CENTENE® Corporation

CONCERT GENETIC TESTING: GENERAL APPROACH TO GENETIC TESTING

See Important Reminder at the end of this policy for important regulatory and legal information.

OVERVIEW

Genetic testing refers to the use of technologies that identify genetic variation, which include genomic, transcriptional, proteomic, and epigenetic alterations, for the prevention, diagnosis, and treatment of disease. Germline variants or mutations are defined as genetic alterations that occur within the germ cells (egg or sperm), such that the alteration becomes incorporated into the DNA of every cell in the body of the offspring.

Genetic disorders can result when there is an alteration, or pathogenic variant, in a DNA sequence which causes the cell to produce an altered protein.

Some conditions, such as sickle cell disease, are caused by a single germline pathogenic variant. Other conditions, such as diabetes and heart disease, are more complex. These complex conditions are referred to as multifactorial conditions, meaning that there is a combination of different inherited and environmental factors. Environmental factors, such as nutrition, exercise, weight, smoking, drinking alcohol, and medication use may influence the observable characteristics of the condition.

Single gene testing, targeted variant analysis, and multigene panels are all examples of the types of genetic tests used to identify germline pathogenic or likely pathogenic variants that cause hereditary and multifactorial conditions.

The general approach to genetic testing criteria is intended for the evaluation of genetic testing that has not been more specifically addressed by other coverage criteria.

POLICY REFERENCE TABLE

Below is a list of higher volume tests and the associated laboratories for each coverage criteria section. This list is not all inclusive.

Coding Implications

This clinical policy references Current Procedural Terminology (CPT®). CPT® is a registered trademark of the American Medical Association. All CPT codes and descriptions are copyrighted 2022, American Medical Association. All rights reserved. CPT codes and CPT descriptions are from the current manuals and those included herein are not intended to be all-inclusive and are included for informational purposes only. Codes referenced in this clinical policy are for informational purposes only. Inclusion or exclusion of any codes does not guarantee coverage. Providers should reference the most up-to-date sources of professional coding guidance prior to the submission of claims for reimbursement of covered services.

Coverage Criteria Sections	Example Tests (Labs)	Common CPT Codes	Common ICD Codes	Ref
General Approach to Genetic Testing				
Known Familial Variant Analysis	Targeted Mutation Analysis for a Known Familial Variant	81403	Q86, Q87, Q89, Q95, Q97, Q98, Q99, Z15.89	6
Single Gene or Multigene Panel Analysis	Varies	0004M, 0006M, 0007M, 0009U, 0011M, 0014M, 0015M, 0016M, 0017M, 0019U, 0035U, 0049U, 0058U, 0059U, 0062U, 0063U, 0084U, 0087U, 0088U, 0094U, 0095U, 0105U, 0154U, 0170U, 0181U, 0182U, 0183U, 0184U, 0185U, 0186U, 0187U, 0188U, 0189U, 0190U, 0191U, 0192U, 0193U, 0194U, 0195U, 0196U, 0197U, 0198U, 0199U, 0200U, 0201U, 0206U, 0222U, 0228U, 0229U, 0230U, 0231U, 0232U, 0246U, 0248U, 0249U, 0252U, 0253U, 0255U, 0256U, 0257U, 0258U, 0260U, 0261U, 0262U, 0263U, 0264U, 0266U, 0269U, 0270U, 0271U, 0272U, 0273U, 0274U, 0276U, 0277U, 0278U, 0279U, 0280U, 0281U, 0282U, 0283U, 0284U, 0285U, 0286U, 0287U,		1, 2, 3, 4, 5

