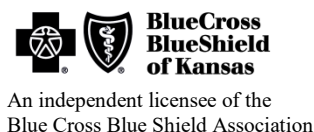


Medical Policy



Title: Genetic Cancer Susceptibility Panels Using Next Generation Sequencing

Professional

Original Effective Date: February 7, 2014
 Revision Date(s): February 7, 2014;
 October 28, 2014; August 5, 2015;
 January 1, 2016; July 7, 2016;
 November 8, 2017; January 1, 2018;
 July 1, 2018; November 7, 2018
 Current Effective Date: February 7, 2014

Institutional

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Populations	Interventions	Comparators	Outcomes
Individuals: <ul style="list-style-type: none"> With a personal and/or family history suggesting an inherited cancer syndrome 	Interventions of interest are: <ul style="list-style-type: none"> Next generation sequencing panel testing 	Comparators of interest are: <ul style="list-style-type: none"> Individual variant testing 	Relevant outcomes include: <ul style="list-style-type: none"> 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 technology to analyze multiple genes at one time (panel testing) can optimize genetic testing in these patients compared with sequencing single genes.

OBJECTIVE

The objective of this policy 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 well-characterized variants based on a clinical suspicion of which gene(s) may be the cause of the familial cancer. Panel testing involves testing for multiple variants in multiple genes at one time.

Multiple commercial companies and medical center laboratories offer genetic testing panels that use next generation sequencing (NGS) methods for hereditary cancers. NGS is one of several methods that use massively parallel platforms to allow the sequencing of large stretches of DNA. Panel testing is potentially associated with greater efficiencies in the evaluation of genetic diseases; however, it may provide information on genetic variants that are of unclear clinical significance or which would not lead to changes in patient management. Currently available panels do not include all genes associated with hereditary cancer syndromes. In addition, these panels do not test for variants (ie, single nucleotide polymorphisms [SNPs]), which may be associated with a low, but increased cancer risk.

NGS Cancer Panels

A list of the genes that are included in these panels is given in Tables 1 to 3. Table 4 provides a list of other hereditary cancer test panels. A brief description of each gene follows the tables. These panels are constantly evolving and the tables below may not represent what the test currently includes.

Table 1. Ambry Genetics Hereditary Cancer Panel Tests

Gene Tested	CancerNext (34 gene)	TumorNext (11 gene)	ColoNext (17 gene)	ProstateNext (14 gene)	BRCaPlus (8 gene)	OvaNext (25 gene)	BreastNext (17 gene)
ALK							
APC	X						
AKT1							
APC			X				
ATM	X	X		X	X	X	X
ATR							
AXIN2							
BAP1							

Gene Tested	CancerNext (34 gene)	TumorNext (11 gene)	ColoNext (17 gene)	ProstateNext (14 gene)	BRCaPlus (8 gene)	OvaNext (25 gene)	BreastNext (17 gene)
<i>BARD1</i>	X	X				X	X
<i>BLM</i>							
<i>BMPR1A</i>	X		X				
<i>BRCA1</i>	X	X		X	X	X	X
<i>BRCA2</i>	X	X		X	X	X	X
<i>BRIP1</i>	X	X				X	X
<i>CDH1</i>	X		X		X	X	X
<i>CDK4</i>	X						
<i>CDKN2A</i>	X						
<i>CHEK1</i>							
<i>CHEK2</i>	X	X	X	X	X	X	X
<i>CTNNA1</i>							
<i>DICER1</i>	X					X	
<i>EGFR</i>							
<i>EPCAM</i>	X		X	X		X	
<i>FAM175A</i>							
<i>FANCP</i>							
<i>FH</i>							
<i>FLCN</i>							
<i>GALNT12</i>							
<i>GATA2</i>							
<i>GEN1</i>							
<i>GREM1</i>	X		X				
<i>HOXB13</i>	X			X			
<i>HRAS</i>							
<i>JAK2</i>							
<i>KIT</i>							
<i>KRAS</i>							
<i>MAX</i>							
<i>MEN1</i>							
<i>MET</i>							
<i>MITF</i>							
<i>MLH1</i>	X		X	X		X	
<i>MLH2</i>							
<i>MLH3</i>							
<i>MRE11A</i>	X	X				X	X
<i>MSH2</i>	X		X	X		X	
<i>MSH6</i>	X		X	X		X	
<i>MUTYH</i>	X		X			X	X
<i>NBN</i>	X	X		X		X	X
<i>NF1</i>	X					X	X
<i>NF2</i>							
<i>NRAS</i>							
<i>PALB2</i>	X	X	X	X	X	X	X
<i>PAX5</i>							
<i>PDGFRA</i>							
<i>PHOX2B</i>							
<i>PIK3CA</i>							
<i>PMS2</i>	X		X	X		X	
<i>POLD1</i>	X		X				
<i>POLE</i>	X		X				
<i>PPM1D</i>							
<i>PRSS1</i>							
<i>PTCH1</i>							
<i>PTEN</i>	X		X		X	X	X
<i>RAD50</i>	X					X	X

Gene Tested	CancerNext (34 gene)	TumorNext (11 gene)	ColoNext (17 gene)	ProstateNext (14 gene)	BRCaPlus (8 gene)	OvaNext (25 gene)	BreastNext (17 gene)
<i>RAD51</i>							
<i>RAD51B</i>							
<i>RAD51C</i>	X	X				X	X
<i>RAD51D</i>	X	X		X		X	X
<i>RB1</i>							
<i>RECQL4</i>							
<i>RET</i>							
<i>RUNX1</i>							
<i>SDHA</i>							
<i>SDHAF2</i>							
<i>SDHB</i>							
<i>SDHC</i>							
<i>SDHD</i>							
<i>SMAD3</i>							
<i>SMAD4</i>	X		X				
<i>SMARCA4</i>	X					X	
<i>SMARCB1</i>							
<i>STK11</i>	X		X			X	
<i>SUFU</i>							
<i>TERT</i>							
<i>TGFBR1</i>							
<i>TGFBR2</i>							
<i>TMEM127</i>							
<i>TP53</i>	X		X	X	X	X	X
<i>TP53BP1</i>							
<i>TSC1</i>							
<i>TSC2</i>							
<i>VHL</i>							
<i>WT1</i>							
<i>XRCC2</i>							

