Medical Policy

Blue Cross Blue Shield Blue Care Network of Michigan

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***Current Policy Effective Date: 5/1/24**
(See policy history boxes for previous effective dates)

Title: GT-Maturity-Onset Diabetes of the Young (MODY)

Description/Background

Maturity-onset diabetes of the young (MODY) is a clinically and genetically heterogeneous form of diabetes that is characterized by impaired insulin secretion.[1] MODY, which is inherited in an autosomal dominant manner, is estimated to account for between 1% and 5% of non-insulin-dependent diabetes cases.[1,2]

MODY is diagnosed clinically in patients with hyperglycemia or diabetes who have a family history of abnormal glucose metabolism in at least 2 consecutive generations, with the patient or 1 or more family members diagnosed before age 25.[2-4] Currently, there are nine known subtypes of MODY that differ with regard to average age at disease presentation, pattern of hyperglycemia, response to the various treatment modalities, and the presence of extrapancreatic features.[5] The penetrance of disease-causing variants may also vary depending on the subtype, but the overall penetrance of MODY gene variants is reported to be > 90%.[4]

The most common types of MODY are MODY2 and MODY3.[2] MODY2 is caused by variants in the glucokinase gene (*GCK*), and is characterized by mild fasting hyperglycemia that is generally stable but persistent.[3] It is suspected that *GCK* variants are relatively common among the general population, but that most carriers are asymptomatic and, thus, undiagnosed.[2,6] Because of the mild manifestations, complications are rare in MODY2 patients.[7,8] Furthermore, MODY2 does not typically require treatment with medication or insulin, although treatment may be warranted in affected women during pregnancy, depending on the growth of the fetus.[1,2,8,9]

MODY 3 is caused by mutations of the hepatocyte nuclear factor 1alpha (HNF1-alpha) gene, a homeobox gene on human chromosome 12.[11] HNF1α is a transcription factor (also known as transcription factor 1, TCF1) that is thought to control a regulatory network (including, among

other genes, HNF1α) important for differentiation of beta cells. One of the incentives for diagnosing it is that insulin may be discontinued or deferred in favor of oral sulfonylureas. Some people treated with insulin for years due to a presumption of type 1 diabetes have been able to switch to oral medication and discontinue injections.

Testing for the major types of MODY often involves analysis of the coding sequences, intron-exon boundaries, and minimal promoter of each MODY gene by direct sequencing.[8,27] However, gene scanning techniques, such as denaturing high-performance liquid chromatography (dHPLC) and single-strand conformation polymorphism (SSCP) analysis, may be used prior to sequence analysis.[28-32] Testing for deletions and duplications of the genes for MODY is performed by multiplex ligation-dependent probe amplification (MLPA).[26,33]

Regulatory Status

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments (CLIA). Laboratories that offer laboratory-developed tests must be licensed by the CLIA for high-complexity testing. To date, the U.S. FDA has chosen not to require any regulatory review of these tests. *Therefore, no FDA approvals will be found or listed on their website.*

Medical Policy Statement

The safety and effectiveness of genetic testing for maturity-onset diabetes of the young (MODY) have been established. It may be considered a useful diagnostic option when indicated for individuals meeting specified guidelines.

Inclusionary and Exclusionary Guidelines

Inclusions:
For the diagnosis of MODY in individuals with:

- Early-onset diabetes in children or young adulthood (typically age <45 years); **AND**
- Have a family history of diabetes in successive generations (suggestive of an autosomal dominant pattern of inheritance); **AND**
- **Any one** of the following atypical features for **Type 1 diabetes**:
    - Absence of pancreatic islet autoantibodies (e.g., GAD and IA2)
    - Evidence of endogenous insulin production beyond the honeymoon period (i.e., 3-5 years after the onset of diabetes)
    - Measurable C-peptide in the presence of hyperglycemia (C-peptide ≥0.60 ng/mL or 0.2 nmol/L)
    - Low insulin requirement for treatment (i.e., <0.5 U/kg/d)
    - Lack of ketoacidosis when insulin is omitted from treatment;

OR

- **Any one** of the following atypical features for **Type 2 Diabetes**:

- Lack of significant obesity
- Lack of acanthosis nigricans
- Normal triglyceride levels and/or normal or elevated high-density lipoprotein cholesterol (HDL-C)

OR

- Any one of the following:
  - Mild, stable fasting hyperglycemia that does not progress or respond appreciably to pharmacologic therapy
  - Extreme sensitivity to sulfonylureas
  - A personal history or family history of neonatal diabetes or neonatal hypoglycemia

Exclusions:

- MODY testing for all other indications not meeting the criteria above.

