Medical Policy

Blue Cross Blue Shield Blue Care Network of Michigan

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Title: Genetic Cancer Susceptibility Panels Using Next Generation Sequencing

Description/Background

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 involves evaluating sequence variants in multiple genes at once.

Multiple commercial companies and medical center laboratories offer genetic testing panels that use next-generation sequencing (NGS) methods for hereditary cancers. NGS is one of several methods that use massively parallel platforms to allow the sequencing of large stretches of DNA. Panel testing is potentially associated with greater efficiencies in the evaluation of genetic diseases; however, it may provide information on genetic variants of uncertain clinical significance or findings that would not lead to changes in patient management.

Genes included in NGS Panels

The following is a summary of the function and disease association of major genes included in the next generation sequencing panels. This is not meant to be a comprehensive list of all genes included in all panels.

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 ~1% of all colorectal cancers.

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.

AXIN2 variants have been associated with familial adenomatous polyposis syndrome, although the phenotypes associated with AXIN2 variants do not appear to be well characterized.

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 are genes mutated in juvenile polyposis syndrome (JPS) and account for 45-60% 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 9-50%.

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.

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.

CDK4 (cyclin-dependent kinase-4) is a protein-serine kinase involved in cell cycle regulation. Variants in this gene have been associated with a variety of cancers, particularly cutaneous melanoma.

CDKN2A (cyclin-dependent kinase inhibitor 2A) 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.

CHEK1 gene variants have been shown to be over expressed in a numerous tumors including breast, colon, liver, gastric and nasopharyngeal carcinoma.

CHEK2 gene variants confer an increased risk of developing several different types of cancer, including breast, prostate, colon, thyroid and kidney.

EPCAM, MLH1, MSH2, MSH6 and PMS2 are mismatch repair genes associated with Lynch syndrome (hereditary nonpolyposis colon cancer or HNPCC). Lynch syndrome is estimated to cause 2-5% 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 risk of other types of cancer, including small intestine, hepatobiliary tract, upper urinary tract and brain, are also elevated.

FANCC (Fanconi-anemia complementation group C) is one of several DNA repair genes that are mutated in Fanconi anemia, which is characterized by bone marrow failure and a high predisposition to multiple types of cancer.

FH (fumarate hydratase) variants have been associated with renal cell and uterine cancers.

FLCN (folliculin) acts as a tumor suppressor gene; variants in this gene are associated with the autosomal dominant syndrome Birt-Hogg-Dube syndrome, which is characterized by hair follicle hamartomas, kidney tumors, and colorectal cancer.

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 *(microphthalmia-associated transcription factor)* is a transcription factor involved in melanocyte differentiation. MITF variants lead to several auditory-pigmentary syndromes, including Waardenburg syndrome Type 2 and Tietz syndrome. MITF variants are also associated with melanoma and renal cell carcinoma.

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.

NF1 (neurofibromin 1) encodes a negative regulator in the *ras* signal transduction pathway. Variants in the *NF1* gene have been associated with neurofibromatosis Type 1, juvenile myelomonocytic leukemia, and Watson syndrome.

PALB2 germline variants have been 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 have been associated with PTEN hamartoma tumor syndrome, 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 individuals have a lifetime risk of up to 50% for breast cancer, 10% for thyroid cancer and 5-10% for endometrial cancer.

RAD51D – (RAD51 paralog D) - germline variants have been associated with familial breast and ovarian cancer.

RET encodes a receptor tyrosine kinase; variants in this gene have been associated with multiple endocrine neoplasia syndromes (types IIA and IIB) and medullary thyroid carcinoma.

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 have been associated with the development of paragangliomas, pheochromocytomas, gastrointestinal stromal tumors, and a *PTEN*-negative Cowden syndrome (Cowden-like syndrome).

STK11 germline variants have been associated with Peutz-Jegher syndrome (PJS), an autosomal dominant disorder, with a 57-81% risk of developing cancer by age 70, of which gastrointestinal and breast are the most common.

TMEM127 (transmembrane protein 127) germline variants have associated with risk of pheochromocytomas.

TP53 has been associated with Li-Fraumeni syndrome. Individuals 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 cancer.

TSC1 (tuberous sclerosis 1) and TSC2 (tuberous sclerosis 2) encode the proteins hamartin and tuberin, which are involved in cell growth, differentiation, and proliferation. Variants in these genes are associated with the development of tuberous sclerosis complex, an autosomal dominant syndrome characterized by skin abnormalities, developmental delay, seizures, and multiple types of cancers, including central nervous system tumors, renal tumors (including angiomyolipomas, renal cell carcinomas), and cardiac rhabdomyomas.

