BlueCross BlueShield Federal Employee Program.

FEP Medical Policy Manual

FEP 2.04.93 Genetic Cancer Susceptibility Panels Using Next Generation Sequencing

Annual Effective Policy Date: April 1, 2024

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Related Policies:

2.04.02 - Germline Genetic Testing for Hereditary Breast/Ovarian Cancer Syndrome and Other High-Risk Cancers (BRCA1, BRCA2, PALB2)
2.04.08 - Genetic Testing for Lynch Syndrome and Other Inherited Colon Cancer Syndromes
2.04.101 - Genetic Testing for Li-Fraumeni Syndrome
2.04.126 - Germline Genetic Testing for Gene Variants Associated With Breast Cancer in Individuals at High Breast Cancer Risk (CHEK2, ATM, and BARD1)
2.04.148 - Germline Genetic Testing for Pancreatic Cancer Susceptibility Genes
2.04.149 - Molecular Testing for Germline Variants Associated with Ovarian Cancer (BRIP1, RAD51C, RAD51D, NBN)
2.04.44 - Genetic Testing for Familial Cutaneous Malignant Melanoma
2.04.63 - Use of Common Genetic Variants (Single Nucleotide Variants) to Predict Risk of Nonfamilial Breast Cancer
2.04.88 - Genetic Testing for PTEN Hamartoma Tumor Syndrome
2.04.92 - General Approach to Evaluating the Utility of Genetic Panels

Genetic Cancer Susceptibility Panels Using Next Generation Sequencing

Description

Description

Commercially available cancer susceptibility gene panels can test for multiple variants associated with a specific type of cancer or can include variants associated with a wide variety of cancers. Some of these variants are associated with inherited cancer syndromes. The cancer type(s), as well as a cancer history involving multiple family members, increase the clinical concern for the presence of a heritable genetic variant. It has been proposed that variant testing using next-generation sequencing (NGS) technology to analyze multiple genes at one time (panel testing) can optimize genetic testing in these patients compared with sequencing single genes.

OBJECTIVE

The objective of this evidence review is to evaluate whether genetic testing with cancer susceptibility panels improves the net health outcome in individuals suspected of having an inherited cancer syndrome.

POLICY STATEMENT

General genetic cancer susceptibility panel testing is considered **investigational**; however, when the coverage criteria of other policies is met (see related policies), then limited genetic cancer susceptibility panels including only the gene variants for which a given member qualifies may be considered **medically necessary**.

POLICY GUIDELINES

Genetics Nomenclature Update

The Human Genome Variation Society nomenclature is used to report information on variants found in DNA and serves as an international standard in DNA diagnostics. It is being implemented for genetic testing medical evidence review updates starting in 2017 (see Table PG1). The Society's nomenclature is recommended by the Human Variome Project, the Human Genome Organization, and by the Human Genome Variation Society itself.

The American College of Medical Genetics and Genomics and the Association for Molecular Pathology standards and guidelines for interpretation of sequence variants represent expert opinion from both organizations, in addition to the College of American Pathologists. These recommendations primarily apply to genetic tests used in clinical laboratories, including genotyping, single genes, panels, exomes, and genomes. Table PG2 shows the recommended standard terminology - "pathogenic," "likely pathogenic," "uncertain significance," "likely benign," and "benign" - to describe variants identified that cause Mendelian disorders.

Table PG1. Nomenclature to Report on Variants Found in DNA

Previous	Updated	Definition
Mutation	Disease-associated variant	Disease-associated change in the DNA sequence
	Variant	Change in the DNA sequence
	Familial variant	Disease-associated variant identified in a proband for use in subsequent targeted genetic testing in first-degree relatives

Table PG2. ACMG-AMP Standards and Guidelines for Variant Classification

Variant Classification	Definition
Pathogenic	Disease-causing change in the DNA sequence
Likely pathogenic	Likely disease-causing change in the DNA sequence
Variant of uncertain significance	Change in DNA sequence with uncertain effects on disease
Likely benign	Likely benign change in the DNA sequence
Benign	Benign change in the DNA sequence

ACMG: American College of Medical Genetics and Genomics; AMP: Association for Molecular Pathology.

Genetic Counseling

Genetic counseling is primarily aimed at individuals who are at risk for inherited disorders, and experts recommend formal genetic counseling in most cases when genetic testing for an inherited condition is considered. The interpretation of the results of genetic tests and the understanding of risk factors can be very difficult and complex. Therefore, genetic counseling will assist individuals in understanding the possible benefits and harms of genetic testing, including the possible impact of the information on the individual's family. Genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing. Genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.

BENEFIT APPLICATION

Experimental or investigational procedures, treatments, drugs, or devices are not covered (See General Exclusion Section of brochure).

Screening (other than the preventive services listed in the brochure) is not covered. Please see Section 6 General exclusions.

Benefits are available for specialized diagnostic genetic testing when it is medically necessary to diagnose and/or manage a patient's existing medical condition. Benefits are not provided for genetic panels when some or all of the tests included in the panel are not covered, are experimental or investigational, or are not medically necessary.

FDA REGULATORY STATUS

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments (CLIA). Laboratories that offer laboratory-developed tests must be licensed by the CLIA for high-complexity testing. To date, the U.S. Food and Drug Administration has chosen not to require any regulatory review of these tests.

