Maturity-Onset Diabetes of the Young (MODY) Testing

Procedures addressed

The inclusion of any procedure code in this table does not imply that the code is under management or requires prior authorization. Refer to the specific Health Plan's procedure code list for management requirements.

<table>
<thead>
<tr>
<th>Procedures addressed by this guideline</th>
<th>Procedure codes</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABCC8 Sequencing</td>
<td>81407</td>
</tr>
<tr>
<td>BLK Sequencing</td>
<td>81479</td>
</tr>
<tr>
<td>CEL Sequencing</td>
<td>81479</td>
</tr>
<tr>
<td>CEL Exon 11 Sequencing</td>
<td>81403</td>
</tr>
<tr>
<td>GCK Sequencing</td>
<td>81406</td>
</tr>
<tr>
<td>GCK Deletion/Duplication</td>
<td>81479</td>
</tr>
<tr>
<td>HNF1A Sequencing</td>
<td>81405</td>
</tr>
<tr>
<td>HNF1A Deletion/Duplication</td>
<td>81479</td>
</tr>
<tr>
<td>HNF1B Sequencing</td>
<td>81405</td>
</tr>
<tr>
<td>HNF1B Deletion/Duplication</td>
<td>81404</td>
</tr>
<tr>
<td>HNF4A Sequencing</td>
<td>81406</td>
</tr>
<tr>
<td>HNF4A Deletion/Duplication</td>
<td>81479</td>
</tr>
<tr>
<td>INS Sequencing</td>
<td>81404</td>
</tr>
<tr>
<td>KCNJ11 Sequencing</td>
<td>81403</td>
</tr>
<tr>
<td>KLF11 Sequencing</td>
<td>81479</td>
</tr>
<tr>
<td>NEUROD1 Sequencing</td>
<td>81479</td>
</tr>
<tr>
<td>PAX4 Sequencing</td>
<td>81479</td>
</tr>
<tr>
<td>PDX1 Sequencing</td>
<td>81404</td>
</tr>
</tbody>
</table>
What is MODY

Definition

Maturity-onset diabetes of the young (MODY) is a type of monogenic diabetes characterized by non-insulin-dependent diabetes and early onset (usually before age 35).\(^1\)\(^-\)\(^4\)

Incidence and Prevalence

Diabetes affects 29.1 million people in the United States, or 9.3% of the population.\(^5\) The most common types of diabetes are type 1 and type 2. The genetic basis of these types of diabetes is largely unknown. The disease is thought to be the result of a combination of multiple genetic and environmental risk factors.\(^5\) Monogenic forms of diabetes are rare, accounting for approximately 2% of all diabetes cases.\(^1\)\(^-\)\(^3\)

Symptoms

Diabetes is a disorder that results in elevated blood glucose. Over time, the disorder can cause various health problems, including diseases of the heart, kidneys, eyes, and nervous system.

Cause

Monogenic forms of diabetes are caused by a mutation in a single gene. There are 14 known MODY genes, and three account for the majority of cases.\(^1\)\(^-\)\(^3\)

- MODY3: Mutations in the hepatocyte nuclear factor-1 alpha (HNF1A) gene are the most common cause of MODY, accounting for about half of cases. This type is characterized by a progressive insulin secretory defect due to beta-cell failure. Laboratory evaluations are negative for pancreatic islet cell antibodies (ruling out type 1) and glycosuria is detectable even at low blood glucose levels (<10 mmol/l). Treatment of choice for people with this type of MODY is sulfonylureas, and a majority of patients can be transferred from insulin to oral agents.

- MODY2: Mutations in the glucokinase gene (GCK) are the next most common cause of MODY, accounting for about 20-25% of cases. GCK encodes the glucokinase enzyme, which acts as the pancreatic glucose sensor. Mutations result in lifelong, stable, mild fasting hyperglycemia. HbA1C values are usually just above the high normal range. People with GCK mutations rarely require treatment. This type of MODY may be detected during pregnancy, when glucose tolerance testing is routinely performed.

