Prior Authorization Review Panel
MCO Policy Submission

A separate copy of this form must accompany each policy submitted for review.
Policies submitted without this form will not be considered for review.

Plan: AmeriHealth Caritas Pennsylvania	**Submission Date**: 7/1/2024
Policy Number: ccp.1235	**Effective Date:** 7/2016 **Revision Date:** June 1, 2024
Policy Name: Genetic testing for hereditary cancer susceptibility	

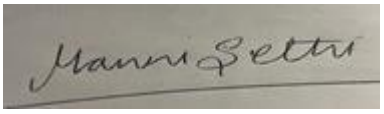
Type of Submission – Check all that apply:

- **New Policy**
- **X Revised Policy***
- **Annual Review – No Revisions**
- **Statewide PDL**

***All revisions to the policy must be highlighted using track changes throughout the document.**

Please provide any clarifying information for the policy below:

See tracked changes below.

Name of Authorized Individual (Please type or print): Manni Sethi, MD, MBA, CHCQM	**Signature of Authorized Individual:** 

Genetic testing for hereditary cancer susceptibility

Clinical Policy ID: CCP.1235

Recent review date: 6/2024

Next review date: 10/2025

Policy contains: Breast cancer; colon cancer; genetic testing; hereditary cancer; ovarian cancer; polyposis; prostate cancer.

AmeriHealth Caritas Pennsylvania has developed clinical policies to assist with making coverage determinations. AmeriHealth Caritas Pennsylvania clinical policies are based on guidelines from established industry sources, such as the Centers for Medicare & Medicaid Services (CMS), state regulatory agencies, the American Medical Association (AMA), medical specialty professional societies, and peer-reviewed professional literature. These clinical policies along with other sources, such as plan benefits and state and federal laws and regulatory requirements, including any state- or plan-specific definition of "medically necessary," and the specific facts of the particular situation are considered by AmeriHealth Caritas Pennsylvania on a case by case basis when making coverage determinations. In the event of conflict between this clinical policy and plan benefits and/or state or federal laws and/or regulatory requirements, the plan benefits and/or state and federal laws and/or regulatory requirements shall control. AmeriHealth Caritas Pennsylvania clinical policies are for informational purposes only and not intended as medical advice or to direct treatment. Physicians and other health care providers are solely responsible for the treatment decisions for their patients. AmeriHealth Caritas Pennsylvania clinical policies are reflective of evidence-based medicine at the time of review. As medical science evolves, AmeriHealth Caritas Pennsylvania will update its clinical policies as necessary. AmeriHealth Caritas Pennsylvania clinical policies are not guarantees of payment.

Coverage policy

As the landscape of molecular testing is rapidly evolving, guideline-directed genetic testing for hereditary cancer susceptibility is phenotype-directed (personal and family history) and focuses on identifying gene mutations that are clinically actionable to avoid overtreatment or overscreening. A tiered approach starting with known familial mutations (e.g., single-gene testing, syndrome-specific panels, cancer-specific panels), with reflex to more detailed multigene testing based on next-generation sequencing, may be medically necessary (Bedrosian, 2024; National Comprehensive Cancer Network, 2023, 2024; Poylin, 2024).

Genetic testing for hereditary cancer susceptibility is clinically proven and, therefore, may be medically necessary, when pre- and post-test genetic counseling is provided, and any of the following criteria are met (National Comprehensive Cancer Network, 2023, 2024; Poylin, 2024):

- Member has a blood relative with a known pathogenic or likely pathogenic variant in a cancer susceptibility gene.
- Member meets any of the criteria below but tested negative or indeterminate with previous limited testing (e.g., single gene and/or absent deletion duplication analysis) and are interested in pursuing multi-gene testing:
    - When a pathogenic or likely pathogenic variant identified on tumor genomic testing or circulating tumor deoxyribonucleic acid (DNA) assays has clinical implications if also identified in the germline.

- To aid in systemic therapy and surgical decision-making.
- When one or more genes may explain a member's medical and family history.
- When member's medical or family history meets criteria for more than one syndrome.
- When member's medical and family history is strongly suggestive of an inherited susceptibility, for example, suspected Li-Fraumeni syndrome, Cowden syndrome/PTEN hamartoma tumor syndrome, or Lynch syndrome; Ashkenazi Jewish ancestry without additional risk factors; serous endometrial cancer; and history of breast, ovarian, pancreatic, prostate, or colorectal cancers.

