

(20493)

<b>Medical Benefit</b>		<b>Effective Date:</b> 01/01/18	<b>Next Review Date:</b> 09/19
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***This protocol considers this test or procedure investigational. If the physician feels this service is medically necessary, preauthorization is recommended.***

*The following protocol contains medical necessity criteria that apply for this service. The criteria are also applicable to services provided in the local Medicare Advantage operating area for those members, unless separate Medicare Advantage criteria are indicated. If the criteria are not met, reimbursement will be denied and the patient cannot be billed. Please note that payment for covered services is subject to eligibility and the limitations noted in the patient's contract at the time the services are rendered.*

Populations	Interventions	Comparators	Outcomes
Individuals: <ul style="list-style-type: none"> <li>• With a personal and/or family history suggesting an inherited cancer syndrome</li> </ul>	Interventions of interest are: <ul style="list-style-type: none"> <li>• Next-generation sequencing panel testing</li> </ul>	Comparators of interest are: <ul style="list-style-type: none"> <li>• Individual variant testing</li> </ul>	Relevant outcomes include: <ul style="list-style-type: none"> <li>• Overall survival</li> <li>• Disease-specific survival</li> <li>• Test validity</li> </ul>

### DESCRIPTION

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

### 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 sequencing 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.

## POLICY

Genetic cancer susceptibility panel testing using next generation sequencing is considered **investigational**.

## POLICY GUIDELINES

Although genetic cancer susceptibility panel testing using NGS is 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 protocol review updates starting in 2017 (see Table PG1). The Society's nomenclature is recommended by the Human Variome Project, the HUman Genome Organization, and by the Human Genome Variation Society itself.

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

Table PG1. Nomenclature to Report on Variants Found in DNA

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

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

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

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

## GENETIC COUNSELING

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.

## MEDICARE ADVANTAGE

For Medicare Advantage genetic cancer susceptibility panels using next generation sequencing are unlikely to impact therapeutic decision-making in the clinical management of the patient and are considered **not medically necessary**.

**Note:** For information on the use of genomic sequential analysis panels as they relate to non-small-cell-lung cancer under Medicare Advantage, please see the Molecular Analysis for Targeted Therapy of Non-Small-Cell-Lung Cancer Protocol.

## 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 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 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 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 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 mutated in juvenile polyposis syndrome (JPS) and account for 45% to 60% of cases of JPS. JPS 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 colorectal cancer). 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 (PJS), 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 (LFS). 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 two 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 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 risk of pheochromocytomas.

#### *VHL Variants*

VHL germline variants are associated with Hippiel-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 the Genetic Testing for Hereditary Breast and Ovarian Cancer Syndrome and the Use of Common Genetic Variants (Single Nucleotide Variants) to Predict Risk of Nonfamilial Breast Cancer Protocols.

Genetic testing for Li-Fraumeni syndrome is evaluated in the Genetic Testing for Li-Fraumeni Syndrome Protocol.

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 the Genetic Testing for PTEN Hamartoma Tumor Syndrome Protocol.

### *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 two 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 the Genetic Testing for Lynch Syndrome and Other Inherited Colon Cancer Syndrome Protocol). 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.<sup>1</sup>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.<sup>2</sup> 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.

### REGULATORY STATUS

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

### RELATED PROTOCOLS

General Approach to Evaluating the Utility of Genetic Panels

Genetic Testing for FAP and Lynch Syndrome

Genetic Testing for Hereditary Breast/Ovarian Cancer Syndrome

Genetic Testing for Li-Fraumeni Syndrome

Genetic Testing for PTEN Hamartoma Tumor Syndrome

Use of Common Genetic Variants (Single Nucleotide Polymorphisms) to Predict Risk of Nonfamilial Breast Cancer

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Services that are the subject of a clinical trial do not meet our Technology Assessment Protocol criteria and are considered investigational. *For explanation of experimental and investigational, please refer to the Technology Assessment Protocol.*

It is expected that only appropriate and medically necessary services will be rendered. We reserve the right to conduct prepayment and postpayment reviews to assess the medical appropriateness of the above-referenced procedures. **Some of this protocol may not pertain to the patients you provide care to, as it may relate to products that are not available in your geographic area.**

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We are not responsible for the continuing viability of web site addresses that may be listed in any references below.

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