- MODY1: Mutations in the hepatocyte nuclear factor-4 alpha (HNF4A) gene cause a clinical presentation similar to HNF1A. However, mutations in this gene are much less common (less than 10% of MODY). Age of onset may be later, and there is not a low renal threshold. HNF4A mutations can also cause high birth weight in newborns and transient neonatal hypoglycemia. These patients are also more sensitive to sulfonylurea treatment.
The remaining genes are rare causes of MODY, each accounting for less than 1% of cases:¹⁻³

- **MODY5**: Caused by heterozygous mutations in HNF1B. The vast majority of HNF1B mutations cause Renal Cysts and Diabetes Syndrome, which is associated with diabetes, renal cysts, genitourinary malformations, pancreatic atrophy, hyperuricemia, and abnormal liver function tests.

- **MODY8**: Caused by heterozygous mutations in CEL. Affected individuals also have pancreatic exocrine dysfunction (diabetes-pancreatic-exocrine dysfunction syndrome).

- Others include: MODY4 (PDX1/IPF-1), MODY6 (NEUROD1), MODY7 (KLF11), MODY9 (PAX4), MODY10 (INS), MODY11 (BLK), MODY12 (ABCC8) and MODY13 (KCNJ11), APPL1 (MODY14).

Other monogenic causes of pediatric diabetes include the following (not meant to be an all-inclusive list):²⁻⁸

- Permanent neonatal diabetes mellitus (PNDM), defined as persistent hyperglycemia in the first 6 months of life. It is most commonly caused by mutations in the ABCC8, KCNJ11, and INS genes. Biallelic mutations in GCK and PDX1 are less common causes.

- Transient neonatal diabetes mellitus (TNDM), which accounts for ~50% of all neonatal diabetes. Affected individuals are at risk for recurrence later in life. 70% of TNDM cases are due to 6q24 methylation defects, while ABCC8 and KCNJ11 combined account for an additional 26% of cases.

- Cystic fibrosis, caused by biallelic CFTR mutations (for more information, see test-specific guideline, *Cystic Fibrosis Testing*).

- Immune dysregulation, polyendocrinopathy, and enteropathy, X-linked (IPEX syndrome), due to mutations in FOXP3.

- Maternally inherited diabetes and deafness (MIDD), caused by mutations in mitochondrial genes: MT-TL1, MT-TK, or MT-TE.

- Wolcott-Rallison syndrome, due to mutations in EIF2AK3.

- Wolfram syndrome, caused by mutations in WFS1 and less often CISD2.

- Other genes associated with PNDM and extra-pancreatic features include GATA6, GLIS3, IER3IP1, NEUROG3, PTF1A, and RFX6.

### Inheritance

MODY is typically inherited in an autosomal dominant manner. When a parent has a MODY mutation, each of her/his offspring have a 50% risk of inheriting the mutation.¹⁻⁴ Mutations that occur de novo in an affected individual, reduced penetrance, and variable expressivity have been reported.⁴ Thus, the absence of a family history does not, by itself, rule out a diagnosis of MODY.
Diagnosis

Diabetes evaluations may include assessment of pancreatic autoantibodies, plasma glucose levels, hemoglobin A1C assessment (HbA1C), and oral glucose tolerance testing (OGTT). For young individuals in whom a diagnosis of type 1 or type 2 diabetes is considered unlikely, genetic testing for monogenic diabetes may be considered, especially in the presence of a strong family history.\textsuperscript{5}

Treatment

Like other forms of diabetes, monogenic diabetes is treated with diet, oral antidiabetic agents, and/or insulin, as required for blood sugar regulation.\textsuperscript{4} Most patients with MODY are not insulin-dependent. Knowledge of the specific genetic cause of MODY may help guide management.

