Genetic Cancer Susceptibility Panels Using Next-Generation Sequencing

Policy # 00382
Original Effective Date: 09/18/2013
Current Effective Date: 01/11/2021

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc.(collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

Note: Genetic Testing for Hereditary Breast and or Ovarian Cancer is addressed separately in medical policy 00047.

Note: Genetic Testing for Lynch Syndrome and Other Inherited Colon is addressed separately in medical policy 00190.

Note: Genetic Testing for Li-Fraumeni Syndrome is addressed separately in medical policy 00424.

Note: Moderate Penetrance Variants Associated With Breast Cancer in Individuals at High Breast Cancer Risk is addressed separately in medical policy 00504.

Note: Use of Common Genetic Variants (single nucleotide polymorphisms) to Predict Risk of Nonfamilial Breast Cancer is addressed separately in medical policy 00268.

Note: Genetic Testing for PTEN Hamartoma Tumor Syndrome is addressed separately in medical policy 00417.

Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers genetic cancer susceptibility panel testing to be **investigational.***

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Policy Guidelines

Although genetic cancer susceptibility panel testing is considered investigational, there may be individual components of the panel that are medically necessary.

Genetic Counseling

Experts recommend formal genetic counseling for patients who are at risk for inherited disorders and who wish to undergo genetic testing. Interpreting the results of genetic tests and understanding risk factors can be difficult for some patients; genetic counseling helps individuals understand the impact of genetic testing, including the possible effects the test results could have on the individual or their family members. It should be noted that genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing; further, genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.

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. 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.

Background/Overview

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 clinical suspicion of which gene(s) may be the cause of the heritable or familial cancer. Panel testing involves evaluating 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. Currently available panels do not include all genes associated with hereditary cancer syndromes. Also, these panels may not test for variants (ie, single nucleotide variants), which may be associated with a low, but increased cancer risk.

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 *BCRA2* 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 one and four 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 four-fold increase in the risk of 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 the 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 are 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. 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 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 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 the 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 one 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 the risk of pheochromocytomas.

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 variants are associated with renal cell and uterine cancers.

FLCN Variants
Folliculin 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 and tuberous sclerosis 2 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 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.

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 separate evidence reviews.

CS is a part of PHTS and is the only PHTS disorder associated with a documented predisposition to malignancies.

Hereditary Diffuse Gastric Cancer
Hereditary DGC is an autosomal dominant trait. Up to 50% of familial cases may be caused by variants in the *CDH1* gene. In kindred families with *CDH1*-positive hereditary DGC, the risk of developing DGC is as high as 80% by 80 years of age. Other candidate genes include *CTNNA1*, *BRCA2*, *STK11*, *SDHB*, *PRSS1*, *ATM*, *MSR1*, and *PALB2*. Guidelines from the International Gastric Cancer Linkage Consortium have proposed genetic testing in families with 2 or more patients with gastric cancer at any age, in individuals with DGC before the age of 40, or in families with diagnoses of both DGC and invasive lobular cancer. Because of the high lifetime risk, prophylactic total gastrectomy between the ages of 20 and 30 is usually advised.

Hereditary Colon Cancer Syndromes
Genetic testing for hereditary colon cancer syndromes are addressed in a related policy. Hereditary colon cancer syndromes are thought to account for approximately 10% of all CRCs. Another 20% have a familial predilection for CRC without a clear hereditary syndrome identified. The hereditary CRC syndromes can be divided into the polyposis and nonpolyposis syndromes. Although there may be polyps in the nonpolyposis syndromes, they are usually less numerous; the presence of ten colonic polyps is used as a rough threshold when considering genetic testing for a polyposis syndrome. The polyposis syndromes can be further subdivided by polyp histology, which includes the adenomatous (FAP, attenuated FAP, *MUTYH*-associated) and hamartomatous (juvenile polyposis syndrome, Peutz-Jeghers syndrome, PHTS) polyposis syndromes. The nonpolyposis syndromes include Lynch syndrome.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)
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. FDA has chosen not to require any regulatory review of these tests.

Rationale/Source

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 technology to analyze multiple genes at one time (panel testing) can optimize genetic testing in these patients compared with sequencing single genes.

For individuals who have a personal and/or family history suggesting an inherited cancer syndrome who receive next-generation sequencing panel testing, the evidence includes reports describing the frequency of detecting variants in patients referred for panel testing. The relevant outcomes are overall survival, disease-specific survival, and test validity. The accuracy of next-

generation sequencing may be reduced in complex genomic regions, and the interpretation of the significance of the variant (ie, pathogenic, benign, or variants of uncertain significance) can differ between laboratories. Clinical validity studies have reported on the results of 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. Published data on clinical utility is lacking, and it is unknown whether the use of these panels improves health outcomes. Variants included in these panels are associated with varying levels of risk of developing cancer. 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 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 significance increases the potential for harm. The evidence is insufficient to determine the effects of the technology on health outcomes.

Supplemental Information

Practice Guidelines and Position Statements

American Society of Clinical Oncology

The American Society of Clinical Oncology (2015) issued a policy statement on genetic and genomic testing for cancer susceptibility. The update addressed the application of next-generation sequencing 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 as 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.

