Medical Policy

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Title: Genetic Cancer Susceptibility Panels Using Next Generation Sequencing

Related Policies:	▪ *Germline Genetic Testing for Hereditary Breast/Ovarian Cancer Syndrome and Other High-Risk Cancers (BRCA1, BRCA2, PALB2)* ▪ *Genetic Testing for Lynch Syndrome and Other Inherited Colon Cancer Syndromes* ▪ *General Approach to Evaluating the Utility of Genetic Panels*

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Populations	Interventions	Comparators	Outcomes
Individuals: • With a personal and/or family history suggesting an inherited cancer syndrome	Interventions of interest are: • Expanded gene panel testing	Comparators of interest are: • Individual gene testing • Limited panel testing	Relevant outcomes include: • Overall survival • Disease-specific survival • Test validity

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 once (panel testing) can optimize genetic testing in these individuals compared with sequencing single genes.

OBJECTIVE

The objective of this evidence review is to evaluate whether genetic testing with cancer susceptibility panels improves the net health outcome in individuals suspected of having an inherited cancer syndrome.

BACKGROUND

Genetic Testing for Cancer Susceptibility

Genetic testing for cancer susceptibility may be approached by a focused method that involves testing for gene(s) that may be the cause of the heritable or familial cancer. Panel testing with next-generation sequencing (NGS) involves evaluating sequence variants in multiple genes at once.

Multiple commercial companies and medical center laboratories offer genetic testing panels that use NGS methods for hereditary cancers. Next-generation sequencing is 1 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 Next-Generation Sequencing 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. Familial adenomatous polyposis 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 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 mutated in juvenile polyposis syndrome and account for 45% to 60% of cases. 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 is a tumor suppressing gene located on chromosome 16q22.1 that encodes the cell-to-cell adhesion protein E-cadherin. Germline variants in the CDH1 gene have been associated with an increased risk of developing hereditary diffuse gastric cancer (DGC) and lobular breast cancer. A diagnosis of HDGC can be confirmed by genetic testing, although 20% to 40% of families with suspected HDGC do not have a CDH1 variant on genetic testing. Pathogenic CDH1 variants have been described in Māori families in New Zealand, and individuals of Maori ethnicity have a higher prevalence of diffuse-type gastric cancer than non-Maori New Zealanders. 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% to 80% lifetime risk), uterine/endometrial cancer (20% to 60% lifetime risk), gastric cancer (11% to 19% lifetime risk), and ovarian cancer (4% to 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. Cowden syndrome 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 variants are associated with Li-Fraumeni syndrome. People with *TP53* variants have a 50% risk of developing any of the associated cancers by age 30 and a lifetime risk up to 90%, including sarcomas, breast cancer, brain tumors, and adrenal gland cancers.

***NF1* Variants**

The *NF1* gene 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 the *CDK4* gene are associated with a variety of cancers, particularly cutaneous melanoma.

CDKN2A Variants
The *CDKN2A* gene 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 a 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
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
FH variants are associated with renal cell and uterine cancers.

FLCN Variants
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 (encoded by the *MITF* gene) 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**

TSC1 and *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**

FANCC is 1 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.

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 (CLIA). Laboratories that offer laboratory-developed tests 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.

POLICY

General genetic cancer susceptibility panel testing is considered **experimental / investigational**; however, when the coverage criteria of other policies is met (see related policies), then limited genetic cancer susceptibility panels including only the gene variants for which a given member qualifies may be considered medically necessary.

POLICY GUIDELINES

Genetics Nomenclature Update

The Human Genome Variation Society nomenclature is used to report information on variants found in DNA and serves as an international standard in DNA diagnostics. It is being implemented for genetic testing medical evidence review updates starting in 2017 (see Table 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

Genetic counseling is primarily aimed at individuals 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.

Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

RATIONALE

This evidence review has been updated regularly with searches of the PubMed database. The most recent literature update was performed through September 1, 2023.

Evidence reviews assess whether a medical test is clinically useful. A useful test provides information to make a clinical management decision that improves the net health outcome. That is, the balance of benefits and harms is better when the test is used to manage the condition than when another test or no test is used to manage the condition.

The first step in assessing a medical test is to formulate the clinical context and purpose of the test. The test must be technically reliable, clinically valid, and clinically useful for that purpose. Evidence reviews assess the evidence on whether a test is clinically valid and clinically useful. Technical reliability is outside the scope of these reviews, and credible information on technical reliability is available from other sources.

Promotion of greater diversity and inclusion in clinical research of historically marginalized groups (e.g., People of Color [African-American, Asian, Black, Latino and Native American]; LGBTQIA (Lesbian, Gay, Bisexual, Transgender, Queer, Intersex, Asexual); Women; and People with Disabilities [Physical and Invisible]) allows policy populations to be more reflective of and findings more applicable to our diverse members. While we also strive to use inclusive language related to these groups in our policies, use of gender-specific nouns (e.g., women, men, sisters, etc.) will continue when reflective of language used in publications describing study populations.

EXPANDED CANCER SUSCEPTIBILITY PANELS

Clinical Context and Test Purpose

The purpose of predictive testing for cancer susceptibility is to predict cancer risk from a gene variant associated with a cancer syndrome in an affected member or in a family member of an affected person. The criteria under which predictive testing may be considered clinically useful are as follows:

- An association of the marker with the natural history of the disease has been established; and
- The clinical utility of identifying the variant has been established (e.g., by demonstrating that testing will lead to changes in the clinical management of the condition or changes in surveillance).

The following PICO was used to select literature to inform this review.

Populations
The relevant population of interest is individuals with a personal and/or family history suggesting an inherited cancer syndrome.

Intervention
The test being considered is an expanded gene testing panel.

Comparator
The following tests are currently being used to make decisions about managing cancer susceptibility: individual gene variant testing and limited panel testing for genes with high clinical validity.

