Oncologic Genetic Testing Panels

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Disclaimer

Highmark Health Options 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 Health Options may provide coverage under medical surgical benefits of the Company's Medicaid products for medically necessary oncologic genetic testing panels.

This policy is designed to address medical necessity guidelines that are appropriate for most 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 Delaware Department of Health and Social Services (DHSS) and all applicable state and federal regulations.

DEFINITIONS

Highmark Health Options (HHO) – Managed care organization serving vulnerable populations that have complex needs and qualify for Medicaid. Highmark Health Options members include individuals and families with low income, expecting mothers, children, and people with disabilities. Members pay nothing to very little for their health coverage. Highmark Health Options currently services Delaware Medicaid: Delaware Health Children (DHCP) and Diamond State Health Plan Plus members.

Genetic Testing Panel – A laboratory test that evaluates multiple genes simultaneously compared to sequential testing of individual genes. There are multiple uses of the testing results including but not limited to: to establish a clinical diagnosis, confirmation of a specific clinical diagnosis, the diagnosis of a hereditary disorder, to determine when a known cancer diagnosis is part of a hereditary cancer syndrome or to assist in the identification of a cancer type/subtype and in the selection of the most appropriate treatment of a cancer type/subtype.

Germline Mutation – An alteration in the DNA that is transmissible from parent to offspring.

Panel Testing Technology – A genetic testing method that examines multiple genes or mutations simultaneously. Testing methods can include next-generation sequencing and chromosomal microarray.

Next Generation Sequencing (NGS) – Non-Sanger-based high-throughput DNA sequencing technologies. Millions or billions of DNA strands can be sequenced in parallel, yielding more throughput and minimizing the need for the fragment-cloning methods that are often used in Sanger sequencing of genomes.

Chromosomal Microarray Analysis (CMA) – a technique that identifies chromosomal abnormalities, including submicroscopic abnormalities that are too small to be detected by conventional karyotyping.

Variant of Unknown/Uncertain Significance (VUS) – An allele, or variant form of a gene that has been identified via genetic testing. The significance of the finding is not established and the connection to a human disease has not been identified.

Clinical Utility – How likely the testing is to significantly improve patient outcomes that reflect the balance between health-related benefits and/or harms that can ensue from using the information made available from the testing.

Genetic Counseling – A service that is provided by a Clinical Geneticist, Certified Genetic Counselor, or other approved medical provider who is independent and not employed by any clinical or genetic laboratory, who bears no conflict of interest with the entity performing the testing.

1st, 2nd, and 3rd Degree Relatives:

Blood relatives on the same side of the family (maternal or paternal).

- 1st-degree relatives are parents, siblings, and children.
- 2nd-degree relatives are grandparents, aunts, uncles, nieces, nephews, grandchildren, and half-siblings.
- 3rd-degree relatives are great-grandparents, great-aunts, great-uncles, great-grandchildren, and first cousins.

PROCEDURES

A prior authorization is required.

This policy applies only if there is no separate Highmark Health Options medical policy that addresses criteria for specific oncologic genetic testing. Genetic testing panels are defined as any assay that simultaneously tests for more than one gene associated with a condition. The testing may focus on sequence variants and/or deletions/duplications of those genes. Oncologic genetic panels include panels for hereditary conditions, genetic conditions, or cancer panels.

The ordering provider must validate the clinical utility by considering:

- Will the panel testing offer significant advantages compared to sequential analysis of individual genes (i.e., a genetic testing panel that addresses the disorder in question, rather than the disorder in question plus other disorders, has been considered and discussed)
- How will the panel testing results be used in patient care decision making
- Will the ancillary findings lead to further testing or management changes
- There is reliable evidence in the peer-reviewed scientific literature that health outcomes will be improved as a result of treatment decisions based on molecular genetic testing findings.