Table 2. GeneDx Hereditary Cancer Panel Tests

Gene Tested	Comprehensive Cancer Panel (32 genes)	High/Moderate Risk Panel (23 genes)	Lynch/Colorectal High Risk (7 genes)	Colorectal Cancer (19 genes)	Breast Cancer High/Moderate Risk (8 genes)	Breast/Ovarian Cancer (20 genes)
<i>ALK</i>						
<i>APC</i>						
<i>AKT1</i>						
<i>APC</i>	X	X	X	X		
<i>ATM</i>	X	X		X	X	X
<i>ATR</i>						
<i>AXIN2</i>	X			X		
<i>BAP1</i>						
<i>BARD1</i>	X					X
<i>BLM</i>						
<i>BMPRI1A</i>	X	X		X		
<i>BRCA1</i>	X	X			X	X
<i>BRCA2</i>	X	X			X	X
<i>BRIP1</i>	X	X				X
<i>CDH1</i>	X	X		X	X	X
<i>CDK4</i>	X					
<i>CDKN2A</i>	X	X				
<i>CHEK1</i>						
<i>CHEK2</i>	X	X		X	X	X

Gene Tested	Comprehensive Cancer Panel (32 genes)	High/Moderate Risk Panel (23 genes)	Lynch/Colorectal High Risk (7 genes)	Colorectal Cancer (19 genes)	Breast Cancer High/Moderate Risk (8 genes)	Breast/Ovarian Cancer (20 genes)
CTNNA1						
DICER1						
EGFR						
EPCAM	X	X	X	X		X
FAM175A						
FANCC	X					X
FANCP						
FH						
FLCN						
GALNT12						
GATA2						
GEN1						
GREM1	X			X		
HOXB13						
HRAS						
JAK2						
KIT						
KRAS						
MAX						
MEN1						
MET						
MITF						
MLH1	X	X	X	X		X
MLH2						
MLH3						
MRE11A						
MSH2	X	X	X	X		X
MSH6	X	X	X	X		X
MUTYH	X	X	X	X		
NBN	X					X
NF1						
NF2						
NRAS						
PALB2	X	X			X	X
PAX5						
PDGFRA						
PHOX2B						
PIK3CA						
PMS2	X	X	X	X		X
POLD1	X			X		
POLE	X			X		
PPM1D						
PRSS1						
PTCH1						
PTEN	X	X		X	X	X
RAD50						
RAD51						
RAD51B						
RAD51C	X	X				X
RAD51D	X	X				X
RB1						
RECQL4						
RET						
RUNX1						
SDHA						

Gene Tested	Comprehensive Cancer Panel (32 genes)	High/Moderate Risk Panel (23 genes)	Lynch/Colorectal High Risk (7 genes)	Colorectal Cancer (19 genes)	Breast Cancer High/Moderate Risk (8 genes)	Breast/Ovarian Cancer (20 genes)
<i>SDHAF2</i>						
<i>SDHB</i>						
<i>SDHC</i>						
<i>SDHD</i>						
<i>SMAD3</i>						
<i>SMAD4</i>		X		X		
<i>SMARCA4</i>						
<i>SMARCB1</i>						
<i>STK11</i>		X		X		
<i>SUFU</i>						
<i>TERT</i>						
<i>TGFBR1</i>						
<i>TGFBR2</i>						
<i>TMEM127</i>						
<i>TP53</i>		X		X	X	X
<i>TP53BP1</i>						
<i>TSC1</i>						
<i>TSC2</i>						
<i>VHL</i>		X				
<i>WT1</i>						
<i>XRCC2</i>						X

Table 3. Myriad Hereditary Cancer Panel Tests

Gene Tested	myRisk (27 genes)	Pancreatic (12 genes)	Colorectal High Risk (7 genes)	Colorectal and Polyposis (17 genes)	Breast and Ovarian (17 genes)	Breast Cancer (8 genes)
<i>ALK</i>						
<i>APC</i>			X			
<i>AKT1</i>						
<i>APC</i>	X			X		
<i>ATM</i>	X	X			X	X
<i>ATR</i>						
<i>AXIN2</i>						
<i>BAP1</i>						
<i>BARD1</i>	X					
<i>BLM</i>						
<i>BMPR1A</i>	X			X		
<i>BRCA1</i>	X	X			X	X
<i>BRCA2</i>	X	X			X	X
<i>BRIP1</i>	X					
<i>CDH1</i>	X			X	X	X
<i>CDK4</i>	X					
<i>CDKN2A</i>	X			X		
<i>CHEK1</i>						
<i>CHEK2</i>	X			X	X	X
<i>CTNNA1</i>						
<i>DICER1</i>						
<i>EGFR</i>						
<i>EPCAM</i>	X	X	X	X	X	
<i>FAM175A</i>						
<i>FANCC</i>						
<i>FANCP</i>						
<i>FH</i>						
<i>FLCN</i>						