RATIONALE

Summary of Evidence

For individuals who have a personal and/or family history suggesting an inherited cancer syndrome who receive expanded gene panel testing, the evidence includes reports describing the diagnostic yield of expanded gene panels. Relevant outcomes are overall survival, disease-specific survival, and test validity. Studies of gene panel testing for genetic cancer risk assessment have reported primarily on the frequency with which variants are identified. The rates of variants of uncertain significance for gene panels are significant and increase in proportion with panel size, reaching nearly 50% for large gene panels. Variants included in these panels are associated with varying levels of risk of developing cancer. Published data on clinical utility are lacking, and it is unknown whether the use of these panels improves health outcomes. Only some variants included on panels are associated with a high risk of developing a well-defined cancer syndrome for which there are established clinical management guidelines. Many expanded panels include genetic variants considered to be of moderate or low penetrance, and clinical management recommendations for these genes are not well-defined. The lack of clinical management pathways for variants of uncertain clinical significance increases the potential for harm. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

SUPPLEMENTAL INFORMATION

Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in 'Supplemental Information" if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

American Society of Clinical Oncology

In 2015, the American Society of Clinical Oncology (ASCO) issued a policy statement on genetic and genomic testing for cancer susceptibility.[16,] The update addressed the application of next-generation sequencing (NGS) and confirmed that panel testing may also identify variants in genes associated with moderate or low cancer risks, variants in high-penetrance genes that would not have been evaluated based on the presenting personal or family history, and variants of uncertain significance in a substantial proportion of patient cases. Further, the statement indicated there is little consensus as to which genes should be included on panels for cancer susceptibility testing.

In 2020, ASCO published a guideline on germline and somatic tumor testing in epithelial ovarian cancer.[17,] Based on a systematic review of evidence and expert panel input, ASCO recommended that women with epithelial ovarian cancer should be offered germline testing for *BRCA1/2* and other specified ovarian susceptibility genes with a multi-gene panel. It was considered more practical to evaluate a minimum of the 10 genes that have been associated with inherited risk of ovarian cancer in a panel in comparison to testing *BRCA1 and BRCA2* alone.

National Comprehensive Cancer Network

Breast and Ovarian Cancers

National Comprehensive Cancer Network (NCCN) guidelines on genetic/familial high-risk assessment for breast, ovarian cancers, and/or pancreatic cancer (v.2.2022)[18,] include the following on multi-gene testing:

- "An individual's personal and/or family history may be explained by more than one inherited cancer syndrome; thus, phenotype-directed testing based on personal and family history through a tailored multi-gene panel test is often more efficient and cost-effective and increases the yield of detecting a pathogenic/likely pathogenic variant in a gene that will impact medical management for the individual or their at-risk family members.
- There may also be a role for multi-gene testing in individuals who have tested negative for a single syndrome, but whose personal or family history remains suggestive of an inherited susceptibility.
- Some individuals may carry a pathogenic/likely pathogenic germline variants in more than one cancer susceptibility gene..."

The NCCN defines a "tailored" multi-gene panel test as a "disease-focused multi-gene panel of clinically actionable cancer susceptibility genes, in contrast to large multi-gene panels of uncertain or unknown clinical relevance." The NCCN cautions that multi-gene panels may include moderate-risk genes that have limited data on the degree of cancer risk and no clear guidelines on risk management. As more genes are tested, the likelihood of finding variants of uncertain significance increases. Multi-gene panel testing also increases the likelihood of finding pathogenic/likely pathogenic variants without clear significance.

Colorectal Cancer

The NCCN guidelines on genetic/familial high-risk assessment for colorectal cancer (v.1.2022) state that "when more than one gene can explain an inherited cancer syndrome, multi-gene testing is more efficient than single-gene testing, or sequential single syndrome testing" and "there is also a role for multi-gene testing in individuals who have tested negative (indeterminate) for a single syndrome, but whose personal or family history remains strongly suggestive of an inherited susceptibility."[19,] However, the NCCN cautioned about the increased likelihood of finding variants of uncertain significance, which increases with the number of genes included in the panel, and that gene panels can include moderate-risk genes that may not be clinically actionable.

Collaborative Group of the Americas on Inherited Gastrointestinal Cancer

In 2020, the Collaborative Group of the Americas on Inherited Gastrointestinal Cancer published a position statement on multi-gene panel testing for patients with colorectal cancer and/or polyposis.[20,] Recommendations were based on the evidence, professional society recommendations endorsing testing of a given gene, and opinion of the expert panel. The group noted the variability in genes included in commercially available panels, and recommended that multi-gene panels include a minimum of 11 specific genes associated with defective mismatch repair (Lynch syndrome) and polyposis syndromes. Additional genes to be considered had low to moderately increased risk, had limited data of colorectal cancer risk, or causation for colorectal cancer was not proven.

U.S. Preventive Services Task Force Recommendations

The **U.S. Preventive Services Task Force (2019) has** recommended that primary care providers screen women with a personal or family history of breast, ovarian, tubal, or peritoneal cancer or who have an ancestry associated with *BRCA1/2* gene mutations with an appropriate brief familial risk assessment tool.[21,] Women with positive screening results should receive genetic counseling and if indicated after counseling, *BRCA* testing (grade B recommendation). The use of genetic cancer susceptibility panels was not specifically mentioned.

Medicare National Coverage

In January 2020, the Centers for Medicare and Medicaid Services (CMS) determined that NGS is covered for patients with breast or ovarian cancer when the diagnostic test is performed in a Clinical Laboratory Improvement Amendments (CLIA)-certified laboratory AND the test has approval or clearance by the U.S. Food and Drug Administration (CAG-00450R).

CMS states that local Medicare carriers may determine coverage of NGS for management of the patient for any cancer diagnosis with a clinical indication and risk factor for germline testing of hereditary cancers when performed in a CLIA-certified laboratory.

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POLICY HISTORY - THIS POLICY WAS APPROVED BY THE FEP® PHARMACY AND MEDICAL POLICY COMMITTEE ACCORDING TO THE HISTORY BELOW:

Date	Action	Description
December 2023	New policy - FEP	FEP Benefit change. New FEP Policy