GENETIC TESTING: GENERAL APPROACH TO GENETIC AND MOLECULAR TESTING

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.

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*

COVERAGE CRITERIA

GENERAL APPROACH TO GENETIC TESTING

Known Familial Variant Analysis for a Genetic Condition

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

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

   B. The member 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 for a genetic condition is considered **investigational** for all other indications.

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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 displays clinical features of the suspected genetic condition and the diagnosis remains uncertain after appropriate clinical evaluation and other standard laboratory tests/imaging/etc. have been performed, **AND**

   B. 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, or if a particular intervention may be harmful, **AND**

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

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

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

F. 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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General Tumor Biomarker Analysis

I. General tumor biomarker analysis* is **medically necessary** when:

A. The member has a confirmed neoplasm and/or malignancy, **AND**

B. The test has clinical utility, as demonstrated by at least one of the following:

1. The test will determine if a particular therapeutic intervention is effective (or ineffective) in the member, or if a particular intervention may be harmful, **OR**
2. The test will directly impact the clinical management, **OR**
3. The test will determine prognosis, **AND**

C. The test shows clinical validity, **AND**

D. Testing is being performed in a Clinical Laboratory Improvement Amendments (CLIA) approved laboratory.

II. General tumor biomarker analysis is considered **investigational** for all other indications.

*See the Oncology: Molecular Analysis of Solid Tumors and Hematologic Malignancies policy for criteria regarding common mutation analysis for tumor testing.

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Oncology Algorithmic Tests

I. Oncology algorithmic testing* is **medically necessary** when:

A. The member has a confirmed neoplasm and/or malignancy, **AND**

B. The test demonstrates clinical validity and clinical utility.

II. Oncology algorithmic testing is considered **investigational** for all other indications.

*See the Oncology: Algorithmic testing policy for criteria regarding common algorithmic tests.

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Other Tests

I. Other tests are **medically necessary** when:

A. The member displays relevant clinical features consistent with the intended use of the test, **AND**

B. The test demonstrates clinical validity and clinical utility.

II. Other tests are considered investigational for all other indications.

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NOTES AND DEFINITIONS

1. A **minor** is any person under the age of 18.
2. **Childhood** is the period of development until the 18th birthday.
3. **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.
4. **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.
5. **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.
6. **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.
7. **Copy Number Variant (CNV)** is the most common structural variation, which refers to different amounts of DNA segments in different individuals.
8. **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

9. **Clinical validity,** according to the National Institutes of Health-Department of Energy (NIH-DOE) Task Force on Genetic Testing, describes the accuracy with which a test identifies a particular clinical condition. The components of measuring clinical validity are:

   a. **Sensitivity**: among people with a specific condition, the proportion who have a positive test result

   b. **Specificity**: among people who do not have the condition, the proportion who have a negative test result

   c. **Positive predictive value**: among people with a positive test result, the proportion of people who have the condition

   d. **Negative predictive value**: among people with a negative test result, the proportion who do not have the condition

10. **Clinical utility** refers to the risks and benefits resulting from genetic test use. The most important considerations in determining clinical utility are: (1) whether the test and any subsequent interventions lead to an improved health outcome among people with a positive test result; and (2) what risks occur as a result of testing.

11. An **algorithmic test** is one that combines biomarkers and clinical data into an algorithm to generate a disease risk assessment, prognostic result, or clinical recommendation for treatment.

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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 of the family to see who is also at risk."

National Society of Genetic Counselors (NSGC)

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."

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)

General Tumor Biomarker Analysis

National Comprehensive Cancer Network

The NCCN guidelines for Occult Primary (3.2023) recommend somatic/tumor molecular genetic testing for patients who are candidates for anti-cancer therapy in order to identify uncommon genetic changes within the tumors (p. OCC-1).

Hayes, et al

In an article by Hayes, et al (2020), the authors state that while there is no strict definition of clinical utility for tumor biomarker tests (TBT), there are several factors that should be considered when deciding on the overall clinical utility (p. 238):

(1) What is the intended use of the tumor biomarker test?

(2) What are the endpoints that are used to determine clinical utility?

(3) How substantial does the difference in endpoints between groups defined by the TBT need to be to determine therapeutic strategies?

(4) What is the risk tolerance of the stakeholders?

(5) Who are the stakeholders that make the decision?

The authors note that “for a TBT to have clinical utility, it must have high analytical validity and be shown, with high levels of evidence, to improve outcomes compared with if the TBT results are not known. A pragmatic determination of clinical utility is dependent on several factors, including what end point is considered, how large the difference in that end point must be to apply the TBT, the level of evidence that exists to support the decision to apply the TBT, and the risk tolerance of whichever stakeholder makes the decision to apply it. None of these factors can be the absolute determinant, but they must be included in the deliberations of whether a TBT does or does not have clinical utility.” (p. 239)

Centers for Disease Control and Prevention (CDC)

The CDC’s Office of Public Health Genomics developed the ACCE Model (Analytic Validity, Clinical Validity, Clinical Utility, and Ethical/Legal/Social Implications), which is a clinical framework in which to evaluate a genetic test. The ACCE model process “...is composed of a standard set of 44 targeted questions that address disorder, testing, and clinical scenarios, as well as analytic and clinical validity, clinical utility, and associated ethical, legal, and social issues.” A complete list of the 44 targeted questions referenced can be found at the following website:
https://www.cdc.gov/genomics/gtesting/acce/acce_proj.htm

Burke, et al

This article from the NIH defines clinical validity and clinical utility, provides examples, and considers the implications of these test properties for clinical practice. When a test is used diagnostically, clinical validity measures the accuracy with which the test identifies a person with the clinical condition in question. The positive and negative predictive values of the test are important measures of clinical validity. These measures allow the clinician to determine how reliably the test can confirm or refute a suspected diagnosis. (p. 2-3)

Table 9.15.1 (p. 12) describes the test properties of measuring clinical validity as follows:

- Sensitivity: Among people with a specific condition, the proportion who have a positive test result
- Specificity: Among people who do not have the condition, the proportion who have a negative test result
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Oncology Algorithmic Test

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The American Association for Clinical Chemistry (AACC)

An article released from the AACC in 2018 defined and reviewed the use of multianalyte assays with algorithmic analyses (MAAAs). They state:

"...these tests combine results from two or more biochemical or molecular markers, along with patient demographics and clinical information, into an algorithm to generate diagnostic, prognostic, or predictive information for a disease. In cases where single biomarker tests lack acceptable clinical sensitivity and specificity, MAAAs can improve or refine disease detection through individualized risk assessment.

Incorporating multiple biochemical or molecular analytes into algorithms with or without clinical information allows for a personalized risk assessment of a patient's disease."

Other Genetic Tests

Centers for Disease Control and Prevention (CDC)

The CDC's Office of Public Health Genomics developed the ACCE Model (Analytic Validity, Clinical Validity, Clinical Utility, and Ethical/Legal/Social Implications), which is a clinical framework in which to evaluate a genetic test. The ACCE model process "...is composed of a standard set of 44 targeted questions that address disorder, testing, and clinical scenarios, as well as analytic and clinical validity, clinical utility, and associated ethical, legal, and social issues." A complete list of the 44 targeted questions referenced can be found at the following website:
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