Gene Tested	myRisk (27 genes)	Pancreatic (12 genes)	Colorectal High Risk (7 genes)	Colorectal and Polyposis (17 genes)	Breast and Ovarian (17 genes)	Breast Cancer (8 genes)
<i>GALNT12</i>						
<i>GATA2</i>						
<i>GEN1</i>						
<i>GREM1</i>	X			X		
<i>HOXB13</i>						
<i>HRAS</i>						
<i>JAK2</i>						
<i>KIT</i>						
<i>KRAS</i>						
<i>MAX</i>						
<i>MEN1</i>						
<i>MET</i>						
<i>MITF</i>						
<i>MLH1</i>	X	X	X	X	X	
<i>MLH2</i>						
<i>MLH3</i>						
<i>MRE11A</i>						
<i>MSH2</i>	X	X	X	X	X	
<i>MSH6</i>	X	X	X	X	X	
<i>MUTYH</i>	X	X	X	X		
<i>NBN</i>						
<i>NF1</i>						
<i>NF2</i>						
<i>NRAS</i>						
<i>PALB2</i>	X	X			X	X
<i>PAX5</i>						
<i>PDGFRA</i>						
<i>PHOX2B</i>						
<i>PIK3CA</i>						
<i>PMS2</i>	X	X	X	X	X	
<i>POLD1</i>	X			X		
<i>POLE</i>	X			X		
<i>PPM1D</i>						
<i>PRSS1</i>						
<i>PTCH1</i>						
<i>PTEN</i>	X			X	X	X
<i>RAD50</i>						
<i>RAD51</i>						
<i>RAD51B</i>						
<i>RAD51C</i>	X				X	
<i>RAD51D</i>	X				X	
<i>RB1</i>						
<i>RECQL4</i>						
<i>RET</i>						
<i>RUNX1</i>						
<i>SDHA</i>						
<i>SDHAF2</i>						
<i>SDHB</i>						
<i>SDHC</i>						
<i>SDHD</i>						
<i>SMAD3</i>						
<i>SMAD4</i>	X			X		
<i>SMARCA4</i>						
<i>SMARCB1</i>						
<i>STK11</i>	X	X		X	X	
<i>SUFU</i>						

Gene Tested	myRisk (27 genes)	Pancreatic (12 genes)	Colorectal High Risk (7 genes)	Colorectal and Polyposis (17 genes)	Breast and Ovarian (17 genes)	Breast Cancer (8 genes)
<i>TERT</i>						
<i>TGFBR1</i>						
<i>TGFBR2</i>						
<i>TMEM127</i>						
<i>TP53</i>	X	X		X	X	X
<i>TP53BP1</i>						
<i>TSC1</i>						
<i>TSC2</i>						
<i>VHL</i>						
<i>WT1</i>						
<i>XRCC2</i>						

Table 4. Other Hereditary Cancer Panel Tests

Gene Tested	MSK-IMPACT ^a (76 genes)	Color (30 genes)	Counsyl Reliant Cancer Screen (36 genes)	Mayo Clinic Colon Cancer (19 genes)	U Washington BROCA Cancer (51 genes)	U Washington ColoSeq (20 genes)
<i>ALK</i>	X					
<i>APC</i>	X		X	X	X	
<i>AKT1</i>					X	X
<i>APC</i>		X				X
<i>ATM</i>	X	X	X	X	X	
<i>ATR</i>					X	
<i>AXIN2</i>				X		
<i>BAP1</i>	X	X			X	
<i>BARD1</i>	X	X	X		X	
<i>BLM</i>	X					
<i>BMPR1A</i>	X	X	X	X	X	X
<i>BRCA1</i>	X	X	X		X	
<i>BRCA2</i>	X	X	X		X	
<i>BRIP1</i>	X	X	X		X	
<i>CDH1</i>	X	X	X	X	X	X
<i>CDK4</i>	X	X	X		X	
<i>CDKN2A</i>	X	X	X		X	
<i>CHEK1</i>					X	
<i>CHEK2</i>	X	X	X	X	X	
<i>CTNNA1</i>					X	
<i>DICER1</i>	X					
<i>EGFR</i>	X					
<i>EPCAM</i>	X	X	X	X		X
<i>FAM175A</i>	X				X	
<i>FANCP</i>					X	
<i>FH</i>	X					
<i>FLCN</i>	X					
<i>GALNT12</i>					X	X
<i>GATA2</i>	X					
<i>GEN1</i>					X	
<i>GREM1</i>	X	X	X		X	X
<i>HOXB13</i>					X	
<i>HRAS</i>	X					
<i>JAK2</i>	X					
<i>KIT</i>	X					
<i>KRAS</i>	X					
<i>MAX</i>	X					
<i>MEN1</i>	X		X		X	

