CLINICAL MEDICAL POLICY	
Policy Name:	Testing for Genetic Disease
Policy Number:	MP-010-MD-PA
Responsible Department(s):	Medical Management
Provider Notice/Issue Date:	12/01/2024; 12/01/2023; 12/01/2022; 05/01/2022; 01/15/2021; 01/20/2020; 01/15/2019; 04/15/2018; 10/01/2016
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Next Annual Review:	11/2025
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Products:	Highmark Wholecare℠ Medicaid
Application:	All participating hospitals and providers
Page Number(s):	1 of 10

Policy History

Date	Activity
01/01/2025	Provider Effective date
11/20/2024	QI/UM Committee review
11/20/2024	Annual Review: No changes to clinical criteria. Updated 'Summary of Literature'.
01/01/2024	Provider Effective date
11/15/2023	QI/UM Committee review
11/15/2023	Annual Review: No changes to clinical criteria. Updated 'Summary of Literature' and 'Reference Sources' sections.
01/01/2023	Provider Effective date
11/16/2022	QI/UM Committee review
11/16/2022	Annual Review: No changes to clinical criteria. Reformatted 'Procedure' section numbering. Updated 'Summary of Literature' and 'Reference Sources' sections.
06/01/2022	Provider Effective date
04/06/2022	PARP Approval
11/17/2021	QI/UM Committee review
11/17/2021	Annual Review: No changes to clinical criteria. Updated Summary of Literature and Reference Sources sections.
02/15/2021	Provider effective date

12/02/2020	PARP approval
11/18/2020	QI/UM Committee review
10/21/2020	Annual Review: No changes to clinical criteria, updated Summary of Literature and Reference sections.
01/20/2020	Provider effective date
12/10/2019	PARP Approval
10/16/2019	QI/UM Committee Review
10/16/2019	Annual Review: referenced other genetic testing policies on pg. 1 under the relate policies box; formatting and language adjustments
01/15/2019	Provider effective date

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℠ may cover medically necessary genetic testing under the laboratory services of the medical-surgical benefit of the Company's Medicaid 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.

The qualifications of the policy will meet the standards of the National Committee for Quality Assurance (NCQA) and the Commonwealth of Pennsylvania (PA) Department of Human Services (DHS) and all applicable state and federal regulations.

(Current applicable Pennsylvania HealthChoices Agreement Section V. Program Requirements, B. Prior Authorization of Services, 1. General Prior Authorization Requirements.)

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

1. When Highmark Wholecare℠ does not have a medical policy for a specific genetic test, ALL of the following criteria must be met for the test to be considered medically necessary:
    A. A complete history, physical examination, family history and 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 on the individual's care/treatment plan. This may include the determination of the intensity of surveillance, initiating a new course of treatment of the disease, altering an existing therapy, or the responsible family member/legal guardian intends to use the information in making decisions about the individual's care or treatment plan; AND
    C. The individual 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; AND
    E. The individual displays clinical features as documented in the physical exam, conventional testing are inconclusive, and a definitive diagnosis is uncertain (diagnostic); AND
    F. The individual has not had 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.

2. For tissue-specific or tumor testing, ALL of the following criteria must be met:
    A. The individual is a candidate for targeted drug therapy associated with a specific genetic mutation; AND
    B. There is an established positive association of a specific gene mutation in response to a particular drug therapy.

    Note: This policy is to be used in situations in which there is an absence of a specific medical policy. When available, please reference the separate Highmark Wholecare℠ medical policies for specific genetic tests.

3. Documentation requirements for genetic tests should include ALL of the following:
    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. CPT codes that will be billed for the genetic testing; AND
    E. Complete history, physical and/or consultation notes that addresses 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.

4. When services are not considered medically necessary
    - Services are not medically necessary for conditions other than those listed above, since the scientific evidence has not been established.
    - 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 the 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.
    - Genetic testing is not medically necessary when the clinical diagnosis can be made without the use of a genetic test.
    - Genetic testing is not medically necessary when the results of the testing would not change the diagnosis and/or management of the individual's care (e.g., testing is performed for non-medical reasons or the testing is not expected to provide a definitive diagnosis).

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. Place of Service
   The proper place of service for genetic testing and laboratory services is outpatient.