Outcomes
The general outcomes of interest are overall survival, disease-specific survival, and test validity. Specific outcomes of interest include sensitivity and specificity, positive and negative predictive value, and reductions in morbidity and mortality.

Study Selection Criteria
For the evaluation of clinical validity, studies that meet the following eligibility criteria were considered:

- Reported on the accuracy of the marketed version of the technology;
- Included a suitable reference standard;
- Patient/sample clinical characteristics were described;
- Patient/sample selection criteria were described.

Clinically Valid
A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).
For genetic susceptibility to cancer, clinical validity can be considered at the following levels:

- Does a positive test identify a person as having an increased risk of developing cancer?
- If so, how high is the risk of cancer associated with a positive test?

REVIEW OF EVIDENCE

Hereditary Cancer Panels
The likelihood that someone with a positive test result will develop cancer is affected not only by the presence of the gene variant but also by other modifying factors that can affect the penetrance of the variant (e.g., environmental exposures, personal behaviors) or by the presence or absence of variants in other genes.

Susswein et al (2016) reviewed the genetic test results and clinical data from a consecutive series of 10,030 patients referred for evaluation by 1 of 8 hereditary cancer panels (comprising combinations of 29 genes) between August 2013 and October 2014.[1,] Personal and family histories of cancer were obtained, and patients were categorized as having breast, colon,

stomach, ovarian, endometrial, or pancreatic cancer; other cancer types were not singled out for analysis. Genetic variants were classified as pathogenic, likely pathogenic, variants of uncertain significance (VUS), likely benign, or benign according to the 2007 guidelines from the American College of Medical Genetics and Genomics.[2,]

Genes included in the panels were grouped into 3 risk categories based on penetrance data available in 2012, as follows:

- high risk: *APC*, *BMPR1A*, *BRCA1*, *BRCA2*, *CDH1*, *CDKN2A*, *EPCAM*, *MLH1*, *MSH2*, *MSH6*, *MUTYH*, *PMS2*, *PTEN*, *SMAD4*, *STK11*, *TP53*, and *VHL*
- moderate risk: *ATM*, *CHEK2*, and *PALB2*
- increased but less well-defined risk: *AXIN2*, *BARD1*, *BRIP1*, *CDK4*, *FANCC*, *NBN*, *RAD51C*, *RAD51D*, and *XRCC2*.

Overall, 9.0% (901/10,030) of the patients were found to carry at least 1 pathogenic or likely pathogenic variant, totaling 937 variants. Approximately half of the positive results were in well-established genes (including *BRCA1* and *BRCA2*, Lynch syndrome, and other high-risk genes) and approximately half in genes with moderate or unknown risk. Likely pathogenic variants comprised 10.6% (99/937) of all positive results.

Individuals with colon/stomach cancer had the highest yield of positive results (14.8% [113/764]), the majority of which were in well-established colon cancer genes: *MLH1*, *MSH2*, *MSH6*, *PMS2*, *EPCAM*, *MUTYH*, *APC*, *PTEN*, and *STK11*. However, 28.2% (35/124) were observed in genes not considered classical for gastrointestinal cancers: *BRCA1*, *BRCA2*, *CHEK2*, *ATM*, *PALB2*, *BRIP1*, and *RAD51D*.

For the breast cancer high-risk panels the highest VUS frequency was observed with the largest panel (29 genes), and the lowest VUS rate was observed with the high-risk breast cancer panel with 6 genes (*BRCA1*, *BRCA2*, *CDH1*, *PTEN*, *STK11*, and *TP53)*. For patients with breast cancer, 9.7% (320/3,315) of women without prior *BRCA1* and *BRCA2* testing were found to carry a pathogenic or likely pathogenic variant, of which *BRCA1* and *BRCA2* accounted for 39.1%. Other high-risk genes included *TP53*, *PTEN*, and *CDH1*, and 5.2% (17/330) of the patients carried the Lynch syndrome genes. Moderate and less well-defined risk genes accounted for 50.0% (165/330) of all positive results among women with breast cancer.

Of women with ovarian cancer, *BRCA1* and *BRCA2* accounted for 50.5% of the 89 variants identified, Lynch syndrome genes for 14.3%, and moderate or less well-defined risk genes for 33.0%.

Of the 453 women with endometrial cancer, the yield for identifying a variant was 11.9% (n=54): 7.3% (n=33) were within a Lynch gene, most commonly *MSH6*; *CHEK2* was positive in 7%, with an overall frequency of 1.5%; and 6 positive results (10.9%) were identified in *BRCA1* and *BRCA2*.

Among 190 pancreatic cancer patients, the yield for identifying a variant was 10.5% (n=20), most commonly identified in *ATM* (40.0% [8/20]), *BRCA2* (25.0% [5/20]), and *PALB2* (15.0% [3/20]).

Six (33%) of the 18 patients with positive findings in *TP53* did not meet classic Li-Fraumeni syndrome, Li-Fraumeni-like syndrome, 2009 Chompret, or National Comprehensive Cancer Network (NCCN) guideline criteria for *TP53* testing, resulting in a frequency of 0.06% (6/9,605) unanticipated positive results. Four patients had a positive *CDH1* result, 2 of whom did not meet the International Gastric Cancer Linkage Consortium testing criteria, resulting in a frequency of 0.02% (2/8,708) positive *CDH1* results.

Overall, yields among patients with breast, ovarian, and colon/stomach cancers were 9.7%, 13.4%, and 14.8%, respectively. Approximately 5.8% of positive results among women with breast cancer were in highly penetrant genes other than *BRCA1* and *BRCA2*. The yield in Lynch syndrome genes among breast cancer patients was 0.5% (17/3,315), higher than a published upper estimate of the prevalence of Lynch among the general population (0.2%). More than a quarter of patients with colon cancer tested positive for genes not considered to be classic colorectal cancer (CRC) genes. Over 11% of positive findings among women with endometrial cancer were in *BRCA1* and *BRCA2*. A small number of patients whose personal and family histories were not suggestive of Li-Fraumeni syndrome were positive for pathogenic variants in the *TP53* gene.