Gene Tested	MSK-IMPACT ^a (76 genes)	Color (30 genes)	Counsyl Reliant Cancer Screen (36 genes)	Mayo Clinic Colon Cancer (19 genes)	U Washington BROCA Cancer (51 genes)	U Washington ColoSeq (20 genes)
<i>MET</i>	X					
<i>MITF</i>	X	X				
<i>MLH1</i>	X	X	X	X	X	X
<i>MLH2</i>						X
<i>MLH3</i>				X		
<i>MRE11A</i>	X		X		X	
<i>MSH2</i>	X	X	X	X	X	X
<i>MSH6</i>	X	X	X	X	X	X
<i>MUTYH</i>	X	X	X	X	X	X
<i>NBN</i>	X	X	X		X	
<i>NF1</i>	X					
<i>NF2</i>	X					
<i>NRAS</i>	X					
<i>PALB2</i>	X	X	X		X	
<i>PAX5</i>	X					
<i>PDGFRA</i>	X					
<i>PHOX2B</i>	X					
<i>PIK3CA</i>					X	X
<i>PMS2</i>	X	X	X	X	X	X
<i>POLD1</i>		X	X		X	X
<i>POLE</i>	X	X	X		X	X
<i>PPM1D</i>					X	
<i>PRSS1</i>					X	
<i>PTCH1</i>	X					
<i>PTEN</i>	X	X	X	X	X	X
<i>RAD50</i>	X		X		X	
<i>RAD51</i>	X				X	
<i>RAD51B</i>	X					
<i>RAD51C</i>	X	X	X		X	
<i>RAD51D</i>	X	X	X		X	
<i>RB1</i>	X					
<i>RECQL4</i>	X					
<i>RET</i>	X		X	X	X	
<i>RUNX1</i>	X					
<i>SDHA</i>	X		X			
<i>SDHAF2</i>	X			X		
<i>SDHB</i>	X		X		X	
<i>SDHC</i>	X		X		X	
<i>SDHD</i>	X				X	
<i>SMAD3</i>	X					
<i>SMAD4</i>	X	X	X	X	X	X
<i>SMARCA4</i>	X					
<i>SMARCB1</i>	X					
<i>STK11</i>	X	X	X	X	X	X
<i>SUFU</i>	X					
<i>TERT</i>	X					
<i>TGFR1</i>	X					
<i>TGFR2</i>	X					
<i>TMEM127</i>	X					
<i>TP53</i>	X	X	X	X	X	X
<i>TP53BP1</i>					X	
<i>TSC1</i>	X					
<i>TSC2</i>	X					
<i>VHL</i>	X		X		X	
<i>WT1</i>	X					

Gene Tested	MSK-IMPACT ^a (76 genes)	Color (30 genes)	Counsyl Reliant Cancer Screen (36 genes)	Mayo Clinic Colon Cancer (19 genes)	U Washington BROCA Cancer (51 genes)	U Washington ColoSeq (20 genes)
<i>XRCC2</i>					X	

^a Memorial Sloan Kettering-Integrated Mutation Profiling of Actionable Cancer Targets.

Myriad Genetics (Salt Lake City, UT) offers the myRisk[®] NGS panel. Mayo Clinic (Rochester, MN) also offers a hereditary colon cancer multigene panel analysis, which includes the genes in the Ambry Genetics ColoNext, with the addition of 2 other low-risk genes (*MLH3*, *AXIN2*). The University of Washington (Seattle, WA) offers the BROCA Cancer Risk Panel.¹ The University of Washington also offers the ColoSeq[™] gene panel, which includes 19 genes associated with Lynch syndrome (hereditary nonpolyposis colorectal cancer), familial adenomatous polyposis (FAP), *MUTYH*-associated polyposis, hereditary diffuse gastric cancer (DGC), Cowden syndrome (CS), Li-Fraumeni syndrome (LFS), Peutz-Jeghers syndrome (PJS), Muir-Torre syndrome, Turcot syndrome, and juvenile polyposis syndrome (JPS).² In 2017, the Memorial Sloan Kettering-Integrated Mutation Profiling of Actionable Cancer Targets (MSK-IMPACT[™]; Memorial Sloan Kettering Cancer Center, New York, NY) was reported to include 76 genes implicated in cancer.³ The association of these genes with specific cancers is described in an online supplement to the report. Marketing of the Color cancer susceptibility panel (Color Genomics, Burlingame, CA) is directed at consumers; a physician in their network will order the test when purchased (personal communication).

Genes Included in NGS Panels

The following is a summary of the function and disease association of major genes included in NGS panels. This summary is not comprehensive.

BRCA1 and *BRCA2* Variants

BRCA1 and *BRCA2* germline variants are associated with hereditary breast and ovarian cancer syndrome, which is associated most strongly with increased susceptibility to breast cancer at an early age, bilateral breast cancer, male breast cancer, ovarian cancer, cancer of the fallopian tube, and primary peritoneal cancer. *BRCA1* and *BRCA2* variants are also associated with increased risk of other cancers, including prostate cancer, pancreatic cancer, gastrointestinal cancers, melanoma, and laryngeal cancer.

APC Variants

APC germline variants are associated with FAP and attenuated FAP. FAP is an autosomal dominant colon cancer predisposition syndrome characterized by hundreds to thousands of colorectal adenomatous polyps, and accounts for about 1% of all colorectal cancers (CRCs).

ATM Variants

ATM is associated with the autosomal recessive condition ataxia-telangiectasia. This condition is characterized by progressive cerebellar ataxia with onset between the ages

of 1 and 4 years, telangiectasias of the conjunctivae, oculomotor apraxia, immune defects, and cancer predisposition, particularly leukemia and lymphoma.

BARD1, BRIP1, MRE11A, NBN, RAD50, and RAD51C Variants

BARD1, BRIP1, MRE11A, NBN, RAD50, and RAD51C are genes in the Fanconi anemia/*BRCA* pathway. Variants in these genes are estimated to confer up to a 4-fold increase in the risk for breast cancer. This pathway is also associated with a higher risk of ovarian cancer and, less often, pancreatic cancer.

BMPR1A and SMAD4 Variants

BMPR1A and *SMAD4* are genes mutated in JPS and account for 45% to 60% of cases of JPS. JPS is an autosomal dominant disorder that predisposes to the development of polyps in the gastrointestinal tract. Malignant transformation can occur, and the risk of gastrointestinal cancer has been estimated from 9% to 50%.

CHEK2 Variants

CHEK2 gene variants confer an increased risk of developing several different types of cancer, including breast, prostate, colon, thyroid, and kidney. *CHEK2* regulates the function of BRCA1 protein in DNA repair and has been associated with familial breast cancers.

