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# Undiagnosed MODY: Time for Action

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## Abstract

Maturity-Onset Diabetes of the Young (MODY) is a monogenic form of diabetes that accounts for at least 1% of all cases of diabetes mellitus. MODY classically presents as non-insulin requiring diabetes in lean individuals younger than 25 with evidence of autosomal dominant inheritance, but these criteria do not capture all cases and can also overlap with other diabetes types. Genetic diagnosis of MODY is important for selecting the right treatment, yet ~95% of MODY cases in the U.S. are misdiagnosed. MODY prevalence and characteristics have been well-studied in some populations, such as the UK and Norway, while other ethnicities, like African and Latino, need much more study. Emerging next-generation sequencing methods are making more widespread study and clinical diagnosis increasingly feasible. This review will cover the current epidemiological studies of MODY and barriers and opportunities for moving toward a goal of access to an appropriate diagnosis for all affected individuals.

### Keywords

MODY; monogenic diabetes; epidemiology; prevalence; diagnosis; next-generation sequencing

## Introduction

Diabetes mellitus is commonly known to be divided into type 1 (usually autoimmune-mediated absolute insulin deficiency tending toward early onset) and type 2 (progressive, relative insulin deficiency in the setting of insulin resistance tending toward later onset),(1) both with etiologies involving complex interplay between multiple genetic and environmental factors. In addition and less well-known, there is a third category of diabetes with specific etiologies including diabetes secondary to a drug, transplant, injury, or other genetic or non-genetic illness; and syndromic and non-syndromic forms caused by a mutation in a single gene. MODY is one of the most well-known forms of monogenic diabetes; most neonatal diabetes (diagnosed before the age of six months) also falls into this category. The fourth category of diabetes is gestational diabetes mellitus (GDM), and some GDM results from MODY mutations.(1) Genetic variants of 13 known genes cause MODY

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through pancreatic beta cell dysfunction that leads to elevated blood glucose. MODY is estimated to make up at least 1% of all cases of diabetes. The three most common forms of MODY are caused by mutations in *HNF4A*, *GCK*, and *HNF1A*, and they make up the majority of all MODY cases.(2–4) *HNF4A* and *HNF1A* both encode transcription factors that promote transcription of genes involved in pancreatic beta cell development and insulin production, while *GCK* encodes glucokinase, the enzyme that catalyzes the phosphorylation of glucose and is therefore important for sensing blood glucose levels in the pancreatic beta cell. Other MODY genes include: *PDX1*, *HNF1B*, *NEUROD1*, *KLF11*, *CEL*, *PAX4*, *INS*, *BLK*, *ABCC8*, and *KCNJ11*.(5–14) MODY classically presents in an individual with hyperglycemia before the age of 25 not requiring insulin and having evidence of autosomal dominant inheritance.(15) MODY is particularly suspected in individuals meeting these criteria who are lean and from not from ethnic groups with a high prevalence of type 2 diabetes (e.g., African American, Hispanic, Pacific Islander). Lack of these type 2 diabetes risk factors and type 1-diabetes specific markers including diabetes auto-antibodies and low C-peptide (as a measure of endogenous insulin production) can be evaluated to differentiate the *probability* of MODY from early stage type 1 diabetes and type 2 diabetes, but these risk factors including adiposity do not completely differentiate the diagnoses, and genetic testing is necessary to diagnose MODY.

