Genetic Testing: Maturity-Onset Diabetes of the Young

MEDICAL POLICY NUMBER: 396

Effective Date: 10/1/2023

Last Review Date: 7/2023

Next Annual Review: 7/2024

INSTRUCTIONS FOR USE: Company Medical Policies serve as guidance for the administration of plan benefits. Medical policies do not constitute medical advice nor a guarantee of coverage. Company Medical Policies are reviewed annually and are based upon published, peer-reviewed scientific evidence and evidence-based clinical practice guidelines that are available as of the last policy update. The Company reserves the right to determine the application of medical policies and make revisions to medical policies at any time. The scope and availability of all plan benefits are determined in accordance with the applicable coverage agreement. Any conflict or variance between the terms of the coverage agreement and Company Medical Policy will be resolved in favor of the coverage agreement. Coverage decisions are made on the basis of individualized determinations of medical necessity and the experimental or investigational character of the treatment in the individual case. In cases where medical necessity is not established by policy for specific treatment modalities, evidence not previously considered regarding the efficacy of the modality that is presented shall be given consideration to determine if the policy represents current standards of care.

SCOPE: Providence Health Plan, Providence Health Assurance and Providence Plan Partners as applicable (referred to individually as “Company” and collectively as “Companies”).

PLAN PRODUCT AND BENEFIT APPLICATION

☒ **Commercial** ☒ **Medicaid/OHP*** ☐ **Medicare****

*Medicaid/OHP Members

Oregon: Services requested for Oregon Health Plan (OHP) members follow the OHP Prioritized List and Oregon Administrative Rules (OARs) as the primary resource for coverage determinations. Medical policy criteria below may be applied when there are no criteria available in the OARs and the OHP Prioritized List.

**Medicare Members

This *Company* policy may be applied to Medicare Plan members only when directed by a separate *Medicare* policy. Note that investigational services are considered **"not medically necessary"** for Medicare members.

COVERAGE CRITERIA

I. Genetic testing for the diagnosis of monogenic diabetes (i.e. mature-onset diabetes of the young (MODY)) may be considered **medically necessary** when all of the following criteria are met (A.-D.):

   A. Diabetes is diagnosed at 35 years of age or younger; **and**
   B. Patient has one of the following (1.-2.):
      1. Hyperglycemia; **or**
      2. A family history of diabetes (i.e. the patient plus a family member that is either one generation older or younger); **and**
   C. Patient is non-obese (i.e. BMI < 30 kg/m^2); **and**
   D. Patient lacks autoantibodies (i.e. autoantibodies have been tested and documented as negative).

II. Genetic testing for maturity-onset diabetes of the young (MODY) is considered **not medically necessary** when criterion I. above is not met.

Link to Evidence Summary

POLICY CROSS REFERENCES

- Genetic and Molecular Testing (Company), MP215

The full Company portfolio of current Medical Policies is available online and can be accessed here.

POLICY GUIDELINES

BACKGROUND

Maturity-Onset Diabetes of the Young (MODY)

Maturity-onset diabetes of the young (MODY) is a heritable form of diabetes mellitus that results from a primary defect in insulin secretion. date, 9 different subtypes of MODY have been described. MODY2 and MODY3 account for the majority of genetically diagnosed MODY cases. MODY2 is caused by variants in the glucokinase (GCK) gene and is characterized by mild hyperglycemia that is persistent but stable. It is often treated successfully with dietary and lifestyle changes alone. MODY3 is caused by variants in the hepatocyte nuclear factor 1 alpha (HNF1A) gene, and is characterized by progressive pancreatic beta-cell dysfunction.

Invitae Monogenic Diabetes Panel

According to the Invitae website, the Monogenic Diabetes Panel tests for genes associated with syndromic and nonsyndromic causes of monogenic diabetes and has 28 genes: [1]

- ABCC8, APPL1, BLK, EIF2AK3, FOXP3, GATA4, GATA6, GCK, GLIS3, HNF1A, HNF1B, HNF4A, IER3IP1, INS, KCNJ11, KLF11, MNX1, NEUROD1, NEUROG3, NKX2-2, PAX4, PDX1, PPARG, PTF1A, RFX6, SLC19A2, WFS1, ZFP57.

REGULATORY STATUS

U.S. FOOD AND DRUG ADMINISTRATION (FDA)

Approval or clearance by the Food and Drug Administration (FDA) does not in itself establish medical necessity or serve as a basis for coverage. Therefore, this section is provided for informational purposes only.