Survival

Survival of affected individuals was reduced when compared with unaffected relatives, specifically with regard to cardiovascular-related causes of death.\textsuperscript{6}

Test information

Introduction

Testing for MODY may include single gene sequence analysis, single gene deletion/duplication analysis, or multi-gene panels of various sizes.

Sequence analysis

Until recently, most sequencing tests used the Sanger sequencing methodology that was originally developed in the 1970s. Sanger sequencing is labor intensive and did not lend itself to high-throughput applications.

Next generation sequencing (NGS), which is also sometimes called massively parallel sequencing, was developed in 2005 to allow larger scale and more efficient gene sequencing. NGS relies on sequencing many copies of small pieces of DNA simultaneously and using bioinformatics to assemble the sequence. NGS may not perform as well as Sanger sequencing in some applications.

NGS tests vary in technical specifications (e.g., depth of coverage, extent of intron/exon boundary analysis, methodology of large deletion/duplication analysis).

Sequence analysis detects single nucleotide substitutions and small (several nucleotide) deletions and insertions. Regions analyzed typically include the coding sequence and intron/exon boundaries. Promoter regions and intronic sequences may also be sequenced if disease-causing mutations are known to occur in these regions of a gene.
The efficiency of NGS has led to an increasing number of large, multi-gene testing panels. NGS panels that test several genes at once are particularly well-suited to conditions caused by more than one gene or where there is considerable clinical overlap between conditions.

Results may be obtained that cannot be adequately interpreted based on the current knowledge base. When a sequence variation is identified that has not been previously characterized or shown to cause the disorder in question, it is called a variant of uncertain significance (VUS). VUSs are relatively common findings when sequencing large amounts of DNA with NGS.

Under certain circumstances, technologies used in multi-gene testing may fail to identify mutations that might be identifiable through single-gene testing. If high clinical suspicion exists for a particular syndrome testing for that syndrome should be performed instead of a broad multi-gene panel.

Since genes can be easily added or removed from multi-gene tests over time by a given lab, medical records must document which genes were included in the specific multi-gene test used and in which labs they were performed.

Additionally, tests should be chosen to

• maximize the likelihood of identifying mutations in the genes of interest
• contribute to alterations in patient management
• minimize the chance of finding variants of uncertain clinical significance

**MODY gene sequence analysis**

MODY multi-gene panels include a wide variety of genes associated with MODY and monogenic diabetes in general. Some panels may also include genes associated with other types of monogenic diabetes and glycemic disorders, such as neonatal diabetes, syndromic diabetes, and familial hyperinsulinism.

**Deletion/duplication analysis**

Analysis for deletions and duplications can be performed using a variety of technical platforms including exon array, MLPA, and NGS data analysis.

These assays detect gains and losses too large to be identified through sequencing technology, often single or multiple exons or whole genes.
Guidelines and evidence

American Diabetes Association

The American Diabetes Association (2017) states: “Children and adults, diagnosed in early adulthood, who have diabetes not characteristic of type 1 or type 2 diabetes that occurs in successive generations (suggestive of an autosomal dominant pattern of inheritance) should have genetic testing for maturity-onset diabetes of the young” (Grade A recommendation).9

National Academy of Clinical Biochemistry


- Routine measurement of genetic markers is not of value at this time for the diagnosis or management of patients with type 1 diabetes. For selected diabetic syndromes, including neonatal diabetes, valuable information can be obtained with definition of diabetes-associated mutations. A (moderate)

- There is no role for routine genetic testing in patients with type 2 diabetes. These studies should be confined to the research setting and evaluation of specific syndromes. A (moderate)

International Society for Pediatric and Adolescent Diabetes

The International Society for Pediatric and Adolescent Diabetes (2014) makes the following recommendations:2

- “The diagnosis of maturity-onset diabetes of the young (MODY) should be suspected in cases with”
  
  o “A family history of diabetes in one parent and first degree relatives of that affected parent in patients who lack the characteristics of type 1 diabetes [no islet autoantibodies, low or no insulin requirements 5 yr after diagnosis (stimulated C-peptide >200 pmol/L)] and lack the characteristics type 2 diabetes (marked obesity, acanthosis nigricans).”
  
  o “Mild stable fasting hyperglycemia which does not progress. Such cases should be tested for glucokinase (GCK) gene mutations, which is the commonest cause of persistent, incidental hyperglycemia in the pediatric population (B).”