## Importance of genetic MODY diagnosis

Distinguishing MODY from other forms of diabetes represents an already available opportunity for so-called personalized or precision medicine as it creates an opportunity to select the treatment based on etiology. Insulin injections are the first line of type 1 diabetes treatment, while metformin is the first line of treatment for type 2 diabetes. On the other hand, *HNF1A*-MODY and sometimes *HNF4A*-MODY and are effectively treated with low-dose sulfonylureas, which are inexpensive oral diabetes medications.(16, 17) *GCK*-MODY has been shown to cause a mildly elevated baseline blood glucose that usually does not require pharmacologic management. The mild elevation of blood glucose does not lead to the common sequelae of diabetes such as nephropathy, neuropathy, microvascular or macrovascular complications.(18) Personalized management of the 3 most common forms of MODY therefore results in improved patient care, through avoiding invasive insulin injections in favor of less expensive and more effective treatment methods. Multiple studies have demonstrated the improved patient experience resulting from a genetic diagnosis of MODY.(16, 19, 20) A recent study modeling the cost-effectiveness of MODY genetic testing in all type 2 diabetes patients determined that the practice would surpass the cost-effectiveness thresholds that are used for resource-allocation decisions.(21) In addition to the benefits of MODY genetic testing, genetic diagnoses for *KCNJ11* or *ABCC8* mutations in most NDM patients allows them to transition from insulin injections to high-dose sulfonylureas, which have dramatic effects on glycemic control.(22, 23) These clinical implications have provided the motivation for studies of MODY epidemiology in several different parts of the world, which have shown that MODY, while comparatively less common than T1DM and T2DM, affects an appreciable number of individuals (e.g., at least 1% of the nearly 30 million individuals with diabetes in the United States, or 300,000 people), and the vast majority of these individuals are not receiving a correct diagnosis.

## MODY Epidemiology Studies

In select areas of the world, MODY has been very well-studied due to the strong genetic resources, availability of clinical care, and research directives.

### Europe

The United Kingdom (UK) and the Netherlands have centralized locations for monogenic diabetes testing, which creates the opportunity for large population studies. In the UK, The Molecular Genetic Laboratory at the Royal Devon and Exeter Hospital is the referral center for monogenic diabetes testing. In a study analyzing data from 1996 through 2009, there were 2,072 MODY-phenotype probands in the UK and 564 (27%) confirmed genetically with mutations in *HNF4A, GCK, HNF1A, PDX1, HNF1B, NEUROD1,* and *INS*. This projects to 68–108 individuals with a genetic diagnosis of MODY per million. Of the relatives with diabetes, 613 of 745 had the same mutation, while 71 of 535 relatives without diabetes carried the mutation. *HNF1A* mutations accounted for the majority (52%) of the probands, while *GCK* made up 32%, *HNF4A* made up 10%, *HNF1B* made up 6%, and *NEUROD1* or *INS* made up <1%.(24) This study revealed vast differences in prevalence by UK province, with fivefold difference in prevalence between the extremes. The prevalence was strongly correlated with referral rate, indicating the use of genetic testing likely underlies the variation between regions. The variation in referral rate in the UK indicates that many MODY cases that are missed even in an area of the world with a comprehensive, centralized referral and testing program. A later investigation by this group of 569 individuals originally diagnosed with either type 1 or type 2 diabetes provided evidence that the number of individuals identified with MODY could be doubled through the systematic application of diagnostic criteria, modified to include all individuals diagnosed before age 30 with C-peptide at 3 years duration, to all individuals with diabetes.(25)

In the Netherlands, the Laboratory for Diagnostic Genome Analysis at the Department of Clinical Genetic at Leiden University Hospital provides the majority of genetic testing for MODY. A study from 2001 to 2010 discovered that 502 of 1319 individuals referred by physicians based on clinical judgment had either *HNF4A*-MODY (N = 76), *GCK*-MODY (N = 204), or *HNF1A*-MODY (N = 222). This translated to a prevalence of 30 per million in the entire Netherlands population. As genetic testing for MODY increased over the span of the study, more cases were discovered and the average age of referral for testing increased in *HNF1A*-MODY cases (25.7 during 2003–2004 to 29.2 during 2009–2010, p=0.022).(26) These examples of centralized monogenic diabetes testing facilities allow relatively comprehensive population studies regarding the patient characteristics, physician criteria, and testing outcome dynamics of MODY diagnosis.

