Genetic Cancer Susceptibility Panels Using Next Generation Sequencing

Policy # 00382
Original Effective Date: 09/18/2013
Current Effective Date: 12/20/2017

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Services Are Considered Investigational
Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers genetic cancer susceptibility panels using next generation sequencing to be **investigational.***

Background/Overview

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.

Several companies, including Ambry Genetics (Aliso Viejo, CA) and GeneDx (Gaithersburg, MD), offer genetic testing panels that use next-generation sequencing (NGS) methods for hereditary cancers. NGS refers to 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 which would not lead to changes in patient management. Currently available panels do not include all genes associated with hereditary cancer syndromes. Also, these panels do not test for variants (ie, single-nucleotide variants [SNVs]), which may be associated with a low, but increased cancer risk.

NGS Cancer Panels

A list of genes 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							

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Gene Tested	CancerNext (34 gene)	TumorNext (11 gene)	ColoNext (17 gene)	ProstateNext (14 gene)	BRCAplus (8 gene)	OvaNext (25 gene)	BreastNext (17 gene)
BAP1							
BARD1	X	X				X	X
BLM							
BMPR1A	X		X				
BRCA1	X	X		X	X	X	X
BRCA2	X	X		X	X	X	X
BRIP1	X	X				X	X
CDH1	X		X		X	X	X
CDK4	X						
CDKN2A	X						
CHEK1							
CHEK2	X	X	X	X	X	X	X
CTNNA1							
DICER1	X					X	
EGFR							
EPCAM	X		X	X		X	
FAM175A							
FANCP							
FH							
FLCN							
GALNT12							
GATA2							
GEN1							
GREM1	X		X				
HOXB13	X			X			
HRAS							
JAK2							
KIT							
KRAS							
MAX							
MEN1							
MET							
MITF							
MLH1	X		X	X		X	
MLH2							
MLH3							
MRE11A	X	X				X	X
MSH2	X		X	X		X	
MSH6	X		X	X		X	
MUTYH	X		X			X	X
NBN	X	X		X		X	X
NF1	X					X	X
NF2							
NRAS							
PALB2	X	X	X	X	X	X	X
PAX5							
PDGFRA							
PHOX2B							
PIK3CA							
PMS2	X		X	X		X	
POLD1	X		X				
POLE	X		X				
PPM1D							
PRSS1							
PTCH1							
PTEN	X		X		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)
RAD50	X					X	X
RAD51							
RAD51B							
RAD51C	X	X				X	X
RAD51D	X	X		X		X	X
RB1							
RECQL4							
RET							
RUNX1							
SDHA							
SDHAF2							
SDHB							
SDHC							
SDHD							
SMAD3							
SMAD4	X		X				
SMARCA4	X					X	
SMARCB1							
STK11	X		X			X	
SUFU							
TERT							
TGFBR1							
TGFBR2							
TMEM127							
TP53	X		X	X	X	X	X
TP53BP1							
TSC1							
TSC2							
VHL							
WT1							
XRCC2							

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)
ALK						
APC						
AKT1						
APC	X	X	X	X		
ATM	X	X		X	X	X
ATR						
AXIN2	X			X		
BAP1						
BARD1	X					X
BLM						
BMPR1A	X	X		X		
BRCA1	X	X			X	X
BRCA2	X	X			X	X
BRIP1	X	X				X
CDH1	X	X		X	X	X
CDK4	X					
CDKN2A	X	X				
CHEK1						
CHEK2	X	X		X	X	X

