



# Monogenic Diabetes: From Genetic Insights to Population-Based Precision in Care. Reflections From a *Diabetes Care* Editors' Expert Forum

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Individualization of therapy based on a person's specific type of diabetes is one key element of a "precision medicine" approach to diabetes care. However, applying such an approach remains difficult because of barriers such as disease heterogeneity, difficulties in accurately diagnosing different types of diabetes, multiple genetic influences, incomplete understanding of pathophysiology, limitations of current therapies, and environmental, social, and psychological factors. Monogenic diabetes, for which single gene mutations are causal, is the category most suited to a precision approach. The pathophysiological mechanisms of monogenic diabetes are understood better than those of any other form of diabetes. Thus, this category offers the advantage of accurate diagnosis of nonoverlapping etiological subgroups for which specific interventions can be applied. Although representing a small proportion of all diabetes cases, monogenic forms present an opportunity to demonstrate the feasibility of precision medicine strategies. In June 2019, the editors of *Diabetes Care* convened a panel of experts to discuss this opportunity. This article summarizes the major themes that arose at that forum. It presents an overview of the common causes of monogenic diabetes, describes some challenges in identifying and treating these disorders, and reports experience with various approaches to screening, diagnosis, and management. This article complements a larger American Diabetes Association effort supporting implementation of precision medicine for monogenic diabetes, which could serve as a platform for a broader initiative to apply more precise tactics to treating the more common forms of diabetes.

Diabetes mellitus is a common disease defined by hyperglycemia but including other metabolic disturbances. It can cause serious medical complications that reduce life expectancy and quality of life and poses a major public health challenge. The lifetime risk of developing diabetes is estimated to be at least one in three for people born in the U.S. (1).

Diabetes is commonly divided into categories (2). These include autoimmune-mediated type 1 diabetes leading to insulin deficiency; diabetes secondary to pancreatic injury; diabetes related to specific genetic disorders; and a broad category termed type 2 diabetes, in which insulin secretion is impaired and resistance to insulin's actions is usually, but not always, present (3). Growing understanding of crucial differences in the pathophysiology underlying these distinct categories has the potential to improve outcomes by allowing for the application of specific therapeutic approaches (4). Such

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evidence-based individualization of therapy is a key component of the current movement toward “precision medicine” (5,6).

There are several barriers to implementing precision medicine in diabetes. These include disease heterogeneity, difficulties in accurately diagnosing different types of diabetes, multiplicity and variability of genetic influences, incomplete understanding of pathophysiology, limitations of current therapies, and environmental, social, and psychological factors that affect clinical management (7,8). Therefore, a stepwise approach is needed.

Monogenic forms of diabetes, for which single gene mutations are causal, are the ones best suited to more precise interventions. More than 50 genetic subtypes have been described in which the disease-causing mutation appears to be minimally affected by behavioral and environmental factors. Because the etiology of monogenic forms is known, their pathophysiological mechanisms are also understood better than those of other forms of diabetes. Although these disorders account for a relatively small proportion of all cases of diabetes, ranging from 1% to 5% in reports of pediatric and young-adult populations (9–14), they present an opportunity to demonstrate the feasibility of precise diagnostic and therapeutic strategies (15). Despite the demonstrated importance of making a correct diagnosis, it is estimated that at least 80% of all monogenic cases of diabetes remain undiagnosed (16).

In June 2019, the editors of *Diabetes Care* convened a group of experts to discuss this opportunity. The group was asked to consider the present scientific understanding of the main monogenic forms of diabetes, current experience with diagnostic and therapeutic approaches to the management of each of these, and the challenges to applying these insights at a population level. The American Diabetes Association and the European Association for the Study of Diabetes recently established the Precision Medicine in Diabetes Initiative to consider the potential for precision medicine in diabetes more generally (6), and this *Diabetes Care* Editors’ Expert Forum was intended to complement that initiative. This article summarizes the major themes that arose at the forum.

## MONOGENIC DIABETES: AN OVERVIEW

### Clinical Subtypes of Monogenic Diabetes

An unusually strong genetic component causing diabetes in certain individuals was suspected decades ago by astute clinicians who observed two main clinical phenotypes that continue to be most suggestive of a possible monogenic cause: 1) onset of diabetes in neonates or infants (termed neonatal diabetes mellitus [NDM]) and 2) families with several generations of diabetes occurring in adolescents or young adults suggestive of an autosomal dominant pattern of inheritance (termed maturity-onset diabetes of the young [MODY]) (17). Other subtypes of monogenic diabetes include multisystem syndromes, severe insulin resistance (in the absence of obesity), and lipodystrophy (both full and partial).

### Evolving Classification Systems

In the past three decades, the classification of monogenic diabetes disorders has evolved from one based on clinical characteristics (e.g., MODY) to one based on molecular genetics (e.g., glucokinase gene [*GCK*] status). This evolution has improved the robustness of diagnoses and enhanced our ability to define the etiology, likely clinical course, and best treatment in any given patient.

The order in which causative loci and genes were described in the literature was used originally in the nomenclature of MODY subtypes. Thus, a disorder involving the *HNF4A* gene was termed “MODY1,” one involving *GCK* was called “MODY2,” and so forth up to at least MODY14 at present (18). This approach has broken down, however, as more genes have been described. In some cases, new MODY numbers have been assigned without convincing rigorous evidence of causality (19), and in others, new genes involved in MODY have been described but not assigned a number (20).

A more useful classification combines the standard abbreviation for the gene involved, followed by a term or abbreviation of the clinical phenotype (because the same gene can result in multiple phenotypes). Clinical phenotypes include MODY, PNDM (permanent NDM), TNDM (transient NDM), lipodystrophy, severe insulin resistance, and so forth. Examples of this combined nomenclature, then, are

*GCK-MODY*, *KCNJ11-TNDM*, and *PPARG*-partial lipodystrophy (i.e., lipodystrophy caused by mutations in *PPARG*). When a clinical diagnosis is made but genetic testing has not been performed, the clinical classification can be used without an associated gene (e.g., MODY alone).

