' as well as having several genetic causes unique to congenital forms. There are over 20 known genetic causes of neonatal diabetes mellitus and 14 genes that have been implicated as causes of MODY (Table 1). While monogenic diabetes is uncommon, accurately diagnosing monogenic diabetes through genetic testing has important clinical and economic considerations for the patient, and often for first-degree relatives as well. For the most common subtypes of monogenic diabetes, gene-directed management improves outcomes, alerts the physician of non-pancreatic features that may accompany diabetes, and identifies affected and at-risk family members who may benefit from diagnostic or predictive genetic testing, respectively.

Table 1. Genetic Causes of Monogenic Diabetes

Common Causes of Neonatal Diabetes	Common Causes of MODY
KCNJ11, ABCC8, INS, 6q24 chromosome abnormalities	GCK, HNF1A, HNF4A, HNF1B
Rare Causes of Neonatal Diabetes	**Rare Causes of MODY**
GATA6, EIF2AK3, PTF1A, GLIS3, FOXP3, GCK, PDX1, HNF1B, GATA4, SLC2A2, SLC19A2, NEUROD1, NEUROG3, NKX2.2, RFX6, IER3IP1, MNX1, ZFP57, STAT3	PDX1, NEUROD1, KLF11*, CEL, PAX4*, INS, BLK*, ABCC8, KCNJ11, APPL1

*Evidence for these as MODY genes is limited

There have now been several economic evaluations of genetic testing for monogenic diabetes. In children, testing for monogenic diabetes has been found to be cost-saving, a rare feat in medicine (4-6). The addition of cascade testing in MODY- that is testing of first-degree relatives of affected individuals- further enhances this cost-effectiveness (6). In adults, routine screening for monogenic diabetes has not yet proven to be cost-effective, which is due to both the absolute number of affected adults and the high percentage of T2DM, where costs of gene-targeted therapy compared to some T2DM regimens, particularly metformin alone, are not substantially different (7,8). However, results strongly suggest that testing only those patients with a high pre-test probability of monogenic diabetes would be cost-effective (7). Thus, genetic testing for adults should still be carried out when careful consideration of the clinical picture is inconsistent with a diagnosis of T1DM or T2DM and is suggestive of MODY or another form of monogenic diabetes.

HOW SHOULD GENETIC TESTING FOR MONOGENIC DIABETES BE CARRIED OUT?

Medical insurance coverage for genetic testing varies not only by insurance company but also by disease. Thus, a prior authorization should be sought before ordering diabetes genetic testing and patients should

be instructed to contact their insurance companies to clearly understand any co-pays for which they will be responsible. Some commercial testing companies offer patient protection programs to limit out-of-pockets expenses but typically patients must enroll in such programs prior to ordering genetic testing.

In the past, genetic testing was accomplished through Sanger sequencing, typically of one gene at a time until a causative mutation was determined or all relevant genes were tested without detected abnormality. This process was labor and time intensive and costly. Now, monogenic diabetes panel are frequently used in place of Sanger sequencing of a single gene (5,9,10). There are a number of CLIA-certified commercial labs offering monogenic diabetes panels, including Ambry, Athena Diagnostics, Blueprint Genetics, Prevention Genetics, Invitae, and GeneDx (this list is non-exhaustive and will change over time). Laboratories at some academic institutions also have the capability to provide CLIA-certified genetic testing for monogenic diabetes. The genes carried on panels vary by laboratory and are often divided into a neonatal diabetes panel and a MODY panel. In general, gene panels will be the appropriate test to order because of the overlapping clinical features between various types of monogenic diabetes, but there are cases where the clinical features clearly fit with a distinct gene. Research-based genetic testing for monogenic diabetes is available through a number of different studies. The methodology does not differ from that used in clinical laboratories, but results are not CLIA certified. While it is at a provider's discretion to act on research findings based on clinical judgment, CLIA confirmation of the finding is advised. In such cases, clinicians must specify that they are confirming a previous research finding so that labs will only sequence the affected gene and look for the specific variant identified. This testing is also appropriate for cascade genetic testing of first-degree relatives. Confirmation of a known genetic finding is relatively inexpensive and typically approved by insurance (authors' practice experience).

HOW SHOULD GENETIC TESTING RESULTS BE INTERPRETED?