		0289U, 0290U, 0291U, 0292U, 0293U, 0294U, 0295U, 0296U, 0297U, 0298U, 0299U, 0300U, 0306U, 0307U, 0314U, 0315U, 0317U, 0318U, 0319U, 0320U, 0331U, 0332U, 0333U, 0335U, 0337U, 0338U, 0340U, 0341U, 0342U, 0343U, 0355U, 0356U, 0360U, 0362U, 0376U, 0378U, 0385U, 81105, 81106, 81107, 81108, 81109, 81110, 81111, 81112, 81168, 81171, 81172, 81173, 81174, 81175, 81176, 81177, 81187, 81188, 81189, 81190, 81191, 81192, 81193, 81194, 81200, 81204, 81205, 81209, 81233, 81236, 81237, 81250, 81251, 81255, 81260, 81261, 81262, 81263, 81264, 81267, 81268, 81277, 81278, 81283, 81290, 81305, 81312, 81313, 81314, 81315, 81316, 81320, 81330, 81333, 81334, 81340, 81341, 81342, 81343, 81344, 81345, 81347, 81348, 81349, 81357, 81360, 81370, 81371, 81372, 81373, 81374, 81375, 81376, 81377, 81378, 81379, 81380, 81381, 81382, 81383, 81400, 81401, 81402, 81403, 81404, 81405, 81406, 81407, 81408, 81427, 81441, 81479, 81493, 81506, 81554, 81560, 81595, 81599		

OTHER RELATED POLICIES

This policy document provides coverage criteria for the general approach to genetic testing for any genetic testing not specifically addressed in other related policies. Please refer to the following documents for specific criteria:

- *Genetic Testing: Noninvasive Prenatal Screening*
- *Genetic Testing: Prenatal Diagnosis (via amniocentesis, CVS, or PUBS) and Pregnancy Loss*
- *Genetic Testing: Prenatal and Preconception Carrier Screening*
- *Genetic Testing: Hereditary Cancer Susceptibility*
- *Oncology: Molecular Analysis of Solid Tumors and Hematologic Malignancies*
- *Oncology: Cancer Screening*

- *Oncology: Circulating Tumor DNA and Circulating Tumor Cells (Liquid Biopsy)*
- *Oncology: Algorithmic Testing*
- *Oncology: Cytogenetics*
- *Genetic Testing: Pharmacogenetics*
- *Genetic Testing: Exome and Genome Sequencing for the Diagnosis of Genetic Disorders*
- *Genetic Testing: Epilepsy, Neurodegenerative, and Neuromuscular Disorders*
- *Genetic Testing: Hematologic Conditions (non-cancerous)*
- *Genetic Testing: Gastroenterologic Conditions (non-cancerous)*
- *Genetic Testing: Cardiac Disorders*
- *Genetic Testing: Aortopathies and Connective Tissue Disorders*
- *Genetic Testing: Hearing Loss*
- *Genetic Testing: Eye Disorders*
- *Genetic Testing: Immune, Autoimmune, and Rheumatoid Disorders*
- *Genetic Testing: Kidney Disorders*
- *Genetic Testing: Lung Disorders*
- *Genetic Testing: Metabolic, Endocrine, and Mitochondrial Disorders*
- *Genetic Testing: Dermatologic Conditions*
- *Genetic Testing: Skeletal Dysplasia and Rare Bone Disorders*

CRITERIA

It is the policy of health plans affiliated with Centene Corporation® that the specific genetic testing noted below is **medically necessary** when meeting the related criteria:

GENERAL APPROACH TO GENETIC TESTING

Known Familial Variant Analysis for a Genetic Condition

I. Targeted mutation analysis for a known familial variant (81403) for a genetic condition is considered **medically necessary** when:

   A. The member/enrollee is 18 years or older (if the condition is adult-onset), **AND**

   B. The member/enrollee has a close relative with a known pathogenic or likely pathogenic variant causing the condition, **AND**

   C. An association between the gene and disease has been established, **AND**

   D. The genetic condition is associated with a significant health problem or problems.

II. Targeted mutation analysis for a known familial variant of uncertain significance is considered **investigational**.

III. Targeted mutation analysis for a known familial variant (81403) for a genetic condition is considered **investigational** for all other indications.

