

MEDICAL POLICY

POLICY TITLE	GENETIC CANCER SUSCEPTIBILITY PANELS USING NEXT GENERATION SEQUENCING
POLICY NUMBER	MP 2.325

CLINICAL BENEFIT	☐ MINIMIZE SAFETY RISK OR CONCERN. ☒ MINIMIZE HARMFUL OR INEFFECTIVE INTERVENTIONS. ☐ ASSURE APPROPRIATE LEVEL OF CARE. ☐ ASSURE APPROPRIATE DURATION OF SERVICE FOR INTERVENTIONS. ☐ ASSURE THAT RECOMMENDED MEDICAL PREREQUISITES HAVE BEEN MET. ☐ ASSURE APPROPRIATE SITE OF TREATMENT OR SERVICE.
Effective Date:	RETIRED 7/1/2026

POLICY

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 PG 1). 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
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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 patients 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.

Cross-References:

MP 2.211 Genetic Testing for BRCA1 or BRCA2 for Hereditary Breast/Ovarian Cancer Syndrome and Other High-Risk Cancers
MP 2.246 Genetic Testing for Familial Cutaneous Malignant Melanoma
MP 2.255 Genetic Testing for PTEN Hamartoma Tumor Syndrome
MP 2.274 Genetic Testing for Li-Fraumeni Syndrome
MP 2.275 Molecular Markers in Fine Needle Aspirates of the Thyroid
MP 2.323 General Approach to Evaluating the Utility of Genetic Panels
MP 2.384 Germline Genetic Testing for Hereditary Diffuse Gastric Cancer (CHD1, CTNNA1)
MP 5.013 Genetic Testing for Lynch Syndrome and Other Inherited Colon Cancer Syndromes

PRODUCT VARIATIONS

This policy is only applicable to certain programs and products administered by Capital Blue Cross and subject to benefit variations. Please see additional information below.

FEP PPO - Refer to FEP Medical Policy Manual. The FEP Medical Policy manual can be found at: <https://www.fepblue.org/benefit-plans/medical-policies-and-utilization-management-guidelines/medical-policies>

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DESCRIPTION/BACKGROUND

GENETIC TESTING FOR CANCER SUSCEPTIBILITY

Genetic testing for cancer susceptibility may be approached by a focused method that involves testing for well-characterized variants based on a clinical suspicion of which gene(s) may be the cause of the heritable or familial cancer. Panel testing involves evaluating for multiple variants in multiple genes at one time.

Multiple commercial companies and medical center laboratories offer genetic testing panels that use next-generation sequencing (NGS) methods for hereditary cancers. NGS is one of several methods that use massively parallel platforms to allow the sequencing of large stretches of DNA. Panel testing is potentially associated with greater efficiencies in the evaluation of genetic diseases; however, it may provide information on genetic variants of uncertain clinical significance or findings that would not lead to changes in patient management.

HEREDITARY CANCER AND CANCER SYNDROMES

The NCCN does speak to multigene panel testing (MGPT) for several cancers:

Colorectal cancer: “Germline MGPT should include at minimum the following CRC risk-associated genes: APC, MUTYH, MLH1, MSH2, MSH6, PMS2, EPCAM, BMPR1A, SMAD4, PTEN, STK11, and TP53”

Prostate cancer: “If criteria are met, germline multigene testing that includes at least BRCA1, BRCA2, ATM, PALB2, CHEK2, HOXB13, MLH1, MSH2, MSH6, and PMS2 is recommended.”

Genetic testing for breast and ovarian cancer syndromes, single nucleotide variants related to breast cancer, and hereditary breast cancer are evaluated in evidence reviews in **MP 2.211**, and **2.249**.

Genetic testing for Li-Fraumeni syndrome is evaluated in evidence review in **MP 2.274**.

Cowden Syndrome (CS) is a part of *PTEN* hamartoma tumor syndrome (PHTS) and is the only PHTS disorder associated with a documented predisposition to malignancies. Genetic testing for CS is evaluated in evidence review **MP 2.255**.