CPT/HCPCS Level II Codes *(Note: The inclusion of a code in this list is not a guarantee of coverage. Please refer to the medical policy statement to determine the status of a given procedure.)*

Established codes:

81405 81406

Other codes (investigational, not medically necessary, etc.):

N/A

Note: Individual policy criteria determine the coverage status of the CPT/HCPCS code(s) on this policy. Codes listed in this policy may have different coverage positions (such as established or experimental/investigational) in other medical policies.

Rationale

Evidence reviews assess the clinical evidence to determine whether the use of a technology improves the net health outcome. Broadly defined, health outcomes are length of life, quality of life, and ability to function including benefits and harms. Every clinical condition has specific outcomes that are important to patients and to managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of a technology, 2 domains are examined: the relevance and the quality and credibility. To be relevant, studies must represent 1 or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be

adequate. Randomized controlled trials are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

Maturity-Onset Diabetes of the Young (MODY)

Clinical Context and Therapy Purpose
The purpose of testing for MODY variants is to establish a specific diagnosis and whether that specific diagnosis has direct implications for the individual's medical management?

The following **PICO** was used to select literature to inform this review.

Populations
The relevant population of interest is individuals with hyperglycemia or non-insulin dependent diabetes.

Interventions
The testing being considered is MODY.

Comparators
The following are alternatives to MODY gene testing include evaluating fasting plasma glucose (FPG) levels, oral glucose tolerance testing, glycosylated hemoglobin (HbA1c) levels, glutamatedecarboxylase (GAD) and islet antigen-2 (IA-2) antibodies.

Outcomes
The general outcomes of interest are improved medical management.

Study Selection Criteria
Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Consistent with a 'best available evidence approach,' within each category of study design, studies with larger sample sizes and longer durations were sought.
- Studies with duplicative or overlapping populations were excluded.

Review of Evidence
Pearson et al (2003) conducted a randomized crossover trial to assess whether different causes for diabetes change the response to oral hypoglycaemic therapy.[1] In a few cases, patients with diabetes caused by mutations in the hepatocyte nuclear factor 1alpha (HNF-1alpha) gene have been described as sensitive to the hypoglycaemic effects of sulphonylureas. In this trial, glicazide and metformin were used in 36 patients either with diabetes caused by HNF-1alpha mutations or type 2 diabetes, who were matched for body-mass index and fasting plasma glucose. The primary outcome was reduction in fasting plasma glucose. Analysis was by intention to treat. The authors assessed possible mechanisms for

sulphonylurea sensitivity through insulin sensitivity, insulin secretory response to glucose and tolbutamide, and tolbutamide clearance. Patients with HNF-1alpha diabetes had a 5.2-fold greater response to gliclazide than to metformin (fasting plasma glucose reduction 4.7 vs 0.9 mmol/L, p=0.0007) and 3.9-fold greater response to gliclazide than those with type 2 diabetes (p=0.002). Patients with HNF-1alpha diabetes had a strong insulin secretory response to intravenous tolbutamide despite a small response to intravenous glucose, and were more insulin sensitive than those with type 2 diabetes. Sulphonylurea metabolism was similar in both patient groups.

Garin et al (2008) conducted a study to characterize glucokinase (GCK) alterations in maturity-on-set diabetes of the young 2 (MODY2)-suspected patients and to investigate their clinical characteristics in relation to the parental origin of the mutation.[2] A group of 57 unrelated Spanish patients presenting with MODY2 phenotype were studied. Patients without mutation in the coding region of the GCK gene were screened for rearrangements by Multiplex Ligation-dependent Probe Amplification (MLPA). After classification according to the parental origin of the mutation, clinical characteristics were compared between the groups. A point mutation or small deletion or insertion of the GCK gene was detected in 47 patients (82.5%); 19 mutations were novel. In addition, a whole-gene deletion by MLPA was found. Patients carrying a GCK gene defect and those with MODY of unknown genetic origin shows similar phenotypes. Comparison of clinical parameters according to the origin of the mutation did not show any differences in the birth weight (BW) nor in age at diagnosis. Patients who inherited the mutation from the father had higher fasting glucose levels at diagnosis.