Content of genetic testing reports can vary widely based on the laboratory (11). There is a growing recognition by experts in monogenic diabetes and laboratories themselves that hard-to-interpret genetic testing reports are a disservice to clinicians and patients. It is likely that in the relatively near future, testing reports will be easier to interpret. Until then, recommendations for interpretation include:

- Look at the classification of any variants found as well as any provided references of the published literature relevant to the genetic finding. Terminology used includes pathogenic, likely pathogenic, variant of uncertain significance (VUS), likely benign, and benign.
- Determine if testing includes gene dosage analysis. Sanger sequencing and some panels will not detect partial or whole gene deletions. However, many laboratories will employ additional methods to detects deletions, such as Multiplex Ligation-dependent Probe Amplification (MLPA) or exon-level array comparative genomic hybridization (CGH). If this has not been included, and genetic testing returns negative in a highly suspicious case, additional testing for copy number variation is warranted.
- It is important to understand that due to the redundancy in our genetic code, many gene variants are tolerated with no effect on gene production, transcription, or expression. Thus, a variant in a known monogenic gene in a patient with suspected monogenic diabetes does not mean that the variant is causing their diabetes (12). Additionally, some genes and some variants reported in the published literature that were once thought to cause monogenic diabetes have

subsequently proven to be non- causal or have come into question, but they persist in the literature. ClinGen is a NIH-funded resource that defines the clinical relevance of genes and variants (https://www.clinicalgenome.org). There are gene curation expert panels and variant curation expert panels for monogenic diabetes. Currently the work of the gene curation panel is focused on the 14 genes designated as MODY, a number of which have questionable data to support them as legitimate monogenic diabetes genes (*BLK*, *KLF11*, *PAX4*).

- Seek advice from an expert in monogenic diabetes for any level of uncertainty in interpretation of test results before discussing results with the patient and particularly before making changes to diabetes management (monogenicdiabetes@uchicago.edu).

WHO SHOULD YOU TEST FOR MONOGENIC DIABETES?

There are many examples of systemic screening for monogenic diabetes in various populations and the result is always the same: if you conduct genetic testing among those diagnosed as T1DM or T2DM, you will find monogenic diabetes cases (2,13-16). While the clinical overlap between different forms of diabetes can make accurate classification challenging, there are several clinical and laboratory features that should prompt consideration of genetic testing for monogenic diabetes (Table 2) (17,18).

All children with diabetes onset before 6 months of age should receive immediate genetic testing for monogenic diabetes as a genetic cause is very likely. Beyond 6 months, T1DM becomes the predominant diagnosis; however, a percentage of infants will still have a monogenic etiology, and many advocate for genetic testing in all cases diagnosed under 12 months of age (19). Another approach is to test these children for pancreatic autoantibodies, which, if positive, would be consistent with autoimmune type 1 diabetes. Those with negative autoantibodies should undergo testing for monogenic diabetes (18). Importantly, there are monogenic causes of early-onset autoimmune diabetes with additional features that suggest a single gene defect (20). A type 1 diabetes genetic risk score along with age can be helpful in discriminating these monogenic autoimmunity cases from polygenic type 1 diabetes (21). While treatment of monogenic autoimmune diabetes will continue to be replacement doses of insulin, accurate genetic diagnosis will help with prognostication and clinical management decisions.

Table 2. Clinical Features That May Indicate Monogenic Diabetes

Age	Diagnosis of diabetes <6 months of age is strongly suggestive of congenital/neonatal monogenic diabetes MODY onset typically occurs in pubertal children or young adults (diagnosis is typically but not always <35 years)
Body habitus	Obesity does not preclude a monogenic cause of diabetes, but rates of obesity in monogenic diabetes are the same as population frequency
Family history	Multiple generations of diabetes in an autosomal dominant pattern in MODY
Acanthosis nigricans, other metabolic features	Typically absent
Laboratory values	Negative pancreatic autoantibodies,

	Continued presence of c-peptide years after diagnosis for MODY and for some forms of neonatal diabetes
Presence of extra-pancreatic features outside of those associated with T1DM or T2DM	Several forms of monogenic diabetes have associated features that can raise suspicion not only for monogenic diabetes but for specific gene causes, e.g., Renal developmental disease, genitourinary abnormalities in HNF1B-MODY Neurocognitive difficulties, seizures in KATP-related neonatal diabetes Exocrine pancreatic insufficiency, cardiac defects in GATA6- and GATA4-related neonatal diabetes