MEDICAL NECESSITY GUIDELINES

1. All genetic testing panels must be performed in a Clinical Laboratory Improvement Amendment (CLIA) licensed lab; AND
2. Genetic testing panels are to be ordered by or recommended by a physician specialist such as hematology, oncology, a physician with expertise in the treatment of the targeted disease or geneticist; AND
3. The ordering provider must not be employed or contracted by a commercial genetic testing laboratory; AND
4. A recommendation for genetic testing is confirmed by either:
    - An American Board of Medical Genetics or American Board of Genetic Counselor; or
    - An independent Board Certified or Board eligible medical geneticist
5. All components of the specific genetic testing panel must demonstrate positive clinical utility for the medical condition being evaluated; AND
6. All components of panel testing offer substantial advantages in efficiency compared to sequential analysis of individual genes.
7. Genetic testing panels should be considered when clinical evaluation suggests a particular diagnosis, the disorder cannot be identified through clinical evaluation and/or other testing, and not when the diagnosis is unclear or uncertain; AND

8. The provider has had a discussion with the member regarding the scope of the genetic testing panel being ordered and the impact of variants of unknown significance; AND
9. Documentation Requirements:
    - Brief explanation of how the result of genetic testing is necessary to guide treatment decisions relevant to the member's personal medical history for positive patient outcome (i.e., whether to perform surgery, determine chemotherapy treatment, choose between medication options, etc.); s; AND
    - Diagnose an illness when signs/symptoms are displayed, OR
    - Rule out a diagnosis when signs/symptoms are displayed, OR
    - Medical records relevant to the testing being performed are to include:
        - A thorough history and physical examinations by the referring physician.
        - Conventional testing and outcomes; AND
        - A three generation pedigree analysis results; AND
            Conservative treatment provided, if applicable.
10. The following information is required for a genetic or molecular diagnostic test is ordered:
    - The specific name of the test/panel
    - Name of performing CLIA-accredited laboratory
    - The exact gene(s) and/or mutations being tested
    - Correct CPT and/or HCPCS code(s)
    - Estimated cost/quote sheet for the genetic testing panel ordered
11. An informed consent must be signed by the patient prior to testing. The consent must include a statement that the patient agrees to post-test counseling and the consent must be made available upon request.
12. Pre-test genetic counselling has been performed and post-test genetically counselling by an independent genetic professional is planned.

WHEN GENETIC TESTING PANELS ARE NOT COVERED

- Broad-based genetic testing panels are considered not medically necessary when individual components are sufficient for treatment/management of the patient. Testing for multiple genes or multiple conditions, in cases where a tiered approach/method is clinically available, will be covered only for the number of genes or tests that are reasonable to obtain necessary therapeutic decision making and NOT the entire panel.
- More than one multi-gene panel is considered not medically necessary at the same time.
- Genetic testing of children to predict adult onset of diseases is considered not medically necessary.
- In the absence of specific information regarding advances in the knowledge of mutation characteristics for a particular disorder, the current literature indicates that genetic tests for inherited disease need only be conducted once per lifetime of the member.
- If a genetic testing panel was previously performed for medically necessary indications and a larger panel is developed and requested, only the testing for previously untested genes will be considered medically necessary.

GENETIC COUNSELING

Pre- and post-test genetic counseling is required to be performed by an independent (not employed by a genetic testing lab) genetic provider prior to genetic counseling for genetic mutations. This service is necessary to inform people being tested about the benefits and limitations of a specific genetic test for the specific patient. Genetic testing for mutations requires documentation of medical necessity from one of the following providers who has evaluated the member and intends to see the person after testing has been performed for counseling:

- Board Eligible or Board-Certified Genetic Counselor
- Advanced Genetics Nurse
- Genetic Clinical Nurse
- Advanced Practice Nurse in Genetic

- Board Eligible or Board-Certified Clinical Geneticist
- A physician with experience in cancer genetics
- A physician with experience with the suspected medical condition (e.g., neurologist)

POST-PAYMENT AUDIT STATEMENT

The medical record must include documentation that reflects the medical necessity criteria and is subject to audit by Highmark Health Options at any time pursuant to the terms of your provider agreement.