The term MODY itself can result in confusion with childhood-/young-adult-onset type 2 diabetes, which is typically associated with marked obesity, unlike the familial monogenic form of diabetes for which the term was intended. Still, the term persists in the literature, and most diabetes care providers are familiar with it as a disease entity, even if they may not remember many other details. Hence, it is easiest to continue to use it as the clinical descriptor rather than inventing a new nomenclature.

The most common causes of monogenic diabetes (MODY and NDM) are listed in Table 1 and discussed in more detail below.

### GCK-MODY

Nonprogressive hyperglycemia related to *GCK*, or *GCK-MODY*, is the most common cause of monogenic diabetes, with an estimated incidence as high as 1 in 1,000 individuals (21). It is caused by heterozygous inactivating mutations in the enzyme glucokinase, which acts as the  $\beta$ -cell glucose sensor (22,23). Metabolism of glucose initiated by *GCK* activity triggers the cascade of events leading to insulin secretion, but impairment of *GCK* activity causes an increase in the threshold glucose level required for insulin secretion to be initiated, while  $\beta$ -cell function is otherwise completely normal (24,25). The key role of *GCK* in hepatic regulation of glucose release and storage also results in defects in these processes. The overall result is mild fasting hyperglycemia, usually 97–150 mg/dL (5.4–8.3 mmol/L), and an A1C of ~5.8–7.6% (40–60 mmol/mol) (26).

This pattern is present from birth and remains remarkably stable over time, although there can be an age-related increase in A1C that is parallel to that seen in aging populations (27). Individuals are asymptomatic and are not diagnosed until incidental laboratory testing or routine screening reveals hyperglycemia, often as pediatric incidental hyperglycemia (28–30), during pregnancy, or during incidental illness (21,31,32).

**Table 1—Clinical implications of some common and important causes of monogenic diabetes**

Gene	Inheritance/phenotypes	Disease mechanism/special features	Importance of genetic diagnosis
<i>GCK</i>	AD: <i>GCK</i> -MODY (common) AR: <i>GCK</i> -NDM (very rare)	Reduced function of glucokinase enzyme raises set point for insulin secretion that is otherwise normal; high population prevalence of causal variants (~1 in 1,000)	<b>No treatment needed</b> for most patients (except possibly during pregnancy)
<i>HNF1A</i>	AD: <i>HNF1A</i> -MODY (common)	LOF of $\beta$ -cell transcription factor; glucosuria is common; risk for benign hepatic adenomas (rarely can become large and/or complicated)	Excellent glycemic control usually possible with low-dose oral sulfonylureas
<i>HNF4A</i>	AD: <i>HNF4A</i> -MODY (uncommon)	LOF of $\beta$ -cell transcription factor; carriers may have history of large birth weights and/or hyperinsulinemic hypoglycemia	Often responsive to low-dose oral sulfonylureas
<i>HNF1B</i>	AD: <i>HNF1B</i> -MODY (uncommon)	LOF of pancreatic/renal transcription factor; renal cysts/genitourinary malformations (may be more penetrant than diabetes); hypomagnesemia; exocrine pancreatic insufficiency, altered liver function tests, hyperuricemia, developmental delay (as part of chromosome 17q deletion syndrome)	Optimal treatment for diabetes not well established; genetic diagnosis will inform monitoring and management of other features
<i>ABCC8</i>	AD/AR: <i>ABCC8</i> -NDM (common) <i>ABCC8</i> -MODY (rare)	Activating missense mutations in $\beta$ -cell $K_{ATP}$ channel SUR1 subunit impair glucose-stimulated insulin secretion; NDM may have a spectrum of neurodevelopmental dysfunction	Usually responds to high-dose oral sulfonylureas; genetic diagnosis facilitates monitoring/intervention for neurodevelopmental problems
<i>KCNJ11</i>	AD: <i>KCNJ11</i> -NDM (common) <i>KCNJ11</i> -MODY (rare)	Activating missense mutations in $\beta$ -cell $K_{ATP}$ channel Kir6.2 subunit impair glucose-stimulated insulin secretion; NDM often have a spectrum of neurodevelopmental dysfunction	Usually responds to high-dose oral sulfonylureas; genetic diagnosis facilitates monitoring/intervention for neurodevelopmental problems
6q24 (imprinted locus)	Most common cause of transient NDM	Overexpression of maternally imprinted 6q24 genes causes impairment of $\beta$ -cell development and function; after remission of NDM within first year of life, diabetes will often recur in adolescence or adulthood	Diabetes recurring later in life is often responsive to noninsulin therapies
<i>INS</i>	AD/AR: <i>INS</i> -NDM (common) AD: <i>INS</i> -MODY (rare)	Missense mutations cause insulin protein misfolding and progressive $\beta$ -cell death (other mechanisms occur more rarely)	Early intensive insulin treatment; future treatments may feasibly target molecular mechanism(s)

AD, autosomal dominant; AR, autosomal recessive; Kir6.2, inward rectifier potassium channel 6.2; SUR, sulfonylurea receptor.

Experts advise that no treatment is required, except possibly under certain circumstances during pregnancy in women with *GCK*-MODY (33,34). Nontreatment is advised because mild hyperglycemia is not sufficient to cause the microvascular or macrovascular complications associated with other forms of diabetes (26), and therapy does not lower glucose as it is regulated at the higher fasting level (35,36). This advice can sometimes be difficult for both people with *GCK*-MODY and earnest diabetologists to accept, yet the weight of the evidence showing the absence of diabetes complications and a lack of treatment response is clear. The urgent need to improve our recognition of this disorder is seen in the high percentage of individuals who are unnecessarily treated with a variety of medications before genetic diagnosis, for whom cessation

of treatment usually has no effect on overall glycemia (35,37,38).