Ellard et al (2008) along with 22 clinicians and scientists held a workshop to discuss clinical criteria for testing and the interpretation of molecular genetic test results in mutations in the GCK and HNF1A genes which are the most common cause of the MODY diabetic.[3] GCK encodes the glucokinase enzyme, which acts as the pancreatic glucose sensor, and mutations result in stable, mild fasting hyperglycaemia. A progressive insulin secretory defect is seen in patients with mutations in theHNF1A and HNF4A genes encoding the transcription factors hepatocyte nuclear factor-1 alpha and -4alpha. A molecular genetic diagnosis often changes management, since patients with GCK mutations rarely require pharmacological treatment and HNF1A/4A mutation carriers are sensitive to sulfonylureas. These monogenic forms of diabetes are often misdiagnosed as type 1 or 2 diabetes. Best practice guidelines for genetic testing were developed to guide testing and reporting of results.

Bellanne-Chantelot et al (2011) conducted a retrospective multicenter study including 487 unrelated patients referred because of suspicion of MODY3.[4] Genetic analysis identified 196 MODY3 and 283 non-MODY3 cases. Criteria associated with MODY3 were assessed by multivariate analysis. The capacity of the model to predict MODY3 diagnosis was assessed by the area under the receiver-operating characteristic curve and was further validated in an independent sample of 851 patients (165 MODY3 and 686 non-MODY3). In the MODY3 patients, diabetes was revealed by clinical symptoms in 25% of the cases and was diagnosed by screening in the others. Age at diagnosis of diabetes was more than 25 years in 40% of the MODY3 patients. There was considerable variability and overlap of all assessed parameters in MODY3 and non-MODY3 patients. The best predictive model was based on criteria available at diagnosis of diabetes, including age, body mass index, number of affected generations, presence of diabetes symptoms, and geographical origin. The area under the curve of the receiver-operating characteristic analysis was 0.81. When sensitivity was set to 90%, specificity was 49%.

According to McDonald et al (2011), MODY is rare (~1% diabetes) and may be misdiagnosed as Type 1 diabetes and inappropriately treated with insulin.[5] Type 1 diabetes is characterized by the presence of islet autoantibodies, including glutamatedecarboxylase (GAD) and islet antigen-2 (IA-2) antibodies. The prevalence of islet autoantibodies is unknown in maturity-onset diabetes of the young and may have the potential to differentiate this form of diabetes from Type 1 diabetes. In this study, plasma GAD and IA-2 antibodies was measured in 508 patients with the most common forms of maturity-onset diabetes of the young (GCK: n = 227; HNF1A: n = 229; HNF4A: n = 52) and 98 patients with newly diagnosed Type 1 diabetes (diagnosed<6 months). Autoantibodies were considered positive if ≥99th centile of 500 adult control subjects. GAD and/or IA-2 antibodies were present in 80/98 (82%) patients with Type 1 diabetes and 5/508 (<1%) patients with maturity-onset diabetes of the young. In the cohort with Type 1 diabetes, both GAD and IA-2 antibodies were detected in 37.8% of patients, GAD only in 24.5% and IA-2 only in 19.4%. All five patients with maturity-onset diabetes of the young with detectable antibodies had GAD antibodies and none had detectable IA-2 antibodies.

In 2019, GoodSmith et al. assessed the cost-effectiveness of genetic testing, preceded by biomarker screening and followed by cascade genetic testing of first-degree relatives, for subtypes of MODY in U.S. pediatric patients with diabetes.[6] Simulation models of distinct forms of diabetes were used to forecast the clinical and economic consequences of a systematic genetic testing strategy compared with usual care over a 30-year time horizon. In the genetic testing arm, patients with MODY received treatment changes (sulfonylureas for HNF1A- and HNF4A-MODY associated with a 1.0% reduction in HbA_{1c}; no treatment for GCK-MODY). Study outcomes included costs, life expectancy (LE), and quality-adjusted life years (QALY). The strategy of biomarker screening and genetic testing was cost-saving as it increased average quality of life (+0.0052 QALY) and decreased costs (-$191) per simulated patient relative to the control arm. Adding cascade genetic testing increased quality-of-life benefits (+0.0081 QALY) and lowered costs further (-$735).