PLACE OF SERVICE: OUTPATIENT

CODING REQUIREMENTS

CPT code	Description
81400	Molecular pathology procedure, Level 1.
81401	Molecular pathology procedure, Level 2.
81404	Molecular pathology procedure, Level 5.
81432	Hereditary breast cancer-related disorders (e.g., hereditary breast cancer, hereditary ovarian cancer, hereditary endometrial cancer); genomic sequence analysis panel, must include sequencing of at least 14 genes, including ATM, BRCA1, BRCA2, BRIP1, CDH1, MLH1, MSH2, MSH6, NBN, PALB2, PTEN, RAD51C, STK11, and TP53.
81433	Hereditary breast cancer-related disorders (e.g., hereditary breast cancer, hereditary ovarian cancer, hereditary endometrial cancer); duplication/deletion analysis panel, must include analyses for BRCA1, BRCA2, MLH1, MSH2, and STK11.
81437	Hereditary neuroendocrine tumor disorders (e.g., medullary thyroid carcinoma, parathyroid carcinoma, malignant pheochromocytoma or paraganglioma); genomic sequence analysis panel, must include sequencing of at least 6 genes, including MAX, SDHB, SDHC, SDHD, TMEM127, and VHL.
81438	Hereditary neuroendocrine tumor disorders (e.g., medullary thyroid carcinoma, parathyroid carcinoma, malignant pheochromocytoma or paraganglioma); duplication/deletion analysis panel, must include analyses for SDHB, SDHC, SDHD, and VHL.
81504	Oncology (tissue of origin), microarray gene expression profiling of > 2000 genes, utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as tissue similarity scores.
81520	Oncology (breast), mRNA gene expression profiling by hybrid capture of 58 genes (50 content and 8 housekeeping), utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as a recurrence risk score.
81521	Oncology (breast), mRNA, microarray gene expression profiling of 70 content genes and 465 housekeeping genes, utilizing fresh frozen or formalin-fixed paraffin-embedded tissue, algorithm reported as index related to risk of distant metastasis.
81540	Oncology (tumor of unknown origin), mRNA, gene expression profiling by real-time RT-PCR of 92 genes (87 content and 5 housekeeping) to classify tumor into main cancer type and subtype, utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as a probability of a predicted main cancer type and subtype.
81541	Oncology (prostate), mRNA gene expression profiling by real-time RT-PCR of 46 genes (31 content and 15 housekeeping), utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as a disease-specific mortality risk score.
S3854	Gene expression profiling panel for use in the management of breast cancer treatment.

REIMBURSEMENT

Participating facilities will be reimbursed per their Highmark Health Options contract.

GOVERNING BODIES APPROVAL

Three federal agencies play a role in the regulation of genetic tests: CMS, FDA and the Federal Trade Commission (FTC). The Centers for Medicare and Medicaid Services is responsible for regulating all clinical laboratories performing genetic testing, ensuring their compliance with the Clinical Laboratory Improvement Amendments of 1988.

The FDA has the broadest authority in terms of regulating the safety and effectiveness of genetic tests as medical devices under the Federal Food, Drug, and Cosmetic Act.

Compared to the FDA and CMS, the Federal Trade Commission's regulatory authority is narrow, and is limited to how tests are advertised. The Commission has the authority to regulate advertising that delivers health-related information to consumers to ensure that it is not false or misleading.

Genetic testing panels are typically laboratory derived tests that are not subject to the United States Food and Drug Administration (FDA) approval. Due to the large numbers of mutations contained in expanded panels, it is not possible to determine clinical validity for the panels.