#### ***HNF1A*-MODY and *HNF4A*-MODY**

*HNF1A*-MODY is the most common cause of symptomatic, treatment-requiring MODY (39). Less common mutations in another  $\beta$ -cell transcription factor (*HNF4A*) have a similar clinical presentation and treatment requirement (40). These genes encode transcription factors present in many tissues. Although originally named as hepatocyte nuclear factors after being identified as transcription factors in a liver cDNA library, these genes play more important roles in the  $\beta$ -cell and are also expressed in multiple other organs such as the kidney.

Individuals with either *HNF1A*-MODY or *HNF4A*-MODY usually have an excellent glucose-lowering response to low

doses of inexpensive oral sulfonylurea medications, but there are key differences in other associated clinical features of these two subtypes. Before a genetic diagnosis, patients are often treated with a variety of less effective medications such as metformin or insulin, and switching to a sulfonylurea is not only cheaper but also tends to improve glycemic control (41–44). The response to sulfonylurea treatment can be so dramatic that hypoglycemia can cause a provider to switch to a different treatment, when in fact this response could be recognized as a reason to adjust dosing and pursue genetic testing.

A reduction in *HNF1A* regulation of sodium–glucose cotransporter 2 (SGLT2) levels in the kidney results in glycosuria despite near-normal blood glucose levels (45). This response means that glycosuria

can be an early marker of children who have inherited an *HNF1A* mutation (46). Given the effects of *HNF1A* on SGLT2 expression, caution should be observed in administering SGLT2 inhibitor medications to such individuals (46).

*HNF4A*-MODY has a similar diabetes phenotype to *HNF1A*-MODY with one clinically very important difference: fetuses and newborns with an *HNF4A* mutation have excessive insulin secretion. The increased fetal insulin secretion results in a marked increase in birth weight (~800 g) and a very high risk of macrosomia even when a fetus has inherited the mutation from the father (47). The neonatal hyperinsulinism can result in persistent and prolonged hypoglycemia in some patients (47,48). The management of *HNF4A*-MODY in pregnancy is discussed later in this article. The mechanisms underlying neonatal hyperinsulinemia but subsequent diabetes resulting from reduced  $\beta$ -cell function in *HNF4A*-MODY remain unexplained.

#### ***HNF1B*-MODY**

*HNF1B*-MODY is typically characterized by renal cysts and diabetes but can feature developmental anomalies in multiple systems (49). This form of diabetes typically starts in adolescence or early adulthood, is usually insulin-requiring, and may be insulin-dependent because the etiology is a reduced number of  $\beta$ -cells in development. Frequently, there is also reduced pancreatic exocrine function, which may require treatment. Reduced pancreatic tail size or low fecal elastase can aid diagnosis of exocrine pancreatic insufficiency. Although renal cysts are typical, multiple subtypes of developmental kidney disease have been described. *HNF1B*-MODY is the most common genetic etiology of childhood kidney disease, accounting for 20–30% of cases (49).

#### ***KCNJ11*-NDM and *ABCC8*-NDM**

Activating heterozygous mutations in either gene encoding the subunits of the  $\beta$ -cell  $K_{ATP}$  channel (*KCNJ11* or *ABCC8*) are the most common cause of PNDM and a major cause of TNDM (50–55). Mutated channels maintain membrane hyperpolarization even in the face of extreme hyperglycemia, but treatment with high doses of a sulfonylurea can overcome these defects, enabling transition off insulin (56) and restoring meal-stimulated insulin secretion (57) with minimal hypoglycemia (58).

Excellent glycemic control commonly persists even after >10 years of treatment (59).

The clinical phenotype is correlated with the severity of mutation, with more damaging variants also causing a spectrum of neurodevelopmental disabilities that can be at least partially ameliorated by early initiation of sulfonylurea treatment once a genetic diagnosis is revealed (60–62). More mildly activating mutations are a common cause of TNDM (*ABCC8* more often than *KCNJ11*) or may present as a rare form of MODY in individuals or family members who are not known to have had neonatal hyperglycemia but later in life develop MODY-like diabetes that is also usually responsive to a sulfonylurea (63,64). Other rare causes of NDM from  $K_{ATP}$  mutations include biallelic mildly activating mutations (usually homozygous), as well as compound heterozygous mutations, in which one is activating and the other is a loss-of-function (LOF) variant (65). However, homozygous LOF variants in either gene cause congenital hyperinsulinism (66).

#### **Imprinted Locus at Chromosome 6q24**

Overexpression of maternally methylated genes at chromosome 6q24 is the most common cause of TNDM, in which the diabetes spontaneously resolves within the first year of life but usually recurs in adolescence or young adulthood (67). When diabetes recurs, clinicians must recognize the significance of the TNDM history because these patients will often respond to oral medications and not require insulin (68).

#### ***INS*-NDM and *INS*-MODY**

With certain subtypes of monogenic diabetes, a genetic diagnosis may not lead to changes in treatment of diabetes but could still allow for a precision-based approach. For example, heterozygous mutations in the proinsulin gene (*INS*) are the second most common cause of PNDM, stemming from a progressive loss of  $\beta$ -cell functional capacity resulting from accumulation of misfolded proinsulin protein (69). Although treatment is currently limited to insulin, minimizing the stimulus for excessive production of the mutated protein by minimizing hyperglycemia through early intensive insulin management may allow for slowing of the progressive loss of  $\beta$ -cell function and better long-term outcomes (70).

Recessive nonsense or promoter *INS* variants preventing or greatly reducing insulin secretion also cause PNDM or TNDM (71,72). Rare *INS* variants also cause a form of MODY through distinct mechanisms such as reduced binding at the insulin receptor, but the best therapeutic options for these rare patients have not yet been established (73,74).