VHL germline variants are associated with the autosomal dominant familial cancer syndrome Von Hippel-Lindau syndrome, which is associated with a variety of malignant and benign tumors, including central nervous system tumors, renal cancers, pheochromocytomas, and pancreatic neuroendocrine tumors.

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.

Regulatory Status

Clinical laboratories may develop and validate tests in-house (“home-brew”) and market them as a laboratory service; such tests must meet the general regulatory standards of the Clinical Laboratory Improvement Act (CLIA). The laboratory offering the service must be licensed by CLIA for high-complexity testing. Ambry Genetics is CLIA licensed.

Medical Policy Statement

Limited genetic cancer susceptibility panels that include only gene variants for which the member meets criteria in other policies may be considered established (see related policies in the Inclusionary and Exclusionary Guidelines).

Genetic cancer susceptibility panel testing is considered experimental/investigational in all other situations.

Inclusionary and Exclusionary Guidelines

Related Policies:

- Genetic Testing for Hereditary Breast/Ovarian Cancer Syndrome (BRCA1 or BRCA2)
- Genetic Testing for Lynch Syndrome and Other Inherited Colon Cancer Syndromes
- Genetic Testing (Single Nucleotide Variants) To Predict Risk of Nonfamilial Breast Cancer
- Gene Expression Profiling for Cutaneous Melanoma
- Gene Variants Associated with Breast Cancer in Individuals at High Breast Cancer Risk
- Moderate Penetrance Variants Associated With Breast Cancer in Individuals at High Breast Cancer Risk
- Circulating Tumor DNA Management of Non-Small-Cell Lung Cancer (Liquid Biopsy)
- Genetic Testing for PTEN Hamartoma Tumor Syndrome
- Genetic Testing-NGS Testing of Multiple Genes (Panel) to Identify Targeted Cancer Therapy

CPT/HCPCS Level II Codes *(Note: The inclusion of a code in this list is not a guarantee of coverage. Please refer to the medical policy statement to determine the status of a given procedure.)*

Established codes:

81201	81202	81203	81210	81288	81292
81293	81294	81295	81296	81297	81298
81300	81301	81307	81308	81317	81318
81319	81401	81403	81406	81435	81436
81445	81450				

Other codes (investigational, not medically necessary, etc.):

81327	81437	81438	81455	81479	81437
81438	0236U*	0238U*	0333U*		

*Proprietary panels are considered experimental/investigational until the laboratory test the code represents is formally documented as established in an interim Medical Policy or Joint Uniform Medical Policy document. Covered CPT codes may be used to represent and reimburse testing for incremental codes or multi-target codes.

Note: There are no specific codes for molecular pathology testing by panels. If the specific analyte is listed in CPT codes 81200-81355 or 81400-81408, the specific CPT code would be reported. If the specific analyte is not listed in the more specific CPT codes, unlisted code 81479 would be reported. The unlisted code would be reported once to represent all of the unlisted analytes in the panel.

Rationale

The assessment of a genetic test typically focuses on 3 categories of evidence: (1) analytic validity (including test-retest reliability or interrater reliability); (2) clinical validity (sensitivity, specificity, positive and negative predictive values) in relevant populations of patients; and (3) clinical utility (i.e., demonstration that the diagnostic information can be used to improve patient outcomes).

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** were used to select literature to inform this review.

Populations

The relevant population of interest is individuals who are diagnosed with a heritable cancer or have a family member who has been diagnosed with a heritable cancer syndrome or have a family member(s) with heritable cancer(s).

Intervention

The test being considered is an expanded cancer susceptibility panel.

Comparator

The following test is currently being used to make decisions about managing cancer susceptibility: individual gene variant testing.

Limited panel testing for genes with high clinical validity.

Outcomes

The outcomes of interest are 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 on 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.

In 2016, Susswein et al reviewed the genetic test results and clinical data from a consecutive series of 10,030 patients referred for evaluation by one 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 or variants 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*; and
- 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 one 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. For patients with breast cancer, 9.7% (320/3315) of female patients 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 (including *TP53*, *PTEN*, and *CDH1*) 5.8% (19/330), and 5.2% (17/330) in 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* and accounted for 50.5%, 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) of these were within a Lynch gene, most commonly *MSH6*, *CHEK2* was positive in 7%, with an overall frequency of 1.5%, and 6 positive results were identified in *BRCA1* and *BRCA2*; 10.9% (6/55) of all positive variants identified.