*__NOTE__: This policy may not apply to multi-gene panel testing for indications that are addressed in test-specific policies. For genetic test-specific policies, please see the following link:
https://highmarkhealthoptions.com/providers/MedicalAndPaymentPolicy

The following is a list of existing genetic testing policies:

- BCR-ABL1 Testing in Chronic Myelogenous Leukemia and Acute Lymphoblastic Leukemia
- BRCA 1 & 2 Genetic Mutation Testing and Related Genetic Counseling
- Chromosomal Microarray Analysis: Comparative Genomic Hybridization (CGH) and Single Nucleotide Polymorphism (SNP)
- Fetal Aneuploidy Testing using Noninvasive Cell-Free Fetal DNA
- Genetic Testing for Colorectal Cancer Susceptibility
- Genetic Testing for Cystic Fibrosis
- Genetic Testing for Warfarin
- Molecular Markers for Fine Needle Aspirates of Thyroid Nodules
- Molecular Tumor Markers for Non-Small Cell Lung Cancer
- Testing for Genetic Disease
- Whole Exome and Whole Genome Sequencing for Diagnosis of Genetic Disorders

SUMMARY OF LITERATURE

The role of genetic testing in the medical profession has continued to grow rapidly. With the completion of the Human Genome Project (HGP) and continued advances in the field of genomics, the use of genetic testing has become widespread. The World Health Organization (WHO) has published criteria to be met for any genetic test to be considered valuable: the disease is an important health problem, the risk in mutation carriers is high in the general population (not just in a high-risk group), mutations for the disease can be accurately identified, and effective interventions exist.

Genetic testing was first introduced as a clinical tool in the 1960s with chromosomal karyotyping. (Satya-Murti, et al. 2013) More advanced testing includes: Chromosomal microarray analysis or comparative genomic hybridization (array CDG) testing, fluorescence-in-situ-hybridization (FISH), letter-by-letter sequencing of specific genes (Sanger technology) and the new technology where huge panels of genes as large as the entire exome can be sequenced (NexGen technology).

Genetic testing includes the following:

- Single gene-targeted mutation/sequence analysis, deletion/duplication testing
- Gene Panels
- Whole Exome Sequencing (WES)-sequencing of exome but interpretation focuses on genes related to phenotype
- Whole Genome Sequencing (WGS)-sequences all genetic material

Genetic testing uses next-generation sequencing (NGS) technology, massive parallel sequencing, or chromosomal microarray analysis (CMA) testing to perform genetic panels. NGS and CMA are new genetic technologies. The intended use for genetic panels is variable. Existing genetic testing panels are available for the following areas: cancer, cardiovascular disease, neurologic disease, psychiatric conditions and for reproductive testing. As of October 10, 2017, the Genetic Testing Registry listed more than 2,600 diagnostic testing panels representing 3 laboratories.

When scientists test for mutations in large numbers of genes with a single test, known as a gene panel, they are virtually guaranteed to find at least one VUS, says Colleen Caleshu, a genetic counsellor at Stanford University's Center for Inherited Cardiovascular Disease. "The more genes you look at, the more variation you'll find," she adds. "We all have tons of variations in our genes, most of which are extremely rare and, by the very nature of rarity, uninterpretable." In short, there isn't enough data to know what you are seeing.
https://arstechnica.com/science/2017/07/the-uncertain-future-of-genetic-testing/

Several methods can be used for genetic testing:

- Molecular genetic tests (or gene tests) study single genes or short lengths of DNA to identify variations or mutations that lead to a genetic disorder.
- Chromosomal genetic tests analyze whole chromosomes or long lengths of DNA to see if there are large genetic changes, such as an extra copy of a chromosome, that cause a genetic condition.
- Biochemical genetic tests study the amount or activity level of proteins; abnormalities in either can indicate changes to the DNA that result in a genetic disorder.