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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)
SDHAF2						
SDHB						
SDHC						
SDHD						
SMAD3						
SMAD4		X		X		
SMARCA4						
SMARCB1						
STK11		X		X		
SUFU						
TERT						
TGFBR1						
TGFBR2						
TMEM127						
TP53		X		X	X	X
TP53BP1						
TSC1						
TSC2						
VHL		X				
WT1						
XRCC2						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)
ALK						
APC			X			
AKT1						
APC	X			X		
ATM	X	X			X	X
ATR						
AXIN2						
BAP1						
BARD1	X					
BLM						
BMPR1A	X			X		
BRCA1	X	X			X	X
BRCA2	X	X			X	X
BRIP1	X					
CDH1	X			X	X	X
CDK4	X					
CDKN2A	X			X		
CHEK1						
CHEK2	X			X	X	X
CTNNA1						
DICER1						
EGFR						
EPCAM	X	X	X	X	X	
FAM175A						
FANCC						
FANCP						
FH						
FLCN						

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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)
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						
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
RAD50						
RAD51						
RAD51B						
RAD51C	X				X	
RAD51D	X				X	
RB1						
RECQL4						
RET						
RUNX1						
SDHA						
SDHAF2						
SDHB						
SDHC						
SDHD						
SMAD3						
SMAD4	X			X		
SMARCA4						
SMARCB1						
STK11	X	X		X	X	

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)
SUFU						
TERT						
TGFBR1						
TGFBR2						
TMEM127						
TP53	X	X		X	X	X
TP53BP1						
TSC1						
TSC2						
VHL						
WT1						
XRCC2						

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)
ALK	X					
APC	X		X	X	X	
AKT1					X	X
APC		X				X
ATM	X	X	X	X	X	
ATR					X	
AXIN2				X		
BAP1	X	X			X	
BARD1	X	X	X		X	
BLM	X					
BMPR1A	X	X	X	X	X	X
BRCA1	X	X	X		X	
BRCA2	X	X	X		X	
BRIP1	X	X	X		X	
CDH1	X	X	X	X	X	X
CDK4	X	X	X		X	
CDKN2A	X	X	X		X	
CHEK1					X	
CHEK2	X	X	X	X	X	
CTNNA1					X	
DICER1	X					
EGFR	X					
EPCAM	X	X	X	X		X
FAM175A	X				X	
FANCP					X	
FH	X					
FLCN	X					
GALNT12					X	X
GATA2	X					
GEN1					X	
GREM1	X	X	X		X	X
HOXB13					X	
HRAS	X					
JAK2	X					
KIT	X					
KRAS	X					
MAX	X					

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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)
MEN1	X		X		X	
MET	X					
MITF	X	X				
MLH1	X	X	X	X	X	X
MLH2						X
MLH3				X		
MRE11A	X		X		X	
MSH2	X	X	X	X	X	X
MSH6	X	X	X	X	X	X
MUTYH	X	X	X	X	X	X
NBN	X	X	X		X	
NF1	X					
NF2	X					
NRAS	X					
PALB2	X	X	X		X	
PAX5	X					
PDGFRA	X					
PHOX2B	X					
PIK3CA					X	X
PMS2	X	X	X	X	X	X
POLD1		X	X		X	X
POLE	X	X	X		X	X
PPM1D					X	
PRSS1					X	
PTCH1	X					
PTEN	X	X	X	X	X	X
RAD50	X		X		X	
RAD51	X				X	
RAD51B	X					
RAD51C	X	X	X		X	
RAD51D	X	X	X		X	
RB1	X					
RECQL4	X					
RET	X		X	X	X	
RUNX1	X					
SDHA	X		X			
SDHAF2	X			X		
SDHB	X		X		X	
SDHC	X		X		X	
SDHD	X				X	
SMAD3	X					
SMAD4	X	X	X	X	X	X
SMARCA4	X					
SMARCB1	X					
STK11	X	X	X	X	X	X
SUFU	X					
TERT	X					
TGFBR1	X					
TGFBR2	X					
TMEM127	X					
TP53	X	X	X	X	X	X
TP53BP1					X	
TSC1	X					
TSC2	X					
VHL	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)
WT1	X					
XRCC2					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. 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). 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. 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 meant as a comprehensive list of all genes included in all panels.