7. 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

8. Related Policies
    - MP-003-MD-PA Fetal Aneuploidy Testing Using Noninvasive Cell-Free Fetal DNA
    - MP-005-MD-PA Gene Expression Testing for Breast Cancer Treatment
    - MP-006-MD-PA Genetic Testing for Cystic Fibrosis
    - MP-011-MD-PA BCRA Genetic Testing
    - MP-012-MD-PA Chromosomal Microarray Analysis: Comparative Genomic Hybridization (CGH) and Single Nucleotide Polymorphism (SNP)
    - MP-013-MD-PA Whole Exome and Whole Genome Sequencing for Diagnosis of Genetic Disorders
    - MP-017-MD-PA BCR-ABL1 Testing in Chronic Myelogenous Leukemia and Acute Lymphoblastic Leukemia
    - MP-018-MD-PA Genetic Testing for Lynch Syndrome, Familial Adenomatous Polyposis (FAP), Attenuated FAP and MYH-associated Polyposis
    - MP-061-MD-PA Molecular Tumor Markers for Non-Small Cell Lung Cancer (NSCLC)
    - MP-062-MD-PA BRAF Mutation Analysis
    - MP-063-MD-PA Genetic Testing for Warfarin and Clopidogrel Therapy
    - MP-065-MD-PA Molecular Markers for Fine Needle Aspirates of Thyroid Nodules
    - MP-071-MD-PA Non-Oncologic Genetic Testing Panels
    - MP-074-MD-PA Oncologic Genetic Testing Panels
    - MP-100-MD-PA Prostate Cancer Testing

Governing Bodies Approval

The FDA has only regulated a relatively small number of genetic tests sold to laboratories as kits. In 2010, the FDA announced plans to expand regulation to all genetic tests, this expansion has yet to take place (as of April 19, 2016).

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.

Summary of Literature

As medical technology continues to advance, it is not surprising that there is 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 currently four major categories of genetic testing: predictive, diagnostic, prognostic and therapeutic. Genetic testing is conducted using several methods:

- **Molecular tests** look for changes in one or more genes. These types of tests determine the order of DNA building blocks (nucleotides) in an individual's genetic code, a process called DNA sequencing. These tests can vary in scope:

- **Targeted single variant**: Single variant tests look for a specific variant in one gene. The selected variant is known to cause a disorder (for example, the specific variant in the HBB gene that causes sickle cell disease). This type of test is often used to test family members of someone who is known to have a particular variant, to determine whether they have a familial condition. Also, direct-to-consumer genetic testing companies typically analyze a number of specific variants in particular genes (rather than finding all the variants in those genes) when providing health or disease risk information.
- **Single gene**: Single gene tests look for any genetic changes in one gene. These tests are typically used to confirm (or rule out) a specific diagnosis, particularly when there are many variants in the gene that can cause the suspected condition.
- **Gene panel**: Panel tests look for variants in more than one gene. This type of test is often used to pinpoint a diagnosis when a person has symptoms that may fit a wide array of conditions, or when the suspected condition can be caused by variants in many genes. (For example, there are hundreds of genetic causes of epilepsy.)
- **Whole exome sequencing/whole genome sequencing**: These tests analyze the bulk of an individual's DNA to find genetic variations. Whole exome or whole genome sequencing is typically used when single gene or panel testing has not provided a diagnosis, or when the suspected condition or genetic cause is unclear. Whole exome or whole genome sequencing is often more cost- and time-effective than performing multiple single gene or panel tests.

- **Chromosomal tests** analyze whole chromosomes or long lengths of DNA to identify large-scale changes. Changes that can be found include an extra or missing copy of a chromosome (trisomy or monosomy, respectively), a large piece of a chromosome that is added (duplicated) or missing (deleted), or rearrangements (translocations) of segments of chromosomes. Certain genetic conditions are associated with specific chromosomal changes, and a chromosomal test can be used when one of these conditions is suspected. (For example, Williams syndrome is caused by a deletion of a section of chromosome 7.)
- **Gene expression tests** look at which genes are turned on or off (expressed) in different types of cells. When a gene is turned on (active), the cell produces a molecule called mRNA from the instructions in the genes, and the mRNA molecule is used as a blueprint to make proteins. Gene expression tests study the mRNA in cells to determine which genes are active. Too much activity (overexpression) or too little activity (underexpression) of certain genes can be suggestive of particular genetic disorders, such as many types of cancer.
- **Biochemical tests** do not directly analyze DNA, but they study the amount or activity level of proteins or enzymes that are produced from genes. Abnormalities in these substances can indicate that there are changes in the DNA that underlie a genetic disorder. (For example, low levels of biotinidase enzyme activity is suggestive of biotinidase deficiency, which is caused by BTD gene variants.) (NLM, 2021)

The American College of Medical Genetics (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 (ACMG, 2021).