Limitations

All other uses of genetic testing for hereditary cancer susceptibility, including determination of clinical trial eligibility, are not medically necessary.

Polygenic risk scores are investigational/not clinically proven and, therefore, not medically necessary (National Comprehensive Cancer Network, 2024).

In members younger than 18 years of age, germline genetic testing for high-risk colorectal cancer syndromes is generally not medically necessary unless the results will impact medical management. Exception: when familial adenomatous polyposis is suspected, genetic testing in this age group may be medically necessary to guide medical management (National Comprehensive Cancer Network, 2023).

Genetic testing from ancestry services is investigational/not clinically proven and, therefore, not medically necessary, as these tests have not been validated for clinical use (National Comprehensive Cancer Network, 2023, 2024).

Circulating tumor DNA assays are not medically necessary for detecting germline variants, as these assays have not been validated for reporting or interpreting germline variants (National Comprehensive Cancer Network, 2023, 2024).

Germline genetic testing is limited to once per lifetime per condition. Exception: repeat germline genetic testing may be medically necessary if it is non-duplicative to identify different genetic content or information using newer and more sensitive methodologies.

Additional molecular testing may be reviewed on a case-by-case basis for medical necessity.

Alternative covered services

- Guideline-directed medical management for each inherited cancer syndrome.
- Genetic counseling.

Background

A hereditary cancer syndrome is an inherited disorder in which a higher-than-normal risk of certain types of cancer runs in the family. Inherited cancers account for about 5% to 10% of all cancers (American Cancer Society, 2023). Often these cancers present at an early age and may be associated with several clinical manifestations (American Society of Clinical Oncology, 2022).

Hereditary cancer syndromes are caused by germline mutations that generally exhibit an autosomal dominant inheritance pattern (American Society of Clinical Oncology, 2022). This pattern requires only one mutated gene, located on a nonsex chromosome (autosome), to cause disease in offspring. These germline mutations generally emanate from mistakes in DNA replication. Left uncorrected, the mutations may lead to deleterious mutations in tumor suppressor genes or oncogenes that affect cell growth and death. Examples of such mutations are in the BRCA1, BRCA2, and p53 or TP53 genes.

The most common hereditary cancer syndromes include hereditary breast and ovarian cancer syndrome, Lynch syndrome, Li–Fraumeni syndrome, Cowden syndrome, Peutz–Jeghers syndrome, and hereditary diffuse gastric cancer. Familial cancer syndromes, for which heritable risk has been identified and which are particularly notable in the population, occur among those patients suffering from colorectal cancer. Among the diagnoses familiar for well-defined risk of heritable disease in this group are (American Society of Clinical Oncology, 2022):

- Lynch syndrome (also known as hereditary nonpolyposis colorectal cancer).
- Familial adenomatous polyposis.
- MutY human homolog-associated polyposis.
- Peutz–Jeghers syndrome.
- Juvenile polyposis.
- Serrated polyposis syndrome.

Comprehensive hereditary cancer risk assessment and counseling include clinical assessment, predictive germline genetic testing when appropriate, and risk management recommendations as part of one or more genetic counseling sessions (National Cancer Institute, 2022). Germline genetic testing strategies encompass single gene or multigene testing, which can simultaneously test for multiple pathogenic genetic variants.

Multigene testing includes syndrome-specific tests, cancer-specific tests, and comprehensive cancer panels that test for multiple genes associated with a variety of cancers or cancer types using blood or saliva samples. As with single gene testing, the rationale for multigene testing focuses on identifying mutations known to be clinically actionable. When one or more genes may influence clinical management, multigene testing may be more efficient or cost effective.

Direct-to-consumer tests are now available but typically do not include professional genetic counseling or interpretation and may be incomplete or require confirmation with another sample (National Cancer Institute, 2022).