LaDuca et al (2014) reported on the clinical and molecular characteristics of 2,079 patients who underwent panel testing with Ambry's BreastNext (n=874), OvaNext (n=222), ColoNext (n=557), or CancerNext (n=425).[3,] Most (94%) patients had a personal history of cancer or adenomatous polyps, and in 5% of cases, the proband was reported to be clinically unaffected. The positive and inconclusive rates for the panels were, respectively, 7.4% and 20% for BreastNext, 7.2% and 26% for OvaNext, 9.2% and 15% for ColoNext, and 9.6% and 24% for CancerNext.

Hereditary Breast and Ovarian Cancer

O'Leary et al (2017) reported on 1,085 cases with non-*BRCA1* or *BRCA2* breast cancer referred to a commercial laboratory that were found to have a pathogenic or likely pathogenic variant.[4,] The cases were divided into 3 groups based on the panel requested by the ordering physician: genes primarily associated with breast cancer (group A), genes associated with breast, gynecologic, and gastrointestinal cancer types (group B), and large comprehensive panels (group C). The proportion of positive findings in genes with breast management guidelines was inversely related to the size of the panel: 97.5% in group A, 63.6% in group B, and 50% in group C. Conversely, more positive findings and unexpected findings (there was no family history) were identified in actionable non breast cancer genes as the size of the panel increased. Rates of VUS also increased as the size of the panel increased, with 12.7% VUS in group A, 31.6% in group B, and 49.6% in group C.

Couch et al (2017) evaluated 21 genetic predisposition genes for breast cancer in a sample of 38,326 white women with breast cancer who received any one of a variety of genetic test panels (Ambry Genetics).[5,] The frequency of pathogenic variants was estimated at 10.2%. After the exclusion of *BRCA1*, *BRCA2*, and syndromic breast cancer genes (*CDH1*, *PTEN*, *TP53*), 5

additional genes with variants classified as pathogenic by ClinVar were associated with a high or moderately increased risk of breast cancer (Table 1). Notably, of the various panels included in this study, only the BRCA plus panel is limited to the set of genes (*ATM*, *BRCA1*, *BRCA2*, *CDH1*, *CHEK2*, *PALB2*, *PTEN*) that were associated with breast cancer in women of European descent.

Table 1. Moderate-to-High Risk Non-*BRCA1* and *BRCA2*, Nonsyndromic Genes Associated With Breast Cancer

Gene	Odds Ratio	95% Confidence Interval	Risk Category
ATM	2.78	2.22 to 3.62	Moderate
BARD1	2.16	1.31 to 3.63	Moderate
CHEK2	1.48	1.31 to 1.67	Moderate
PALB2	7.46	5.12 to 11.19	High
RAD51D	3.07	1.21 to 7.88	Moderate

Other studies have assessed the prevalence of pathogenic variants among patients with breast cancer who were referred for genetic testing, using a panel of 25 genes associated with inherited cancer predisposition (Myriad Genetics).

A study by Buys et al (2017) included over 35,000 women with breast cancer who were assessed with the Myriad 25-gene panel.[6,] Pathogenic variants were identified in 9.3% of the women tested. Nearly half of those variants were in the *BRCA1* or *BRCA2* genes. The remaining variants were found in other breast cancer genes, Lynch syndrome genes, and other panel genes. The VUS rate was 36.7%.

A similar study by Langer et al (2016) evaluated the frequency of pathogenic variants identified with the 25-gene panel (Myriad Genetics) in 3,088 patients with a personal history of ovarian cancer who were referred for testing.[7,] Pathogenic or likely pathogenic variants were identified in 419 (13.6%) patients, of whom 7 patients had variants in 2 different genes. Nearly all patients (99.2%) met NCCN guidelines for hereditary breast and ovarian cancer testing (78.4%), Lynch syndrome testing (0.3%), or both (20.5%). Of the 419 patients with pathogenic or likely pathogenic variants, 277 (65%) were identified in *BRCA1* or *BRCA2*, 33 (7.8%) in Lynch syndrome-associated genes (*PMS2*, *MSH6*, *MLH1*, *MSH2*), 26.8% in genes with a low-to-moderate increase in cancer risk (*ATM*, *BRIP1*, *CHEK2*, *RAD51C*, *PALB2*, *NBN*), and <1% each in 6 other genes. One or more VUS were reported in 1141 (36.9%) of patients.

Kurian et al (2017) evaluated the association between gene variants on the Myriad 25-gene panel in 95,561 women and documented risk of breast or ovarian cancer from provider-completed test requisition forms.[8,] Pathogenic variants were detected in 6,775 (7%) of the women. Multivariate regression models and case-control analysis estimated that 8 genes were associated with breast cancer with odds ratio (OR) from 2-fold (*ATM*) to 6-fold (*BRCA1*). Eleven genes were associated with ovarian cancer, with OR ranging from 2-fold (*ATM*) to 40-fold (*STK11*), but statistical significance was achieved for only 3 genes (*BRCA1, BRCA2, RAD51C*). The clinical significance of the increase in cancer risk for the other genes is uncertain. Out of the 25 genes tested on the panel, there was overlap of 3 genes (*ATM, BRCA1, BRCA2*) for the association of both breast or ovarian cancer, and not all genes on the panel were associated with risk for either cancer.