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, 2009 Chompret, or National Comprehensive Cancer Network guideline criteria for *TP53* testing, resulting in a frequency of 0.06% (6/9605) unanticipated positive results. Four patients had a positive *CDH1* result, 2 of whom did not meet International Gastric Cancer Linkage Consortium testing criteria, resulting in a frequency of 0.02% (2/8708) 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% (17/3315), 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 genes. Over 11% of the 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.

In 2014, LaDuca et al reported the clinical and molecular characteristics of 2079 patients who underwent panel testing with 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 1085 cases with non-*BRCA1* or *BRCA2* breast cancer referred to their commercial laboratory who were found to have a pathogenic/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 finding 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 nonbreast cancer genes as the size of the panel increased. VUS rates 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.

In a 2017 publication, Couch et al 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 exclusion of *BRCA1*, *BRCA2*, and syndromic breast cancer genes (*CDH1*, *PTEN*, TP*5*3), 5 additional genes with variants classified as pathogenic by ClinVar were associated with high or moderately increased risk of breast cancer (see Table 5). Notably, of the various panels included in this study, only the 8 gene BRCAplus 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-BRACA1 and BRACA2, Nonsyndromic Genes Associated With Breast Cancer

Gene	Odds Ratio	95% Confidence Interval (CI)	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 3088 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 HBOC testing (78.4%), Lynch syndrome testing (0.3%), or both (20.5%). Of the 419 patients with pathogenic/likely pathogenic variants, 277

(65%) were identified in *BRCA1* or *BRCA2*, 33 (7.8%) in Lynch syndrome-associated genes (*PMS2*, *MSH6*, *MLH1*, *MSH2*), and 26.8% in genes with a low to moderate increase in cancer risk: *ATM*, *BRIP1*, *CHEK2*, *RAD51C*, *PALB2*, *NBN* , or one of 6 other genes (<1% each). 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 2014, in an industry-sponsored study, Cragun et al reported the prevalence of clinically significant variants and variants of uncertain significance (VUSs) among patients who underwent ColoNext panel testing.[10] For the period included in the study (March 2012-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 one VUS, including 14 patients who had a least one VUS in addition to a pathologic variant. Of the 42 patients with a pathologic variant, must (30 [71%] patients) clearly met National Comprehensive Cancer Network guidelines for syndrome-based testing, screening, or diagnosis, based on the available clinical and family history. The authors noted that, "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 vs. 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 252223 consecutive individuals, most of whom (92.8%) met testing criteria for hereditary breast and ovarian cancer and/or Lynch syndrome. Pathogenic variants (n=17340) were identified in 17000 (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.

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.
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 improved health outcomes. There are well-defined clinical guidelines on the management of patients who are identified as having a 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). In addition, 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 one of these variants are not well defined. In addition, 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 2000 patients who had been referred for genetic testing at 1 of 3 academic medical centers (see 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, of which 66% was anticipated by the genetic clinician and 34% which 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)	2,000 patients who underwent a multi-gene cancer panel test[a]	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 n (%)			P-value Pathogenic vs. VUS
					Pathogenic	VUS	Negative	
Idos et al (2018) Overall	2000		160/242 (66)	82/142 (34)	242 (12)[a]	689 (34)	1,069 (53)	
Prophylactic surgery		62			30 (16.0)	12 (2.3)	20 (2.4)	
Distress score (0 to 30) -mean (SD)		1,248			6.1 (6.04)	2.1 (4.2)	1.7 (3.5)	<0.001
Uncertainty (0 to 45) mean (SD)		1,223			11.4 (8.8)	7.4 (7.8)	6.3 (7.1)	<0.001

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)	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)		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 (ie, 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.

In 2017, Lumish et al 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/likely pathogenic variant, 14 with a VUS, 104 with normal test results) and 103 had a family history of cancer (14 with a pathogenic/likely pathogenic variant, 20 with a VUS, and 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/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. The authors of this study noted that the VUS rate will increase with the number of genes in a panel and the choice of a panel will need to optimize the chance of receiving results with clinical utility while minimizing the chance of results that have disutility and increase anxiety.