Findings

There is a growing body of evidence regarding genetic testing for hereditary cancer susceptibility. Much of the available medical evidence to date has focused on the study of individuals and families at high risk of cancer, and of selected tumors, to investigate the genetic susceptibility and environmental exposures that may alter cancer risk. As a rule, both genetic and environmental risk factor information specific for the tumor type is obtained to establish a risk score and prediction for heritable susceptibility.

Regarding multigene testing, there are limited data and a lack of clear guidance with respect to the degree of risk associated with some genes in these panels, particularly genes of low or moderate penetrance. There may also be some doubt as to how to best manage and communicate the risk for gene carriers. Choice of testing panel is multifactorial. Considerations include phenotype, the number of genes analyzed, turnaround time, the likelihood of detecting variants of unknown significance, and the potential of next-generation sequencing methods to miss important variants that would be detected with single gene methods. Therefore, multigene testing should be offered in the context of professional genetics expertise (National Comprehensive Cancer Network, 2023, 2024).

Phenotype should direct the testing plan with a focus on identifying gene mutations that are clinically actionable to avoid overtreatment or overscreening. Multigene testing is most useful when: one or more genes can explain a patient’s medical and family history; a patient’s personal or family history meets criteria for more than one syndrome; or the patient’s medical and family history is strongly suggestive of an inherited susceptibility and prior single gene testing is negative or indeterminate (National Comprehensive Cancer Network, 2023, 2024).

National Comprehensive Cancer Network provides general and specific genetic testing criteria for hereditary cancer syndromes in several guidelines. General indications for genetic testing are as follows (National Comprehensive Cancer Network, 2024):

- Individuals with any blood relative with a known pathogenic or likely pathogenic variant in a cancer susceptibility gene.
- Individuals meeting the criteria below but who tested negative with previous limited testing (e.g., single gene and/or absent deletion duplication analysis) and are interested in pursuing multi-gene testing.
    - A pathogenic or likely pathogenic variant identified on tumor genomic testing that has clinical implications if also identified in the germline.
    - To aid in systemic therapy and surgical decision-making.
    - Individual who meets testing criteria for Li-Fraumeni syndrome, Cowden syndrome/PTEN hamartoma tumor syndrome, or Lynch syndrome.
    - Ashkenazi Jewish ancestry without additional risk factors.
    - A personal history of serous endometrial cancer.
    - A personal or family history of breast, ovarian, pancreatic, prostate, or colorectal cancers.

Polygenic risk scores, which are groups of single nucleotide polymorphism associated with a specific disorder or disease used to refine risks in those with hereditary cancer, should not be used to inform clinical management as their clinical value has not been established (National Comprehensive Cancer Network, 2024).

The American Society of Colon and Rectal Surgeons states a family history of polyposis is not required to pursue genetic testing, because the absence of a family history of polyposis or colorectal cancer does not exclude the diagnosis of a polyposis syndrome. The Society recommends testing for the known familial pathologic variant in at-risk family members of a polyposis patient with an identified pathogenic variant. Management of patients with a suspected adenomatous polyposis syndrome should include a thorough family history, referral to genetic counseling, and testing with a multigene panel (Poylin, 2024).

A joint guideline by the American College of Medical Genetics and Genomics and the National Society of Genetic Counselors presents a comprehensive list of referral indications for cancer predisposition assessment based on personal and family history criteria (Hampel, 2015). The purpose of the guideline is to facilitate identification and appropriate referral of at-risk individuals for cancer genetic consultation for a wide range of inherited cancers.

An American College of Medical Genetics and Genomics technical standard provides guidance on a multigene panel testing approach for hereditary colorectal cancer and polyposis. It identified 23 genes associated with hereditary colorectal cancer or polyposis recommended as the minimum list of genes for multigene panel testing (Mao, 2021).

For patients with breast cancer undergoing BRCA1/2 testing, the American Society of Clinical Oncology recommends testing for other cancer predisposition genes as suggested by personal or family history (Bedrosian, 2024). According to the Society, next-generation sequencing can facilitate identification of inherited cancer susceptibility in the course of somatic mutation profiling or through direct germline multigene panel testing. Concurrent multigene panel testing may be efficient for (Robson, 2015):

- Examining multiple high-penetrance genes of established clinical utility to discern possible explanations for a patient's personal or family history of cancer.
- Identifying gene variants associated with moderate or low cancer risks.
- Identifying variants in high-penetrance genes that would not have been evaluated on the basis of the presenting personal or family history need.