Colorectal Cancer

Pearlman et al (2021) reported on the prevalence of germline pathogenic variants among patients with CRC in the Ohio Colorectal Cancer Prevention Initiative.[9,] All 3,310 patients enrolled in the study underwent testing for mismatch repair deficiency, and patients meeting at least 1 clinical criterion (mismatch repair deficiency, CRC diagnosis at less than 50 years of age, multiple primary tumors [CRC or endometrial cancer], or first degree relative with CRC or endometrial cancer) underwent subsequent multigene panel testing. The specific multigene panel test used depended on the results of mismatch repair deficiency testing; patients with mismatch repair deficiency not explained by *MLH1* hypermethylation (n=224) underwent testing with ColoSeq or BROCA panels, while patients with *MLH1* hypermethylated tumors (n=99) and patients without mismatch repair deficiency (n=1,139) underwent testing with a myRisk panel. Panels tested for 25 to 66 cancer genes. Among the 1,462 patients who underwent multigene panel testing, 248 pathogenic or likely pathogenic variants were detected in 234 patients (16% of patients who underwent multigene panel testing, and 7.1% of the entire study population). One hundred forty two pathogenic variants were in mismatch repair deficiency genes, while 101 were in non-mismatch repair deficiency genes. If mismatch repair deficiency testing had been the only method used to screen for hereditary cancer syndromes, 38.6% (91 of 236) of patients with a pathogenic variant in a cancer susceptibility gene or constitutional hypermethylation would have been missed, including 6.3% (9 of 144) of those with Lynch syndrome. One hundred seventy-five patients (5.3% of the entire study population) had pathogenic variants in genes with therapeutic targets. Variants of uncertain significance were found in 422 patients who underwent multigene panel testing (28.9%).

In an industry-sponsored study, Cragun et al (2014) reported on the prevalence of clinically significant variants and VUS among patients who underwent ColoNext panel testing.[10,] For the period included in the study (March 2012 to March 2013), the ColoNext test included the *MLH1*, *MSH2*, *MSH6*, *PMS2*, *EPCAM*, *BMPR1*, *SMAD4*, *STK11*, *APC*, *MUTYH*, *CHEK2*, *TP53*, *PTEN*, and *CDH1* genes. Alterations were classified as follows: (1) pathogenic variant; (2) variant, likely pathogenic; (3) variant, unknown significance; (4) variant, likely benign; and (5) benign. Data were analyzed for 586 patients whose ColoNext testing results and associated clinical data were maintained in a database by Ambry Genetics. Sixty-one (10.4%) patients had genetic alterations consistent with pathogenic variants or likely pathogenic variants; after 8 patients with only *CHEK2* or 1 *MUTYH* variant were removed, 42 (7.2%) patients were considered to have actionable variants. One hundred eighteen (20.1%) patients had at least 1 VUS, including 14 patients who had at least 1 VUS in addition to a pathologic variant. Of the 42 patients with a pathologic variant, most (30 [71%] patients) met NCCN guidelines for syndrome-based testing, screening, or diagnosis, based on the available clinical and family history. The authors noted "The reality remains that syndrome based testing would have been sufficient to identify the majority of patients with deleterious variants. Consequently, the optimal and most cost-effective use of panel-based testing as a first-tier test versus a second-tier test (i.e. after syndrome-based testing is negative), remains to be determined."

Pan-Cancer Panels

Rosenthal et al (2017) published an industry-sponsored study evaluating a 25-gene pan-cancer panel.[11,] The analysis included 252,223 consecutive individuals, most of whom (92.8%) met

testing criteria for hereditary breast and ovarian cancer and/or Lynch syndrome. Pathogenic variants (n=17,340) were identified in 17,000 (6.7%) patients; the most common pathogenic variants were *BRCA1* and *BRCA2* (42.2%), other breast cancer genes (32.9%), Lynch syndrome genes (13.2%), and ovarian cancer genes (6.8%). Among individuals who met only hereditary breast and ovarian cancer or Lynch syndrome testing criteria, half of the pathogenic variants found were genes other than *BRCA1* and *BRCA2* or Lynch syndrome genes, respectively. The study was limited by reliance on providers for personal and family cancer histories and by uncertainty regarding the exact cancer risk spectrum for each gene included on the panel.

Clinically Useful
A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, more effective therapy, or avoid unnecessary therapy or testing.

Direct Evidence
Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from randomized controlled trials.

The following criteria can be used to evaluate the clinical utility of cancer susceptibility panel testing:

- Is decision-making based on potential results of panel testing well-defined?
    - Do positive results on panel testing result in changes in cancer susceptibility that are clinically important?
    - Does this change in cancer susceptibility lead to changes in management that result in health outcome benefits for the patient being tested?
- Is the impact of ancillary information provided by panel testing well-defined?
    - What is the probability that ancillary information leads to further testing or management changes that may have either a positive or a negative impact on the patient being tested?

Identifying a person with a genetic variant that confers a high risk of developing cancer could lead to changes in clinical management and improve health outcomes. There are well-defined clinical guidelines on the management of patients who are identified as having high-risk hereditary cancer syndrome. Changes in clinical management could include modifications in cancer surveillance, specific risk-reducing measures (e.g., prophylactic surgery), and treatment guidance (e.g., avoidance of certain exposures). Also, other at-risk family members could be identified.

On the other hand, identifying variants that have intermediate or low penetrance is of limited clinical utility. Clinical management guidelines for patients found to have 1 of these variants are not well-defined. Also, there is a potential for harm, in that the diagnosis of an intermediate- or low-risk variant may lead to undue psychological stress and unnecessary prophylactic surgical intervention.

