CLINICAL MEDICAL POLICY	
Policy Name:	Testing for Genetic Disease
Policy Number:	MP-035-MC-PA
Responsible Department(s):	Medical Management
Provider Notice/Issue Date:	10/01/2024; 10/01/2023; 11/01/2022; 10/15/2021; 10/19/2020; 10/21/2019
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Revision Date:	09/18/2024; 09/20/2023; 09/21/2022; 09/15/2021; 08/19/2020; 08/21/2019
Products:	Pennsylvania Medicare Assured
Application:	All participating and nonparticipating practitioners and facilities unless contractually precluded
Page Number(s):	1 of 10

Policy History

Date	Activity
11/01/2024	Provider Effective date
09/18/2024	QI/UM Committee review
09/18/2024	Annual Review: No changes to clinical criteria. Updated CMS hyperlink and 'Reference Sources' section.
11/01/2023	Provider Effective date
09/20/2023	QI/UM Committee review
09/20/2023	Annual Review: No changes to clinical criteria. Updated 'Summary of Literature' and 'Reference Sources' sections.
12/01/2022	Provider Effective date
09/21/2022	QI/UM Committee review
09/21/2022	Annual Review: No changes to clinical criteria. Removed the following repetitive statement from the 'Procedure' section: "*The information from the genetic testing is expected to make an impact on the patient's treatment plan or the responsible family member/legal guardian intends to use the information in making decisions about his/her care or treatment plan"*. Removed the word 'covered', replaced with 'medically necessary'. Added related CMS hyperlinks. Updated 'Summary of Literature' and 'Reference Sources' sections.
11/15/2021	Provider effective date

09/15/2021	QI/UM Committee review
09/15/2021	Annual Review: No clinical criteria changes. Minor Procedures section formatting changes. Updates Summary of Literature and Reference Sources sections.
09/15/2017	Initial policy developed

Disclaimer

Highmark Wholecare℠ medical policy is intended to serve only as a general reference resource regarding coverage for the services described. This policy does not constitute medical advice and is not intended to govern or otherwise influence medical decisions.

Policy Statement

Highmark Wholecare℠ covers medically necessary genetic testing under the laboratory services of the medical-surgical benefit of the Company's Medicare products to establish a molecular diagnosis of an inheritable disease. This policy is not inclusive of all known genetic tests.

This policy is designed to address medical necessity guidelines that are appropriate for the majority of individuals with a particular disease, illness or condition. Each person's unique clinical circumstances warrant individual consideration, based upon review of applicable medical records.

Definitions

Biochemical Genetic Test – Diverse spectrum of laboratory analysis of biomolecules (metabolites, enzyme activities and functional assays) in serum or tissue to detect inborn errors of metabolism, genotype, or mutations for clinical purposes (e.g., predict risk of disease, identify carriers, and establish prenatal or clinical diagnoses or prognosis).

Genetic Testing – Genetic testing requires the analysis of human chromosomes, DNA (deoxyribonucleic acid), RNA (ribonucleic acid), genes or gene products in order to detect or predict risk of inherited or non-inherited genetic variants related to disease, identify carriers, establish prenatal and clinical diagnosis or prognosis.

Carrier Testing – Carrier testing is used to determine whether an individual possesses one copy of a gene mutation that, when present in two copies, causes a genetic disorder. This type of testing is offered to individuals who have a family history of a genetic disorder and to people in certain ethnic groups with an increased risk of specific genetic conditions.

Genetic Counseling – The process in which a specially trained professional evaluates family history, medical records, and genetic test results, in the risk assessment of an individual for genetic disease, understanding the limitations and risks of genetic testing.

Genetic Screening – Genetic testing used to identify individuals who do not currently exhibit signs or symptoms but may have an increased risk of developing or transmitting a specific genetic disorder.

Genetic Screening Panels – Screening panels are a grouping of genetic tests that are performed for multiple conditions such as the Ashkenazi Jewish Panel.

Diagnostic/Confirmatory Testing in Symptomatic Individuals – Genetic testing that is performed to rule out, identify, or confirm a suspected genetic disorder in an affected individual.

Direct Risk – When there is documentation in the family history of a disorder that involves an autosomal dominant inheritance which has been demonstrated in either the mother or the father or evidence of a disorder inherited in an autosomal recessive or X-linked recessive manner with supporting documentation suggestive of family history of a suspected disorder.

Family –

- First-degree relatives are defined as the parents, brothers, sisters, or children of an individual patient.
- Second-degree relatives are those people with whom one quarter of the patient's genes is shared (e.g., grandparent, grandchild, uncle, aunt, nephew, niece or half-sibling).
- Third-degree relatives are those people with whom one eighth of a patient's genes is shared (e.g., cousin, great grandparent, great aunt, or great uncle).