CDH1 Variants

CDH1 germline variants are associated with lobular breast cancer in women and with hereditary DGC. The estimated cumulative risk of gastric cancer for *CDH1* variant carriers by age 80 years is 70% for men and 56% for women. *CDH1* variants are associated with a lifetime risk of 39% to 52% of lobular breast cancer.

EPCAM, MLH1, MSH2, MSH6, and PMS2 Variants

EPCAM, MLH1, MSH2, MSH6, and PMS2 are mismatch repair genes associated with Lynch syndrome (hereditary nonpolyposis colorectal cancer). Lynch syndrome is estimated to cause 2% to 5% of all colon cancers. Lynch syndrome is associated with a significantly increased risk of several types of cancer—colon cancer (60%-80% lifetime risk), uterine/endometrial cancer (20%-60% lifetime risk), gastric cancer (11%-19% lifetime risk), and ovarian cancer (4%-13% lifetime risk). The risks of other types of cancer, including small intestine, hepatobiliary tract, upper urinary tract, and brain, are also elevated.

MUTYH Variants

MUTYH germline variants are associated with an autosomal recessive form of hereditary polyposis. It has been reported that 33% and 57% of patients with clinical FAP and attenuated FAP, respectively, who are negative for variants in the *APC* gene, have *MUTYH* variants.

PALB2 Variants

PALB2 germline variants are associated with an increased risk of pancreatic and breast cancer. Familial pancreatic and/or breast cancer due to *PALB2* variants is inherited in an autosomal dominant pattern.

PTEN Variants

PTEN variants are associated with *PTEN* hamartoma tumor syndrome (PHTS), which includes CS, Bannayan-Riley-Ruvalcaba syndrome, and Proteus syndrome. CS is characterized by a high risk of developing tumors of the thyroid, breast, and endometrium. Affected persons have a lifetime risk of up to 50% for breast cancer, 10% for thyroid cancer, and 5% to 10% for endometrial cancer.

STK11 Variants

STK11 germline variants are associated with PJS, an autosomal dominant disorder, with a 57% to 81% risk of developing cancer by age 70, of which gastrointestinal and breast cancers are the most common.

TP53 Variants

TP53 are associated with LFS. People with *TP53* variants have a 50% risk of developing any of the associated cancers by age 30 and a lifetime risk up to 90%, including sarcomas, breast cancer, brain tumors, and adrenal gland cancers.

NF1 Variants

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

RAD51D Variants

RAD51D germline variants are associated with familial breast and ovarian cancers.

CDK4 Variants

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

CDKN2A Variants

Cyclin-dependent kinase inhibitor 2A (*CDKN2A*) encodes proteins that act as multiple tumor suppressors through their involvement in 2 cell cycle regulatory pathways: the p53 pathway and the *RB1* pathway. Variants or deletions in *CDKN2A* are frequently found in multiple types of tumor cells. Germline variants in *CDKN2A* have been associated with risk of melanoma, along with pancreatic and central nervous system cancers.

RET Variants

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

SDHA, SDHB, SDHC, SDHD, and SDHAF2 Variants

SDHA, *SDHB*, *SDHC*, *SDHD*, and *SDHAF2* gene products are involved in the assembly and function of 1 component of the mitochondrial respiratory chain. Germline variants in these genes are associated with the development of paragangliomas, pheochromocytomas, gastrointestinal stromal tumors, and a *PTEN*-negative Cowden-like syndrome.

TMEM127 Variants

Transmembrane protein 127 (*TMEM127*) germline variants are associated with risk of pheochromocytomas.

VHL Variants

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

FH Variants

Fumarate hydratase (*FH*) variants are associated with renal cell and uterine cancers.

FLCN Variants

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

MET Variants

MET is a proto-oncogene that acts as the hepatocyte growth factor receptor. *MET* variants are associated with hepatocellular carcinoma and papillary renal cell carcinoma.

MITF Variants

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

TSC1 Variants

Tuberous sclerosis 1 (*TSC1*) and tuberous sclerosis 2 (*TSC2*) encode the proteins hamartin and tuberin, which are involved in cell growth, differentiation, and proliferation. Variants in these genes are associated with the development of tuberous sclerosis

complex, an autosomal dominant syndrome characterized by skin abnormalities, developmental delay, seizures, and multiple types of cancers, including central nervous system tumors, renal tumors (including angiomyolipomas, renal cell carcinomas), and cardiac rhabdomyomas.

XRCC2 Variants

XRCC2 encodes proteins thought to be related to the RAD51 protein product that is involved in DNA double-stranded breaks. Variants may be associated with Fanconi anemia and breast cancer.

FANCC Variants

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

AXIN2 Variants

AXIN2 variants are associated with FAP syndrome, although the phenotypes associated with *AXIN2* variants do not appear to be well characterized.

Hereditary Cancer and Cancer Syndromes

Hereditary Diffuse Gastric Cancer

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

Hereditary Colon Cancer Syndromes

Hereditary colon cancer syndromes are thought to account for approximately 10% of all CRCs. Another 20% have a familial predilection for CRC without a clear hereditary syndrome identified.¹ The hereditary CRC syndromes can be divided into the polyposis and nonpolyposis syndromes. Although there may be polyps in the nonpolyposis syndromes, they are usually less numerous; the presence of 10 colonic polyps is used as a rough threshold when considering genetic testing for a polyposis syndrome.² The polyposis syndromes can be further subdivided by polyp histology, which includes the adenomatous (*FAP*, attenuated *FAP*, *MUTYH*-associated) and hamartomatous (JPS, PJS, PHTS) polyposis syndromes. The nonpolyposis syndromes include Lynch syndrome.