Idos et al (2018) conducted a prospective study that enrolled 2,000 patients who had been referred for genetic testing at 1 of 3 academic medical centers (Table 2).[12,] Patients underwent differential diagnosis by a genetic clinician prior to cancer panel testing for 25 or 28 genes associated with breast or ovarian cancer, Lynch syndrome, and genes associated with gastric, colon, or pancreatic cancer. Results of the study are shown in Table 3. Twelve percent of the patients were found to have a pathogenic variant; 66% of these findings were anticipated by the genetic clinician and 34% were not anticipated. Most of the unanticipated results were in moderate to low penetrance genes. Thirty-four percent of the patients had a VUS and 53% of patients had benign results. Prophylactic surgery was performed more frequently in patients with a pathogenic variant (16%) compared to patients with a benign (2.4%) or unknown (2.3%) variant. Limitations in relevance and design and conduct are shown in Tables 4 and 5. Information on the actions associated with low to moderate penetrance genes were not reported. One concern with large panels is the increase in VUS. Having a VUS did not increase distress or uncertainty or diminish a positive experience of the testing in this study, and there was no increase in prophylactic surgery in patients with a VUS. However, all patients had received genetic counseling at an academic medical center regarding the outcomes of testing and this study may not be representative of community practice. In addition, a threshold for testing of 2.5% on a risk prediction model is a lower threshold than what is typically recommended. Patients with a positive result were more likely to encourage relatives to undergo testing. Longer-term follow-up for clinical outcomes is ongoing.

Table 2. Study Characteristics

Study	Study Population	Design	Comparator	Outcomes	Blinding of Assessors	Follow-up
Idos et al (2018)[12,]	2,000 patients who underwent a multi-gene cancer panel test[a]; 40.4% non-Hispanic, white; 39.1% Hispanic, white; 11.7% Asian; 3.8% Black or African American	Prospective	Differential diagnosis by a genetic clinician	Post-test survey of decisions and attitudes	No	1,573 surveys were returned at a median of 13 mo after the genetic test

[a] Patients met genetic testing guidelines or had at least a 2.5% risk of cancer on a risk prediction model. Seventy-three percent had a personal history of cancer. Reasons for genetics referral included cancer diagnosis < 50 years of age, > 2 close relatives with cancer, > 1 family member with cancer at < 50 years of age, or history of multiple cancers.

Table 3. Study Results

Study	Initial N	Final N	Clinically Anticipated, n (%)	Test Results not Clinically Anticipated, n (%)	Outcome			p-value, Pathogenic vs VUS
					Pathogenic	VUS	Negative	
Idos et al (2018)[12], Overall	2,000		160/242 (66)	82/142 (34)	242 (12)[a]	689 (34)	1,069 (53)	
Prophylactic surgery, n (%)		62			30 (16.0)	12 (2.3)	20 (2.4)	<.001
Distress score (0 to 30), mean (SD)		1,248			6.1 (6.04)	2.1 (4.2)	1.7 (3.5)	<.001
Uncertainty (0 to 45), mean (SD)		1,223			11.4 (8.8)	7.4 (7.8)	6.3 (7.1)	<.001

SD: standard deviation; VUS: variant of uncertain significance.
[a]31% had a variant in *BRCA1/BRCA2,* 16% had a variant associated with Lynch syndrome, 18% had a pathogenic *MUTYH* variant, and 8% had pathogenic variants in *APC*. Other genes included *TP53, CHEK2, ATM, PALB2, BRIP1, RAD51C, BARD1, NBN, CDH1,* and *CDKN2A.*

Table 4. Study Relevance Limitations

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Follow-Up[e]
Idos et al (2018)[12],	4. The population included patients down to 2.5% of risk on a risk prediction model			1. The outcomes were patient-reported experience	1. Follow-up is continuing for clinical outcomes

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.
[b] Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4. Not the intervention of interest.
[c] Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively.
[d] Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. No CONSORT reporting of harms; 4. Not establish and validated measurements; 5. Clinical significant difference not prespecified; 6. Clinical significant difference not supported.
[e] Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms.

Table 5. Study Design and Conduct Limitations

Study	Selection[a]	Blinding[b]	Delivery of Test[c]	Selective Reporting[d]	Data Completeness[e]	Statistical[f]
Idos et al (2018)[12,]		1. Blinding not described			1. Surveys were completed by 69% of patients at 3 mo and 57% at 12 mo	

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Selection key: 1. Selection not described; 2. Selection not random or consecutive (i.e., convenience).
[b] Blinding key: 1. Not blinded to results of reference or other comparator tests.
[c] Test Delivery key: 1. Timing of delivery of index or reference test not described; 2. Timing of index and comparator tests not same; 3. Procedure for interpreting tests not described; 4. Expertise of evaluators not described.
[d] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.
[e] Data Completeness key: 1. Inadequate description of indeterminate and missing samples; 2. High number of samples excluded; 3. High loss to follow-up or missing data.
[f] Statistical key: 1. Confidence intervals and/or p values not reported; 2. Comparison with other tests not reported.

Lumish et al (2017) evaluated the impact of hereditary breast and ovarian cancer gene panel testing in 232 patients who had undergone gene panel testing after discussion with a genetic counselor.[13,] From this sample, 129 patients had a personal history of cancer (11 with a pathogenic or likely pathogenic variant, 14 with a VUS, 104 with normal test results) and 103 had a family history of cancer (14 with a pathogenic or likely pathogenic variant, 20 with a VUS, 69 with normal test results). The greatest impact of test results was for the 14 patients with a family history of breast or ovarian cancer who received a positive (pathogenic or likely pathogenic) test result, leading to greater distress and more frequent screening in 13 patients and prophylactic surgery in 1. Positive test results for the 11 patients with a personal history of cancer influenced their decision about the type of surgery for 4 (36.4%) patients. For the 20 patients with a family history of cancer and a VUS result, distress increased to an intermediate level, and 7 (35%) patients reported that their test result would impact the decision to have additional screening.

Eliade et al (2017) evaluated the clinical actionability of a multi-gene panel in a cohort of 583 patients with a family history of breast or ovarian cancer.[14,] A pathogenic or likely pathogenic *BRCA1* or *BRCA2* variant was identified in 51 (9%) patients, and a pathogenic or likely pathogenic variant was identified in 10 other genes in the panel for 37 patients. The most frequently mutated genes were *CHEK2* (n=12 [2%]), *ATM* (n=9 [1.5%]), and *PALB2* (n=4 [0.6%]). The identification of a pathogenic/likely pathogenic variant in a high-risk gene or in 2 genes led to a change in surveillance or prophylactic surgery. In patients with a positive finding in a moderate-risk gene, breast magnetic resonance imaging was recommended, while surveillance according to family history was recommended in patients with a negative finding. There was no change in management in the 4 women with a positive finding in a low-risk gene (*BRIP1*, *BARD1*, *RAD50*). Individuals with a negative finding could not be reassured, given the possibility of a pathogenic or likely pathogenic variant in an as-yet-undiscovered gene.