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. Laboratories that offer laboratory-developed tests must be licensed by the Clinical Laboratory Improvement Amendments for high-complexity testing. To date, the U.S. Food and Drug Administration has chosen not to require any regulatory review of these tests.

Genes Included in NGS Panels

The following summarizes the function and disease association of major genes included in NGS panels. The list is alphabetized by gene, but some are grouped with other genes related to condition. This summary is not comprehensive.

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APC Variants are associated with familial adenomatous polyposis (FAP) and attenuated FAP. FAP is an autosomal dominant colon cancer predisposition syndrome characterized by hundreds to thousands of colorectal adenomatous polyps and accounts for about 1% of all colorectal cancers (CRCs).

ATM Variants are associated with the autosomal recessive condition ataxia-telangiectasia. This condition is characterized by progressive cerebellar ataxia with onset between the ages of 1 and 4 years, telangiectasias of the conjunctivae, oculomotor apraxia, immune defects, and cancer predisposition, particularly leukemia and lymphoma.

AXIN2 Variants are associated with FAP syndrome, although the phenotypes associated with AXIN2 variants do not appear to be well-characterized.

BARD1, BRIP1, MRE11A, NBN, RAD50, and RAD51C Variants are genes in the Fanconi anemia/BRCA pathway. Variants in these genes are estimated to confer up to a 4-fold increase in the risk for breast cancer. This pathway is also associated with a higher risk of ovarian cancer and, less often, pancreatic cancer.

BRCA1 and BRCA2 Variants are associated with hereditary breast and ovarian cancer syndrome, which is associated most strongly with increased susceptibility to breast cancer at an early age, bilateral breast cancer, male breast cancer, ovarian cancer, cancer of the fallopian tube, and primary peritoneal cancer. **BRCA1** and **BRCA2** variants are also associated with increased risk of other cancers, including prostate cancer, pancreatic cancer, gastrointestinal cancers, melanoma, and laryngeal cancer.

BMPR1A and SMAD4 Variants are genes that mutate in juvenile polyposis syndrome and account for 45% to 60% of cases of juvenile polyposis syndrome. Juvenile polyposis syndrome is an autosomal dominant disorder that predisposes to the development of polyps in the gastrointestinal tract. Malignant transformation can occur, and the risk of gastrointestinal cancer has been estimated from 9% to 50%.

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CHEK2 Variants confer an increased risk of developing several different types of cancer, including breast, prostate, colon, thyroid, and kidney. *CHEK2* regulates the function of the BRCA1 protein in DNA repair and has been associated with familial breast cancers.

CDH1 Variants are associated with lobular breast cancer in women and with hereditary diffuse gastric cancer (DGC). The estimated cumulative risk of gastric cancer for *CDH1* variant carriers by age 80 years is 70% for men and 56% for women. *CDH1* variants are associated with a lifetime risk of 39% to 52% of lobular breast cancer.

CDK4 Variants Cyclin-dependent kinase-4 (CDK4) is a protein-serine kinase involved in cell cycle regulation. Variants in this gene are associated with a variety of cancers, particularly cutaneous melanoma.

CDKN2A Variants Cyclin-dependent kinase inhibitor 2A (*CDKN2A*) encodes proteins that act as multiple tumor suppressors through their involvement in 2 cell cycle regulatory pathways: the p53 pathway and the RB1 pathway. Variants or deletions in *CDKN2A* are frequently found in multiple types of tumor cells. Germline variants in *CDKN2A* have been associated with risk of melanoma, along with pancreatic and central nervous system cancers.

EPCAM, MLH1, MSH2, MSH6, and PMS2 Variants are mismatch repair genes associated with Lynch syndrome (hereditary nonpolyposis CRC). Lynch syndrome is estimated to cause 2% to 5% of all colon cancers. Lynch syndrome is associated with a significantly increased risk of several types of cancer—colon cancer (60%-80% lifetime risk), uterine/endometrial cancer (20%-60% lifetime risk), gastric cancer (11%-19% lifetime risk), and ovarian cancer (4%-13% lifetime risk). The risks of other types of cancer, including small intestine, hepatobiliary tract, upper urinary tract, and brain, are also elevated.