Advantages of genetic testing panels

- The potential for overall greater sensitivity can provide a comprehensive analysis for multiple diagnoses.
- Enhanced sensitivity over Sanger sequencing

Disadvantages

- There is no standardization in the makeup of genetic panels. The panel compositions are variable with different set of genes for the same condition. This genetic panel composition is determined by the specific lab that developed the test.
- The gene selection of genetic panels is subject to change based on scientific discovery.
- Because of the large number of mutations contained in expanded panels, it is not possible to determine clinical validity for the panels.
- The risk for uncertain and incidental findings with the large numbers of genes on the panels.
- Large percentage of VUS

An example of the number of genes for the same clinical indications is as follows: There are at least four clinical laboratories offering epilepsy gene panels. The number of genes being tested range from 70 to 377 (Xue, et al. 2015). It is suggested that the rationale for the obvious difference in the number of genes tested is that some laboratories may prefer to include all possible genes that are even remotely associated with the phenotype being evaluated in order to procure a higher diagnostic yield. Other laboratories elect to take a conservative approach by only including the genes that have support for association with a disorder. However, it is the responsibility of the clinician and the laboratory geneticist to determine the medically appropriate gene selection for the panels. The clinician needs to be able to understand the results in relation to the clinical case at hand.
Per SGO (2014), advantages of cancer gene panels include decreased cost and improved efficiency of cancer genetic testing by decreasing the time involved, number of patient visits, and number of tests sent. A negative genetic test is more reassuring at eliminating the likelihood of inherited risk when all known genes for that phenotype have been assayed.

In addition, SGO (2014) states that the major drawback of cancer gene panels is the increased complexity of results. For many genes, clear risk reduction strategies for mutation carriers are not established. A major concern is the increased likelihood of identifying results of uncertain clinical significance. Uncertain results occur when a rare variant is identified whose impact on protein function is unknown. Uncertainty can also arise from the identification of a clearly deleterious mutation in a gene of uncertain clinical significance. The more genes that are tested, the greater the chances are of such uncertain results. Clinical management should not be dictated by these uncertain variants; rather, family history should guide recommendations in these cases. However, clinicians may misinterpret uncertain results, treating patients as if a deleterious mutation is present, leading to unnecessary interventions. Given the increased variety of testing options and potential complexity of genetic results with cancer gene panels, genetic counselors or knowledgeable medical professionals should carefully discuss the pros and cons with patients.

Types of Testing

- Testing of affective/symptomatic individual (diagnostic, prognostic and therapeutic)
- Testing asymptomatic individuals to determine risk
- Testing individual to benefit family
- Testing of DNA from cancer cells (diagnostic, prognostic, treatment responses)

While cost is not a primary concern—most panel tests are comparable in price to testing for individual genetic tests—some genetics professionals question the inclusion of emerging-risk genes or variants of undetermined significance on panels, and whether collecting that information is clinically beneficial or possibly harmful to patients. A study published in Genetics in Medicine (LaDuca, et al. 2014) said that multigene panels "play an important role in the diagnosis of hereditary cancer predisposition." However, the authors noted there is a need for careful interpretation of results, particularly for mutations in moderate-risk genes and for patients with negative results.
Oncologists may choose panel testing around hereditary cancer from the following approaches:

- Syndrome-specific gene panel: This approach would include BRCA1 and BRCA2 for hereditary breast and ovarian cancer or testing of mismatch repair genes for Lynch syndrome (MLH1, MSH2, MSH6, PMS2 and EPCAM).
- High-penetrance gene panel: These types of panels include genes with high penetrance and are known to be involved in a specific cancer. One example is high risk breast cancer panel testing for mutations in BRCA1, BRCA2, TP53, PTEN, CDH1 and STK11.
- Cancer-specific gene panel: This panel would include testing of between 17-23 genes. Tested genes include both highly and moderately penetrant genes related to a specific cancer type such as breast cancer or ovarian cancer.
- Comprehensive cancer risk panel: Several companies offer these panels, which include testing of between 25 and 61 highly and moderately penetrant genes known to be associated with risk for many different cancers.

Although multigene tests are gaining in popularity for patients who may be predisposed to hereditary breast and/or ovarian cancer, concerns remain because most of the genes tested are considered low- or moderate-risk genes for which management guidelines either do not exist or have only been recently introduced. Current research indicates that multigene panel testing can provide information in a small subset of patients, however additional studies are necessary to address if clinical interventions are of any benefit to positive less well studied mutations. In addition, there is paucity in the information in addressing the large numbers of variants of uncertain significance generated by multigene panels.