Kurian et al (2014) evaluated the information from a next-generation sequencing (NGS) panel of 42 cancer-associated genes in women previously referred for clinical *BRCA1* and *BRCA2* testing after clinical evaluation of hereditary breast and ovarian cancer from 2002 to 2012.[15,] The authors aimed to assess concordance of the results of the panel with prior clinical sequencing,

the prevalence of potentially clinically actionable results, and the downstream effects on cancer screening and risk reduction. Potentially actionable results were defined as pathogenic variants that cause recognized hereditary cancer syndromes or have a published association with a 2-fold or greater relative risk of breast cancer compared with average-risk women. In total, 198 women participated in the study. Of these, 174 had breast cancer and 57 carried 59 germline *BRCA1* and *BRCA2* variants. Of the women who tested negative for *BRCA1* and *BRCA2* variants (n=141), 16 had pathogenic variants in other genes (11.4%). Overall, a total of 428 VUS were identified in 39 genes, among 175 patients. Six women with variants in *ATM, BLM, CDH1, NBN*, and *SLX4* were advised to consider annual breast magnetic resonance imaging because of an estimated doubling of breast cancer risk, and 6 with variants in *CDH1, MLH1*, and *MUTYH* were advised to consider frequent colonoscopy and/or endoscopic gastroduodenoscopy (once every 1 to 2 years) due to estimated increases in gastrointestinal cancer risk. One patient with an *MLH1* variant consistent with Lynch syndrome underwent risk-reducing salpingo-oophorectomy and early colonoscopy. No clinical outcomes associated with the recommendations were reported.

Chain of Evidence
Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

Because the clinical validity of cancer susceptibility panel testing for inherited cancer syndromes has not been established, a chain of evidence cannot be constructed.

Section Summary: Expanded Cancer Susceptibility Panels
There is limited evidence on clinical validity for many of the genes in expanded panels. Most studies have been retrospective. These studies have reported on the frequency with which well-known cancer susceptibility variants are identified using large panels and variably have reported the VUS rate. The VUS rates increased in proportion with panel size, reaching nearly 50% for large gene panels. Although it may be possible to evaluate the clinical validity of some of the genes found on these panels, the clinical validity of expanded cancer susceptibility panels, which include variants associated with unknown or variable cancer risk, are of uncertain clinical validity.

Data are lacking for the clinical utility of multi-gene panels for inherited cancer susceptibility panels. There are management guidelines for syndromes with high penetrance, which have clinical utility in that they inform clinical decision making and result in the prevention of adverse health outcomes. Clinical management recommendations for the inherited conditions associated with low-to-moderate penetrance are not standardized, and the clinical utility of genetic testing for these variants is uncertain and could potentially lead to harm. Also, high VUS rates have been reported with the use of these panels.

SUPPLEMENTAL INFORMATION
The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

Practice Guidelines and Position Statements
Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US

representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

American Society of Clinical Oncology
In 2015, the American Society of Clinical Oncology (ASCO) issued a policy statement on genetic and genomic testing for cancer susceptibility.[16,] The update addressed the application of next-generation sequencing (NGS) 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 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.

In 2020, ASCO published a guideline on germline and somatic tumor testing in epithelial ovarian cancer.[17,] Based on a systematic review of evidence and expert panel input, ASCO recommended that women with epithelial ovarian cancer should be offered germline testing for *BRCA1/2* and other specified ovarian susceptibility genes with a multi-gene panel. It was considered more practical to evaluate a minimum of the 10 genes that have been associated with inherited risk of ovarian cancer in a panel in comparison to testing *BRCA1 and BRCA2* alone.

NATIONAL COMPREHENSIVE CANCER NETWORK

Breast and Ovarian Cancers
National Comprehensive Cancer Network (NCCN) guidelines on genetic/familial high-risk assessment for breast, ovarian cancers, and/or pancreatic cancer (v1.2024)[18,] include the following on multi-gene testing:

- "An individual's personal and/or family history may be explained by more than one inherited cancer syndrome; thus, phenotype-directed testing based on personal and family history through a tailored multi-gene panel test is often more efficient and cost-effective and increases the yield of detecting a pathogenic/likely pathogenic variant in a gene that will impact medical management for the individual or their family members with increased risk.
- There may also be a role for multi-gene testing in individuals who have tested negative for a single syndrome, but whose personal or family history remains suggestive of an inherited susceptibility.
- Some individuals may carry pathogenic/likely pathogenic germline variants in more than one cancer susceptibility gene..."

The NCCN defines a "tailored" multi-gene panel test as a "disease-focused multi-gene panel of clinically actionable cancer susceptibility genes, in contrast to large multi-gene panels of uncertain or unknown clinical relevance." The NCCN cautions that multi-gene panels may include moderate-risk genes that have limited data on the degree of cancer risk and no clear guidelines on risk management. As more genes are tested, the likelihood of finding variants of uncertain significance increases. Multi-gene panel testing also increases the likelihood of finding pathogenic/likely pathogenic variants without clear significance.

Colorectal Cancer

The NCCN guidelines on genetic/familial high-risk assessment for colorectal cancer (v1.2023) state that "when more than one gene can explain an inherited cancer syndrome, multi-gene testing is more efficient than single-gene testing, or sequential single syndrome 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."[19,] However, the NCCN 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.