FANCC Variants Fanconi anemia complementation group C (*FANCC*) is one of several DNA repair genes that mutate in Fanconi anemia, which is characterized by bone marrow failure and a high predisposition to multiple types of cancer.

FH Variants Fumarate hydratase (*FH*) variants are associated with renal cell and uterine cancers.

FLCN Variants Folliculin (*FLCN*) acts as a tumor suppressor gene; variants in this gene are associated with the autosomal dominant Birt-Hogg-Dube syndrome, which is characterized by hair follicle hamartomas, kidney tumors, and CRC.

MET Variants are proto-oncogenes that acts as the hepatocyte growth factor receptor. *MET* variants are associated with hepatocellular carcinoma and papillary renal cell carcinoma.

MITF Variants Microphthalmia-associated transcription factor (*MITF*) is a transcription factor involved in melanocyte differentiation. *MITF* variants lead to several auditory-pigmentary syndromes, including Waardenburg syndrome type 2 and Tietze syndrome. *MITF* variants are also associated with melanoma and renal cell carcinoma.

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MUTYH Variants are associated with an autosomal recessive form of hereditary polyposis. It has been reported that 33% and 57% of patients with clinical FAP and attenuated FAP, respectively, who are negative for variants in the *APC* gene, have *MUTYH* variants.

PALB2 Variants are associated with an increased risk of pancreatic and breast cancer. Familial pancreatic and/or breast cancer due to *PALB2* variants is inherited in an autosomal dominant pattern.

NF1 Variants Neurofibromin 1 (NF1) encodes a negative regulator in the *ras* signal transduction pathway. Variants in the *NF1* gene have been associated with neurofibromatosis type 1, juvenile myelomonocytic leukemia, and Watson syndrome.

PTEN Variants are associated with *PTEN* hamartoma tumor syndrome (PHTS), which includes Cowden syndrome (CS), Bannayan-Riley-Ruvalcaba syndrome, and Proteus syndrome. CS is characterized by a high risk of developing tumors of the thyroid, breast, and endometrium. Affected persons have a lifetime risk of up to 50% for breast cancer, 10% for thyroid cancer, and 5% to 10% for endometrial cancer.

RAD51D Variants are associated with familial breast and ovarian cancers.

RET Variants encode a receptor tyrosine kinase; variants in this gene are associated with multiple endocrine neoplasia syndromes (types IIA and IIB) and medullary thyroid carcinoma.

SDHA, SDHB, SDHC, SDHD, and SDHAF2 Variants These gene products are involved in the assembly and function of 1 component of the mitochondrial respiratory chain. Germline variants in these genes are associated with the development of paragangliomas, pheochromocytomas, gastrointestinal stromal tumors, and a *PTEN*-negative Cowden-like syndrome.

STK11 Variants are associated with Peutz-Jeghers syndrome, an autosomal dominant disorder, with a 57% to 81% risk of developing cancer by age 70, of which gastrointestinal and breast cancers are the most common.

TP53 Variants are associated with Li-Fraumeni syndrome. People with *TP53* variants have a 50% risk of developing any of the associated cancers by age 30 and a lifetime risk up to 90%, including sarcomas, breast cancer, brain tumors, and adrenal gland cancers.

TMEM127 Variants Transmembrane protein 127 (*TMEM127*) germline variants are associated with risk of pheochromocytomas.

TSC1 Variants Tuberous sclerosis 1 (*TSC1*) and tuberous sclerosis 2 (*TSC2*) encode the proteins hamartin and tuberin, which are involved in cell growth, differentiation, and proliferation. Variants in these genes are associated with the development of tuberous sclerosis complex, an autosomal dominant syndrome characterized by skin abnormalities, developmental delay, seizures, and multiple types of cancers, including central nervous system tumors, renal tumors (including angiomyolipomas, renal cell carcinomas), and cardiac rhabdomyomas

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VHL Variants VHL germline variants are associated with Hippel-Lindau syndrome, an autosomal dominant familial cancer syndrome. This syndrome is associated with various malignant and benign tumors, including central nervous system tumors, renal cancers, pheochromocytomas, and pancreatic neuroendocrine tumors.