Predictive Testing – Predictive testing is used to determine whether individuals who have a family history of a disease but no current symptoms have the gene alteration associated with the disease. Predictive genetic testing includes pre-symptomatic testing and pre-dispositional testing.

Procedures

Medicare coverage for screening of individuals with a family history of certain disease is considered medically necessary only for a limited number of services as listed in the IOM 100-02 *Medicare Benefit Policy Manual, Chapter 15, Section 280 – Preventative and Screening Services*.

Tests performed without relationship to treatment or diagnosis of a patient with no findings or history for a specific illness, symptom, complaint or injury unless set exclusion are so noted in Title 42 CFR, Section 411.15(a)(1).

Local Medicare coverage of such biomarkers must be predicated upon three fundamental principles:

1) There must be an underlying performance of acceptable, high-quality analytical validity for all such laboratory testing. As a result, the laboratory shall have available upon request:
    a) Analytical and clinical validation reports for Clinical Laboratory Improvement Amendments (CLIA), including the test description, intended use, and indications for testing; AND
    b) If applicable, all formal, written minutes and correspondences (including any Q & A and supporting documentation) with the New York State Department of Health (NYSDOH) or the US Food and Drug Administration (FDA); AND

c) Most recent inspection results (including recommendations) or scheduled inspection(s) from CLIA, College of American Pathologists (CAP), or NYSDOH, as applicable.

2) There must be an appreciation of evidence-in-transition where new biomarkers should be brought on-line in harmonization with their proven clinical validity/utility (CVU). Although analytical validity is an equally important metric, it remains more outside of a payer's purview to conduct such detailed evaluations. Therefore, in the absence of a standard CVU referee process (e.g., although FDA labeling of biomarkers can be a helpful adjunct, it may not always be relevant), the key imperative is for medical necessity to be reflected by the clear articulation of a particular biomarker niche.

3) There must be a recognized decision impact of such biomarkers by the clinical community. In other words, there must be acceptance/uptake of specific testing into patient management. It should be taken into account that to reach the medical necessity threshold, such acceptance should be based on the strongest evidence available, ideally from along the spectrum of high-quality masked, randomized controlled clinical trials, and much less preferably from lower levels of evidence, which are predicated upon expert opinion only without primary study data.

The commercial availability does not ensure that a molecular diagnostic test is indicated for clinical application. Molecular diagnostic testing is a rapidly evolving science in which the significance of detecting specific mutations has yet to be clarified in many circumstances. Analytical and clinical validity as well as clinical utility are the responsibility of the provider, and all testing must meet standards of care.

1. When Highmark Wholecare℠ does not have a medical policy for a specific genetic test, the following medical necessity criteria must be met:
    A. A complete history, physical examination, family history, pedigree analysis, laboratory, imaging and other diagnostic testing, and a specific medical differential diagnosis has been established; AND
    B. The results of the genetic testing will have a direct impact and will be used specifically in the patient's care/treatment plan, including the determination of the intensity of surveillance or initiating a new course of treatment of that disease or altering an existing therapy; AND
    C. The patient is at direct risk of inheriting the genetic mutation (pre-symptomatic) as determined on review of family history and risk factors (carrier identification); AND
    D. The genetic disorder is associated with the potential for significant disability or has a lethal natural history; OR
    E. The patient displays clinical features as documented in the physical exam, conventional testing are inconclusive, and a definitive diagnosis is uncertain (diagnostic); AND
    F. The patient has not had like or similar genetic testing previously. This does not apply to requests for comprehensive genetic testing when targeted testing has been previously performed; AND
    G. The providing laboratory is approved by the FDA and/or other professional or governmental agencies; AND
    H. The specific mutation or set of mutations has been established in the scientific literature as a reliable test associated with the disease; AND
    I. Peer reviewed literature is available that provides evidence for the indications and performance of the testing this policy is to be used in situations in which there is an absence of a medical policy; AND
    J. For tissue-specific or tumor testing ALL of the following criteria must be met:

1) The patient is a candidate for targeted drug therapy associated with a specific genetic mutation; AND
2) There is an established positive association of a specific gene mutation in response to a particular drug therapy.

Note: When available, please reference the separate Highmark Wholecare℠ medical policies for specific genetic tests.