- “Specific features can suggest subtypes of MODY, such as renal developmental disease or renal cysts (HNF1B-MODY) and macrosomia and/or neonatal hypoglycemia (HNF4A-MODY) (C).”

- “In familial autosomal dominant symptomatic diabetes, mutations in the hepatocyte nuclear factor 1α (HNF1A) gene (HNF1A-MODY) should be considered as the first diagnostic possibility, while mutations in the GCK gene are the most common cause in the absence of symptoms or marked hyperglycemia (B).”
• “Three genes are responsible for the majority of MODY cases (GCK, HNF1A, and HNF4A) … However, up to 13 different genes have been reported to cause autosomal dominant non-insulin dependent diabetes but these are so unusual they do not need to be tested for in children with diabetes except in a research setting or when there are additional phenotypes such as pancreatic exocrine dysfunction.”

European Molecular Genetics Quality Network

The European Molecular Genetics Quality Network (2008) makes the following recommendations for testing (paraphrased due to their length):³

• Testing for GCK mutations (presentation outside of pregnancy):
  o Persistent, stable elevation of fasting blood glucose (5.5-8 mmol/l)
  o HbA1c just above the upper limit of normal (rarely exceeds 7.5%)
  o Oral glucose tolerance testing demonstrates a small increment (4.6 mmol/l is often used to prioritize testing)
  o May have a family history consistent with autosomal dominant inheritance

• Testing for GCK mutations (for evaluation of gestational diabetes):
  o Persistent elevation of fasting blood glucose (5.5-8 mmol/l) before, during and after pregnancy
  o At least one oral glucose tolerance test with an increment of <4.6 mmol/l (either during or after pregnancy)

• Testing for HNF1A mutations:
  o Young-onset diabetes (<25 years old)
  o Non-insulin-dependent diabetes
  o Family history of diabetes (at least two generations)
  o Absence of pancreatic islet autoantibodies
  o Glycosuria at blood glucose levels <10 mmol/l
  o Marked sensitivity to sulfonylureas
  o Features suggestive of monogenic diabetes (lack of obesity or evidence of insulin resistance, absence of acanthosis nigricans, etc)

• Testing for HNF4A mutations:
  o Should be considered when HNF1A analysis is normal but the clinical features are strongly suggestive of HNF1A
• “When diabetic family members have marked macrosomia (>4.4 kg at term) or if diazoxide-responsive neonatal hyperinsulinism has been diagnosed in the context of familial diabetes.”

• “Macrosomic babies with diazoxide-responsive hyperinsulinism and a strong family history of diabetes should be considered for HNF4A mutation screening.”

• Syndromic forms of diabetes, including HNF1B and CEL mutations, “are not included in these guidelines since testing is guided by the non-endocrine pancreatic or extra-pancreatic clinical features.”

**Literature Review**

An expert-authored review (2018) suggests that MODY has an onset in adolescence or young adulthood, typically less than 35 years.  

• “Molecular genetic testing approaches to determine the associated MODY gene can include a combination of gene-targeted testing (serial single-gene or multigene panel) and comprehensive genomic testing (chromosomal microarray analysis or exome sequencing), depending on the phenotype.”

• “Serial single-gene testing. Sequence analysis of the most likely genes is performed first. If no pathogenic variant is found, gene-targeted deletion/duplication analysis to detect exon-sized deletions could be considered, especially for those genes (CEL, GCK, HNF1A, HNF1B, and HNF4A) in which whole-gene or multiexon deletions have been identified.”