Another useful epidemiological resource for MODY analysis is large MODY or diabetes patient registries found in Norway, Germany, and Poland. The Norwegian MODY Registry was created as a nationwide patient database with over 1500 subjects fulfilling 2 of 5 MODY requirements (first degree relative with diabetes, onset before age 25 in at least 1 family member, low-dose insulin requirement, T2DM diagnosed between ages 25 and 40, or unusual type 1 diabetes). Of this database, 458 patients have a genetic diagnosis of monogenic diabetes. *HNF1A* variants make up 53% of genetic diagnoses in Norway, while

*GCK* is the 2nd most common form (30%) over *HNF4A* (7.5%) and *HNF1B* (5.6%).(27) Another study used the Norwegian Childhood Diabetes Registry to estimate the number of monogenic diabetes cases in the population of diabetic children in Norway. This study used strict filtering criteria to identify children under the age of 15 with suspected MODY or NDM, followed by gene-specific genetic testing, and linked to the Norwegian MODY Registry. They discovered a minimum prevalence of 1.1% of children with diabetes have monogenic forms (0.94% have MODY), while 31 children per million are predicted to be affected in the entire Norwegian childhood population.(28)

German and Austrian databases of adolescent diabetes have also allowed thorough epidemiological studies. The DPV-Wiss (Diabetes-Patienten-Verlaufsdaten) database of 40,757 German and Austrian pediatric and adolescent diabetic patients was surveyed for *HNF4A*-, *GCK*-, and *HNF1A*-MODY. This observational investigation found 339 cases (0.83%) that fit MODY criteria of autosomal dominant inheritance in at least 2 generations, onset prior to age 18, and low-to-no insulin requirement. Of the 272 individuals that underwent genetic testing, 97% had mutations in *GCK* (62%), *HNF1A* (31%), or *HNF4A* (4%). Interestingly, 17% of MODY mutation carriers were positive for pancreatic β-cell antibodies (glutamic acid decarboxylase [GAD], insulinoma antigen 2 [IA-2], and insulin autoantibody [IAA; at onset only]), indicating overlap between MODY and type 1 diabetes phenotypes.(29) The finding of diabetes autoantibodies in MODY patients could indicate inaccuracies in classifying pathogenic MODY variants, inability of autoantibodies to specifically detect T1DM, or combined etiologies.

A study performed in Poland utilized publicly available epidemiologic data from the PolPeDiab Collaboration to study the prevalence of monogenic diabetes in three administrative districts from 2007 to 2011. Patients were selected for testing according to the Best Practice Guidelines by Ellard et al.(30) This study found that 42–46 children per million had monogenic diabetes caused by *GCK*-MODY (84%), *HNF1A/4A*-MODY (4%), *HNF1B*-MODY (2%), neonatal diabetes mellitus (7%), Wolfram syndrome (2%) or Alström syndrome (1%).(31) The high prevalence of *GCK*-MODY could possibly be due to a nationwide advertising campaign to inform physicians, parents and educators that increased referral rate for *GCK*-MODY testing nearly twofold in 2010.(32)

A study in Italy measured the rate of monogenic diabetes diagnosis across four pediatric diabetes clinics from 2003 through 2012. This study found that 4.9% (61 patients) of the pediatric diabetic population of 1244 had genetic causes of MODY, which *GCK*-MODY making up 84.7% of monogenic diabetes diagnoses.(33) These examples display the utility of MODY or diabetes registries to provide epidemiological data about select populations.

Besides centralized MODY genetic testing facilities and diabetes registries, there have been many more studies performed in smaller European populations to estimate the prevalence of MODY. These studies utilize similar designs, selecting groups of probands with suspected MODY and pursuing genetic causes through genetic testing of one or more MODY genes. These studies generally have about 50% success in obtaining genetic diagnoses, although they are generally underpowered to provide accurate population estimates. When assessed with the larger studies above, these studies show a general trend of increased *HNF1A*-

MODY diagnoses in Northern European nations, while *GCK*-MODY predominates in Southern European populations (Table 1). An example Northern European small study of 78 MODY patients in Denmark discovered 74% of MODY patients with genetic diagnoses had *HNF1A*-MODY, while 21% had *GCK*-MODY, and 5% had *HNF4A*-MODY.(34) A Southern European study of *GCK* and *HNF1A* in 172 MODY probands in Italy discovered 63.4% carried *GCK* variants, 6.9% carried *HNF1A* variants, and 29.6% had unexplained MODY.(35) Multiple other Italian studies have produced data to support this study.(36–38) The trend of increased *GCK*-MODY compared to *HNF1A*-MODY is also shown in small studies in the Czech Republic,(39) Spain,(40) and Greece.(41) Between large patient registries, centralized MODY genetic testing facilities, and smaller cohort studies, the landscape of MODY and monogenic diabetes across Europe has been well studied.