The National Comprehensive Cancer Network (NCCN) advises that the decision to offer genetic testing should involve 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. It is recommended that a genetic counselor, clinical geneticist, oncologist, surgeon, oncology nurse, or other

health professional with expertise and experience in cancer genetics be involved at each stage whenever possible. Testing should be considered in appropriate high-risk individuals where it is likely to impact the risk management and/or treatment of the tested individuals and/or their at-risk family members (NCCN, 2023).

The National Society of Genetic Counselors (NSGC) has recommended that genetic testing be performed utilizing the informed decision-making process Issues included in this process should include the following:

1. Obtaining all pertinent personal medical and family history data
2. Psychosocial assessment
3. Discussion of cancer and mutation risk and how personalized risk estimates are derived
4. Facilitation of the informed consent process through discussion of the risks, benefits, limitations, and likelihood of identifying a mutation with genetic susceptibility testing
5. Result disclosure, when appropriate
6. Discussion of medical management options
7. Review of issues related to genetic discrimination (Berliner et al., 2013).

The National Society of Genetic Counselors supports regulation of DNA testing for health-related conditions and hereditary diseases for clinical use. Any decision to regulate genetic testing should be patient-focused and should carefully consider the potential risk of stifling technological advancements that are critical to the fields of genetics, genomics, and precision medicine.

Regulation should not impede patient access to high-quality clinically useful information. Goals should include protecting patients from undue harm by developing clinical utility and analytical validity programs; ensuring that practitioners correctly interpret results; and creating transparency in the use, or intended application, of a genetic test (Berliner et al., 2013).

There are limitations to the testing of genetic and molecular diseases. According to the American College of Medical Genetics and Genomics (2017), 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 (Apolipoprotein E Genotyping) 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.

Direct-to-Consumer Genetic Testing

Traditionally, genetic testing was only available through health care providers. These providers order appropriate genetic tests from a qualified laboratory and interpret the results. Recently direct-to-consumer genetic testing has become available as seen on television, printed advertisements and the Internet. However, direct-to-consumer genetic testing (DTC GT) raises scientific, ethical and regulatory questions. The European Academies of Science Advisory Council (EASAC) and the Federation of European Academies of Medicine (FEAM) has stated that as a whole, DTC GT has little clinical value at present and, on occasion, has potential to be harmful. The EASAC & FEAM would not wish to encourage citizens to use DTC GT at present. The governance of DTC GT should address the concerns expressed about the validity

and completeness of information supplied before testing, consent, test data management, and access to advice and counseling. Developing general principles for the governance of DTC services should include:

- Susceptibility testing for complex disorders should be regulated on the basis that claims about the link between genetic marker and disease are scientifically valid.
- Test quality assurance must cover not only laboratory analytical quality but also the professional interpretation of results and the provision of counselling that is appropriate to the disease risk and burden.
- Information supplied by the DTC GT company should be controlled by the enforcement of advertising standards (truth in labelling), and must emphasize who is advised not to use DTC GT services.
- Implications for the established health services and others need to be assessed, for example in terms of the potential waste of scarce resources in unnecessary follow-up to test results.
- Companies should include proper, additional, consent-seeking (specifying the handling of samples and information) when desiring to use data for research (EASAC & FEAM, 2012).

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.

Recent advances in high-throughput genomics have made large-scale genotyping and sequencing affordable. This has led to an increased number of genetic tests being developed, including tests for clinical use and commercially available direct-to-consumer genetic tests. However, there are still several challenges that limit the widespread use of genetic information in the clinical care setting. In choosing a genetic test, one needs to assess the following:

1. how well the test performs to detect the genetic variation or mutation of interest (technical performance),
2. how well the variant or mutation tested accurately and reliably predicts the clinical disease (clinical validity), and
3. what is the evidence that the genetic test improves clinical outcomes or has added value for patient management decisions (clinical utility)

These criteria for the evaluation of a genetic test are based on the Center for Disease Control and Prevention ACCE model, which also includes ethical, legal, and social implications of genetic testing (Franceschini, 2018).

The American Society of Human Genetics (ASHG) provides the stance that the potential for genetics-based tools to enhance healthcare will only be fully realized if health insurance coverage policies foster their appropriate use. Government health insurance programs and private payers should establish clear policies about the coverage of genetic tests and associated services that improve healthcare. Given the rapid pace of genetic discovery and innovation, policies should allow for the adoption of new tests emerging from novel technologies, advances in our understanding of the relationship between genetic variation and disease, and research demonstrating the clinical utility of a new test in patient care.

Reimbursement

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

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