• “A MODY multigene panel that includes the 14 known MODY-related genes and other genes of interest is most likely to identify the genetic cause of MODY at the most reasonable cost while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype [Ellard et al 2013, Alkorta-Aranburu et al 2016].”

a) “The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time.”

b) “Some custom laboratory-designed multigene panels may include genes not associated with MODY but possibly associated with other types of monogenic diabetes; other custom laboratory-designed panels may not include the genes that rarely cause MODY.”

c) “In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that include genes specified by the clinician.”

**Criteria**

This guideline applies to all MODY testing, including single genes as well as multi-gene panels, which are defined as assays that simultaneously test for more than one MODY
gene. Medical necessity determination generally relies on criteria established for testing individual genes.

Medical necessity criteria differ based on the type of testing being performed (i.e., individual MODY genes separately chosen versus pre-defined panels of MODY genes) and how that testing will be billed (one or more individual MODY gene procedure codes, specific panel procedure codes, or unlisted procedure codes).

These guidelines are for gene testing in the context of MODY evaluation only. For gene testing in non-MODY contexts (e.g., neonatal diabetes, familial hyperinsulinism, etc.), refer to the general policies, Genetic Testing to Diagnose Non-Cancer Conditions and Genetic Testing by Multigene Panels, as appropriate.

HNF1A Sequencing and Deletion/Duplication Analysis

- Genetic Counseling:
  - Pre and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND

- Previous Genetic Testing:
  - No previous HNF1A gene sequencing or deletion/duplication analysis, and
  - No known MODY mutation in biologic relative, AND

- Diagnostic Testing for Symptomatic Individuals:
  - Member has a diagnosis of diabetes prior to 35 years of age, and
  - Member has a biological parent with diabetes, and
  - Member does NOT have symptoms consistent with a specific condition or specific gene mutation, and
  - Member does NOT have any of the following features:
    - Extra-pancreatic manifestations (e.g., congenital malformations and other signs of syndromic diabetes), or
    - Pancreatic autoantibodies suggestive of type 1 diabetes, or
    - Body mass index (BMI) greater than or equal to 35 kg/m², or
    - Acanthosis nigricans, AND

- Rendering laboratory is a qualified provider of service per the Health Plan policy.

HNF4A Sequencing and Deletion/Duplication Analysis

- Genetic Counseling:
  - Pre and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
• Previous Genetic Testing:
  o No previous HNF4A gene sequencing or deletion/duplication analysis, and
  o No known MODY mutation in biologic relative, and
  o Member has previous HNF1A testing with no deleterious mutation found, AND
• Rendering laboratory is a qualified provider of service per the Health Plan policy.

GCK Sequencing and Deletion/Duplication Analysis

• Genetic Counseling:
  o Pre and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
• Previous Genetic Testing:
  o No previous GCK gene sequencing or deletion/duplication analysis, and
  o No known MODY mutation in biologic relative, AND
• Diagnostic Testing for Symptomatic Individuals:
  o Member has previous HNF1A testing with no deleterious mutation found, or
  o Member has a personal history of the following features presenting outside of pregnancy:
    ▪ Persistent, stable elevation of fasting blood glucose (5.5-8 mmol/L), and
    ▪ HbA1C that is no more than mildly elevated (less than or equal to 7.5%), and
    ▪ At least one oral glucose tolerance test demonstrates a small increment (less than 4.6 mmol/L), or
  o Member has a personal history of the following features in the context of gestational diabetes:
    ▪ Persistent elevation of fasting blood glucose (5.5-8 mmol/L) before, during, and after pregnancy, and
    ▪ At least one oral glucose tolerance test demonstrates a small increment (less than 4.6 mmol/L) either during or after pregnancy, AND
• Rendering laboratory is a qualified provider of service per the Health Plan policy.