Multi-gene panels are commonly used when:

- When the family mutation is unknown in a symptomatic patient, OR
- When there are multiple candidate genes and no single gene is significantly more likely than the others, OR
- When personal and family history are suggestive of more than one hereditary syndrome: OR
- When the suspected diagnosis cannot be unequivocally diagnosed otherwise.

Targeted Gene Sequencing

Targeted gene sequencing are focused panels that contain a select number of genes or gene regions that are known or are suspected as associates of the disease or phenotype. These panels can be designed with preselected content or custom designed. Next generation sequencing also evaluated targeted genes of interest however, multiple genes can be assessed.

Shashi and colleagues (2014) noted that it remains unclear which patients should be analyzed with a specific genetic test and in which stage during the evaluation. In a study to assess the diagnostic yield of the traditional comprehensive clinical evaluation and targeted genetic testing, the authors retrospectively analyzed a cohort of 500 unselected consecutive patients. These patients had received traditional genetic diagnostic evaluations at a tertiary facility. The diagnosis rate, number of visits to diagnosis, genetic tests and the cost of testing was calculated. The authors concluded that half of the patients tested with traditional approaches were diagnosed in the initial visit. It is logical that the remaining patients that were undiagnosed may benefit from next generation sequencing. The use of next-generation sequencing utilized after the first clinical visit could result in a higher rate of genetic diagnosis and at a considerable cost savings.

The American Academy of Neurology (AAN) has issued recommendations for genetic test that is ‘guided by the clinical phenotype, inheritance patter (if available), and electrodiagnostic features. As example the AAN does not support complete panels of all known Charcot-Marie Tooth genes but recommends a stepwise evaluation method to improve genetic screening efficiency.

Multiple research documents report that a thorough clinical evaluation is a major step in choosing the best genetic test for the patient's condition.

The National Comprehensive Cancer Network (NCCN, 2017) evidence and consensus-based guidelines recommend the following initial laboratory evaluations for individuals suspected of having MPN:

- “Laboratory evaluations should include complete blood count (CBC), microscopic examination of the peripheral smear, comprehensive metabolic panel with serum uric acid, serum LDH, liver function tests, serum EPO level and serum iron studies.”
- Fluorescence in situ hybridization (FISH) or a reverse transcriptase polymerase chain reaction (RT-PCR) on a peripheral blood specimen to detect BCR-ABL1 transcripts and exclude the diagnosis of CML is recommended for all patients, especially those with left-shifted leukocytosis and/or thrombocytosis with basophilia.”

- "Molecular testing for JAKV617F mutations should be performed in all patients. If JAKV617F mutation is negative, molecular testing for MPL and CALR mutations should be performed for patients with MF and ET; molecular testing for JAK2 exon 12 mutation should be done for those with PV."
  "In the absence of JAK2, CALR and MPL mutations, the presence of another clonal marker is included as one of the major diagnostic criteria for PMF. Additional mutations in ASXL1, EZH2, TET2, IDH1, IDH2, SRSF2, and SF3B1 genes are noted to be of help in determining the clonal nature of the disease."
- "Bone marrow aspirate and biopsy with trichrome and reticulin stain and bone marrow cytogenetics (karyotype, with or without FISH) is necessary to accurately distinguish the bone marrow morphological features between the disease subtypes (early/prefibrotic PMF, ET and masked PV)."

The National Comprehensive Cancer Network (NCCN) guidelines do not contain recommendations for the general strategy of testing a tumor for a wide range of mutations. The guidelines do contain recommendations for specific genetic testing for individual cancers, based on situations where there is a known mutation-drug combination that has demonstrated benefits for that specific tumor type.

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POLICY UPDATE HISTORY

12/21/2021	Approved in Medical Policy Committee
01/2022	Approved in QI/UM
12/28/2022	Annual review; approved in Medical Policy Committee
01/03/2023	Approved in QI/UM