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Medical Policy Manual Genetic Testing, Policy No. 20

Genetic and Molecular Diagnostic Testing

Effective: June 1, 2025

Next Review: February 2026
Last Review: April 2025

IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

Genetic testing, which detects changes in DNA, RNA, and chromosomes, may be performed to diagnose or determine susceptibility to inherited conditions, screen for potential genetic risk factors for common conditions, and aid in the selection of medications or other treatments.

MEDICAL POLICY CRITERIA

Note: This policy only applies when there is not a more specific medical policy available (see the Genetic Testing Section of the Medical Policy Manual). This policy is not intended to address asymptomatic carrier screening, which is addressed in the Carrier Screening for Genetic Diseases policy (Genetic Testing, Policy No. 81).

The following general criteria are applied to genetic and molecular diagnostic testing.

I. Genetic testing to establish a diagnosis or susceptibility for an inherited disease may be considered **medically necessary** when *all* of the following criteria are met:

   A. The genetic test is not a panel test listed in Genetic Testing Policy No. 64, *Evaluating the Utility of Genetic Panels*, as these tests are always investigational. Genetic panel tests that are not listed in GT64 or addressed by another specific policy will be reviewed by the criteria below.

B. There must be a reasonable expectation based on family history (pedigree analysis), risk factors, and symptomatology that a genetically inherited condition exists.

C. Diagnostic results from physical examination, pedigree analysis, and conventional testing are inconclusive and a definitive diagnosis is uncertain.

D. The clinical utility of all requested genes and gene variants must be established (including all genes and gene variants in a panel test, as applicable). The clinical records must document:

1. How test results will guide decisions regarding: disease treatment, prevention, or management, such as averting treatment for other possible diagnoses, and
2. These treatment decisions would not otherwise be made in the absence of the genetic test results.

II. Genetic testing to establish a diagnosis or susceptibility for an inherited disease is considered **not medically necessary** if Criterion I. above is not met.

III. Genetic testing of children to predict adult-onset diseases is considered **not medically necessary** unless test results will guide current decisions concerning prevention and this benefit would be lost by waiting until the child has reached adulthood.

IV. Genetic testing for indications *other than* determining risk or establishing a diagnosis for a genetically inherited disease (e.g., genotyping for drug selection and dosing) may be considered **medically necessary** when *all* of the following criteria are met:

A. The genetic test is not a panel test listed in Genetic Testing Policy No. 64, *Evaluating the Utility of Genetic Panels*, as these tests are always investigational. Genetic panel tests that are not listed in GT64 or addressed by another specific policy will be reviewed by the criteria below.

B. Diagnostic results from physical examination and conventional testing are inconclusive; and

C. The clinical records document how results of genetic testing are necessary to guide treatment decisions; and

D. There is reliable evidence in the peer-reviewed scientific literature that health outcomes are improved as a result of treatment decisions based on molecular genetic test results.

V. Genetic testing for indications other than determining risk or establishing a diagnosis for a genetically inherited disease is considered **not medically necessary** if any of criteria IV. A.-D. above are not met.

LIST OF INFORMATION NEEDED FOR REVIEW

In order to determine the clinical utility of gene test(s), <u>all of the following information must be submitted for review</u>:

1. Name of the genetic test(s) or panel test
2. Name of the performing laboratory and/or genetic testing organization (more than one may be listed)

3. The exact gene(s) and/or variants being tested
4. Relevant billing codes
5. Brief description of how the genetic test results will guide clinical decisions that would not otherwise be made in the absence of testing
6. Medical records related to this genetic test
    - History and physical exam
    - Date of sample collection (e.g., blood draw)
    - Conventional testing and outcomes
    - Conservative treatment provided, if any

CROSS REFERENCES

1. See the Genetic Testing Section of the Medical Policy Manual Table of Contents for additional genetic testing policies.
2. Investigational Gene Expression, Biomarker, and Multianalyte Testing, Laboratory, Policy No. 77

BACKGROUND

GENETIC TESTING

Genetic testing may be performed for several different purposes, including:

- Diagnosing or predicting susceptibility for inherited conditions[1]
- Screening for common disorders
- Selecting appropriate treatments (also known as pharmacogenetic testing)

GENETIC PANEL TESTING

New genetic technology, such as next generation sequencing and chromosomal microarray, has led to the ability to examine many genes simultaneously.[2] This in turn has resulted in a proliferation of genetic panels. Panels using next generation technology are intuitively attractive to use in clinical care because they can screen for numerous variants within a single gene or multiple genes quickly and may lead to greater efficiency in the work-up of genetic disorders. One potential challenge of genetic panel testing is the identification of genetic variants of unknown significance and variants for which the clinical management is uncertain and may lead to unnecessary follow-up testing and procedures.