In 2021, we deleted several references. We modified the coverage based on information from updated National Comprehensive Cancer Network guidelines, as follows. We included statements that comprehensive genetic

testing should include full sequencing and testing for large genomic rearrangements, and should be performed in certified laboratories. Germline testing may also be indicated to confirm a pathogenic variant found on tumor (somatic) testing that has clinical implications if also identified in the germline. We added limitation statements for germline testing in minors, commercial entities that offer ancestry information, and circulating tumor DNA assays.

In 2022, current research investigated validates the present policy content.

In 2023, we deleted references to Centers for Medicare & Medicaid Services and updated the reference list. We added two guidelines to the policy (Mao, 2021; Robson, 2015). No policy changes are warranted.

In 2024, we deleted retired references, updated existing references, and added two guidelines to the policy. Coverage was modified to align with recent guideline changes from the National Comprehensive Cancer Network, the American Society of Colon and Rectal Surgeons, and the American Society of Clinical Oncology.

References

On May 1, 2024, we searched PubMed and the databases of the Cochrane Library, the U.K. National Health Services Centre for Reviews and Dissemination, the Agency for Healthcare Research and Quality, and the Centers for Medicare & Medicaid Services. Search terms were "Neoplastic Syndromes, Hereditary" [MAJR], "Genetic Predisposition to disease" (MeSH), "Genetic Testing" (MeSH), and "Neoplasms" (MeSH)." We included the best available evidence according to established evidence hierarchies (typically systematic reviews, meta-analyses, and full economic analyses, where available) and professional guidelines based on such evidence and clinical expertise.

American Cancer Society. Understanding genetic testing for cancer. https://www.cancer.org/cancer/cancer-causes/genetics/understanding-genetic-testing-for-cancer.html. Last revised October 24, 2023.

American Society of Clinical Oncology. The genetics of cancer. https://www.cancer.net/navigating-cancer-care/cancer-basics/genetics/genetics-cancer. Approved November 2022.

Bedrosian I, Somerfield MR, Achatz MI, et al. Germline testing in patients with breast cancer: ASCO-Society of Surgical Oncology guideline. *J Clin Oncol*. 2024;42(5):584-604. Doi: 10.1200/jco.23.02225.

Hampel H, Bennett RL, Buchanan A, Pearlman R, Wiesner GL. A practice guideline from the American College of Medical Genetics and Genomics and the National Society of Genetic Counselors: Referral indications for cancer predisposition assessment. *Genet Med.* 2015;17(1):70-87. Doi: 10.1038/gim.2014.147.

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National Cancer Institute. The genetics of cancer. https://www.cancer.gov/about-cancer/causes-prevention/genetics. Updated August 17, 2022.

National Comprehensive Cancer Network. Genetic/familial high-risk assessment: Breast, ovarian, and pancreatic. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). Version 3.2024. https://www.nccn.org. Published February 12, 2024.

National Comprehensive Cancer Network. Genetic/familial high-risk assessment: Colorectal. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). Version 2.2023. https://www.nccn.org. Published October 30, 2023.

Poylin VY, Shaffer VO, Felder SI, et al. The American Society of Colon and Rectal Surgeons clinical practice guidelines for the management of inherited adenomatous polyposis syndromes. *Dis Colon Rectum*. 2024;67(2):213-227. Doi: 10.1097/dcr.0000000000003072.

Robson ME, Bradbury AR, Arun B, et al. American Society of Clinical Oncology policy statement update: Genetic and genomic testing for cancer susceptibility. *J Clin Oncol*. 2015;33(31):3660-3667. Doi: 10.1200/jco.2015.63.0996.

Policy updates

5/2016: initial review date and clinical policy effective date: 7/2016

3/2017: Policy references updated.

2/2018: Policy references updated.

5/2019: Policy references updated. The policy ID changed.

3/2020: Policy references updated.

6/2021: Policy references updated. Coverage modified.

6/2022: Policy references updated.

6/2023: Policy references updated.

6/2024: Policy references update. Coverage modified.