Urbanova et al (2020) presented a summary of the actual diagnostic possibilities and differentiation of MODY (Maturity-Onset Diabetes of the Young) from gestational diabetes (GDM) found during routine screening, and specific aspects of care and treatment of MODY during pregnancy and early postpartum period.[7] Many patients with MODY, especially the glucokinase MODY, can be first diagnosed during pregnancy. It is estimated that MODY patients account for up to 5% of GDM cases found in routine screening of GDM. MODY should be considered in lean women around 25 years of age, with a positive family history of diabetes in one of the parents. The differentiation of MODY from GDM is of particular importance not only for the different management and goals of antidiabetic therapy and planning ultrasound controls of fetal growth during pregnancy, but also because of the risk of hyperinsulinemic hypoglycemia in newborns. The authors concluded that recognition of MODY during pregnancy and adherence to existing recommendations concerning specific care of these patients is essential for the optimal course of their pregnancy and proper care of the newborn in the early postpartum period.

Summary of Evidence

MODY is a dominantly inherited form of diabetes that is characterized by defective insulin secretion. The clinical criteria for a diagnosis of MODY are well-established and indicate that the diagnosis of MODY should be considered in certain patients. Studies of the clinical validity of MODY gene testing demonstrate that there is a clear association between variants in

the known MODY genes and the MODY phenotype. In addition, it is apparent that the phenotype of MODY patients, including the age at disease onset and the clinical manifestations, varies depending on the type of MODY each patient has. The evidence supporting the clinical utility of MODY gene testing suggests that the optimal treatment of MODY patients may depend on the subtype. For example, it is possible that MODY3 patients may be able to discontinue or avoid insulin treatment, since these individuals are often sensitive to sulphonylureas. Also, patients in whom a diagnosis of MODY2 is established may be able to discontinue treatment with either insulin or oral hypoglycemic agents, since they are often able to manage the disease with diet and lifestyle changes alone. In addition to the implications for treatment, families report that MODY 2 and 3 gene testing is useful for future or family planning and to reduce uncertainty and anxiety in those at risk of developing the disease. The evidence for MODY 2 & 3 testing is sufficient to determine that the technology results in an improvement in the net health outcome.

SUPPLEMENTAL INFORMATION

PRACTICE GUIDELINES AND POSITION STATEMENTS

American Diabetes Association (ADA)[9]

In 2024, the ADA published Diagnosis and Classification of Diabetes guidelines. The following recommendations were made:

- 2.24a Regardless of current age, all people diagnosed with diabetes in the first 6 months of life should have immediate genetic testing for neonatal diabetes.
- A 2.24b Children and young adults who do not have typical characteristics of type 1 or type 2 diabetes and who often have a family history of diabetes in successive generations (suggestive of an autosomal dominant pattern of inheritance) should have genetic testing for maturity-onset diabetes of the young (MODY).
- A 2.24c In both instances, consultation with a center specializing in diabetes genetics is recommended to understand the significance of genetic mutations and how best to approach further evaluation, treatment, and genetic counseling.

European Molecular Genetics Quality Network (EMQN)[3]

The EMQN (2008) developed guidelines for diagnostic and predictive testing for MODY1, MODY2, and MODY3. MODY2 (due to *GCK* variants) should be considered in patients with an FPG level ≥ 5.5 mmol/L that is persistent and stable, an HbA1c that is just above the upper limit of normal but rarely exceeds 7.5%, and a small (< 4.6 mmol/L) 2-hour increment on oral glucose tolerance test. In addition, MODY2 patients may have a parent diagnosed with hyperglycemia or type 2 DM. MODY3 (due to *HNF1A* variants) should be considered in patients with young-onset non-insulin-dependent diabetes, a family history of DM in at least 2 consecutive generations, and an absence of autoimmune markers of DM. In addition, MODY3 patients often have glycosuria and may exhibit a marked sensitivity to sulphonylureas. Testing for MODY1 (caused by *HNF4A* variants) should be considered in patients who test negative for an *HNF1A* gene variant. Specific recommendations regarding the reporting of test results are also provided by the EMQN.

ONGOING AND UNPUBLISHED CLINICAL TRIALS

Some currently unpublished trials that might influence this policy are listed in Table 1.