#### **Less Common Causes of Monogenic Diabetes**

Monogenic diabetes can result in multisystem syndromes that are usually congenital and hence cause NDM (50,75) but can also result in a later onset of diabetes. The most common multisystem syndromes that present later in life are *HNF1B* (discussed earlier), mitochondrial diabetes, and Wolfram syndrome. These syndromes frequently present with diabetes, which may not be recognized as a first manifestation of a multisystem disease.

Cardinal features of mitochondrial diabetes syndromes, most commonly caused by m.3243A>G mutation, include maternally inherited diabetes (typically diagnosed in the third or fourth decades of life), sensorineural deafness (typically diagnosed before the diabetes), and several other possible problems such as renal manifestations, cardiomyopathy, myopathy, and central neurological features (76). Wolfram syndrome is a rare, severe, multisystem condition characterized by insulin-dependent diabetes (diagnosed in the first decade of life), optic atrophy, diabetes insipidus, and sensorineural deafness. It is usually caused by recessive mutations in *WFS1* (77).

Other subcategories of monogenic diabetes include a growing list of genes causing monogenic autoimmune syndromes in which diabetes is a common feature (78). Lipodystrophies and other syndromes of severe insulin resistance often go unrecognized as clinically distinct from type 2 diabetes even though optimal management may entail vastly different therapeutic approaches (79,80). The heterogeneity of phenotypic presentation and age of onset can hinder recognition of such patients as candidates for genetic testing, but, even if the diabetes can only be treated with insulin, a correct diagnosis can still guide monitoring and treatment of associated features, clarify the long-term prognosis, and lead to testing in family members.

## CHALLENGES AND OPPORTUNITIES IN DIAGNOSIS AND TREATMENT

### Challenges in Diagnosis and Management

The presence of a monogenic form of diabetes should be considered when a patient does not seem to fit with the more common presentations of type 1 or type 2 diabetes. Decades of research on different populations have shown that any stringently defined set of features will be too restrictive to identify all people who carry a highly penetrant genetic variant. Such criteria, originally associated with the research by Stefan S. Fajans on MODY (17), have typically included onset before the age of 25–35 years, lack of insulin dependency (as shown by treatment or C-peptide measurement), absence of obesity or other signs of insulin resistance, and dominant inheritance over several generations. The absence of pancreatic islet-specific autoantibody titers associated with type 1 diabetes has now become another important measure. No approach will be sensitive enough to accurately detect every case or specific enough to ensure that genetic testing is not performed on patients who turn out not to have a monogenic diagnosis.

### Selecting Appropriate Individuals for Genetic Screening

Because no combination of clinical, historical, and biomarker information can reliably identify all cases, there must be a balance between the desire to test more often (even when the chance of a positive result is very low) and the need to control costs (by restricting testing to selected groups). In the absence of clear guidelines, decisions on testing rest with individual clinicians. This dilemma occurs especially with patients in youth or young adulthood, when the more common forms of monogenic diabetes are most likely to become apparent. Some patients who are unlikely to have MODY are tested, whereas many who are very likely to have MODY are not.

There are also barriers to making a diagnosis for certain individuals who are very likely to have MODY, such as those with diabetes who are first- or second-degree relatives of people with known monogenic diabetes. Evaluation of close relatives has not been a priority in diabetes care and can be challenging,

especially when they receive health care from a different medical team or live far away.

### Accessing Genetic Testing

Difficulties in arranging for genetic testing can include a lack of availability and high costs, even when testing is partially covered by insurance plans. In most industrialized countries, molecular genetic testing for MODY is available, but in many regions throughout Asia and Africa, samples must be sent to distant laboratories outside of the patient's country of residence.

Inequities in access may arise when such testing is not provided by a state health care system or not covered by private insurance companies. The cost of genetic testing, like that of other technology-related services, is likely to decline, but a significant decrease has not yet occurred. In systems with commercial payers, cumbersome authorization processes and high direct costs to patients can influence whether testing is done. Even in government-funded health care systems, restrictions due to limited resources dictate that testing be performed only when the likelihood of a positive result is high.

### Ensuring the Quality of Testing and Interpretation of Results

Genetic testing would seem to be a robust procedure, but there are troublesome issues with both the methods used and interpretation of the findings. Many laboratories have offered testing for only a few of the most common genetic disorders. However, improvement in testing methods, particularly the advent of multiple gene sequencing, now allows more subtypes of monogenic diabetes to be assessed with a single test.

Recent studies have demonstrated the importance of comprehensive testing. One used a population-based approach to screen all nonneonatal patients diagnosed with diabetes at <30 years of age and found that up to 18% of those with monogenic diabetes had subtypes other than *GCK*, *HNF1A*, and *HNF4A* (81,82). These rarer but clinically significant forms include *ABCC8/KCNJ11* (which respond to sulfonylurea treatment), *HNF1B* (diabetes with renal cysts and/or other genitourinary defects and other associated features) (49), and m.3243A>G (the most common mitochondrial mutation causing maternally inherited diabetes and deafness [76]).

Errors in the interpretation of sequencing are also common in diagnostic laboratories with limited experience with monogenic diabetes and when the clinical presentation of patients and the pretest likelihood of a monogenic diagnosis are not considered (19). The increase in the number of genes assessed has exacerbated problems of interpretation. With the more common MODY genes, mutations frequently lead to haploinsufficiency, and causality of novel variants is therefore easier to predict. For genes including *PDX1*, *CEL*, *ABCC8*, *KCNJ11*, and *INS*, in which a heterozygous nonsense mutation causing haploinsufficiency does not result in the diabetes phenotype, more sophisticated interpretation is needed. In contrast, certain missense mutations may be causal, whereas other missense variants and protein-truncating variants may be benign. Other genes being tested do not actually meet robust criteria for causing monogenic diabetes (83). These issues were reviewed in a recent commentary by Ellard et al. (19).