Sequencing and Deletion/Duplication Analysis of ABCC8, BLK, CEL, HNF1B, INS, KCNJ11, KLF11, NEUROD1, PAX4, and PDX1

Sequencing and deletion/duplication analysis of these genes in the context of MODY testing is not a covered benefit.
• The clinical utility of these tests for the evaluation of MODY has not been well established. Mutations in HNF1A, GCK, and HNF4A are responsible for the majority of cases of MODY, making them the most common known genetic causes of the disorder. There are other genes associated with MODY, but mutations in each gene account for greater than 1% of cases of MODY, therefore incremental mutation yield of individual gene testing is expected to be very low. In addition, medical management guidelines have not been established for most of these forms of MODY.

• Gene testing is not covered strictly for the indication of MODY testing. Testing in other contexts may meet medical necessity criteria (e.g., HNF1B testing for individuals with symptoms of Renal Cysts and Diabetes Syndrome, CEL testing for individuals with diabetes and pancreatic exocrine dysfunction, or certain gene tests for individuals with neonatal diabetes or familial hyperinsulinism). For gene testing in non-MODY contexts, refer to Genetic Testing for Non-Cancer Conditions.

MODY Multi-Gene Panels

When separate procedure codes will be billed for individual MODY genes (e.g., Tier 2 MoPath codes 81400-81408), each individually billed test will be evaluated separately. The below criteria for single gene testing will be applied.

If the member meets the following criteria, the entire panel will be approved. However, the laboratory will be redirected to use a panel CPT code for billing purposes (e.g. 81479):

• Genetic Counseling:
  o Pre and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND

• Previous Genetic Testing:
  o No previous MODY genetic testing, and
  o No known MODY mutation in biologic relative, AND

• Diagnostic Testing for Symptomatic Individuals:
  o Member has a diagnosis of diabetes prior to 35 years of age, and
  o Member has a family history of diabetes consistent with autosomal dominant inheritance, and
  o Member does NOT have symptoms consistent with a specific condition or specific gene mutation, and
  o Member does NOT have any of the following features:
    ▪ Extra-pancreatic manifestations (e.g., congenital malformations and other signs of syndromic diabetes), or
    ▪ Pancreatic autoantibodies suggestive of type 1 diabetes, or
- Body mass index (BMI) greater than or equal to 35 kg/m$^2$, or
- Acanthosis nigricans, AND

- Rendering laboratory is a qualified provider of service per the Health Plan policy.

When a multi-gene panel is being requested and will be billed with a single panel CPT code (e.g. 81479), the panel will be considered medically necessary when the following criteria are met:

- Genetic Counseling:
  - Pre and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND

- Previous Genetic Testing:
  - No previous MODY genetic testing, and
  - No known MODY mutation in biologic relative, AND

- Diagnostic Testing for Symptomatic Individuals:
  - Member has a diagnosis of diabetes prior to 35 years of age, and
  - Member has a family history of diabetes consistent with autosomal dominant inheritance, and
  - Member does NOT have symptoms consistent with a specific condition or specific gene mutation, and
  - Member does NOT have the following features:
    - Extra-pancreatic manifestations (e.g., congenital malformations and other signs of syndromic diabetes), or
    - Pancreatic autoantibodies suggestive of type 1 diabetes, or
    - Body mass index (BMI) greater than or equal to 35 kg/m$^2$, or
    - Acanthosis nigricans, AND

- Rendering laboratory is a qualified provider of service per the Health Plan policy.

**Billing and reimbursement considerations**

- When multiple CPT codes are billed for components of a panel and there is a more appropriate CPT code representing the panel, eviCore will redirect to the panel code(s).
- If the laboratory will not accept redirection to a panel code, the medical necessity of each billed component procedure will be assessed independently.
In general, only a limited number of panel components that are most likely to explain the member's presentation will be reimbursable. The remaining panel components will not be reimbursable.

When a MODY multi-gene panel is billed with multiple stacked codes, only the following genes may be considered for reimbursement:

- HNF1A
- GCK
- HNF4A

References