## Asia

In contrast to the European MODY studies, there has been a relative dearth of MODY or monogenic diabetes studies in other ethnicities. Asian populations have been studied, but not as extensively as European Caucasian groups. A study from 2005–2011 selected 80 Japanese youths through the nationwide school urinalysis program (N = 56/80), incidental glucosuria identification (N = 21/80), or primary care referrals (N = 3/80). This study confirmed MODY diagnosis in 38 participants; 3 *HNF4A*, 18 *GCK*, 11 *HNF1A*, and 6 *HNF1B* mutations.(42) These results indicated similar rates of MODY prevalence compared to Caucasian populations, in opposition to earlier studies on *HNF1A* only.(43) Recent studies have expanded to study a specific cohort of *GCK*-MODY Japanese patients, determining that they have similar clinical symptoms to Caucasian counterparts, although insulin resistance may be more common in the Japanese.(44) Small studies from Chinese populations have also been performed. The findings indicate that *HNF1A*-MODY, *GCK*-MODY, and *HNF4A*-MODY all appear to be much less common in Chinese populations compared to Caucasians, although variants in *GCK* and *HNF1A* still explain a small number of cases.(45–47) Small studies of *HNF1A* in Korean populations have shown *HNF1A*-MODY is present, but other MODY genes have not been assessed.(48, 49) The study of MODY in India is just in its infancy, but the large proportion of young people with diabetes is increasing in that population. A previous study in India described a large number of cases with suspected MODY diagnoses.(50) A study of *HNF1A* in Indian suspected MODY patients found 9% of cases have *HNF1A* mutations.(51) Similar studies for *HNF4A* have shown the prevalence to be 3.4% of suspected MODY cases.(52) However, when 49 children and adolescents from a study in Chennai, India with hyperglycemia were sequenced for *GCK* mutations, none were discovered, despite other case reports of *GCK*-MODY in Indian patients.(53) A recent study of MODY in India utilized next-generation sequencing to attain sequence data for 10 MODY genes, rather than only the 3 most common.(54) This study found potentially damaging variants in *HNF4A*, *GCK*, *HNF1A*, *PDX1*, *HNF1B*, *NEUROD1*, and *PAX4* in 11 of 56 patients tested. This could indicate a much more complex landscape of MODY disease etiology in India, or it may suggest the difficulty of determining pathogenicity of variants found large-scale sequencing projects. Many more studies on larger population and richer datasets will be necessary to determine the genetic factors behind monogenic diabetes and MODY in Asian populations.

## African, Latino and Middle Eastern Populations

There have been very few studies beyond case reports about the epidemiology of MODY in African, Latino, and Middle Eastern populations. A study of 59 suspected MODY cases in Israel were sequenced for the 3 most common forms of MODY. Only 20.3% of patients had a genetic diagnosis, with 1.7% as *HNF4A*-MODY, 8.5% as *GCK*-MODY, and 10.1% as *HNF1A*-MODY.(55) Another study specifically of *GCK*-MODY in Israelis discovered the same rare variant, p.T206P, in suspected MODY cases of 6 unrelated families of Jewish-Ashkenazi descent.(56) A study in the country of Oman examined 20 patients with suspected MODY diagnosis, but found no mutations in *HNF4A*, *GCK*, or *HNF1A*.(57) These studies provide interesting clues about the genetic makeup of MODY in the Middle East that need to be further studied. Due to their general predisposition to diabetes mellitus, Latino and African ethnicities represent two major groups that are in desperate need for study in the field of monogenic diabetes. There has only been a single study searching for *HNF1A* variants in an African American population.(58) There have been multiple small studies of Brazilian populations, but they are generally underpowered and have conflicting results.(59–61) A small Mexican cohort has been studied, but no follow up studies have been performed to validate any findings.(62) It is unclear why MODY epidemiological studies have not been pursued in these ethnic populations. However, the American Diabetes Association (ADA) suggests that monogenic diabetes diagnosis should be considered when the patient has a “Strong family history of diabetes but without typical features of type 2 diabetes (non-obese, low-risk ethnic group),” which may deter physicians from testing or studying monogenic diabetes in these populations.(1)