Assessment of allele frequency in people not selected for disease in databases such as gnomAD (84) has helped to rule out alleles that are too frequent to cause MODY (1 in 60,000 alleles or 1 in 30,000 people), and several variants previously published as mutations can now be excluded. Despite the availability of this information, the lack of widespread understanding results in common polymorphisms still being reported as causal mutations.

In short, there is still a long way to go in achieving consistent, high-quality interpretation of genetic testing. Fortunately, efforts are underway to address these problems. For example, all laboratories should be encouraged to take part in quality assurance programs such as the European Molecular Genetics Quality Network MODY Group (85). The National Institutes of Health-supported Clinical Genome Resource (86) includes a long-term effort to bring together disease-specific clinical and genetic experts to evaluate the evidence for gene-disease relationships and to establish the likelihood that known variants are causal or benign, using recently established American College of Medical Genetics and Genomics/Association for Molecular Pathology guidelines (87). The Monogenic Diabetes Variant Curation Expert Panel is developing a systematic process for reviewing pathogenicity and submission to ClinVar (88).

Even as reporting of genetic testing improves, the clinical significance of reports may not be understood by medical providers, even those who are diabetes specialists. This occurs most often when “variants of uncertain significance” (VUS) are reported, leaving the ordering providers to draw their own conclusions about possible causality. Whereas some laboratories thoroughly review and report all possible evidence, others may report a variant as a VUS if their review is less complete. Some laboratories lack a standard process for obtaining clinical data that might improve the relevance of their reported conclusions.

#### **Taking Appropriate Clinical Action**

Additional problems arise when a genetic diagnosis is established but appropriate changes in clinical management are not made. Many diabetes health care professionals do not have experience with genetic subgroups, and genetic reports often do not provide clinical guidance. Failure to recognize the implications of a diagnosis of *GCK*-MODY can result in initiation of glucose-lowering treatment that will be ineffective (Table 1) (35). Similarly, insulin therapy may be prescribed unnecessarily for *HNF1A*-MODY, which is highly responsive to sulfonylurea therapy (43). Informed therapeutic decisions are particularly needed in the setting of pregnancy accompanying *GCK*-MODY. Moreover, clinicians should be aware that not all patients in specific monogenic diabetes subgroups will respond well to what is considered optimal therapy, and those who respond initially may require changes to therapy later (89).

Beyond glycemic control, appropriate management of monogenic diabetes also can include examining other organs that may be affected. Examples include renal function with *HNF1B*-MODY (49) and echocardiographic or electrocardiographic changes due to cardiomyopathy associated with mitochondrial mutations that cause maternally inherited diabetes and deafness (76).

#### **Opportunities in Diagnosis and Management**

##### **Improving Recognition of Potential Monogenic Diabetes Patients**

Understanding which individuals are most likely to have a monogenic etiology is centrally important. One consideration in

genetic screening is the age at which a patient is diagnosed with diabetes. Other considerations include clinical features and laboratory test results.

##### **Diagnosing Monogenic NDM**

Identifying monogenic NDM is relatively easy because the only alternative diagnosis is type 1 diabetes, which is very rare before the age of 6 months. Using a cutoff age of 6 months identifies a group of patients in which at least 82% have an identifiable form of monogenic NDM (50). There is absolutely no doubt that every patient diagnosed in the first 6 months of life should be genetically tested.

It is uncertain whether testing patients diagnosed with diabetes between 6 and 12 months of age is economically justified. The answer will depend on the frequency of pathogenic  $K_{ATP}$  channel mutations. Correct diagnosis of such mutations, allowing for inexpensive treatment with sulfonylureas and improved long-term glycemic outcomes, may make a policy of testing cost-saving as long as at least 3% of those screened have treatable defects (90). One study found that 4% of patients presenting between the ages of 6 and 9 months had  $K_{ATP}$  channel-related NDM, suggesting that a policy of testing up to 9 months of age likely remains cost-saving (91). Very few  $K_{ATP}$  channel mutation cases have been reported as being diagnosed after 9 months of age (92,93), and such cases have not been found in systematic surveys of this age-group (91). Thus, at present, it is not cost-effective to test after 9 months of age, but this cut point may change with future studies.

##### **Distinguishing MODY From Type 1 Diabetes and Type 2 Diabetes**

Diagnostic criteria must be able to discriminate MODY from both type 1 diabetes and type 2 diabetes. Efforts to do so are complicated by the fact that clinical features differ among the common subtypes of MODY. Selection of appropriate patients for genetic testing must consider a combination of clinical considerations and laboratory tests, with the latter primarily being used to exclude type 1 diabetes.

Although no algorithm will be perfect, the MODY probability calculator (<https://www.diabetesgenes.org/mody-probability-calculator>), which estimates the likelihood of a patient having MODY based on clinical criteria, is a robust and widely used

method of assessing the clinical likelihood of genetic etiology (94). Further refinement and validation for different populations in different countries and/or clinical settings should yield reasonable estimates of the probability that testing will reveal a monogenic diagnosis. Health systems could consider using such tools to establish policies allowing for genetic testing in patients whose probability of having an underlying monogenic cause meets an established cost-effectiveness threshold, while allowing for exceptions based on individual circumstances.

##### **Establishing the Cost-Effectiveness of Genetic Testing for MODY**

Distinguishing certain forms of MODY from both type 1 and type 2 diabetes can result in significant treatment differences and improvements in outcome that have the potential to greatly reduce costs. One study modeled the potential cost differences of distinguishing MODY from type 2 diabetes based on the assumption of improved glycemic control using sulfonylurea therapy for *HNF1A*-/*HNF4A*-MODY and no treatment for *GCK*-MODY (95). This analysis suggested that a policy limiting testing to individuals who have at least a 6% chance of having MODY will be cost-effective. If the criteria used can identify a group of patients in which 30% will have a monogenic cause, genetic testing will be cost-saving. Interestingly, genetic testing of all patients with type 2 diabetes diagnosed at <40 years of age could potentially be cost-effective if the cost of testing were reduced to <\$700 (95).