In older children, cost-effectiveness analyses suggest that a reasonable approach to diabetes classification would be to test for pancreatic autoantibodies and endogenous insulin production (as measured by c-peptide) in all pediatric patients, and to test those with negative antibodies and positive c-peptide for monogenic diabetes (5,6). Using this biomarker approach reveals a monogenic diabetes prevalence of 2.5%-6.5%, including a monogenic diabetes prevalence of 4.5% in overweight and obese children, who would fall under the radar of many clinicians for monogenic diabetes consideration (2,3,22). If there are barriers to universal biomarker testing, age at diagnosis in older children may be helpful in considering monogenic diabetes versus T1DM and T2DM. The predominant diagnosis between 1 year of age and puberty will be T1DM. In the peripubertal period both T2DM and monogenic diabetes become higher considerations and T1DM remains a consideration. Additional clinical features of normal weight, lack of acanthosis nigricans or features of metabolic syndrome can identify patients who should undergo genetic testing. Family history is expected to be positive in both monogenic diabetes and type 2 diabetes so asking specific details for each affected family member, including age at diabetes diagnosis, body habitus at the time of diagnosis, and treatment are necessary to make family history useful.

In adults, the substantial burden of type 2 diabetes precludes universal biomarker screening to identify individuals who may have monogenic diabetes (8). However, the same clinical features of body habitus, features of insulin resistance or metabolic syndrome, paired with personal and detailed family history are useful to screen in people for additional evaluation. Age at diabetes onset is also an important consideration, as MODY onset is rarely beyond 35 years of age. There is a prediction model for MODY, known as the MODY calculator, which is available by website and as an app (https://www.diabetesgenes.org/exeter-diabetes-app/). The calculator was developed in an European white population and so must be used with caution for other groups, but on-going work will help to clarify its use in non-white populations (23) (24).

Importantly, until universal genetic testing is available for diabetes classification, some cases will be missed by applying these 'clinical filters' for selecting patients for testing, particularly those who have both monogenic diabetes and obesity. Because of the selection bias that results from excluding obese patients from testing, the impact of obesity on management and outcomes of specific subtypes of monogenic diabetes is not well understood.

HOW SHOULD YOU MANAGE SPECIFIC SUBTYPES OF MONOGENIC DIABETES?

Several of the common forms of monogenic diabetes have specific management as discussed below and in Table 3.

KATP-Related Neonatal Diabetes

Mutations in the *KCNJ11* and *ABCC8* genes, encoding the subunits of the KATP channel, most commonly manifest as neonatal diabetes, and can cause permanent or transient forms (mutations in *KCNJ11* and *ABCC8* are also rare causes of MODY) (25,26). Transient forms have a median onset of 4 weeks and remit at a median age of 35 weeks, but may relapse later in life. Neurodevelopmental difficulties are a common feature of mutations in these genes. KATP-related neonatal diabetes can usually be treated with high doses of sulfonylureas, which also helps with the neurodevelopmental phenotype (26). Frequently people can achieve excellent diabetes control on sulfonylureas (27). More severe mutations and longer duration of misdiagnosis are associated with decreased success in transitioning from insulin therapy to sulfonylureas (28).

6q24-Related Transient Neonatal Diabetes

6q24-related transient neonatal diabetes is an imprinted disorder diagnosed through methylation analysis of the 6q24 differentially methylated region of chromosome 6. It has a more severe phenotype than KATP-related transient neonatal diabetes with severe intra-uterine growth restriction and earlier diabetes onset, but earlier remission. Diabetes onset occurs in the first 6 weeks of life, and often within the first week of life. Affected individuals may have macroglossia and/or umbilical hernia. Typically, insulin is used for treatment during the infancy period. Insulin needs then decline and diabetes remits at an average of 4 months but can persist beyond a year (29,30). Relapse frequently occurs-usually in adolescence, pregnancy or adulthood. The best treatment for relapsed diabetes is not clearly defined, but many patients will respond to sulfonylureas and/or other oral medications such as dipeptidyl peptidase-4 (DPP-4) inhibitors, without need for insulin therapy (31).

Table 3. Features and Treatment of the Common Forms of Monogenic Diabetes

Name	Gene & Protein	Clinical Characteristics	Laboratory Findings	Treatment
Neonatal Diabetes				
KCNJ11-related neonatal diabetes	*KCNJ11*, Kir6.2	Can cause transient & permanent neonatal diabetes Low birth weight Developmental delay, seizures		High doses of sulfonylureas Insulin if there is no response to sulfonylureas
ABCC8-related neonatal	*ABCC8*, SUR1	Can cause transient & permanent		High doses of sulfonylureas

