MEDICAL POLICY

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

Original Issue Date (Created):	**8/1/2014**
Most Recent Review Date (Revised):	**11/6/2019**
Effective Date:	**1/1/2020**

I. POLICY

Genetic cancer susceptibility panels using next generation sequencing are considered **investigational**. There is insufficient evidence to support a conclusion concerning the health outcomes or benefits associated with this procedure.

Note: This policy does not address focused testing for individual cancers.

Policy Guidelines

Although genetic cancer susceptibility panels using next generation sequencing are considered investigational, there may be individual components of the panel that are medically necessary.

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.

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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

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

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.

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-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 and subject to benefit variations as discussed in Section VI. Please see additional information below.

FEP PPO - The FEP program dictates that all drugs, devices or biological products approved by the U.S. Food and Drug Administration (FDA) may not be considered investigational. Therefore, FDA-approved drugs, devices or biological products may be assessed on the basis of medical necessity.

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. Currently available panels do not include all genes associated with hereditary cancer syndromes. Also, these panels may not test for variants (i.e., 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 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 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. 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.

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.

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 2.04.02, 2.04.63, and 2.04.126, respectively.

Genetic testing for Li-Fraumeni syndrome is evaluated in evidence review 2.04.101.

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 2.04.88.

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 (see evidence review 2.04.08). 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.[1] 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 10 colonic polyps is used as a rough threshold when considering genetic testing for a polyposis syndrome.[2] 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.

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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 NGS panel testing, the evidence includes reports describing the frequency of detecting variants in patients referred for panel testing. Relevant outcomes are overall survival, disease-specific survival, and test validity. The accuracy of NGS may be reduced in complex genomic regions, and the interpretation of the significance of the variant (i.e., 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.

V. DEFINITIONS

TOP

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

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 the 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:

CPT Codes®								
0022U	0048U	0101U	0102U	0103U	0129U	0130U	0131U	0132U
0133U	0134U	0135U	0136U	81308	81432	81433	81435	81436
81437	81438	81445	81450	81455				

IX. REFERENCES

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X. POLICY HISTORY

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MP 2.235	**CAC 3/25/14** New policy. Adopting BCBSA. Previously silent now investigational.
	CAC 11/25/14 Minor review. Added policy guidelines and information on other panels including PancNext. No change to policy statement. References and rationale updated. No coding changes.
	CAC 11/24/15 Consensus. No change to policy statements. Added Medicare variation to reference LCD L35396 Biomarkers for Oncology. References and rationale updated. Coding reviewed.
	CAC 11/29/16 Consensus review. No changes to policy statements. References and rational updated. Coding reviewed. Variation reformatting.
	10/1/17 Administrative Update: Added new code 0022U with effective date 10/1/17.

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	CAC 12/19/17 Consensus. No change to policy statements. References and rationale updated.
	CAC 1/30/2018 Consensus review. No change to policy statements.
	Admin Update 7/1/2018: Added new code 0048U; effective date 7/1/2018. Rationale to include only the Summary of Evidence.
	11/28/18 Consensus review. No change to policy statements. Background, references and rationale summary updated. **3/19/19** Code review. No changes.
	Admin Update 7/1/2019: Added new codes 0101U- 0104U, effective 7/1/19
	10/1/19 Coding Update: Added new codes 0129U-0136U effective 10/1/19. Deleted coded 0104U removed. Also added codes 81432, 81433, 81435, 81436, 81437, 81438 for consistency with policy statements.
	11/6/19 Consensus review. No change to policy statements. References updated. Coding reviewed. 2020 Coding update: Added new code 81308. Effective 1/1/2020.

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