REGULATORY STATUS

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments (CLIA). Laboratories that offer laboratory-developed tests must be licensed by 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

Genetic cancer susceptibility panel testing using next generation sequencing are considered **experimental / investigational**.

Policy Guidelines

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.

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

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

RATIONALE

Updated literature reviews were conducted most recently through August 8, 2018.

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.

Cancer Susceptibility Panels

Cancer susceptibility panels may be either diagnostic or prognostic.

Clinical Context and Test Purpose

The purpose of diagnostic testing symptomatic patients for genetic or heritable pathogenic variants is to establish a molecular diagnosis defined by the presence of a known pathologic variant(s). For genetic testing, a symptomatic individual is defined as one with a clinical phenotype that correlates with a known pathologic variant but who has not yet developed a malignancy. The criteria under which testing for genetic cancer susceptibility may be considered clinically useful are as follows:

- An association of the marker with the disorder has been established;
- Symptoms of the disease are present;

- A definitive diagnosis cannot be made based on history, physical examination, pedigree analysis, and/or standard diagnostic studies or tests; and
- The clinical utility of a diagnosis has been established (eg, by demonstrating that a definitive diagnosis will lead to changes in clinical management of the condition, changes in surveillance, or changes in reproductive decision making, and these changes will lead to improved health outcomes).

The purpose of prognostic testing for cancer susceptibility is to predict whether a cancer is likely to occur in a family member of an affected person. The criteria under which prognostic 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 (eg, by demonstrating that testing will lead to changes in clinical management of the condition or changes in surveillance).

The question addressed in this evidence review is: Does testing for genetic cancer susceptibility improve the net health outcome?

The following PICOTS were used to select literature to inform this review.

Patients

The relevant population of interest is patients being evaluated for clinical signs or symptoms that may be associated with a risk for the presence of a heritable cancer variant (diagnostic testing) or have a family member(s) diagnosed with a heritable cancer(s) (prognostic testing).

Intervention

The test being considered is a cancer susceptibility panel.

Comparator

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

Outcomes

The outcomes of interest are sensitivity and specificity, positive and negative predictive value, and reductions in morbidity and mortality.

Timing

Follow-up varies by whether testing is diagnostic or prognostic.

Setting

These tests are offered commercially through various manufacturers and institutions.

Technically Reliable

Assessment of technical reliability focuses on specific tests and operators and requires review of unpublished and often proprietary information. Review of specific tests, operators, and unpublished data are outside the scope of this evidence review and alternative sources exist. This evidence review focuses on the clinical validity and clinical utility.

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).

The published literature provides no guidance on the assessment of the clinical validity of panel testing for cancer susceptibility with next-generation sequencing (NGS), and the usual approach to establishing the clinical validity of genetic testing is difficult to apply to panel testing.

Although it may be possible to evaluate the clinical validity of sequencing of individual genes found on these panels, the clinical validity of NGS for cancer susceptibility panels, which include variants associated with an unknown or variable cancer risk, are of uncertain clinical validity.

For genetic susceptibility to cancer, clinical validity can be considered at the following levels:

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

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 (eg, 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 a hereditary cancer panel between August 2013 and October 2014.³ 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. Patients with breast and ovarian cancers were stratified according to previous *BRCA1* and *BRCA2* genetic testing. Patients with colon or stomach cancers were combined because of the small number of patients with stomach cancers. Eight multigene cancer panels comprising combinations of 29 genes were included. 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.⁴

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

- high risk: *APC*, *BMP1A*, *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*.

Over half of the individuals referred for testing were women with breast cancer (n=5209), of whom 3315 (63.6%) had not had previous *BRCA1* and *BRCA2* testing. Unaffected individuals comprised 25.2% of the study population. 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, with *CHEK2* accounting for the majority of all likely pathogenic variants (68.7% [68/99]).

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*. *BRCA1* and *BRCA2* accounted for 9.7% (12/124) of positive variants identified in individuals diagnosed with colon cancer. The Lynch syndrome/colorectal cancer (CRC) panel (GeneDx), containing *MLH1*, *MSH2*, *MSH6*, *PMS2*, *EPCAM*, *APC*, and *MUTYH*, had the highest yield (13.7% overall; 17.6% among affected individuals). The panel's high yield was likely a result of the well-established association of all genes on this panel with CRC and the specific clinical history or tumor characteristics (microsatellite instability and/or immunohistochemistry) that prompted providers to order this focused panel.

The breast cancer high-risk panel containing *BRCA1*, *BRCA2*, *CDH1*, *PTEN*, *STK11*, and *TP53* had the lowest yield (3.8% overall, 4.2% among individuals with breast cancer). 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 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 (including *TP53*, *PTEN*, and *CDH1*) accounted for 5.8% (19/330), 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 without previous *BRCA1* and *BRCA2* testing, 13.4% (89/663) had variants, of which *BRCA1* and *BRCA2* 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]). Of 901 patients with positive results, 28 (3.1%) had more than 1 positive finding, reflecting 0.3% (28/10,030) of the total testing population; 5 had positive results in 2 highly penetrant genes; 12 had 1 positive result in a high-risk gene, and 1 in a gene with moderate or unknown risk; and 11 had 2 positive findings in genes with moderate or unknown risk.

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 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 the International Gastric Cancer Linkage Consortium testing criteria, resulting in a frequency of 0.02% (2/8708) positive *CDH1* results. In summary, among patients with specific cancers, yields were 9.7%, 13.4%, and 14.8% in patients with breast, ovarian, and colon/stomach cancers, 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 CRC 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.