diabetes		neonatal diabetes Low birth weight		Insulin if there is no response to sulfonylureas
INS- related neonatal diabetes	*INS*, Insulin	Can cause transient & permanent neonatal diabetes Low birth weight		Insulin
6q24-related neonatal diabetes		Causes transient neonatal diabetes that may relapse in adolescence or adulthood IUGR, Low birth weight Earlier presentation compared to KATP-related neonatal diabetes Macroglossia, umbilical hernia		Typically insulin, use of sulfonylureas has been reported Sulfonylureas have successfully been used in relapsed cases
MODY				
HNF1A-MODY (previously referred to as MODY3)	*HNF1A,* Hepatocyte nuclear factor 1-alpha	Macrosomia and congenital hyperinsulinemic hypoglycemia (commonly seen in HNF4A-MODY) has been described in a small number of cases. Diabetes onset is typically in adolescence or young adulthood Progressive insulin	Glucosuria without significant hyperglycemia Elevated HDL Low hsCRP	Sulfonylureas are first line therapy GLP1 agonists and DPP4 inhibitors have also been shown to be effective in HNF1A-MODY

		secretory defect. Increased risk for cardiovascular disease Liver adenomas may occur		
HNF4A-MODY (previously referred to as MODY1)	*HNF4A,* Hepatocyte nuclear factor 4-alpha	Macrosomia and congenital hyperinsulinemic hypoglycemia may occur in affected infants Diabetes onset is typically in adolescence or young adulthood	Low apolipoproteins and triglycerides	Sulfonylureas are first line therapy DPP4 inhibitors have also been shown to be effective in HNF4A-MODY
HNF1B-MODY (previously referred to as MODY5)	*HNF1B,* Hepatocyte nuclear factor 1-beta	Developmental renal disease, especially cysts, genitourinary malformations, gout, pancreatic insufficiency	Elevated liver enzymes Elevated uric acid Low magnesium	Most patients will require insulin therapy Oral hypoglycemic agents may be successful
GCK-MODY (previously referred to as MODY2)	*GCK,* Glucokinase	Mild, non-progressive hyperglycemia is present at birth Diagnosis is often incidental (routine screening or investigation for an unrelated symptom)	FBG typically ranges from 99-144 mg/dL HbA1c ranges from 5.6-7.6%	

HNF1A-MODY

HNF1A-MODY is the most common form of MODY worldwide. It is characterized by a progressive insulin secretory defect with diabetes onset often in adolescence or young adulthood (32,33). Laboratory features include a low renal glucose threshold resulting in glucosuria at lower-than-expected blood

glucose levels (34). There is often a large incremental increase between fasting and 2-hour glucose on oral glucose tolerance tests. Additionally, hsCRP levels are lower than in other diabetes types (35).

Cardiovascular disease is higher in individuals with HNF1A-MODY compared to their unaffected relatives. Thus, despite a typically high HDL level, related to the activity of the transcriptional factor, statins should be considered in individuals with HNF1A-MODY (36).

Hepatic adenomas can also be a feature of HNF1A-MODY, and liver adenomatosis has been reported in 6.5% of those with HNF1A-MODY in one study. While routine screening for liver adenomatosis in HNF1A-MODY hasn't been a universal recommendation, it can present with intra-abdominal or intratumoral bleeding in 25% of cases, making asymptomatic screening clinically reasonable (37).

First line diabetes treatment for HNF1A-MODY is low-dose sulfonylureas, which partly bypass the defective insulin secretory response (38). Individuals with HNF1A-MODY can be very sensitive to sulfonylureas and experience hypoglycemia even on very small doses. Guidelines for transitioning patients can be found here. Studies of HNF1A-MODY have shown good maintenance on sulfonylurea therapy and lower rates of diabetes-related complications. Predictors of treatment success include shorter duration of diabetes, lower HbA1c, and lower BMI at the time of genetic diagnosis and less weight gain over time (39,40).

Meglitinides can be used in place of sulfonylureas, as they have a similar mechanism of action but bind less strongly to the receptor (41). GLP-1 agonists and DPP-IV inhibitors have also been studied in HNF1A-MODY, and have been shown to be efficacious and may be useful adjunctive therapy (42,43). These can be used for adjunctive therapy in cases where glycemic control is inadequate with sulfonylurea monotherapy or when hypoglycemia precludes use of sulfonylureas and meglitinides (typically early in diabetes).

HNF4A-MODY

HNF4A-MODY is similar in phenotype to HNF1A-MODY, but much less common (5-10% of MODY) (33). One distinct feature is a family history of macrosomia in about half of affected individuals and diazoxide-responsive hypoglycemia in neonates due to hyperinsulinism, which can last for days to years. This hyperinsulinemic hypoglycemia occurs in ~15% of HNF4A-MODY but has only rarely been reported to occur in HNF1A-MODY (44).

Again, first line treatment for HNF4A-MODY is a sulfonylurea (45). DPP-4 inhibitors and GLP-1 agonists have also been studied to a limited extent in HNF4A-MODY (46,47).