Table 1. Clinical Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT05586594	Identifying Maturity-onset Diabetes of the Young in Emirati Patients	150	Aug 2025
NCT06111833	Optimized Diagnosis and Precision Medicine of MODY	1500	May 2028
Unpublished			
NCT03246828	Glucagon in MODY (Maturity Onset Diabetes of the Young)	10	Aug 2022
NCT05918484	Usefulness of Continuous Glucose Monitoring in MODY Diagnosis (UCMODY)	4000	Dec 2023

Government Regulations

National:

There is no NCD for this testing.

Local:

There is no LCD for this testing.

(The above Medicare information is current as of the review date for this policy. However, the coverage issues and policies maintained by the Centers for Medicare & Medicare Services [CMS, formerly HCFA] are updated and/or revised periodically. Therefore, the most current CMS information may not be contained in this document. For the most current information, the reader should contact an official Medicare source.)

Related Policies

N/A

References

1. Pearson ER, Starkey BJ, Powell RJ, et al. Genetic cause of hyperglycemia and response to treatment in diabetes. Lancet. Oct 2003;362(9392):1275-1281.
2. Garin I, Rica I, Estalella I, et al. Haploinsufficiency at GCK gene is not a frequent event in MODY2 patients. Clin Endocrinol. June 2008;68(6):873-878.
3. Ellard S, Bellanne-Chantelot C, Hattersley AT. Best practice guidelines for the molecular genetic diagnosis of maturity-onset diabetes of the young. Diabetologia. April 2008;51(4):546-553.
4. Bellanne-Chantelot C, Levy DJ, Carette C, et al. Clinical characteristics and diagnostic criteria of maturity-onset diabetes of the young (MODY) due to molecular anomalies of the HNF1A gene. J Clin Endorinol Metab. Aug 2011;96(8):E1346-1351.
5. McDonald TJ, Colclough K, Brown R, et al. Islet autoantibodies can discriminate maturity-onset diabetes of the young (MODY) from type 1 diabetes. Diabet Med. Sep 2011;28(9):1028-1033.
6. GoodSmith MS, Skandari MR, Huang ES, Naylor RN. The impact of biomarker screening and cascade genetic testing on the cost-effectiveness of MODY genetic testing. Diabetes Care. Dec 2019; 42(12):2247-2255.

7. Urbanova J, Brunerova L, Nunes MA, Broz J. MODY diabetes and screening of gestational diabetes. Ceska Gynekol. 2020;85(2):124-130.
8. Balasubramanyam A, Nathan DM, et al. Classification of diabetes mellitus and genetic diabetic syndromes. UpToDate. 2024.
9. American Diabetes Association. Diagnosis and classification of diabetes: standards of care in diabetes-2024. Diabetes Care. 2024;47(1):S20-S42.
10. Frayling TM, Evans JC, Bulman MP, et al. Molecular and Clinical Characterization of Mutations in Transcription Factors. Diabetes. 2001;50(1):S94-S100.

The articles reviewed in this research include those obtained in an Internet based literature search for relevant medical references through January 2024, the date the research was completed.

Joint BCBSM/BCN Medical Policy History

Policy Effective Date	BCBSM Signature Date	BCN Signature Date	Comments
5/1/24	3/4/24		Joint policy established

Next Review Date: 1st Qtr., 2025

Pre-Consolidation Medical Policy History

Original Policy Date	Comments
BCN:	Revised:
BCBSM:	Revised:

BLUE CARE NETWORK BENEFIT COVERAGE
POLICY: GT-MATURITY-ONSET DIABETES OF THE YOUNG (MODY)

I. Coverage Determination:

Commercial HMO (includes Self-Funded groups unless otherwise specified)	Per policy
BCNA (Medicare Advantage)	See government section
BCN65 (Medicare Complementary)	Coinsurance covered if primary Medicare covers the service.

II. Administrative Guidelines:

- The member's contract must be active at the time the service is rendered.
- Coverage is based on each member's certificate and is not guaranteed. Please consult the individual member's certificate for details. Additional information regarding coverage or benefits may also be obtained through customer or provider inquiry services at BCN.
- The service must be authorized by the member's PCP except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Services must be performed by a BCN-contracted provider, if available, except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Payment is based on BCN payment rules, individual certificate and certificate riders.
- Appropriate copayments will apply. Refer to certificate and applicable riders for detailed information.
- CPT - HCPCS codes are used for descriptive purposes only and are not a guarantee of coverage.