A more recent study used real-world data from several studies of pediatric diabetes to model the cost-effectiveness of systematic biomarker screening and genetic testing of patients diagnosed with diabetes between the ages of 10 and 20 years who are C-peptide-positive and anti-islet autoantibody-negative (96). Based on the assumption of improved glycemic control with sulfonylurea therapy (in most cases instead of insulin) for those found to have *HNF1A*-/*HNF4A*-MODY and cessation of all treatment in those found to have *GCK*-MODY, the model suggested that such a screening approach would be cost-saving, and the savings would increase for every additional family member who could be identified.

A recent study based on data from the U.K. (97), including data from the UNITED

(Using pharmacogenetics to Improve Treatment in Early-onset Diabetes) study (81), further assessed the potential of systematic screening of adults with diabetes. The analysis was based on C-peptide and autoantibodies in insulin-treated patients diagnosed with diabetes at <30 years of age. Health economic modeling established that an algorithm-based strategy using these biomarkers, together with the MODY probability calculator, saved ~£100–200 (US\$123–246) per person tested over a lifetime (97). Based on the population of England and Wales, applying this approach in those with diabetes diagnosed before the age of 30 years who are currently <50 years of age would be predicted to save the health care system £20–40 million (US\$25–49 million).

#### **Identifying MODY in Pediatric and Young-Adult Age-Groups**

The main alternative diagnosis in the pediatric age-group is type 1 diabetes. Cases of type 2 diabetes usually stand out because of obesity, parental family history, high-risk racial/ethnic group, or some combination of these characteristics. Many pediatric patients with diabetes are treated with insulin immediately, even when they have modest hyperglycemia, making it difficult to assess their underlying  $\beta$ -cell function. Even if C-peptide measurement confirms that a patient has significant endogenous insulin secretion, type 1 diabetes in an early stage or honeymoon period remains a possibility.

Testing for multiple islet autoantibodies that are present in type 1 diabetes can help greatly. These include islet antigen 2 autoantibodies, insulin autoantibodies, GAD autoantibodies, and zinc transporter 8 autoantibodies. Individuals with titers greater than the 97.5th percentile for one or more autoantibodies do not need to be tested for MODY (11,13). However, 12–15% of individuals with pediatric diabetes are anti-islet autoantibody-negative at the time of diagnosis, the majority of whom have autoimmune diabetes (11,13); this proportion decreases with repeat testing (98). Additionally, GAD autoantibodies can be positive in 1–2% of people without diabetes (99).

Beyond autoantibody status, two other key factors that raise the likelihood of a monogenic disorder are an A1C <7.5% at diagnosis and a parental history of diabetes (13).

#### **Identifying MODY in Middle-Aged Adults**

Although MODY can present later in life, the vast majority of cases involve diabetes diagnosed before the age of 35 years. Individuals diagnosed after the age of 40 years should only exceptionally be tested; the person in a family who was diagnosed at the youngest age with non-insulin-dependent diabetes should be tested first. In patients <40 years of age who are not treated with insulin, the major differential diagnosis is familial type 2 diabetes, with the key discriminatory factors for MODY being low BMI and earlier age of diagnosis, as is well assessed by the MODY probability calculator (94). For patients <40 years of age who start insulin therapy immediately upon diagnosis, the main differential diagnosis is type 1 diabetes, and testing for islet autoantibodies, C-peptide levels, or both can help to discriminate, along with clinical features.

#### **Elucidating the Epidemiology of Monogenic Diabetes**

Population-based intervention for any disorder requires information on its epidemiology. Defining the epidemiology of monogenic diabetes is difficult because there have been few population-based studies, and those done have been mostly in populations that are predominantly White and of European origin.

PNDM is one of the better-studied categories of monogenic diabetes. In most population studies in high-income countries with a low prevalence of consanguineous marriages, its prevalence is 1 in 100,000–200,000 live births, and most cases are heterozygous, with ~80% being de novo mutations (50). Low-income countries have a much lower frequency of recognized cases. In regions having high rates of consanguineous marriage, the prevalence of PNDM is much higher (~1 in 20,000–40,000 live births), and recessive causes are found in the majority of cases (50).

The prevalence of MODY has been best investigated in population-based studies of pediatric cases in Europe and the U.S., with prevalence rates ranging from 0.6% to 6.3%, as reviewed by Shepherd et al. (89). A major cause of variation in prevalence is how many individuals with *GCK* mutations are identified, which has ranged from 20% of MODY when there is a MODY prevalence of 0.6% (100) to 75% of MODY when there is a MODY

prevalence of 6.3% (101). *GCK* mutations were more prevalent when pediatric patients with persistent incidental hyperglycemia were included as well as patients diagnosed with diabetes.

There have been few systematic epidemiologic studies of adults because of the large numbers involved. The only study of which we are aware is the previously mentioned UNITED study (81). This study was conducted in two regions of the U.K. where all patients who had been diagnosed with diabetes at <30 years of age who were still <50 years of age were genetically screened if they did not have a low C-peptide level or high-titer pancreatic autoantibodies. Using this approach, 3.6% of this young-onset group had monogenic diabetes.

Because systematic studies of monogenic diabetes have focused on populations of people who are relatively younger and/or known to have features suggestive of a monogenic cause, the actual population-wide prevalence over the full range of ages remains uncertain.

### **CURRENT EXPERIENCE WITH SCREENING, DIAGNOSIS, AND MANAGEMENT**

#### **Physician-Based Approaches**

The study of monogenic diabetes is a relatively new field. At present, monogenic diabetes is not generally diagnosed via systematic population screening, but rather by investigation of cases referred by individual physicians based on a likely clinical presentation. This approach is still missing as many as 80% of monogenic diabetes cases, which are instead being misdiagnosed as type 1 or type 2 diabetes (16,102).