## United States

Perhaps surprisingly, diagnosis of MODY in the United States has lagged behind the UK and other nations. New studies are beginning to emerge that show the prevalence of monogenic diabetes in the United States. Two recent studies have been reports on the results of monogenic diabetes testing at two separate facilities, the Barbara Davis Center (BDC) at the University of Colorado and the Seattle Children’s Hospital Molecular Genetics Laboratory (SCHMGL). The BDC tested 97 participants that fit inclusion criteria (non-syndromic [except renal cysts and diabetes, MODY5] diabetes onset before age 25, random C-peptide measure of >0.1 ng/mL, and negative for GADA, IA-2, ZnT8 and IAA antibodies) for MODY types 1–5 using a commercial testing agency. They discovered 21% (N = 20) had pathogenic genetic variants in *HNF4A* (N = 3), *GCK* (N = 8), or *HNF1A* (N = 9), while there were none found in *PDX1* or *HNF1B*.(63) The SCHMGL, a diagnostic laboratory that has performed molecular diagnostic testing for MODY, NDM, and congenital hyperinsulinemia since 2009, tested 331 referred probands and discovered 115 reportable variants. In addition to MODY, they also discovered multiple genetic etiologies for neonatal diabetes, a case of mosaic MODY presentation, and a case of digenic MODY presentation. An important point made by the study showed that 30% of the reportable variants changed classification between pathogenic, benign, or “variant of undetermined significance” over the 4 years of the study.(64) This displays the important point that as the clinical knowledge base grows, genetic classification must constantly be updated to reflect the newest information available.

While the BDC and SCHMGL studies have started to reveal some of the genetic architecture of patients with a classic MODY presentation, a landmark study with important implications for clinical practice and public health occurred as part of the SEARCH for Diabetes in Youth study. This multicenter collaboration studied 5,963 pediatric diabetes patients. A subset of 586 antibody-negative, C-peptide positive patients were tested for *HNF4A*, *GCK*, or *HNF1A* variants. Genetic MODY diagnoses were found in 8% (N = 47) of patients, with *HNF1A*-MODY being the most common form (N = 26) followed by *GCK*-MODY (N = 14) and *HNF4A*-MODY (N = 7). Importantly, only three (6%) of these patients had been diagnosed with MODY by their providers; most had been diagnosed with either T1DM (36%) or T2DM (51%). Consequently, most were being treated with insulin or metformin, and few with the treatment indicated by genetic etiology (sulfonylureas for *HNF1A/4A* and no treatment for *GCK*). This study is unique in that patients were unselected by ethnicity, adiposity, or family history of diabetes. Sixty-four percent of genetic MODY cases were minorities (African American: 20%, Hispanic: 31%, and Asian/Pacific Islander: 11%), similar to the MODY-negative tested population (67% minority), but higher than that of the entire SEARCH childhood diabetes population (64% vs. 31%, $p < 0.01$, apparently due to the high higher prevalence of T1DM in non-Hispanic whites). Prevalence of parental history of diabetes was similar between MODY and non-MODY patients. While mean BMI was lower in the MODY group, the MODY group contained individuals in the overweight range. The authors also extrapolated a prevalence of MODY of at least 1.2% in the pediatric diabetes population. Taken together, these findings indicate that MODY has an appreciable prevalence and the vast majority of cases (~95%) in the United States are currently going misdiagnosed. (65)

