

MEDICAL POLICY

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

Effective Date:	5/1/2023
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I. 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**.

The National Comprehensive Cancer Network (NCCN) is a nonprofit alliance of cancer centers throughout the United States. NCCN develops the Clinical Practice Guidelines in Oncology which are recommendations aimed to help health care professionals diagnose, treat and manage patients with cancer. Guidelines evolve continuously as new treatments and diagnostics emerge and may be used by Capital BlueCross when determining medical necessity according to this policy.

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

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		in subsequent targeted genetic testing in first-degree relatives
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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 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 2.249** Use of Common Genetic Variants (Single Nucleotide Polymorphisms) to Predict Risk of Non-Familial Breast Cancer
- MP 2.255** Genetic Testing for PTEN Hamartoma Tumor Syndrome
- MP 2.274** Genetic Testing for Li-Fraumeni Syndrome
- MP 2.323** General Approach to Evaluating the Utility of Genetic Panels
- MP 2.377** Molecular Testing for Variants Associated with Hereditary Ovarian Cancer
- MP 5.013** Genetic Testing for Lynch Syndrome and Other Inherited Colon Cancer Syndromes

II. PRODUCT VARIATIONS

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This policy is only applicable to certain programs and products administered by Capital BlueCross please see additional information below, and subject to benefit variations as discussed in Section VI below.

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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>.

III. DESCRIPTION/BACKGROUND

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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.

Genes Included in NGS Panels

The following summarizes the function and disease association of major genes included in NGS panels. This summary is not comprehensive.

BRCA1 and BRCA2 Variants

BRCA1 and *BRCA2* germline 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.

APC Variants

APC germline 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

ATM is 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.

BARD1, BRIP1, MRE11A, NBN, RAD50, and RAD51C Variants

BARD1, BRIP1, MRE11A, NBN, RAD50, and RAD51C 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

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breast cancer. This pathway is also associated with a higher risk of ovarian cancer and, less often, pancreatic cancer.

BMPR1A and SMAD4 Variants

BMPR1A and *SMAD4* are genes 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%.

CHEK2 Variants

CHEK2 gene 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

CDH1 germline 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.

EPCAM, MLH1, MSH2, MSH6, and PMS2 Variants

EPCAM, *MLH1*, *MSH2*, *MSH6*, and *PMS2* 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.

MUTYH Variants

MUTYH germline 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

PALB2 germline 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.

PTEN Variants

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.

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Affected persons have a lifetime risk of up to 50% for breast cancer, 10% for thyroid cancer, and 5% to 10% for endometrial cancer.

STK11 Variants

STK11 germline 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

TP53 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.

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.

RAD51D Variants

RAD51D germline variants are associated with familial breast and ovarian cancers.

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.

RET Variants

RET encodes 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

SDHA, *SDHB*, *SDHC*, *SDHD*, and *SDHAF2* 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.

TMEM127 Variants

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

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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.

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

MET is a proto-oncogene 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.

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.

XRCC2 Variants

XRCC2 encodes 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.

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

AXIN2 Variants

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

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Hereditary Cancer and Cancer Syndromes

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 MPs 2.211, 2.249 and 2.279.

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

CS is a part of 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.

IV. RATIONALE

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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.

V. DEFINITIONS

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NA

VI. BENEFIT VARIATIONS

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The existence of this medical policy does not mean that this service is a covered benefit under the member's health benefit plan. Benefit determinations should be based in all cases on the

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applicable health benefit plan language. Medical policies do not constitute a description of benefits. A member's health benefit plan governs which services are covered, which are excluded, which are subject to benefit limits and which require preauthorization. There are different benefit plan designs in each product administered by Capital BlueCross. Members and providers should consult the member's health benefit plan for information or contact Capital BlueCross for benefit information.

VII. DISCLAIMER

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Capital BlueCross's medical policies are developed to assist in administering a member's benefits, do not constitute medical advice and are subject to change. Treating providers are solely responsible for medical advice and treatment of members. Members should discuss any medical policy related to their coverage or condition with their provider and consult their benefit information to determine if the service is covered. If there is a discrepancy between this medical policy and a member's benefit information, the benefit information will govern. If a provider or a member has a question concerning the application of this medical policy to a specific member's plan of benefits, please contact Capital BlueCross' Provider Services or Member Services.

Capital BlueCross considers the information contained in this medical policy to be proprietary and it may only be disseminated as permitted by law.

VIII. CODING INFORMATION

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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								
0022U	0048U	0101U	0102U	0103U	0129U	0130U	0131U	0132U
0133U	0134U	0135U	0329U	0379U	81432	81433	81435	81436
81437	81438	81445	81449	81450	81451	81455	81456	

IX. REFERENCES

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MP 2.235	9/2/20 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.
	6/10/2022 Admin update. Added new code 0329U effective 7/1/2022
	11/23/2022 Consensus Review. No change to policy statement. References updated. Coding reviewed.
	12/1/2022 Administrative update. Added new codes 81449, 81451 & 81456 effective 1/1/23
	3/16/2023 Administrative update. Added new code 0379U; effective 4-1-23.

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