LaDuca et al (2014) reported on the clinical and molecular characteristics of 2079 patients who underwent panel testing with BreastNext, OvaNext, ColoNext, or CancerNext (Ambry Genetics).⁵ 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. A total of 2079 cases were included: 874 BreastNext, 222 OvaNext, 557 ColoNext, and 425 CancerNext. 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 a commercial laboratory who were found to have a pathogenic or likely pathogenic variant.⁶ 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.

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).⁷ The frequency of pathogenic variants was estimated at 10.2%. After 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 high or moderately increased risk of breast cancer (see Table 5). Notably, of the various panels included in this study, only the 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 5. Moderate-to-High Risk Non-*BRCA1* and *BRCA2*, Nonsyndromic Genes Associated With Breast Cancer

Gene	Odds Ratio	95% Confidence Interval	Risk Category
<i>ATM</i>	2.78	2.22 to 3.62	Moderate
<i>BARD1</i>	2.16	1.31 to 3.63	Moderate
<i>CHEK2</i>	1.48	1.31 to 1.67	Moderate
<i>PALB2</i>	7.46	5.12 to 11.19	High
<i>RAD51D</i>	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.⁸ 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.⁹ 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 National Comprehensive Cancer Network 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*), 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.

Tung et al (2015) included 2 cohorts: 1781 patients referred for commercial testing for *BRCA1* and *BRCA2* variants and whose samples were consecutively submitted to Myriad between November 2012 and April 2013 (cohort 1), and 377 DNA samples from patients who were referred to Beth Israel Deaconess Medical Center for genetic testing between 1998 and 2013 and had previously tested negative for *BRCA1* and *BRCA2* (cohort 2).¹⁰ Variants were identified in 16 genes, with the most frequent being *BRCA1*, *BRCA2*, *CHEK2*, *ATM*, and *PALB2*.

Colorectal Cancer

Hansen et al (2017) published a retrospective analysis using multigene panel testing to identify genetic causes for increased CRC risk.¹¹ A custom gene panel targeting 112 genes, including both well-known and candidate CRC susceptibility genes, was designed, and variants were validated by Sanger sequencing. DNA samples from 274 familial CRC patients who fulfilled the Amsterdam I/II and/or the Revised Bethesda guidelines were included. All had previously been screened for variants in 1 or more of the MMR genes (*MLH1*, *MSH2*, *MSH6*, *PMS2*) without any pathogenic findings. In well-known cancer susceptibility genes, 17 pathogenic variants and 19 VUS were identified. Thirty-seven potentially pathogenic variants in candidate CRC susceptibility genes were also identified. Clinical correlations were not available.

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.¹² For the period included in the study (March 2012-March 2013), the ColoNext test included the *MLH1*, *MSH2*, *MSH6*, *PMS2*, *EPCAM*, *BMP1*, *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 National Comprehensive Cancer Network

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 *vs* a second-tier test (i.e. after syndrome-based testing is negative), remains to be determined.”

Section Summary: Clinically Valid

Clinical validity studies have studied mixed populations; high-risk individuals due to clinical presentation or family history as well as cancer affected persons with or without prior variant testing. 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. VUS rates increased in proportion with panel size, reaching nearly 50% for large gene panels.

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, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary 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.

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.

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

- Does panel testing offer substantial advantages in efficiency compared with sequential analysis of individual genes?
- 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 a high-risk hereditary cancer syndrome. Changes in clinical management could include modifications in cancer surveillance, specific risk-reducing measures (eg, prophylactic surgery), and treatment guidance (eg, 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 one 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.

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 one. 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 would increase with the number of genes in a panel and that the choice of a panel would 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 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.

Rosenthal et al (2017) published an industry-sponsored study evaluating the clinical utility of a 25-gene pan-cancer panel.¹⁵ 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.

Kurian et al (2014) evaluated the information from an 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 2012.¹⁶ 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. Testing with the panel confirmed 57 of 59 of the pathogenic *BRCA1* and *BRCA2* variants; of the 2 others, one was detected but reclassified as a VUS, and the other was a large insertion that would not be picked up by NGS panel testing. Of the women who tested negative for *BRCA1* and *BRCA2* variants (n=141), 16 had pathogenic variants in other genes (11.4%). The affected genes were *ATM* (n=2), *BLM* (n=1), *CDH1* (n=1), *CDKN2A* (n=1), *MLH1* (n=1), *MUTYH* (n=5), *NBN* (n=2), *PRSS1* (n=1), and *SLX4* (n=2). Eleven of these variants had been previously reported in the literature and 5 were novel. Eighty percent of the women with pathogenic variants in the non-*BRCA1* and -*BRCA2* genes had a personal history of breast cancer. 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 an *MLH1* variant consistent with Lynch syndrome underwent risk-reducing salpingo-oophorectomy and early colonoscopy, which identified a tubular adenoma that was excised (she had previously undergone hysterectomy for endometrial carcinoma). 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: Clinically Useful

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

pathogenic, benign, or variants of uncertain significance) can differ between laboratories. Clinical validity studies have reported on the results of the frequency with which variants are identified. The rates of variants of uncertain significance for gene panels are significant and increase in proportion with panel size, reaching nearly 50% for large gene panels. Published data on clinical utility is lacking, and it is unknown whether the use of these panels improves health outcomes. Variants included in these panels are associated with varying levels of risk of developing cancer. Only some variants included on panels are associated with a high risk of developing a well-defined cancer syndrome for which there are established clinical management guidelines. Many panels include genetic variants considered to be of moderate or low penetrance, and clinical management recommendations for these genes are not well-defined. The lack of clinical management pathways for variants of uncertain significance increases the potential for harm. The evidence is insufficient to determine the effects of the technology on health outcomes.