GENETIC COUNSELING

Due to the complexity of interpreting genetic test results, patients should receive pre- and post-test genetic counseling from a qualified professional when testing is performed to diagnose or predict susceptibility for inherited diseases. The benefits and risks of genetic testing should be fully disclosed to individuals prior to testing, and counseling concerning the test results should be provided.

REGULATORY STATUS

The majority of genetic tests and genetic panel tests are laboratory derived tests that are not subject to U.S. Food and Drug Administration (FDA) approval.[3] The degree of oversight by the FDA depends on the intended use of the test and risk of inaccurate results. Clinical laboratories may develop and validate tests in-house (“lab-developed tests”) and market them as a laboratory service; such tests must meet the general regulatory standards of the Clinical

Laboratory Improvement Act (CLIA). The laboratory offering the service must be licensed by CLIA for high-complexity testing.

Note: Separate Medical Policies may apply to some specific genetic tests and panels. See the Genetic Testing Section of the Medical Policy Manual Table of Contents for additional genetic testing policies.

REFERENCES

1. Clinical utility of genetic and genomic services: a position statement of the American College of Medical Genetics and Genomics. *Genetics in medicine : official journal of the American College of Medical Genetics.* 2015;17:505-7. PMID: 25764213
2. Choi M, Scholl UI, Ji W, et al. Genetic diagnosis by whole exome capture and massively parallel DNA sequencing. *Proceedings of the National Academy of Sciences of the United States of America.* 2009;106(45):19096-101. PMID: 19861545
3. National Institutes of Health. Regulation of Genetic Tests. Secondary National Institutes of Health. Regulation of Genetic Tests [cited 03/27/2025]. 'Available from:' http://www.genome.gov/10002335.

CODES

NOTE: If the specific analyte (gene or gene variant) is listed with a CPT code, the specific CPT code should be reported. If the specific analyte is not listed with a specific CPT code, unlisted code 81479 should be reported.

Codes	Number	Description
CPT	0032U	COMT (catechol-O-methyltransferase)(drug metabolism) gene analysis, c.472G>A (rs4680) variant
	0232U	CSTB (cystatin B) (eg, progressive myoclonic epilepsy type 1A, Unverricht-Lundborg disease), full gene analysis, including small sequence changes in exonic and intronic regions, deletions, duplications, short tandem repeat (STR) expansions, mobile element insertions, and variants in non-uniquely mappable regions
	0234U	MECP2 (methyl CpG binding protein 2) (eg, Rett syndrome), full gene analysis, including small sequence changes in exonic and intronic regions, deletions, duplications, mobile element insertions, and variants in non-uniquely mappable regions
	0235U	PTEN (phosphatase and tensin homolog) (eg, Cowden syndrome, PTEN hamartoma tumor syndrome), full gene analysis, including small sequence changes in exonic and intronic regions, deletions, duplications, mobile element insertions, and variants in non-uniquely mappable regions
	0236U	SMN1 (survival of motor neuron 1, telomeric) and SMN2 (survival of motor neuron 2, centromeric) (eg, spinal muscular atrophy) full gene analysis, including small sequence changes in exonic and intronic regions, duplications and deletions, and mobile element insertions
	0238U	Oncology (Lynch syndrome), genomic DNA sequence analysis of MLH1, MSH2, MSH6, PMS2, and EPCAM, including small sequence changes in exonic and intronic regions, deletions, duplications, mobile element insertions, and variants in non-uniquely mappable regions
	0244U	Oncology (solid organ), DNA, comprehensive genomic profiling, 257 genes, interrogation for single-nucleotide variants, insertions/deletions, copy number