Single Gene or Multigene Panel Analysis

I. Genetic testing for a genetic condition via single-gene or multigene panel analysis may be considered **medically necessary** when:

A. The member/enrollee displays clinical features of the suspected genetic condition and the diagnosis remains uncertain after appropriate conventional diagnostic testing, **AND**

1. At least one of the following:

(1) The test will confirm or establish a diagnosis for the genetic condition, **OR**

(2) The test will provide or refine estimates of the natural history, recurrence risk, or the predicted course of the genetic condition, **OR**

(3) The test will determine if a particular therapeutic intervention is effective (or ineffective) in the member/enrollee, or if a particular intervention may be harmful, **AND**

B. There is no known pathogenic or likely pathogenic familial variant for the genetic condition for which targeted variant analysis would be more appropriate, **AND**

C. Non-genetic causes for the member's/enrollee's clinical features have been ruled out (e.g., pathogens, drug toxicity, environmental factors, etc), **AND**

D. An association with the gene or multigene panel and disease has been established, **AND**

E. Genetic testing for the suspected genetic condition has been scientifically validated to improve health outcomes (i.e., the test has been shown to have clinical utility).

II. Genetic testing in an individual under the age of 18 for an adult-onset condition is considered **not medically necessary**.

III. Genetic testing via single-gene or multigene panel analysis is considered **investigational** or **not medically necessary** when the above criteria are not met.

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NOTES AND DEFINITIONS

A minor is any person under the age of 18.

Childhood is the period of development until the 18th birthday.

Germline pathogenic or likely pathogenic variants are mutations that occur in the egg and sperm cells, also known as the germ cells. These variants are inherited; that is, passed down in families by blood relatives. Most germline mutations do not result in disease.

Multifactorial conditions are complex conditions that are inherited and may be caused by a combination of the effects of multiple genes or by interactions between genes and the environment.

Single Nucleotide Polymorphisms (SNPs) are the most common type of genetic mutation and occur when one nucleotide is replaced with a different nucleotide. Over 65% of the disease caused by genetic mutations are due to SNPs.

Structural Variations are classified as larger than 1000 base pairs and include deletions, duplications, inversions, and translocations. Due to the large number of genes affected, these variations commonly lead to severe genetic abnormalities.

Copy Number Variant (CNV) is the most common structural variation, which refers to different amounts of DNA segments in different individuals.

Close relatives include first, second, and third degree blood relatives on the same side of the family:

a. **First-degree relatives** are parents, siblings, and children

b. **Second-degree relatives** are grandparents, aunts, uncles, nieces, nephews, grandchildren, and half siblings

c. **Third-degree relatives** are great grandparents, great aunts, great uncles, great grandchildren, and first cousins

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CLINICAL CONSIDERATIONS

Genetic counseling is recommended for patients who are at risk for inherited disorders and who are interested in undergoing genetic testing. Interpreting the results of genetic tests and understanding risk factors can be challenging. Genetic counseling helps in the understanding of the potential impacts of genetic testing, including possible effects the test results could have on the individual or their family members. Genetic counseling may alter the utilization of genetic testing substantially and has been shown to reduce inappropriate testing and should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.

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BACKGROUND AND RATIONALE

Known Familial Variant Analysis

Genetic Support Foundation

The Genetic Support Foundation's Genetics 101 information on inheritance patterns says the following about testing for familial pathogenic variants:

> "Genetic testing for someone who may be at risk for an inherited disease is always easier if we know the specific genetic cause. Oftentimes, the best way to find the genetic cause is to start by testing someone in the family who is known or strongly suspected to have the disease. If their testing is positive, then we can say that we have found the familial pathogenic (harmful) variant. We can use this as a marker to test other members/enrollees of the family to see who is also at risk."

Single Gene or Multigene Panel Analysis

American College of Medical Genetics and Genomics (ACMG) and the Association for Molecular Pathology (AMP)

- The ACMG and AMP released criteria on the types and severity of mutations, which are as follows:

- **Very strong evidence of pathogenicity:** Null variants in a gene where loss of function (LOF) is a known mechanism of disease. The guidelines note to use caution in genes where LOF is not a mechanism, if LOF variants are at the 3' end, if exon skipping occurs, and if multiple transcripts are present.
- **Strong:** Amino acid change to a pathogenic version, de novo mutations, established studies supporting a damaging gene or gene product, or if the prevalence of the variant is increased in affected individuals compared to healthy controls. The guidelines note to be careful of changes impacting splicing and if only the paternity has been confirmed.
- **Moderate:** Located in a mutational hot spot or well-established functional domain without a benign variant, absent from controls in Exome Sequencing Project, 1000 Genomes Project, or Exome Aggregation Consortium, detected in trans with pathogenic variants for a recessive disorder, protein length changes, novel missense changes where a different missense change has been pathogenic before, and a possible de novo mutation.
- **Supporting:** Cosegregation with disease in multiple affected family members in a gene definitively known to cause the disease, missense variant in a gene with low rate of benign missense variation, if the mutation has evidence that it is deleterious, or if the patient's phenotype is highly specific for disease with a single genetic cause. (p. 412)

American College of Medical Genetics and Genomics (ACMG)

The American College of Medical Genetics and Genomics Board of Directors (2015) published a position statement regarding the clinical utility of genetic and genomic services that stated the following regarding individuals and situations where a definitive genetic diagnosis has clinical utility:

Clinical Utility for Individual Patients

- Situations in which definitive diagnosis specifically informs causality, prognosis, and treatment
- Newborn screening for conditions recommended by the Secretary's Discretionary Advisory Committee on Heritable Disorders of Newborns and Children
- The discovery of medically actionable secondary findings in the course of genomic testing that have associated treatments that improve/affect outcome
- Patients with complex and often poorly understood clinical disorders such as autism spectrum disorders and intellectual disability

- Patients with rare disorders, including those diagnosed by chromosome analysis (such as karyotype) or microarray
- Patients with genetic conditions such that definitive and specific guidance regarding prognosis and medical management is not yet available

Clinical Utility for Families

- Enables at-risk family members to obtain testing to determine whether they carry a causative mutation, offering the possibility for early intervention. This clinical utility is independent of whether the affected family member has benefited directly from this diagnosis.
- Enables specific and informed reproductive decision-making and family planning.
- Brings resolution to the costly (in terms of both psychosocial and financial contexts) and wasteful (for the medical system at large) diagnostic odyssey that is often pursued in a quest to establish a diagnosis. There are countless examples of economic and psychological costs to the health-care system and to patients and families during the quest to obtain a diagnosis.
- Enables involvement in disease support groups and other types of social support for families.

Clinical Utility for Society

- Understanding the etiology of disease and increased accrual into clinical trials will propel research, benefitting society as a whole.
- Many genetic disease risks can be identified decades before the time when benefits accrue to the individual or their family members. In the current health-care environment, cost-effectiveness often is measured by return on investment to payers and is measured over much shorter time periods, despite long-term benefits to population health. (p. 506)

National Society of Genetic Counselors (NSGC)

The National Society of Genetic Counselors released a position statement (2017) endorsing the use of multi-gene panels when clinically warranted and appropriately applied, stating the following:

> "These tests can provide a comprehensive and efficient route to identifying the genetic causes of disease. Before ordering a multi-gene panel test, providers should thoroughly evaluate the analytic and clinical validity of the test, as well as its clinical utility. Additional factors to consider include, but are not limited to: clinical and family history information, gene content of the panel, limitations of the sequencing and informatics technologies, and variant interpretation and reporting practices.

> Panels magnify the complexities of genetic testing and underscore the value of experts, such as genetic counselors, who can educate stakeholders about appropriate utilization of the technology to mitigate risks of patient harm and unnecessary costs to the healthcare system. NSGC supports straightforward and transparent pricing so that patients, providers, laboratories, and health plans can easily weigh the value of genetic testing in light of its cost."

The National Society of Genetic Counselors updated a position statement (2017) regarding the genetic testing of minors for adult-onset conditions, stating the following:

> "[NSGC] encourages deferring predictive genetic testing of minors for adult-onset conditions when results will not impact childhood medical management or significantly benefit the child. Predictive testing should optimally be deferred until the individual has the capacity to weigh the associated risks, benefits, and limitations of this information, taking his/her circumstances, preferences, and beliefs into account to preserve his/her autonomy and right to an open future."