National Comprehensive Cancer Network

National Comprehensive Cancer Network guidelines on genetic/familial high-risk assessment for breast and ovarian cancers (v.3.2019) state the following on multigene testing:

- "Patients who have a personal or family history suggestive of a single inherited cancer syndrome are most appropriately managed by genetic testing for that specific syndrome. When more than one gene can explain an inherited cancer syndrome, then multi-gene testing may be more efficient and/or cost-effective.

- There may be a role for multi-gene testing in individuals who have tested negative (indeterminate) for a single syndrome, but whose personal or family history remains suggestive of an inherited susceptibility.
- As commercially available tests differ in the specific genes analyzed (as well as classification of variants and many other factors), choosing the specific laboratory and test panel is important.
- Multi-gene testing can include "intermediate" penetrant (moderate-risk) genes. For many of these genes, there are limited data on the degree of cancer risk and there are no clear guidelines on risk management for carriers of mutations. Not all genes included on available multi-gene test are necessarily clinically actionable.
- As is the case with high-risk genes, it is possible that the risks associated with moderate-risk genes may not be entirely due to that gene alone, but may be influenced by gene/gene or gene/environment interactions…. Therefore, it may be difficult to use a known mutation alone to assign risk for relatives.
- In many cases, the information from testing for moderate penetrance genes does not change risk management compared with that based on family history alone…."
- There is an increased likelihood of finding variants of unknown significance when testing for pathogenic/likely pathogenic variants in multiple genes.
- It is for these and other reasons that multigene testing is ideally offered in the context of professional genetic expertise for pre- and post-test counseling."

National Comprehensive Cancer Network guidelines on genetic/familial high-risk assessment for colorectal cancer (v.2.2019) state that "when more than one gene can explain an inherited cancer syndrome, then multi-gene testing may be more efficient and/or cost-effective than single-gene 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." However, the Network 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.

U.S. Preventive Services Task Force Recommendations

The U.S. Preventive Services Task Force (2015) has recommended that primary care providers screen women who have family members with breast, ovarian, tubal, or peritoneal cancer with one

of several screening tools designed to identify a family history that may be associated with an increased risk for potentially harmful variants in breast cancer and susceptibility genes (*BRCA1* or *BRCA2*). 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
There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

Ongoing and Unpublished Clinical Trials
Some currently ongoing and unpublished trials that might influence this review are listed in Table 1.

Table 1. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT03688204	Clinical Implementation of a Polygenic Risk Score (PRS) for Breast Cancer: Impact on Risk Estimates, Management Recommendations, Clinical Outcomes, and Patient Perception	2,000	Sep 2025
Unpublished			

NCT01850654	Ohio Colorectal Cancer Prevention Initiative: Universal Screening for Lynch Syndrome	3470	Jun 2018

NCT: national clinical trial.

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Policy History

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09/05/2013	Medical Policy Committee review
09/18/2013	Medical Policy Implementation Committee approval. New policy.
09/04/2014	Medical Policy Committee review
09/17/2014	Medical Policy Implementation Committee approval. No change to coverage.
01/01/2015	Coding Update
09/03/2015	Medical Policy Committee review
09/23/2015	Medical Policy Implementation Committee approval. No change to coverage.
09/08/2016	Medical Policy Committee review
09/21/2016	Medical Policy Implementation Committee approval. No change to coverage.
01/01/2017	Coding update: Removing ICD-9 Diagnosis Codes
12/07/2017	Medical Policy Committee review
12/20/2017	Medical Policy Implementation Committee approval. No change to coverage.
12/06/2018	Medical Policy Committee review
12/19/2018	Medical Policy Implementation Committee approval. No change to coverage. Added policy guidelines.
06/17/2019	Coding update
12/05/2019	Medical Policy Committee review
12/11/2019	Medical Policy Implementation Committee approval. No change to coverage. Coding update
12/03/2020	Medical Policy Committee review
12/09/2020	Medical Policy Implementation Committee approval. No change to coverage.

Next Scheduled Review Date: 12/2021

Coding

The five character codes included in the Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®)‡, copyright 2019

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Codes used to identify services associated with this policy may include (but may not be limited to) the following:

Code Type	Code
CPT	0012M, 0048U, 0049U, 0131U, 0132U, 0133U, 0134U, 0135U, 81162, 81163, 81164, 81165, 81166, 81167, 81201, 81202, 81203, 81206, 81207, 81208, 81210, 81212, 81215, 81216, 81217, 81235, 81270, 81275. 81276, 81287, 81292, 81293, 81294, 81295, 81296, 81297, 81298, 81299, 81300, 81317, 81318, 81319, 81321, 81322, 81323, 81345, 81432, 81433, 81437, 81438, 81443, 81455, 81479 Code added eff date 1/1/2020: 81309
HCPCS	No codes
ICD-10 Diagnosis	All related diagnoses

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
    1. Consultation with the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated technology evaluation center(s);
    2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
    3. Reference to federal regulations.

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NOTICE: If the Patient's health insurance contract contains language that differs from the BCBSLA Medical Policy definition noted above, the definition in the health insurance contract will be relied upon for specific coverage determinations.

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