Eliade et al (2017) evaluated the clinical actionability of a multigene panel in a cohort of 583 patients with family history of breast or ovarian cancer.[14] A pathogenic/likely pathogenic *BRCA1* or *BRCA2* variant was identified in 51 (9%) patients and a pathogenic/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 MRI 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/likely pathogenic variant in an as-yet discovered gene.

In 2014, Kurian et al evaluated the information from a NGS panel of 42 cancer-associated genes in women who had been previously referred for clinical *BRCA1/2* 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 caner 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 *BRCA1/2* variants. Of the women who tested negative for *BRCA1/2* 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 1-2 years) due to estimated increases in gastrointestinal cancer risk. One patient with a *MLH1* variant consistent with LS underwent risk-reducing salpingooophorectomy and early colonoscopy.

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 multigene 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. In addition, high rates of VUSs have been reported with the use of these panels.

SUMMARY OF EVIDENCE

For individuals who have a personal and/or family history suggesting an inherited cancer syndrome who receive testing with a next-generation sequencing panel, the evidence includes reports describing the diagnostic yield of expanded gene panels. Relevant outcomes are overall survival, disease-specific survival, test accuracy, and test validity. Studies of gene panel testing for genetic cancer risk assessment have reported primarily on the frequency with which variants are identified. The rates of variants of uncertain significant 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 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 that are considered to be of moderate or low penetrance, and clinical management recommendations for these genes are not well-defined. In addition, high rates of variants of uncertain significance have been reported with these panels, leading to the potential for harm. The evidence is insufficient to determine the effects of the technology on health outcomes.

SUPPLEMENTAL INFORMATION

PRACTICE GUIDELINES AND POSITION STATEMENTS

American Society of Clinical Oncology (ASCO)

A 2015 update of a policy statement on genetic and genomic testing for cancer susceptibility from the American Society of Clinical Oncology (ASCO) addresses the application of next-generation sequencing.[18] The update addressed the application of next-generation sequencing and confirmed that panel testing may also identify variants in genes associated with moderate or low cancer risks, variants in high-penetrance genes that would not have been evaluated based on the presenting personal or family history, and as variants of uncertain significance in a substantial proportion of patient cases. Further, the statement indicated there is little consensus as to which genes should be included on panels for cancer susceptibility testing.

In 2020, ASCO published a guideline on germline and somatic tumor testing in epithelial ovarian cancer.[19] 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 multigene panel. ASCO considered it 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

National Comprehensive Cancer Network (NCCN) guidelines on genetic/familial high-risk assessment for breast, ovarian, and/or pancreatic cancer (v.3.2024)[20] include the following on multigene 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 multi-gene panel test may be more efficient and/or cost-effective and increase the likelihood of detecting a pathogenic/likely pathogenic variant in a gene that will impact medical management for the individual or his/her at-risk family members.
- There may be a role for multigene testing in individuals who have tested negative (indeterminate) for a single syndrome, but whose personal or family history remains suggestive of an inherited susceptibility.
- Some individuals may carry a 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 testing, 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.

NCCN guidelines on genetic/familial high risk assessment for colorectal cancer (v.4.2024) state that “when more than one gene can explain an inherited cancer syndrome, then 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.” However, NCCN cautions about the increased likelihood of finding VUS, which increases with the number of genes included in the panel, and that gene panels can include moderate-risk genes which may not be clinically actionable. In addition, the panel believes that there are insufficient data to recommend the use of multigene assays, Immunoscore, or post-surgical ctDNA to estimate risk of recurrence or determine adjuvant therapy.[21]

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 multigene panel testing for patients with colorectal cancer.[22] 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 multigene 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, updated 2024) recommends 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.[23] Women with a positive screening results should receive genetic counseling and, if indicated after counseling, *BRCA* testing (grade B recommendation). The use of genetic cancer susceptibility panels is not specifically mentioned.

Ongoing and Unpublished Clinical Trials

Some currently unpublished trials that might influence this policy 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			
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

Government Regulations National/Local:

National Coverage Determination. 100-3, Manual Section Number 90.2 implementation date 11/13/2020.