2. Documentation Requirements:
   A. A physician order for the specific genetic test being requested; AND
   B. Name of the laboratory performing the testing; AND
   C. Name and description of the genetic testing; AND
   D. All applicable CPT codes that will be billed for the genetic testing; AND
   E. Complete history and physical and/or consultation notes that address ALL of the following:
      1) Necessity of the test to be performed; AND
      2) Symptoms and/or test results related to need for specific genetic testing; AND
      3) Family history when applicable; AND
      4) Explanation of the impact of genetic testing results in clinical care decision making (e.g., testing method is as targeted as possible); AND
      5) The technical and the clinical performance of the genetic test is supported by published peer-reviewed medical literature.

3. Any services for conditions other than those listed above are considered not medically necessary, because the scientific evidence has not been established. Conditions considered not medically necessary may include, but are not limited to, ANY of the following:
   - Generally, genetic testing for a particular disease should be performed once per lifetime; however, there are rare circumstances in which testing may be performed more than once in a lifetime (e.g., previous testing methodology is inaccurate or a new discovery has added significant relevant mutations for a disease).
   - Direct-to-consumer testing including, but not limited to, 'in-home' test kits or genetic tests ordered by patient over the phone or Internet.
   - Genetic testing of children to predict adult onset diseases is considered not medically necessary unless test results will guide current decisions concerning prevention which would be lost by waiting until the patient has reached adulthood.
   - Genetic testing or gene mapping in the screening of the general population.
   - When the clinical diagnosis can be made without the use of a genetic test.
   - When the results of the testing would not change the diagnosis and/or management of the patient's care (e.g., testing is performed for non-medical reasons or the testing is not expected to provide a definitive diagnosis).
   - Genetic testing for the establishment of paternity.

4. Place of Service

   The proper place of service for these genetic testing/laboratory services is outpatient.

5. Post-payment Audit Statement
   The medical record must include documentation that reflects the medical necessity criteria and is subject to audit by Highmark Wholecare℠ at any time pursuant to the terms of your provider agreement.

6. Genetic Counseling
   Pre- and post-test genetic counseling is required to be performed by an independent genetic provider (not employed by a genetic testing lab) prior to genetic testing for mutations. This service is necessary in order to inform patient being tested about the benefits and limitations of specific genetic tests. Genetic testing for mutations requires documentation of medical necessity from at least one of the following providers who has previously evaluated the patient, and intends to see the patient after genetic testing has been performed:
   - Board Eligible or Board Certified Genetic Counselor
   - Advanced Genetics Nurse
   - Genetic Clinical Nurse
   - Advanced Practice Nurse in Genetics
   - Board Eligible or Board Certified Clinical Geneticist
   - A physician of appropriate expertise or other obstetrical provider specializing in the care for the indication(s) for genetic testing

Governing Bodies Approval

The list of nucleic acid-based tests that have been cleared or approved by the Center for Devices and Radiological Health is available on the FDA's Nucleic Acid Based Tests webpage. These tests analyze variations in the sequence, structure, or expression of deoxyribonucleic acid (DNA) and ribonucleic acid (RNA) in order to diagnose disease or medical conditions, infection with an identifiable pathogen, or determine genetic carrier status.

The majority of genetic testing are laboratory developed tests that do not require premarket approval by the FDA. These types of tests are regulated under the Clinical Laboratory Improvement Amendments (CLIA) Act of 1998. The regulations of the CLIA Amendments do not include validation of specific test, but rather there is procedural compliance.

Coverage Determination and Links

Highmark Wholecare℠ follows the coverage determinations made by CMS as outlined in either the NCD or state-specific LCD/LCA.

CMS Link
- CMS Website

NCD/LCD Link
- There are no current NCDs related to this topic.
- Related LCD: Biomarkers for Oncology (L35396)

Article Link

- Related LCA: Billing and Coding: Biomarkers for Oncology (A52986)

Summary of Literature

As medical technology continues to advance, it is not surprising that there is a parallel advancement and utilization of genetic testing. Due to the rapidly evolving field of genetic testing, every genetic test must be thoroughly evaluated in order to determine whether or not the identified genetic mutation represents a genetic disorder.

There are several types of genetic tests, including molecular tests, targeted single variant, single gene, gene panel, whole exome sequencing/whole genome sequencing, chromosomal tests, gene expression tests, and biochemical tests. The uses of genetic tests include:

- Newborn screening – used just after birth to identify genetic disorders that can be treated early in life.
- Diagnostic testing – used to identify or rule out a specific genetic or chromosomal condition. Can be used to confirm a diagnosis when a particular condition is suspected based on physical signs or symptoms.
- Carrier testing – used to identify people who carry one copy of a gene mutation that, when present in two copies, causes a genetic disorder.
- Prenatal testing – used to detect changes in a fetus's genes or chromosomes before birth.
- Preimplantation testing – also called preimplantation genetic diagnosis (PGD), is a specialized technique that can reduce the risk of having a child with a particular genetic or chromosomal disorder.
- Predictive and Presymptomatic testing – used to detect gene mutations associated with disorders that appear after birth, often later in life.
- Forensic testing – uses DNA sequences to identify an individual for legal purposes. (MedlinePlus, 2021).