XRCC2 Variants encode proteins thought to be related to the RAD51 protein product that is involved in DNA double-stranded breaks. Variants may be associated with Fanconi anemia and breast cancer.

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.

DEFINITIONS

NA

DISCLAIMER

Capital Blue Cross' medical policies are used to determine coverage for specific medical technologies, procedures, equipment, and services. These medical policies do not constitute medical advice and are subject to change as required by law or applicable clinical evidence from independent treatment guidelines. Treating providers are solely responsible for medical advice and treatment of members. These policies are not a guarantee of coverage or payment. Payment of claims is subject to a determination regarding the member's benefit program and eligibility on the date of service, and a determination that the services are medically necessary and appropriate. Final processing of a claim is based upon the terms of contract that applies to the members' benefit program, including benefit limitations and

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exclusions. If a provider or a member has a question concerning this medical policy, please contact Capital Blue Cross' Provider Services or Member Services.

CODING INFORMATION

Note: This list of codes may not be all-inclusive, and codes are subject to change at any time. The identification of a code in this section does not denote coverage as coverage is determined by terms of member benefit information. In addition, not all covered services are eligible for separate reimbursement.

Genetic cancer susceptibility panels using next generation sequencing are considered investigational:

	Procedure Codes								
0048U	0101U	0102U	0103U	0129U	0130U	0133U	0134U	0329U	0379U
0475U	81437	81445	81449	81450	81451	81455	81456		

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I. POLICY HISTORY

[TOP](#)

MP 2.235	09/02/2020 Consensus Review. No change to policy statement. References updated. Coding reviewed, removed code 81308 and 0136U.
	01/01/2020 Administrative Update. Added new codes 81351-81353.
	11/17/2021 Minor Review. Update to criteria, updated cross references, coding, background, rationale, and coding. Removed codes 81351-81353 as these are on MP 2.274.
	06/10/2022 Administrative Update. Added new code 0329U effective 07/01/2022
	11/23/2022 Consensus Review. No change to policy statement. References updated. Coding reviewed.
	12/01/2022 Administrative Update. Added new codes 81449, 81451 & 81456; effective 01/01/2023
	03/16/2023 Administrative Update. Added new code 0379U; effective 04/01/2023.
	12/01/2023 Minor Review. Statement now reads “when the coverage criteria of other policies is met (see related policies), then genetic cancer susceptibility panels may be considered medically necessary .”. Removed code 0022U, 81432, 81433, 81435, 81436. Reformatted list of genes in policy guidelines. Updated background and references.
	06/11/2024 Administrative Update. New code 0475U, effective 07/01/2024.
	09/20/2024 Consensus Review. Removed 0129U, minor formatting changes. Updated references.
	12/11/2024 Administrative Update. Removed code 81438. Effective

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	01/01/2025.
	07/17/2025 Administrative Update. Added code 0129U, as code applicable to indications addressed in this policy.
	08/07/2025 Consensus Review. minor formatting changes.
	09/23/2025 Administrative Update. Removed Benefit Variations Section and updated Disclaimer.
	12/04/2025 Administrative Update. Removed codes 0131U, 0132U & 0135U as they have been deleted effective 01/01/2026.
	03/09/2026 Retirement Review. Services managed by EviCore.

Health care benefit programs issued or administered by Capital BlueCross and/or its subsidiaries, Capital Advantage Insurance Company®, Capital Advantage Assurance Company® and Keystone Health Plan® Central. Independent licensees of the BlueCross BlueShield Association. Communications issued by Capital BlueCross in its capacity as administrator of programs and provider relations for all companies.