Studies of physician referrals to specialist centers for genetic diagnosis have shown that there is a marked degree of regional variation in referral for (and therefore in diagnosis of) monogenic diabetes (16,102). Factors that contribute to this problem include differences in awareness of monogenic forms of diabetes among clinicians and differences in access to appropriate screening and genetic testing services. The existence of specialist networks and the geographic distribution of expert centers have clear effects on identification of new cases (16,101). For these reasons, the reported prevalence of monogenic diabetes as a percentage of all cases varies widely among different regions and countries.



A more systematic screening approach using a predefined protocol to examine consecutive pediatric cases was reported by an Italian group who conducted a retrospective analysis (101). This study was conducted through a network of pediatric centers providing good coverage and access throughout Italy, and it followed a sequence of investigations from type 1 diabetes–associated autoantibodies through to genetic testing based on presenting “metabolic phenotype.” This method identified a higher proportion of monogenic cases, 6.3% of the total (101), than has been reported elsewhere in similar age-groups.

Education of clinical providers has been shown to greatly improve the effectiveness of the physician-based approach to the diagnosis of monogenic diabetes. In one ongoing project, the monogenic diabetes specialist team at the Royal Devon and Exeter National Health Service Foundation Trust and University of Exeter Medical School trained a cohort of 52 diabetes nurse specialists across the U.K. to serve as genetic diabetes nurses (103). This project has been highly effective at spreading the necessary clinical expertise from specialist testing centers to routine clinical care settings. Such a nurse-led approach to clinician education seems ideal for translation to other countries and regions in support of a more precise approach to diabetes care.

### Systematic Population-Based Screening

An alternative approach used in the UNITED trial (81) is systematic population-based screening to identify young patients for possible MODY sequencing, using low C-peptide and positive autoantibodies to exclude likely type 1 diabetes. This approach has been shown to be highly effective and cost-effective (97). Applied at scale, it should ensure that there are no inequities in screening and diagnosis of monogenic diabetes in the population tested.

A similar strategy of C-peptide testing in individuals with >3 years' duration of assumed type 1 diabetes and autoantibody testing at diagnosis, with monogenic gene sequencing then performed in those who are autoantibody-negative or have a persistently robust C-peptide level, is now being implemented in Scotland, making it the first country to implement

population-wide testing for monogenic diabetes.

### Screening in the Pediatric Population

Making a correct diagnosis of MODY in pediatric diabetes is important because these patients will spend almost their whole life living with diabetes, and increasing attention is directed to this problem. However, the correct diagnosis often is made years after an incorrect initial diagnosis, when assumed type 1 diabetes fails to progress. Making a MODY diagnosis close to the initial diagnosis of diabetes is a priority.

Currently, recognition of possible MODY cases is based on clinical features at follow-up rather than on any sort of assessment at the time of diabetes diagnosis. There is clear evidence of the need for systematic testing; the multicenter SEARCH for Diabetes in Youth study in the U.S. (11) showed that *HNF1A*, *HNF4A*, and *GCK* mutations accounted for 1.2% of diabetes cases in the pediatric population, but the vast majority of these patients with MODY were misdiagnosed and inappropriately treated with insulin. Screening procedures or algorithms based on islet autoantibodies that are reliable discriminatory factors at diagnosis (104) could be used to direct genetic testing for MODY sooner. Using such protocols would reduce delays in recommended treatment and potentially reduce both personal and clinical costs.

Comprehensive autoantibody testing close to the time of diagnosis to guide testing for MODY has been performed in pediatric populations in a large multicenter study in the U.S. (11) and in national studies in Sweden (13) and Norway (100). Testing for MODY was systematically performed in the 12–15% in whom islet antibodies were not detected. The overall prevalence of MODY in these three studies was 0.8–1.2%. No cases were reported when patients were autoantibody positive (13). In these studies, the absence of autoantibodies was the strongest predictor of MODY in these populations, being more discriminatory than any clinical criteria. Because MODY is detected in 7–15% of all autoantibody-negative children, 85–93% of these patients do not have MODY; the majority have type 1 diabetes, but some have type 2 diabetes, and this proportion varies depending on the population studied (11).

In the most comprehensive study at diagnosis to date (13), individuals with MODY had lower random plasma glucose and A1C levels than those without MODY and did not present with diabetic ketoacidosis. These indications of severity of presentation discriminated better than the other good predictor—a parental history of diabetes. Using this information could reduce the number of autoantibody-negative patients who need testing for MODY near the time of diabetes diagnosis in pediatric populations, but this reduction will be at the cost of missing some cases.

### Diagnosis and Management of MODY in Pregnancy

MODY patients, especially those with *GCK*-MODY, are often identified during pregnancy. Monogenic disorders account for 1–2% of all cases of diabetes diagnosed during pregnancy, with *GCK*-MODY being found in one in three patients with a fasting glucose  $\geq 100$  mg/dL (5.5 mmol/L) and normal weight (BMI  $< 25$  kg/m<sup>2</sup>) (21). It is important to correctly identify patients with *GCK*-MODY because its clinical course and management differ substantially from those of other types of diabetes in pregnancy.

In *GCK*-MODY, the primary determinant of fetal growth is the fetal genotype, with affected fetuses having normal birth weight and unaffected fetuses being ~500–600 g heavier than normal (33). Fetal genotype is not usually known, although an exciting new development is the use of noninvasive testing using cell-free DNA in maternal blood to assess whether a fetus is affected (105). In the absence of cell-free DNA testing, serial fetal ultrasound measurements can help determine likely fetal genotype. If accelerating fetal abdominal circumference—a sign of macrosomia—is present on serial ultrasounds, it can be assumed that the fetus does not have the *GCK* mutation. Insulin therapy is usually recommended to reduce the risk of macrosomia, and delivery could be induced at 38 weeks. However, well-designed studies have not proven that this approach leads to fewer complications, whereas insulin treatment may be associated with episodes of hypoglycemia, including severe hypoglycemia (33,34). If serial ultrasounds show normal fetal growth, the fetus has



probably inherited the *GCK* mutation and will have an elevated glucose set point similar to that of the mother. In that setting, mild maternal hyperglycemia is desired (31,106), and treatment is not indicated and may be harmful by resulting in low birth weight (34).