## Implications of Epidemiological Studies of MODY

The epidemiological studies of the prevalence of MODY reveal many challenges and opportunities for improvement regarding MODY genetic testing. Most of the studies listed identify mutations in fewer than 50% of patients with suspected MODY. Failure to identify a mutation may result from diagnostic overlap with more complex forms of diabetes or causation by a mutation in a gene not yet identified. Some of the targeted studies, such as those in Germany, Italy, and Spain, had a 70–90% hit rate, but such high specificity could be accompanied by compromised sensitivity; i.e., ability to detect true positives.(29, 35, 36, 40) Delineating monogenic diabetes from type 1 or type 2 diabetes is challenging and is becoming more difficult in general due to similarity of clinical features including monogenic diabetes patients with elevated BMI, fasting glucose and HbA1c levels similar to type 2 diabetics, incomplete penetrance,(65) and even islet autoantibodies in some monogenic diabetes cases.(29) Available screening algorithms for MODY are based on the best interpretation of currently available epidemiological studies, but the ideal screening algorithm would be based on comprehensive sequencing of a large number of diabetic individuals unselected for any particular risk factors. To date, such an effort has been cost-prohibitive, but advances in genetic testing technology and decreasing costs will allow this deficit to be remedied. Emerging studies, especially those incorporating whole genome sequencing or exome sequencing, will enable a comprehensive description of the prevalence

and characteristics of patients with MODY, allowing approaches to selection of patient for testing with the optimal combination of sensitivity and specificity

The prevalence and characteristics of monogenic diabetes need to be further described in ethnicities that have not been well-studied to this point, including those of African, Latin American, Middle Eastern, and Asian descent. Some of which exhibit high prevalence of type 2 diabetes, and it is particularly important to be mindful that MODY does affect these groups and to understand how to differentiate the two diagnoses.

An underlying issue of all of these studies is the pathogenicity of discovered variants. Pathogenicity can be difficult to define, especially for variants seen in one or two families. New American College of Medical Genetics (ACMG) Standards and Guidelines were recently released in order to provide standardized methods to review the evidence, including familial, epidemiological, computational and functional, for or against the pathogenicity of genetic variants.(66)

## MODY Diagnosis

General guidelines and recommendations have been created to aid in MODY diagnosis. The ADA suggests that a diagnosis of monogenic diabetes should be considered in children with the following characteristics: 1) diabetes diagnosed in the first 6 months of life, 2) family history of diabetes without type 2 diabetes risk factors (nonobese, low-risk ethnicity), 3) mild fasting hyperglycemia if young and nonobese, and 4) diabetes with negative autoantibodies and without signs of obesity or insulin resistance.(1) Clinical centers for monogenic diabetes in Exeter and Chicago also have published (15, 67) and posted online (http://diabetesgenes.org/ and http://monogenicdiabetes.uchicago.edu/) suggested criteria for the clinical diagnosis of monogenic diabetes. In addition to those sources, there have been multiple publications suggesting algorithms for diagnosis.(68–70) The low rate of diagnosis of MODY cases such as that seen in the SEARCH Study (~6%) suggest that these criteria are not in wide use. Moreover, epidemiological studies cited above suggest the criteria, even if applied, are likely to miss cases (e.g., those with obesity or from an ethnicity at high risk for type 2 diabetes).

Some types of MODY have specific clinical, sometimes extra-pancreatic features that can help to place a patient on the pipeline to diagnosis. For example, patients with *HNF1A*-MODY may have lower renal function in terms of glucose reabsorption, which can be detected as postprandial glycosuria.(71) *HNF4A*-MODY can cause macrosomia at birth in 50% of cases,(72) and some *HNF4A* mutations (p.R76W) can cause atypical Fanconi syndrome in addition to diabetes.(73) *HNF1B*-MODY often presents with MODY characteristics as well as renal cysts, and as a result, is also called renal cysts and diabetes (RCAD).(74) Additionally, *pectus excavatum* is also a part of the *HNF1B*-MODY clinical spectrum.(75) Largely beyond the scope of this review are the many monogenic syndromes that include diabetes as a symptom, including Wolfram Syndrome, Roger's Syndrome, and Wolcott-Rallison Syndrome, among others.