HNF1B-MODY

Heterozygous mutations in the *HNF1B* gene present with variable phenotypes which include isolated developmental cystic kidney disease, isolated diabetes, the combination of both (known as RCAD-renal cysts and diabetes), and may additionally have a number of other features. These include asymptomatic elevation of liver enzymes, genital tract malformations, hypomagnesemia wasting, hyperuricemia and gout. Typically, there is hypoplasia of the pancreas which is frequently accompanied by pancreatic exocrine dysfunction, which can be subclinical or overt (48,49).

Importantly, the same gene variant can lead to any of the above presentations. It is not uncommon to have families with a mixture of phenotypes. Thus, a family

history of cystic renal disease in a patient presenting with young-onset diabetes atypical for either type 1 or type 2 diabetes should prompt consideration of this gene.

Unlike the other hepatic nuclear transcription factor-MODY subtypes, HNF1B-MODY is not typically sensitive to sulfonylureas (50). There have not been rigorous studies of other non-insulin therapies in HNF1B-MODY. The majority of affected individuals require insulin therapy (51).

The *HNF1B* gene resides on the long arm of chromosome 17. Deletions of 17q12 lead to neurologic features, including cognitive impairment and autism spectrum disorder and may also include HNF1B-MODY (52,53). There is a 17q12 foundation that such patients can be directed to for additional support as their neurologic features are often challenging.

GCK-MODY

GCK-MODY is the second most common subtype of MODY and is distinctive from other MODY types and polygenic forms of diabetes. It is characterized by stable, mild hyperglycemia owing to an increased set-point for glucose stimulated insulin release. HbA1c ranges from 5.6-7.6%(54). The microvascular and macrovascular complications typical of other polygenic and monogenic forms of diabetes are exceedingly rare in GCK-MODY (55). Pharmacologic treatment is not effective or needed for GCK-MODY, with the exception of pregnancy in a woman with GCK-MODY (56). In pregnancy, appropriate management is predicated on the genotype of the fetus. If the fetus inherits the *GCK* mutation, mildly elevated maternal blood glucose levels are sensed as normal by the fetus and treatment is not needed. If the fetus does not carry the mutation, the mildly elevated maternal blood glucose levels will prompt increased insulin secretion by the fetus which can lead to macrosomia. Unfortunately, fetal genotype is usually unknown, although this should change with advancing fetal cDNA applications. Current practice is to infer fetal genotype based on abdominal circumference (FAC) on second trimester ultrasound, with a FAC >75% suggestive of unaffected status. In these cases, insulin therapy should be considered. However, blood glucose targets should be adjusted to higher levels than typical for pregnancy to account for the counterregulatory response that is altered in GCK-MODY (57). It is important to note that best management of GCK-MODY in pregnancy is debated, with some favoring universal early insulin administration. However, given the risks of maternal hypoglycemia, risk of impaired fetal growth in affected babies, and lack of demonstrated efficacy, these authors endorse the former management, guided by known or inferred fetal genotype (58).

ADDITIONAL BENEFITS OF ACCURATE MONOGENIC DIABETES DIAGNOSIS

There are several monogenic diabetes subtypes where insulin is the best or only treatment available. Additionally, for those subtypes with genetically-targeted therapy discussed above, not all affected individuals will respond or be maintained on these therapies and insulin may be necessary. However, genetic testing for accurate diagnosis is still beneficial for multiple reasons. Establishing a molecular diagnosis can often provide a unifying diagnosis for multiple, seemingly unrelated medical conditions, such as in the case of HNF1B-MODY. It also allows for earlier and proactive medical surveillance of extra-pancreatic manifestations, such as early referral to developmental specialists for children with KATP-related neonatal diabetes and neurodevelopmental challenges. Additionally, at-risk and affected family members can be identified and conception counseling can be provided.

CONCLUSIONS

The substantial worldwide burden of diabetes, in terms of sheer numbers and also cost, make it imperative that outcomes are optimized. Early accurate classification to direct management is a crucial step. Since the conception of the Precision Medicine Initiative in 2015, more attention and excitement has been garnered toward tailoring treatment to the individual characteristics of patients. Monogenic diabetes represents an opportunity to use a precision medicine approach to improve therapy selection and management of diabetes to improve glycemic outcomes for affected individuals, often while lowering burden and cost of care (59). The lessons that we learn from the continued investigation into the single gene causes of diabetes will inform our understanding of polygenic diabetes, including how to best subclassify the heterogeneous presentations of type 2 diabetes to guide first-line therapy selection and add-on therapies, expanding the scope of precision medicine in diabetes.

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