It is crucial to recognize *HNF4A*-MODY in pregnancy because fetuses that inherit the *HNF4A* mutation will be ~800 g heavier than those that do not inherit the mutation. This tendency to gain weight, especially if combined with maternal hyperglycemia, can result in massive macrosomia (>5 kg), which can cause severe fetal and maternal complications (47). Thus, repeated ultrasound scans are needed, with early delivery if they reveal evidence of excessive fetal growth (47). It is also important to monitor the fetus carefully when the father has MODY, even though the mother is unaffected and has normal glucose levels, because, if the fetus is affected, the risk of macrosomia is as high as or higher than in conventional gestational diabetes mellitus (47).

The excessive fetal insulin secretion caused by the *HNF4A* mutation that leads to macrosomia can also result in prolonged and severe neonatal hypoglycemia. For this reason, a pediatrician should be present at delivery, and urgent *HNF4A* testing for the specific mutation in the fetus should be performed rapidly. The emerging method of determining fetal mutation status using cell-free DNA from the mother allows for prediction of fetal outcome before delivery without relying on indirect evidence from maternal ultrasound scans (105).

In *HNF1A*-MODY and *HNF4A*-MODY, as in all other forms of diabetes during pregnancy, maternal glycemic control is a major determinant of fetal outcomes. The challenges in both MODY subtypes are twofold: uncontrolled hyperglycemia during the first trimester (the time of organogenesis) and a risk of macrosomia and neonatal hypoglycemia accompanying sulfonylurea therapy in the third trimester (107). Therefore, different treatment strategies have been proposed: either stopping sulfonylurea therapy before pregnancy and switching to insulin, or continuing sulfonylurea in the preconception period and early pregnancy and then switching to insulin in the second trimester (108). The latter

option has been suggested for patients with excellent glycemic control on sulfonylureas prior to pregnancy. Glyburide has been the most extensively studied sulfonylurea in pregnancy and is therefore recommended as the agent of choice (107).

In general, however, studies of pregnancy affected by monogenic diabetes are scarce, and data from prospective studies are needed to better define the need for and timing of insulin treatment during pregnancy (31,106).

## SUMMARY AND A WAY FORWARD

The promise of precision medicine is based on the individual or groups of individuals. The approach incorporates aspects of family history (genetics), lifestyle, and environment, such that the health care provider can customize interventions, diagnostics, and therapeutics to permit a healthier life for the patient and reduce health care utilization and costs. In diabetes, there are numerous forms of the disease at presentation, ranging from monogenic (involving single gene mutations) to those with complex etiologies (such as autoimmune type 1 diabetes) that require exogenous insulin for survival, to the most common form (type 2 diabetes) that itself results from dysregulation of multiple, incompletely understood metabolic processes.

Monogenic diabetes is currently the form of diabetes that is most relevant for the application of precision medicine in terms of diagnosis and treatment. However, the growing understanding of monogenic diabetes alone will not lead to much change in clinical practice. Practical application of this information requires several additions to diabetes management as it occurs in most places. It is also important to recognize that the distribution of various forms of monogenic diabetes relative to type 1 diabetes or type 2 diabetes may differ across global populations. As a preliminary proposal, this expert panel suggests that three programs are needed to accomplish and sustain population-based diagnosis and management of these disorders.

### 1. A Regional Infrastructure

There should be basic agreement on definitions and guidelines developed by professional societies or governmental agencies. The American Diabetes

Association's Precision Medicine in Diabetes Initiative (6), including this *Diabetes Care* Editors' Expert Forum, represents a step in this direction. Regional collection, storage, and management of data will be necessary. Such efforts are being undertaken in some countries in the form of disease-specific registries, but prospective management of data are insufficient in most locations. Depending on the size and geography of a given region, one or multiple specialized centers are needed. Ongoing financial support is necessary, and the case for providing it must be made based on the results of cost-effectiveness studies.

### 2. Specialized Expertise

Regional centers must be staffed by adequately trained professionals who are expert in the epidemiologic, genetic, and clinical aspects of diabetes. These specialty groups could manage the data, oversee laboratory methods, train personnel, and interact with clinical providers. Primary care providers need and will continue to need education and consultative support regarding individual cases, all of which can be provided by specialized diabetes centers.

### 3. Research Toward Population-Based Management of Other Forms of Diabetes

The infrastructure and expert center networks might be expected, over time, to expand their activities to study of the genetic factors underlying other forms of diabetes. At present, combined clinical and genetic risk scores are in development to assess risks of developing type 1 diabetes and type 2 diabetes and to predict individuals' need for and responses to various pharmacotherapies. In the future, clinical investigation of various kinds could be carried out efficiently through these centers of expertise. Ongoing screening for and treatment of individuals with monogenic disorders will naturally accrue data that bear on the population-based management of all forms of diabetes. It may be feasible to develop prospective trials of new methods of prevention or treatment of the more common types of diabetes using the same infrastructure and personnel.

It should be recognized that all forms of diabetes evolve over time for every affected individual. The pathophysiology and appropriate treatments change

over time and can be altered by the appearance of other comorbid conditions, complications, changes in lifestyle or environmental factors, and patients' perceptions of their disease. Therefore, services provided by the systems just described are relevant not just at the time of screening and diagnosis but longitudinally throughout the life span of each individual.

In summary, we suggest that a systematic approach to screening for and appropriately treating monogenic diabetes could establish a platform on which to base a broader initiative toward precision treatment of diabetes in general. For the present, it seems appropriate to go for the low-hanging fruit: the easily diagnosed cases of monogenic diabetes for which specific therapeutic approaches are already established, yet all too seldom correctly applied.

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