CLINICAL EVIDENCE AND LITERATURE REVIEW

EVIDENCE REVIEW

A review of the ECRI, Hayes, Cochrane, and PubMed databases was conducted regarding the use of MODY gene testing for diabetes. Below is a summary of the available evidence identified through June 2023.

Systematic Reviews

- In 2018, GeneReviews published an overview of MODY gene testing for diabetes.[2] Authors stated that MODY has an onset in adolescence or young adulthood, typically less than 35 years and issued the following findings:

- Molecular genetic testing approaches to determine the associated MODY gene can include a combination of gene-targeted testing (serial singe-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:
    - 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."
    - 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.

- In 2014, Hayes published a molecular test assessment of MODY gene testing for diabetes.[3] Authors wrote that studies involving patients with MODY2 and MODY3 reveal a relatively high prevalence of these subtypes among MODY patients, and indicate that genetic testing for diagnostic purposes is accurate and reliable. Furthermore, the data suggest there is clinical utility in MODY2 and MODY3 gene testing, as the diagnosis of these specific subtypes may impact treatment decisions. Authors found evidence supporting the clinical utility of MODY gene testing in patients who are clinically diagnosed. Studies of the clinical utility of MODY gene testing are limited in that they only address the most common MODY subtypes. Also, the studies that have been performed include only a small number of patients who were followed for a relatively short period of time. Hayes assigned a B rating for MODY2 and MODY3 gene testing in patients with a clinical diagnosis of MODY and a C rating for MODY1 and MODY5 gene testing for diagnostic purposes in diabetes patients. Studies examining the clinical validity and clinical utility of gene testing for the rarest subtypes are currently insufficient. Authors assigned a D2 rating for MODY4, MODY6, MODY7, MODY8, and MODY9 gene testing.

CLINICAL PRACTICE GUIDELINES

American Diabetes Association

In 2019, the American Diabetes Association published guidelines addressing the classification and diagnosis of diabetes, including the following recommendations:[4]

- All children diagnosed with diabetes in the first 6 months of life should have immediate genetic testing for neonatal diabetes.

- 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.
- In both instances, consultation with a center specializing in diabetes genetics is recommended to understand the significance of these mutations and how best to approach further evaluation, treatment, and genetic counseling.
- A diagnosis of one of the three most common forms of MODY, including GCK-MODY, HNF1A-MODY, and HNF4A-MODY, allows for more cost-effective therapy (no therapy for GCK-MODY; sulfonylureas as first-line therapy for HNF1A-MODY and HNF4A-MODY). Additionally, diagnosis can lead to identification of other affected family members.
- A diagnosis of MODY should be considered in individuals who have atypical diabetes and multiple family members with diabetes not characteristic of type 1 or type 2 diabetes…
- Readily available commercial genetic testing following the criteria listed below now enables a cost-effective, often cost-saving, genetic diagnosis that is increasingly supported by health insurance.
- It is critical to correctly diagnose one of the monogenic forms of diabetes because these patients may be incorrectly diagnosed with type 1 or type 2 diabetes, leading to suboptimal, even potentially harmful, treatment regimens and delays in diagnosing other family members. The correct diagnosis is especially critical for those with GCK-MODY mutations where multiple studies have shown that no complications ensue in the absence of glucose-lowering therapy. Genetic counseling is recommended to ensure that affected individuals understand the patterns of inheritance and the importance of a correct diagnosis.
- The diagnosis of monogenic diabetes should be considered in children and adults diagnosed with diabetes in early adulthood with the following findings:
    - Diabetes diagnosed within the first 6 months of life (with occasional cases presenting later, mostly *INS* and *ABCC8* mutations)
    - Diabetes without typical features of type 1 or type 2 diabetes (negative diabetes-associated autoantibodies, nonobese, lacking other metabolic features especially with strong family history of diabetes)
    - Stable, mild fasting hyperglycemia (100–150 mg/dL [5.5–8.5 mmol/L]), stable A1C between 5.6 and 7.6% (between 38 and 60 mmol/mol), especially if nonobese

<u>International Society for Pediatric and Adolescent Diabetes</u>

In 2022, the ISPAD published clinical practice consensus guidelines addressing the diagnosis and management of monogenic diabetes in children and adolescents.[5] Authors made the following recommendations:

- The diagnosis of maturity onset diabetes of the young (MODY) is recommended in the following scenarios:
    - A family history of diabetes in a parent and first-degree relatives of that affected parent in persons with diabetes who lack the characteristics of T1D and T2D.
- Testing for GCK-MODY, which is the commonest cause of persistent, incidental hyperglycemia in the pediatric population, is recommended for mild stable fasting hyperglycemia that does not progress.