Collaborative Group of the Americas on Inherited Gastrointestinal Cancer

In 2020, the Collaborative Group of the Americas on Inherited Gastrointestinal Cancer published a position statement on multi-gene panel testing for patients with colorectal cancer and/or polyposis.[20,] Recommendations were based on the evidence, professional society recommendations endorsing testing of a given gene, and opinion of the expert panel. The group noted the variability in genes included in commercially available panels, and recommended that multi-gene panels include a minimum of 11 specific genes associated with defective mismatch repair (Lynch syndrome) and polyposis syndromes. Additional genes to be considered had low to moderately increased risk, had limited data of colorectal cancer risk, or causation for colorectal cancer was not proven.

U.S. Preventive Services Task Force Recommendations

The U.S. Preventive Services Task Force (2019) has recommended that primary care providers screen women with a personal or family history of breast, ovarian, tubal, or peritoneal cancer or who have an ancestry associated with *BRCA1/2* gene mutations with an appropriate brief familial risk assessment tool.[21,] 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.

Ongoing and Unpublished Clinical Trials

Some currently ongoing and unpublished trials that might influence this review are listed in Table 6.

Table 6. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT05681416	Prostate Cancer Prevention Clinic for Men With Risk of Familial Prostate Cancer	300	Feb 2027
Unpublished			

NCT No.	Trial Name	Planned Enrollment	Completion Date
NCT03688204	Clinical Implementation of a Polygenic Risk Score (PRS) for Breast Cancer: Impact on Risk Estimates, Management Recommendations, Clinical Outcomes, and Patient Perception	118	Nov 2020

NCT: national clinical trial.

CODING

The following codes for treatment and procedures applicable to this policy are included below for informational purposes. This may not be a comprehensive list of procedure codes applicable to this policy.

Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

The code(s) listed below are medically necessary ONLY if the procedure is performed according to the "Policy" section of this document.

CPT/HCPCS	
81432	Hereditary breast cancer-related disorders (e.g., hereditary breast cancer, hereditary ovarian cancer, hereditary endometrial cancer); genomic sequence analysis panel, must include sequencing of at least 10 genes, always including *BRCA1*, *BRCA2*, *CDH1*, *MLH1*, *MSH2, MSH6*, *PALB2*, *PTEN*, *STK11*, and *TP53*
81433	Hereditary breast cancer-related disorders (e.g., hereditary breast cancer, hereditary ovarian cancer, hereditary endometrial cancer); duplication/deletion analysis panel, must include analyses for BRCA1, BRCA2, MLH1, MSH2, and STK11
81435	Hereditary colon cancer disorders (e.g., Lynch syndrome, PTEN hamartoma syndrome, Cowden syndrome, familial adenomatosis polyposis); genomic sequence analysis panel, must include sequencing of at least 10 genes, including APC, BMPR1A, CDH1, MLH1, MSH2, MSH6, MUTYH, PTEN, SMAD4, and STK11
81436	Hereditary colon cancer disorders (e.g., Lynch syndrome, PTEN hamartoma syndrome, Cowden syndrome, familial adenomatosis polyposis); duplication/deletion analysis panel, must include analysis of at least 5 genes, including MLH1, MSH2, EPCAM, SMAD4, and STK11
81437	Hereditary neuroendocrine tumor disorders (e.g., medullary thyroid carcinoma, parathyroid carcinoma, malignant pheochromocytoma or paraganglioma); genomic sequence analysis panel, must include sequencing of at least 6 genes, including MAX, SDHB, SDHC, SDHD, TMEM127, and VHL
81438	Hereditary neuroendocrine tumor disorders (e.g., medullary thyroid carcinoma, parathyroid carcinoma, malignant pheochromocytoma or paraganglioma); duplication/deletion analysis panel, must include analyses for SDHB, SDHC, SDHD, and VHL
81445	Solid organ neoplasm, genomic sequence analysis panel 5-50 genes, interrogation for sequence variants and copy number variants or rearrangements, if performed; DNA analysis or combined DNA and RNA analysis (eff. 01-01-2024)
81450	Hematolymphoid neoplasm or disorder, genomic sequence analysis panel, 5-50 genes, interrogation for sequence variants, and copy number variants or rearrangements, or isoform expression or mRNA expression levels, if performed; DNA analysis or combined DNA and RNA analysis (eff. 01-01-2024)

CPT/HCPCS	
81455	Solid organ or hematolymphoid neoplasm or disorder, 51 or greater genes, interrogation for sequence variants and copy number variants or rearrangements, or isoform expression or mRNA expression levels, if performed; DNA analysis or combined DNA and RNA analysis (eff. 01-01-2024)
81479	Unlisted molecular pathology procedure
0048U	Oncology (solid organ neoplasia), DNA, targeted sequencing of protein-coding exons of 468 cancer-associated genes, including interrogation for somatic mutations and microsatellite instability, matched with normal specimens, utilizing formalin-fixed paraffin-embedded tumor tissue, report of clinically significant mutation(s)
0049U	NPM1 (nucleophosmin) (e.g., acute myeloid leukemia) gene analysis, quantitative
0101U	Hereditary colon cancer disorders (e.g., Lynch syndrome, PTEN hamartoma syndrome, Cowden syndrome, familial adenomatosis polyposis); genomic sequence analysis panel utilizing a combination of NGS, Sanger, MLPA and array CGH, with MRNA analytics to resolve variants of unknown significance when indicated [15 genes (sequencing and deletion/duplication), EPCAM and GREM1 (deletion/duplication only)]
0102U	Hereditary breast cancer-related disorders (e.g., hereditary breast cancer, hereditary ovarian cancer, hereditary endometrial cancer), genomic sequence analysis panel utilizing a combination of NGS, Sanger, MLPA, and array CGH, with MRNA analytics to resolve variants of unknown significance when indicated (17 genes [sequencing and deletion/duplication])
0103U	Hereditary ovarian cancer (e.g., hereditary ovarian cancer, hereditary endometrial cancer), genomic sequence analysis panel utilizing a combination of NGS, Sanger, MLPA, and array CGH, with MRNA analytics to resolve variants of unknown significance when indicated (24 genes [sequencing and deletion/duplication], *EPCAM* [deletion/duplication only])
0129U	Hereditary breast cancer–related disorders (e.g., hereditary breast cancer, hereditary ovarian cancer, hereditary endometrial cancer), genomic sequence analysis and deletion/duplication analysis panel (ATM, BRCA1, BRCA2, CDH1, CHEK2, PALB2, PTEN, and TP53)
0130U	Hereditary colon cancer disorders (e.g., Lynch syndrome, PTEN hamartoma syndrome, Cowden syndrome, familial adenomatosis polyposis), targeted mRNA sequence analysis panel (APC, CDH1, CHEK2, MLH1, MSH2, MSH6, MUTYH, PMS2, PTEN, and TP53)
0131U	Hereditary breast cancer–related disorders (e.g., hereditary breast cancer, hereditary ovarian cancer, hereditary endometrial cancer), targeted mRNA sequence analysis panel (13 genes)
0132U	Hereditary ovarian cancer–related disorders (e.g., hereditary breast cancer, hereditary ovarian cancer, hereditary endometrial cancer), targeted mRNA sequence analysis panel (17 genes)
0133U	Hereditary prostate cancer–related disorders, targeted mRNA sequence analysis panel (11 genes)
0134U	Hereditary pan cancer (e.g., hereditary breast and ovarian cancer, hereditary endometrial cancer, hereditary colorectal cancer), targeted mRNA sequence analysis panel (18 genes)