American Academy of Pediatrics (AAP) and American College of Medical Genetics and Genomics (ACMG)

> "Decisions about whether to offer genetic testing and screening should be driven by the best interest of the child." (p. 234)
>
> "The AAP and the ACMG do not support routine carrier testing or screening for recessive conditions when carrier status has no medical relevance during minority". (p. 236)
>
> "Predictive genetic testing for adult onset conditions generally should be deferred unless an intervention initiated in childhood may reduce morbidity or mortality". (p. 238)

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Reviews, Revisions, and Approvals	Revision Date	Approval Date
Policy developed	03/23	03/23

REFERENCES

1. ACMG Board of Directors. Clinical utility of genetic and genomic services: a position statement of the American College of Medical Genetics and Genomics. Genet Med. 2015;17(6):505-507. doi:10.1038/gim.2015.41

2. "Genetic Testing of Minors for Adult-Onset Conditions". Position Statement from National Society of Genetic Counselors. https://www.nsgc.org/Policy-Research-and-Publications/Position-Statements/Position-Statements/Post/genetic-testing-of-minors-for-adult-onset-conditions. Released February 15, 2017. Updated April 18, 2018.
3. Ross LF, Saal HM, David KL, Anderson RR; American Academy of Pediatrics; American College of Medical Genetics and Genomics. Technical report: Ethical and policy issues in genetic testing and screening of children [published correction appears in Genet Med. 2013 Apr;15(4):321. Ross, Laine Friedman [corrected to Ross, Lainie Friedman]]. Genet Med. 2013;15(3):234-245. doi:10.1038/gim.2012.176
4. Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17(5):405-424. doi:10.1038/gim.2015.30
5. "Use of Multi-Gene Panel Testing." Position Statement from National Society of Genetic Counselors. https://www.nsgc.org/Policy-Research-and-Publications/Position-Statements/Position-Statements/Post/use-of-multi-gene-panel-tests. Released March 14, 2017.
6. Genetic Support Foundation. Genetics 101 Inheritance Patterns: Familial Pathogenic Variant. Accessed 10/4/2022. https://geneticsupportfoundation.org/genetics-101/#

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Important Reminder

This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information. The Health Plan makes no representations and accepts no liability with respect to the content of any external information used or relied upon in developing this clinical policy. This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. "Health Plan" means a health plan that has adopted this clinical policy and that is operated or administered, in whole or in part, by Centene Management Company, LLC, or any of such health plan's affiliates, as applicable.

The purpose of this clinical policy is to provide a guide to medical necessity, which is a component of the guidelines used to assist in making coverage decisions and administering benefits. It does not constitute a contract or guarantee regarding payment or results. Coverage decisions and the administration of benefits are subject to all terms, conditions, exclusions and limitations of the coverage documents (e.g., evidence of coverage, certificate of coverage, policy,

contract of insurance, etc.), as well as to state and federal requirements and applicable Health Plan-level administrative policies and procedures.

This clinical policy is effective as of the date determined by the Health Plan. The date of posting may not be the effective date of this clinical policy. This clinical policy may be subject to applicable legal and regulatory requirements relating to provider notification. If there is a discrepancy between the effective date of this clinical policy and any applicable legal or regulatory requirement, the requirements of law and regulation shall govern. The Health Plan retains the right to change, amend or withdraw this clinical policy, and additional clinical policies may be developed and adopted as needed, at any time.

This clinical policy does not constitute medical advice, medical treatment or medical care. It is not intended to dictate to providers how to practice medicine. Providers are expected to exercise professional medical judgment in providing the most appropriate care, and are solely responsible for the medical advice and treatment of members/enrollees. This clinical policy is not intended to recommend treatment for members/enrollees. Members/enrollees should consult with their treating physician in connection with diagnosis and treatment decisions.

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Note: For Medicaid members/enrollees, when state Medicaid coverage provisions conflict with the coverage provisions in this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.

Note: For Medicare members/enrollees, to ensure consistency with the Medicare National Coverage Determinations (NCD) and Local Coverage Determinations (LCD), all applicable NCDs, LCDs, and Medicare Coverage Articles should be reviewed prior to applying the criteria set forth in this clinical policy. Refer to the CMS website at http://www.cms.gov for additional information.