PRACTICE GUIDELINES AND POSITION STATEMENTS

American Society of Clinical Oncology

The American Society of Clinical Oncology (2015) updated its policy statement on genetic and genomic testing for cancer susceptibility.¹⁷ 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 that there is little consensus as to which genes should be included on panels for cancer susceptibility testing.

National Comprehensive Cancer Network

National Comprehensive Cancer Network guidelines on genetic/familial high-risk assessment for breast and ovarian cancers (v.2.2019)¹⁸ state the following on multigene testing:

- “Patients who have a personal or family history suggestive of a single inherited cancer syndrome are most appropriately managed by genetic testing for that specific syndrome. When more than one gene can explain an inherited cancer syndrome, then multi-gene testing may be more efficient and/or cost effective.
- There may be a role for multi-gene testing in individuals who have tested negative (indeterminate) for a single syndrome, but whose personal or family history remains suggestive of an inherited susceptibility.
- As commercially available tests differ in the specific genes analyzed (as well as classification of variants and many other factors), choosing the specific laboratory and test panel is important.
- Multi-gene testing can include “intermediate” penetrant (moderate-risk) genes. For many of these genes, there are limited data on the degree of cancer risk and there are no clear guidelines on risk management for carriers of mutations. Not all genes included on available multi-gene test are necessarily clinically actionable.
- As is the case with high-risk genes, it is possible that the risks associated with moderate-risk genes may not be entirely due to that gene alone, but may be influenced by gene/gene or gene/environment interactions.... Therefore, it may be difficult to use a known mutation alone to assign risk for relatives.
- In many cases, the information from testing for moderate penetrance genes does not change risk management compared with that based on family history alone....”

- There is an increased likelihood of finding variants of unknown significance when testing for mutations in multiple genes.
- It is for these and other reasons that multigene testing is ideally offered in the context of professional genetic expertise for pre- and post-test counseling.”

National Comprehensive Cancer Network guidelines on genetic/familial high-risk assessment for colorectal cancer (v.1.2018) state that “when more than one gene can explain an inherited cancer syndrome, then multi-gene testing may be more efficient and/or cost-effective than single gene testing,” and “there is also a role for multi-gene testing in individuals who have tested negative (indeterminate) for a single syndrome, but whose personal or family history remains strongly suggestive of an inherited susceptibility.”¹⁹ However, the Network cautioned about the increased likelihood of finding variants of uncertain significance, which increases with the number of genes included in the panel, and that gene panels can include moderate-risk genes that may not be clinically actionable.

U.S. PREVENTIVE SERVICES TASK FORCE RECOMMENDATIONS

The U.S. Preventive Services Task Force (2015) has recommended that primary care providers screen women who have family members with breast, ovarian, tubal, or peritoneal cancer with one of several screening tools designed to identify a family history that may be associated with an increased risk for potentially harmful variants in breast cancer and susceptibility genes (*BRCA1* or *BRCA2*).²⁰ 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 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			
NCT01850654	Ohio Colorectal Cancer Prevention Initiative: Universal Screening for Lynch Syndrome	3470	Jan 2018

NCT: national clinical trial.

CODING

The following codes for treatment and procedures applicable to this policy are included below for informational purposes. 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.

CPT/HCPCS

- 81432 Hereditary breast cancer-related disorders (eg, 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 (eg, 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 (eg, 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 (eg, 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 (eg, 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 (eg, medullary thyroid carcinoma, parathyroid carcinoma, malignant pheochromocytoma or paraganglioma); duplication/deletion analysis panel, must include analyses for SDHB, SDHC, SDHD, and VHL
- 81445 Targeted genomic sequence analysis panel, solid organ neoplasm, DNA analysis, and RNA analysis when performed, 5-50 genes (eg, ALK, BRAF, CDKN2A, EGFR, ERBB2, KIT, KRAS, NRAS, MET, PDGFRA, PDGFRB, PGR, PIK3CA, PTEN, RET), interrogation for sequence variants and copy number variants or rearrangements, if performed
- 81450 Targeted genomic sequence analysis panel, hematolymphoid neoplasm or disorder, DNA analysis, and RNA analysis when performed, 5-50 genes (eg, BRAF, CEBPA, DNMT3A, EZH2, FLT3, IDH1, IDH2, JAK2, KRAS, KIT, MLL, NRAS, NPM1, NOTCH1), interrogation for sequence variants, and copy number variants or rearrangements, or isoform expression or mRNA expression levels, if performed
- 81455 Targeted genomic sequence analysis panel, solid organ or hematolymphoid neoplasm, DNA analysis, and RNA analysis when performed, 51 or greater genes (eg, ALK, BRAF, CDKN2A, CEBPA, DNMT3A, EGFR, ERBB2, EZH2, FLT3, IDH1, IDH2, JAK2, KIT, KRAS, MLL, NPM1, NRAS, MET, NOTCH1, PDGFRA, PDGFRB, PGR, PIK3CA, PTEN, RET), interrogation for sequence variants and copy number variants or rearrangements, if performed
- 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)
- If the panel does not meet the criteria in the specific code descriptors or if the specific analyte is not listed in the more specific CPT codes, then the following unlisted code would be reported: 81479. The unlisted code would be reported once to represent all of the unlisted analytes in the panel.

ICD-10 Diagnoses

Experimental / Investigational for all diagnoses related to this medical policy.

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: <ul style="list-style-type: none"> ▪ 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: <ul style="list-style-type: none"> ▪ Revised nomenclature to CPT code: 81432.
07-01-2018	In Coding section: <ul style="list-style-type: none"> ▪ Added CPT code: 0048U.
11-07-2018	Updated Description section.
	In Policy section: <ul style="list-style-type: none"> ▪ 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: <ul style="list-style-type: none"> ▪ Updated coding bullets.
	Updated References section.

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