CPT/HCPCS	
0135U	Hereditary gynecological cancer (e.g., hereditary breast and ovarian cancer, hereditary endometrial cancer, hereditary colorectal cancer), targeted mRNA sequence analysis panel (12 genes)
0136U	ATM (ataxia telangiectasia mutated) (e.g., ataxia telangiectasia), mRNA sequence analysis
0137U	PALB2 (partner and localizer of BRCA2) (e.g., breast and pancreatic cancer), mRNA sequence analysis
0138U	BRCA1 (BRCA1, DNA repair associated), BRCA2 (BRCA2, DNA repair associated) (e.g., hereditary breast and ovarian cancer), mRNA sequence analysis

REVISIONS	
02-07-2014	Policy added to the bcbsks.com web site on 01-08-2014 for an effective date of 02-07-2014.
10-28-2014	Updated Description section.
	Added Policy Guideline section.
	Updated Rationale section.
	Updated References section.
08-05-2015	Updated Description section.
	Updated Rationale section.
	In Revisions section, removed "Updated Summary section" from 10-28-2014.
	Updated References section.
01-01-2016	In Coding section: ▪ Added CPT codes: 81432, 81433, 81435, 81436, 81437, 81438, 81445, 81450, 81455. ▪ Removed CPT codes: 81200, 81201, 81202, 81203, 81205, 81206, 81207, 81208, 81209, 81210, 81211, 81212, 81213, 81214, 81215, 81216, 81217, 81220, 81221, 81222, 81223, 81224, 81225, 81226, 81227, 81228, 81229, 81235, 81240, 81241, 81242, 81243, 81244, 81245, 81250, 81251, 81252, 81253, 81254, 81255, 81256, 81257, 81260, 81261, 81262, 81263, 81264, 81265, 81266, 81267, 81268, 81270, 81275, 81280, 81281, 81282, 81290, 81291, 81292, 81293, 81294, 81295, 81296, 81297, 81298, 81299, 81300, 81301, 81302, 81303, 81304, 81310, 81315, 81316, 81317, 81318, 81319, 81321, 81322, 81323, 81324, 81325, 81326, 81330, 81331, 81332, 81340, 81341, 81342, 81350, 81355, 81400, 81401, 81402, 81403, 81404, 81405, 81406, 81407, 81408.
07-07-2016	Updated Description section.
	Updated Rationale section.
	Updated References section.
11-08-2017	Updated Description section.
	Updated Rationale section.
	Updated References section.
01-01-2018	In Coding section: ▪ Revised nomenclature to CPT code: 81432.
07-01-2018	In Coding section: ▪ Added CPT code: 0048U.
11-07-2018	Updated Description section.
	In Policy section:

REVISIONS	
	▪ Added "testing" to read, "Genetic cancer susceptibility panel testing using next generation sequencing are considered experimental / investigational." ▪ Updated Policy Guidelines.
	Updated Rationale section.
	In Coding section: ▪ Updated coding bullets.
	Updated References section.
07-01-2019	In Coding section: ▪ Added new CPT codes: 0102U, 0103U, 0104U.
05-14-2021	Updated Description section.
	In Policy section: • Replaced previous statement "Genetic cancer susceptibility panel testing using next generation sequencing are considered **experimental / investigational."** with the following policy statement: "General genetic cancer susceptibility panel testing is considered **experimental / 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." • Removed "Although genetic cancer susceptibility panels using next generation sequencing are considered experimental / investigational, there may be individual components of the panel that are medically necessary." From the Policy Guidelines.
	Updated Rationale section.
	In coding section: • Added CPT codes: 0049U, 0101U, 0129U, 0130U, 0131U, 0132U, 0133U, 0134U, 0135U, 0136U, 0137U, 0138U • Removed CPT code: 0104U
	Updated References section.
12-02-2021	Updated Description Section
	Updated Rationale Section
	Updated References Section
11-22-2022	Updated Description Section
	Updated Rationale Section
	Updated Coding Section Updated Nomenclature for 81445, 81450, and 81455
	Updated References Section
11-17-2023	Updated Description Section
	Updated Rationale Section
	Updated Coding Section ▪ Removed ICD-10 Diagnoses Box ▪ Updated nomenclature for 81445, 81450, and 81455 (eff. 01-01-2024)
	Updated References Section

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