The American College of Medical Genetics and Genomics (ACMG) recommends that genetic testing should only be requested by a qualified health care professional who is responsible for both ordering and interpreting the genetic tests as well as pretest and post-test counseling of individuals and families regarding the medical significance of the test results and the need for follow-up, if any.

The National Comprehensive Cancer Network (NCCN) recommends that risk assessment and discussion of genetic testing involves three related stages:

1. Pre-test counseling done prior to ordering testing
2. Consideration of the most appropriate tests to order; and
3. Post-test counseling done when results are disclosed.

Pre-test counseling includes the following elements:

- Evaluate the patient's needs and concerns regarding:
    - Knowledge of genetic testing for cancer risk, including benefits, risks, and limitations
    - Variant-specific cancer risks
    - Goals for cancer family risk assessment

- Detailed family history including:
    - Collection of a comprehensive family history
        - Assessment of family history close blood relatives include first-, second-, and third-degree relatives on each side of the family, particularly around individuals with a diagnosis of cancer
        - Types of cancer, bilaterality, age at diagnosis, subtype, and pathology report confirmation
        - Ethnicity (specifically Ashkenazi Jewish ancestry)
- Detailed medical and surgical history, including:
    - Documentation of prior genetic testing results for patients and their family members
    - Personal cancer history (eg, age, histology, laterality)
    - Pathology reports of primary cancers and/or benign lesions (eg, breast biopsies)
    - Carcinogen exposure (eg, history of RT)
    - Reproductive history
    - Hormone or oral contraceptive use
    - History of risk-reducing surgeries
    - Smoking, alcohol, or other exposures related to cancer risk
- Focused physical exam (conducted by qualified clinician) when indicated
- Generate a differential diagnosis and educate the patient on inheritance patterns, penetrance, variable expressivity, and the possibility of genetic heterogeneity

Post-test counseling includes the following elements:

- Discussion of results and associated medical risks
- Interpretation of results in context of personal and family history of cancer
- Discussion of recommended medical management options s including discussion of therapeutic implications by a qualified health care provider if positive
- Discussion of the importance of notifying family members and offering materials/resources for informing and testing family members who also have increased risk
- Discussion of available resources such as high-risk clinics, disease-specific support groups, and research studies. (NCCN, 2023)

There are limitations to the testing of genetic and molecular diseases. According to the ACMG, there are 5 key things patients and providers should question in regards to genetic testing, including:

1. Don't order a duplicate genetic test for an inherited condition unless there is uncertainty about the validity of the existing test result.
2. Don't order APOE genetic testing as a predictive test for Alzheimer disease.
3. Don't order MTHFR genetic testing for the risk assessment of hereditary thrombophilia.
4. Don't order HFE genetic testing for a patient without iron overload or a family history of HFE-associated hereditary hemochromatosis.
5. Don't order exome or genome sequencing before obtaining informed consent that includes the possibility of secondary findings (ACMG, 2015)

Direct-to-Consumer Genetic Testing

Direct-to-Consumer genetic tests (DTC-GT) are genetic tests sold directly to consumers to provide information about their genetic information (generally ancestry, some health traits, and health risks) from a saliva sample. Ordering and return of results for DTC-GT typically does not involve health care professional engagement or the use of health insurance to cover the costs of testing. In recent years,

multiple types of genetic testing products have emerged, including provider-mediated genetic testing (PM-GT) engages a healthcare professional in a non-traditional role as part of the testing process. The professional's involvement may be limited to placing the test order or approving the order for genetic testing with minimal interaction or discussion of the test with the consumer. This professional may be employed by the company that conducts the genetic test and may not know the consumer, or the healthcare professional may already care for the consumer (NIH, 2023). Highmark Wholecare does not consider any direct-to-consumer tests medically necessary.

Consumers may be misled by results of DTC testing if the results are unproven or the testing is invalid. Consumer treatment decisions may be based on inaccurate, incomplete or misunderstood information without the guidance of a trained healthcare provider. More research is needed to fully understand the benefits and limitations of DTC.

Reimbursement

Participating facilities will be reimbursed per their Highmark Wholecare℠ contract.

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