Codes	Number	Description
		alterations, gene rearrangements, tumor-mutational burden and microsatellite instability, utilizing formalin-fixed paraffin embedded tumor tissue
	81105 – 81112	HPA genotyping code range
	81170	ABL1 (ABL proto-oncogene 1, non-receptor tyrosine kinase) (eg, acquired imatinib tyrosine kinase inhibitor resistance), gene analysis, variants in the kinase domain
	81200 – 81257	Molecular pathology code range
	81260 – 81268	Molecular pathology code range
	81270 – 81276	Molecular pathology code range
	81287	MGMT (O-6-methylguanine-DNA methyltransferase) (eg, glioblastoma multiforme) promoter methylation analysis
	81290 – 81300	Molecular pathology code range
	81302 – 81304	Molecular pathology code range
	81310 – 81332	Molecular pathology code range
	81336 – 81355	Molecular pathology code range
	81370 - 81408	Molecular pathology code range
	81413	Cardiac ion channelopathies (eg, Brugada syndrome, long QT syndrome, short QT syndrome, catecholaminergic polymorphic ventricular tachycardia); genomic sequence analysis panel, must include sequencing of at least 10 genes, including ANK2, CASQ2, CAV3, KCNE1, KCNE2, KCNH2, KCNJ2, KCNQ1, RYR2, and SCN5A
	81419	Epilepsy genomic sequence analysis panel, must include analyses for ALDH7A1, CACNA1A, CDKL5, CHD2, GABRG2, GRIN2A, KCNQ2, MECP2, PCDH19, POLG, PRRT2, SCN1A, SCN1B, SCN2A, SCN8A, SLC2A1, SLC9A6, STXBP1, SYNGAP1, TCF4, TPP1, TSC1, TSC2, and ZEB2
	81441	Inherited bone marrow failure syndromes (IBMFS) (eg, Fanconi anemia, dyskeratosis congenita, Diamond-Blackfan anemia, Shwachman-Diamond syndrome, GATA2 deficiency syndrome, congenital amegakaryocytic thrombocytopenia) sequence analysis panel, must include sequencing of at least 30 genes, including BRCA2, BRIP1, DKC1, FANCA, FANCB, FANCC, FANCD2, FANCE, FANCF, FANCG, FANCI, FANCL, GATA1, GATA2, MPL, NHP2, NOP10, PALB2, RAD51C, RPL11, RPL35A, RPL5, RPS10, RPS19, RPS24, RPS26, RPS7, SBDS, TERT, and TINF2
	81470	X-linked intellectual disability (XLID) (eg, syndromic and non-syndromicXLID); genomic sequence analysis panel, must include sequencing of at least60 genes, including ARX, ATRX, CDKL5, FGD1, FMR1, HUWE1,IL1RAPL, KDM5C, L1CAM, MECP2, MED12, MID1, OCRL, RPS6KA3,and SLC16A2
	81471	;duplication/deletion gene analysis, must include analysis of at least 60 genes, including ARX, ATRX, CDKL5, FGD1, FMR1, HUWE1, IL1RAPL, KDM5C, L1CAM, MECP2, MED12, MID1, OCRL, RPS6KA3, and SLC16A2
	81479	Unlisted molecular pathology procedure
HCPCS	G0452	Molecular pathology procedure; physician interpretation and report

Codes	Number	Description
	S3800	Genetic testing for amyotrophic lateral sclerosis (ALS)
	S3840	DNA analysis for germline mutations of the RET proto-oncogene for susceptibility to multiple endocrine neoplasia type 2
	S3841	Genetic testing for retinoblastoma
	S3842	Genetic testing for Von Hippel-Lindau disease
	S3844	DNA analysis of the connexin 26 gene (GJB2) for susceptibility to congenital, profound deafness
	S3845	Genetic testing for alpha thalassemia
	S3846	Genetic testing for hemoglobin E beta-thalassemia
	S3849	Genetic testing for Niemann-Pick disease
	S3850	Genetic testing for sickle cell anemia
	S3853	Genetic testing for muscular dystrophy
	S3861	Genetic testing, sodium channel, voltage-gated, type V, alpha subunit (SCN5A) and variants for suspected Brugada syndrome
	S3865	Comprehensive gene sequence analysis for hypertrophic cardiomyopathy
	S3866	Genetic analysis for a specific gene mutation for hypertrophic cardiomyopathy (HCM) in an individual with a known HCM mutation in the family

Date of Origin: *September 1999*