Several standard blood markers are established or under study to clarify which patients will be most likely to benefit from genetic testing. *GCK*-MODY is known to cause only mild

elevation of HbA1c (5.5–8 mmol/L), but it has also been associated with decreased lipid levels, including HDL cholesterol.(76) While the HbA1c range has already been used in some diagnostic algorithms (77), HDL cholesterol levels were shown in one study to enhance differentiation between *GCK*-MODY and type 1 diabetes.(78) Two genome-wide association studies of *HNF1A* variants discovered an association with serum C-reactive protein (CRP), which is used clinically as an inflammatory marker.(79, 80) Because HNF1-α binds to the *CRP* promoter, decreased function would predict a decrease in CRP. While multiple studies initially supported the use of CRP to diagnose *HNF1A*-MODY,(81, 82) a recent study has shown that comparisons of *HNF1A*-MODY patients to familial young-onset type 2 diabetes found that over half of the study participants were within the zone of diagnostic uncertainty, indicating it does not improve diagnosis.(83) Since HNF1-α is a regulator of fucosylation of proteins, examination of plasma glycoprotein profiles can indicate *HNF1A* damaging variants.(84) A major downside of this metabolite marker is that there is no high-throughput technique for this measure. Other metabolites, including CD36, cystatin C, and ghrelin, have also been studied for the same purpose, but to less extent than CRP or glycoprotein profiles.(85–87)

The field of genetics is rapidly advancing due to decreasing costs and increasing capabilities of next-generation sequencing (NGS). Currently, monogenic diabetes is often genetically diagnosed with Sanger sequencing of one to a few genes of interest. However, increased capacity of NGS allows sequencing to be performed on collections of genes, exomes, or even whole genomes. Several studies have purported the usefulness of gene panels for diagnosis of monogenic diabetes.(88–90) As part of the Implementing Genomics in Practice (IGNITE) network of the NHGRI, the Personalized Diabetes Medicine Program (PDMP) at the University of Maryland is implementing such a panel as part of a project to implement, disseminate and evaluate (including from a payer perspective) a comprehensive approach to the detection, diagnosis and individualized treatment for monogenic diabetes. The PDMP uses screening questionnaires, patient medical history, family history, and routine bloodwork to identify patients suspicious for having monogenic diabetes. Patients fulfilling criteria undergo genetic sequencing for 40 genes that cause MODY, NDM, syndromic diabetes, and lipodystrophy. After validation in a CLIA/CAP-certified laboratory, the sequencing results are returned to the patient and physician through the electronic health record. A small number of studies have also used exome sequencing for monogenic diabetes diagnosis.(91, 92) As the cost of sequencing decreases and the efficiency increases, exome and whole genome will likely be the future of genetic diagnosis, with the ability to interpret and classify pathogenicity of variants expected to improve over time.

## Barriers and Opportunities

While there are many opportunities for widespread implementation of genetic testing for monogenic diabetes, there are also many barriers that need to be overcome. Limited provider awareness of monogenic diabetes is a major obstacle for attaining proper diagnosis, especially in the context of overlapping clinical characteristics with type 1 and type 2 diabetes and the clinical heterogeneity of patients with monogenetic diabetes diagnoses. Although awareness is improving as more studies are performed, it is important that all

clinicians treating diabetes patients are considering monogenic etiologies as a potential diagnosis, especially when diagnosis can occur in adults that have been diabetic since youth.

Given that current and existing diagnoses of monogenic diabetes are being missed, an additional opportunity for case identification may lie in the clinical genetics setting, where patients are being seen for other indications. Through training of geneticists and genetic counselors to ask targeted questions upon encountering patients with diabetic relatives, it may be possible to identify patients and families for further evaluation. In a recent review, one of the authors of the current report (TIP) gives an overview of how patient clinical symptoms, family history and teamwork among providers can be utilized to direct genetic testing for specific forms of diabetes.(93)

Anecdotally, patients and providers have also noted difficulties with insurance reimbursement for genetic testing. It is important that healthcare payers are engaged in order to demonstrate the patient care and economic benefits of monogenic diabetes testing, as is currently being performed by projects like the PDMP. The cost effectiveness of MODY testing and the impact on patient outcomes and lifestyle provide a great opportunity for healthcare payers to initiate reimbursement practices for genetic testing.