- In familial autosomal dominant symptomatic diabetes, mutations in the HNF1A gene (HNF1A-MODY) should be considered as the first diagnostic possibility.
- Specific features can suggest subtypes of MODY, such as renal developmental disease or renal cysts (HNF1B-MODY), macrosomia and/or neonatal hypoglycemia (HNF4A-MODY), exocrine pancreatic dysfunction or pancreatic cysts (CEL-MODY), or hearing impairment and maternal inheritance of diabetes (mitochondrial diabetes).
- Obesity alone should not preclude genetic testing in young persons, especially if:
    - family history is strongly suggestive of autosomal dominant inheritance of diabetes
    - if some affected family members are NOT obese
    - and/or, there are no other features of metabolic syndrome.
- Some forms of MODY are sensitive to SU, such as HNF1A-MODY and HNF4A-MODY.
- Mild fasting hyperglycemia due to GCK-MODY is not progressive during childhood. These persons do not develop complications.

EVIDENCE SUMMARY

Evidence is sufficient to support the clinical utility of MODY gene testing for diabetes. Peer-reviewed literature and evidence-based clinical practice guidelines have demonstrated that identifying monogenic diabetes usually improves patients' clinical care. The correct diagnosis also informs familial genetic counseling, triggering extended genetic testing in other family members with diabetes or hyperglycemia who may also carry a causal mutation.

BILLING GUIDELINES AND CODING

CODES*		
CPT	81404	Molecular pathology procedure, level 5 (e.g., analysis of 2-5 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 6-10 exons, or characterization of a dynamic mutation disorder /triplet repeat by southern blot analysis
	81405	Molecular pathology procedure, level 6 (e.g., analysis of 6-10 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 11-25 exons)
	81406	Molecular pathology procedure, Level 7 (e.g., analysis of 11-25 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 26-50 exons, cytogenomic array analysis for neoplasia)
	81479	Unlisted molecular pathology procedure

***Coding Notes:**

- The above code list is provided as a courtesy and may not be all-inclusive. Inclusion or omission of a code from this policy neither implies nor guarantees reimbursement or coverage. Some codes may not require routine review for medical necessity, but they are subject to provider contracts, as well as member benefits, eligibility and potential utilization audit.
- All unlisted codes are reviewed for medical necessity, correct coding, and pricing at the claim level. If an unlisted code is submitted for non-covered services addressed in this policy then it will be **denied as not covered**. If an unlisted code is submitted for potentially covered services addressed in this policy, to avoid post-service denial, **prior authorization is recommended**.

- **See the non-covered and prior authorization lists on the Company Medical Policy, Reimbursement Policy, Pharmacy Policy and Provider Information website for additional information.**
- HCPCS/CPT code(s) may be subject to National Correct Coding Initiative (NCCI) procedure-to-procedure (PTP) bundling edits and daily maximum edits known as "medically unlikely edits" (MUEs) published by the Centers for Medicare and Medicaid Services (CMS). This policy does not take precedence over NCCI edits or MUEs. Please refer to the CMS website for coding guidelines and applicable code combinations.

REFERENCES

1. Invitae Labs. Invitae Monogenic Diabetes Panel. https://www.invitae.com/en/providers/test-catalog/test-55001. Published 2023. Accessed 6/16/2023.
2. GeneReviews. Maturity-Onset Diabetes of the Young Overview. https://www.ncbi.nlm.nih.gov/books/NBK500456/. Published 2018. Accessed 6/16/2023.
3. Hayes Inc. Molecular Test Assessment: Maturity-Onset Diabetes Of The Young (MODY). https://evidence.hayesinc.com/report/gte.mody1748. Published 2014 (Archived). Accessed 6/16/2023.
4. American Diabetes Association. Standards of Medical Care in Diabetes-2019 Abridged for Primary Care Providers. *Clin Diabetes.* 2019;37(1):11-34.
5. Greeley SAW, Polak M, Njølstad PR, et al. ISPAD Clinical Practice Consensus Guidelines 2022: The diagnosis and management of monogenic diabetes in children and adolescents. 2022.

POLICY REVISION HISTORY

DATE	REVISION SUMMARY
10/2023	New policy.