1. Somatic (Acquired) Cancer
   Centers for Medicare & Medicaid Services (CMS) has determined that **NEXT GENERATION SEQUENCING** (NGS) as a diagnostic laboratory test is reasonable and necessary and covered nationally, when performed in a Clinical Laboratory Improvement Amendments (CLIA)-certified laboratory, when ordered by a treating physician, and when all of the following requirements are met:
   a. Patient has:
      i. either recurrent, relapsed, refractory, metastatic, or advanced stage III or IV cancer; and
      ii. not been previously tested with the same test using NGS for the same cancer genetic content, and
      iii. decided to seek further cancer treatment (e.g., therapeutic chemotherapy).
   b. The diagnostic laboratory test using NGS must have:
      i. Food & Drug Administration (FDA) approval or clearance as a companion in vitro diagnostic; and,
      ii. an FDA-approved or -cleared indication for use in that patient's cancer; and,
      iii. results provided to the treating physician for management of the patient using a report template to specify treatment options.

2. Germline (Inherited) Cancer
   Effective for services performed on or after January 27, 2020, CMS has determined that NGS as a diagnostic laboratory test is reasonable and necessary and covered nationally for patients with germline (inherited) cancer, when performed in a CLIA-certified laboratory, when ordered by a treating physician and when all of the following requirements are met:
   a. Patient has:
      i. ovarian or breast cancer; and,
      ii. a clinical indication for germline (inherited) testing for hereditary breast or ovarian cancer; and,
      iii. a risk factor for germline (inherited) breast or ovarian cancer; and
      iv. not been previously tested with the same germline test using NGS for the same germline genetic content.
   b. The diagnostic laboratory test using NGS must have all of the following:
      i. FDA-approval or clearance; and,
      ii. results provided to the treating physician for management of the patient using a report template to specify treatment options.

Nationally Non-Covered Indications

Somatic (Acquired) Cancer

NGS as a diagnostic laboratory test for patients with acquired *(somatic)* cancer are non-covered if the cancer patient does not meet the criteria noted in section above.

Other

Somatic (Acquired) Cancer

Medicare Administrative Contractors (MACs) may determine coverage of NGS as a diagnostic laboratory test for patients with *advanced* cancer only when the test is performed in a CLIA-certified laboratory, *when* ordered by a treating physician, and when the patient has:

a. either recurrent, relapsed, refractory, metastatic, or advanced stages III or IV cancer; and,
b. *not been previously tested with the same test using NGS for the same cancer genetic content, and*
c. decided to seek further cancer treatment (e.g., therapeutic chemotherapy).

Germline (Inherited) Cancer
MACs may determine coverage of NGS as a diagnostic laboratory test for patients with germline (inherited) cancer only when the test is performed in a CLIA-certified laboratory, when ordered by a treating physician, when results are provided to the treating physician for management of the patient and when the patient has:

a. any cancer diagnosis; and,
b. a clinical indication for germline (inherited) testing of hereditary cancers; and,
c. a risk factor for germline (inherited) cancer; and,
d. not been previously tested with the same germline test using NGS for the same germline genetic content.

Local Coverage Determination, L38158, effective 06/08/23. MolDX: Next-Generation Sequencing for Solid Tumors.
All the following must be present for coverage eligibility:

- As per NCD 90.2, this test is reasonable and necessary when:
    - the patient has either:
        - Recurrent cancer
        - Relapsed cancer
        - Refractory cancer
        - Metastatic cancer
        - Advanced cancer (stages III or IV)
    - AND has not been previously tested by the same test for the same genetic content
    - AND is seeking further treatment
- The test has satisfactorily completed a TA by MolDX for the stated indications of the test
- The assay performed includes at *least* the minimum genes and genomic positions required for the identification of clinically relevant FDA-approved therapies with a companion diagnostic biomarker as well as other biomarkers known to be necessary for clinical decision making for its intended use that can be reasonably detected by the test. Because these genes and variants will change as the literature and drug indications evolve, they are listed separately in associated documents such as the MolDX TA forms.

Situations in which Test should not be used or coverage is denied:
The test in question will be non-covered if:

- It does not fulfill all the criteria set forth in the NCD 90.2 as stated above
- Another CGP test was performed on the same tumor specimen (specimen obtained on the same date of service)
- A TA is not completed satisfactorily by MolDX for new tests
- For tests that are currently covered but a TA submission has not been made, providers must submit completed TA materials by February 10th, 2020, or coverage will be denied

Local Coverage Determination, L38176. MolDX: Next Generation Sequencing Lab-Developed Tests for Myeloid Malignancies and Suspected Myeloid Malignancies, effective 03/28/2024.
The following must be present for coverage eligibility:

- For tests that are specifically indicated in patients whom are known to have a myeloid malignancy at the time of testing, NCD 90.2 applies
- The patient has a diagnosis of AML, MDS, or MPN. AML, MDS, and MPN are herein classified as refractory and/or metastatic cancers and fulfill the NCD 90.2 criteria.
- The test has satisfactorily completed a TA by MolDX for the stated indications of the test.
- The assay performed includes *at least* the minimum genes and positions indicated for its intended use, as described in an associated coverage Article, and found in the TA forms.
- For patients that do not have a diagnosis of a myeloid malignancy, where one is suspected, the patient must have an undefined cytopenia for greater than 4 months, other possible causes have been reasonably excluded.
- Testing is performed on bone marrow biopsies, bone marrow aspirates, bone marrow clots, peripheral blood samples, or extramedullary sites suspected of harboring a myeloid malignancy.

Situations in which Test should not be used or coverage is denied:
The test in question will be non-covered if:

- A TA has not been satisfactorily completed by MolDX. For tests that are currently covered but a TA submission has not been made, providers must submit complete TA materials by February 10th, 2020, or coverage will be denied.
- Another NGS test was performed on the same surgical specimen/ blood draw (specimen obtained on the same date of service).
- Testing falls within scope of NCD 90.2 and has been tested with the same test for the same genetic content.

(The above Medicare information is current as of the review date for this policy. However, the coverage issues and policies maintained by the Centers for Medicare & Medicare Services [CMS, formerly HCFA] are updated and/or revised periodically. Therefore, the most current CMS information may not be contained in this document. For the most current information, the reader should contact an official Medicare source.)

Related Policies

- Genetic Testing and Counseling
- GT-BCR-ABL1 in CML and AML
- GT-BRAF for Melanoma Targeted Therapy
- GT-Circulating DNA Colon CA Recurrence
- GT-NGS for Assessment of Measurable Residual-Hematological
- GT-NGS of Multiple Genes Panel for Solid and Hematolymphoid Malignant Conditions
- General Approach to Evaluating the Utility of Genetic Panels

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The articles reviewed in this research include those obtained in an Internet based literature search for relevant medical references through July 2024, the date the research was completed.

Joint BCBSM/BCN Medical Policy History

Policy Effective Date	BCBSM Signature Date	BCN Signature Date	Comments
11/1/13	8/20/13	9/10/13	Joint policy established
1/1/15	10/21/14	11/3/14	Routine maintenance; no change in policy status. Added information regarding additional gene panels. References updated.
3/1/16	12/10/15	12/10/15	Routine maintenance, updated rationale and references. No change in policy status.
1/1/17	10/11/16	10/11/16	Routine policy maintenance, updated rationale and references.
3/1/17	12/13/16	12/13/16	Added codes 81437 and 81438.
3/1/18	12/12/17	12/12/17	Updated background and rationale sections. Added reference# 3, 13, 18, 19, 22, 24-26, 30-32, 34 and 35. "Mutations" changed to "Variants" throughout policy. VOUS (variants of unknown significance) changed to VUS throughout policy. No change in policy status
11/1/18	8/21/18	8/21/18	Added code 0048U as E/I, effective 7/1/18.
11/1/19	8/20/19		Some editing for content and clarification that the policy focus is utility of genetic panel testing. Reference 44 added. No change in policy status.
11/1/20	8/18/20		Routine policy maintenance. No change in policy status.
11/1/21	8/17/21		Policy statement added that limited genetic cancer susceptibility panels may be considered established. Expanded panels remain E/I. References #16, 18 and 21 added. Rationale updated.
11/1/22	8/16/22		Routine policy maintenance, added reference #9, added code 0236U as E/I, no change in policy status.
11/1/23	8/15/23		Added codes 0333U, 0334U as E/I, nomenclature revised for 81445, 81450

			and 81455, Updated CMS and NCCN guidelines. Vendor managed: N/A (ds)
11/1/24	8/20/24		Routine policy maintenance, removed codes 0037U, 0048U, 0244U and 0334U. Vendor managed: N/A (ds)

Next Review Date: 3rd Qtr. 2025

BLUE CARE NETWORK BENEFIT COVERAGE
POLICY: GENETIC CANCER SUSCEPTIBILITY PANELS USING NEXT GENERATION SEQUENCING

I. Coverage Determination:

Commercial HMO (includes Self-Funded groups unless otherwise specified)	Not covered.
BCNA (Medicare Advantage)	See government section.
BCN65 (Medicare Complementary)	Coinsurance covered if primary Medicare covers the service.

II. Administrative Guidelines:

N/A