New studies using research tools such as exome sequencing and whole genome sequencing will allow genetic diagnoses to expand into unknown or unrecognized genes, and increasing numbers of patients with high-quality phenotype data in monogenic diabetes registries will allow better definition of the range of clinical presentations. The rapidly increasing technology in NGS platforms is creating powerful tools for detecting genetic etiologies of a large number of individuals at moderate costs. The implementation of electronic health records has also created opportunities for large sources of information that can link genetic data to clinical patient data. While methods for diagnosing MODY are continuing to improve, the majority of existing opportunities to provide life-changing re-diagnoses using existing tools are being missed. Existing data on the prevalence of MODY in and outside the United States indicate there are a large number of undiagnosed cases that would currently benefit from widespread implementation of genetic testing.

## Conclusion

MODY is a highly penetrant genetic form of diabetes that represents an under-utilized opportunity for immediate clinical implementation of genetic testing. The characteristics of the most common forms of MODY have been well-defined and specific clinical guidelines are in place after a genetic diagnosis has been made. Since etiology-specific treatment of MODY can have such a drastic improvement in patient care, implementation of genetic testing needs to be more widespread. While the prevalence of MODY in some populations in Europe have been well-studied, further study is necessary in populations on nearly all other continents. Immediate implementation of large-scale MODY genetic testing for suspected individuals can both improve patient treatment directly and provide data to target genetic testing for the future. Large-scale efforts to genetically diagnose MODY will lead to improved targeted screening algorithms, additional metabolic marker studies, and utilization of NGS capabilities further improve the proportion and number of patients with genetic

MODY diagnoses. While improving MODY diagnosis will certainly improve the clinical care for patients, it will also have broader implications. Screening and genetic testing for MODY among patients with diabetes will provide a model for identifying and diagnosing highly penetrant forms of other otherwise common complex diseases to the power of genetics and genomics for improving patient care and public health.

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**Table 1**

European Studies of *HNF4A*-, *GCK*-, and *HNF1A*-MODY by Nation

| Nation | Latitude | Study Participants | Undiag. MODY | Genetic MODY | *HNF4A*-MODY | *GCK*-MODY | *HNF1A*-MODY | Ratio of *GCK*/*HNF1A* MODY | Source |
|---|---|---|---|---|---|---|---|---|---|
| Norway | 57°57′–80°49′ | >1500[†] | >69% (>1,042) | <31% (458) | <3% (40) | <9% (139) | <14% (208) | 0.67 | (27) |
| Denmark | 54°34′–57°45′ | 78 | 51% (40) | 49% (38) | 3% (2) | 10% (8) | 36% (28) | 0.29 | (34) |
| Netherlands | 50°45′–53°32′ | 1,319 | 65% (817) | 39% (502) | 6% (76) | 15% (204) | 17% (222) | 0.92 | (26) |
| UK | 49°51′–60°51′ | 2,072 | 73% (1,508) | 27% (564) | 3% (56) | 9% (180) | 14% (293) | 0.61 | (24) |
| Poland | 49°00′–54°50′ | 1351 | 93% (1251) | 7% (100) | <0.3% (4[*]) | 6.2% (84) | <0.3% (4[*]) | 21[*] | (31) |
| Germany/Austria | 47°17′–55°03′, 46°23′–49°01′ | 272 | 3% (9) | 97% (263) | 4% (10) | 62% (169) | 31% (84) | 2.0 | (29) |
| Czech Rep. | 48°33′–51°02′ | 61 | 52% (32) | 48% (29) | 5% (3) | 31% (19) | 11.5% (7) | 2.7 | (39) |
| Italy | 35°30′–47°05′ | 172, 58 | 30% (51), 22% (13) | 70% (121), 78% (45) | N/A, 5% (3) | 63% (109), 53% (31) | 7% (12), 16% (9) | 9.1, 3.4 | (35, 36) |
| Greece | 34°49′–41°43′ | 134 | 34% (46) | 66% (88) | N/A | 54% (72) | 12% (16) | 4.5 | (41) |
| Spain | 28°38′–43°47′ | 95 | 11% (10) | 89% (85) | 0% (0) | 80% (76) | 8% (8) | 9.5 | (40) |

[†]Study did not provide precise number of registry participants

[*]Study did not differentiate between *HNF1A* and *HNF4A* mutations