BRCA1 and BRCA2 Variants
BRCA1 and *BRCA2* germline variants are associated with hereditary breast and ovarian cancer syndrome, which is associated most strongly with increased susceptibility to breast cancer at an early age, bilateral breast cancer, male breast cancer, ovarian cancer, cancer of the fallopian tube, and primary peritoneal cancer. *BRCA1* and *BCRA2* variants are also associated with increased risk of other cancers, including prostate cancer, pancreatic cancer, gastrointestinal cancers, melanoma, and laryngeal cancer.

APC Variants
APC germline variants are associated with 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 Hippel-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
*F*olliculin (*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
*F*anconi 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 Breast Cancer
Breast cancer can be classified as sporadic, familial, or hereditary. Sporadic breast cancer accounts for 70% to 75% of cases and is thought to be due to nonhereditary causes. Familial breast cancer, in which there are more cases within a family than statistically expected, but with no specific pattern of inheritance, accounts for 15% to 25% of cases. Hereditary breast accounts for 5% to 10% of cases and is characterized by well-known susceptibility genes with apparently autosomal dominant transmission.

The “classic” inherited breast cancer syndrome is hereditary breast and ovarian cancer syndrome, most cases of which are due to variants in the *BRCA1* and *BRCA2* genes. Other hereditary cancer syndromes such as LFS (associated with *TP53* variants), CS (associated with *PTEN* variants), PJS (associated with *STK11* variants), hereditary DGC, and, possibly, Lynch syndrome also predispose patients to varying degrees of risk for breast cancer. Other variants and SNVs are associated with increased risk of breast cancer.

Variants associated with breast cancer vary in their penetrance. Highly penetrant variants in the *BRCA1*, *BRCA2*, *TP53*, and *PTEN* genes may be associated with a lifetime breast cancer risk ranging from 40% to 85%. Only about 5% to 10% of all cases of breast cancer are attributable to a highly penetrant cancer predisposition gene. In addition to breast cancer, variants in these genes may also confer a higher risk for other cancers.

Other variants may be associated with intermediate penetrance and a lifetime breast cancer risk of 20% to 40% (eg, *CHEK2*, *APC*, *CDH1*). Low-penetrance variants discovered in genome-wide association studies (eg, SNVs), are common and confer a modest increase in risk, although penetrance can vary based on environmental and lifestyle factors.

An accurate and comprehensive family history of cancer is essential for identifying people who may be at risk for inherited breast cancer and should include a 3-generation family history with information on both maternal and paternal lineages. The focus should be on both people with malignancies and family members without a personal history of cancer. It is also important to document the presence of nonmalignant findings in the proband and the family, because some inherited cancer syndromes are also associated with other nonmalignant physical characteristics (eg, benign skin tumors in CS).

Further discussion on the diagnostic criteria of hereditary breast and ovarian cancer will not be addressed in this evidence review. Criteria for a presumptive clinical diagnosis of LFS and CS have been established.

Li-Fraumeni Syndrome

LFS has been estimated to be involved in approximately 1% of hereditary breast cancer cases. LFS is a highly penetrant cancer syndrome associated with a high lifetime risk of cancer. People with LFS often present with certain cancers (soft tissue sarcomas, brain tumors, adrenocortical carcinomas) in early childhood and have an increased risk of developing multiple primary cancers during their lifetime.

Classic LFS is defined by the following criteria:

- A proband with a sarcoma diagnosed before age 45 years AND
- A first-degree relative with any cancer before age 45 years AND
- A first- or second-degree relative with any cancer before age 45 years or a sarcoma at any age.

The 2009 Chompret criteria for LFS (*TP53*) testing are as follows:

- A proband who has:
  - A tumor belonging to the LFS tumor spectrum (soft tissue sarcoma, osteosarcoma, premenopausal breast cancer, brain tumor, adrenocortical carcinoma, leukemia, or lung bronchoalveolar cancer) before age 46 years AND
  - At least one first- or second-degree relative with an LFS tumor (except breast cancer if the proband has breast cancer) before age 56 years or with multiple tumors; OR
- A proband with multiple tumors (except multiple breast tumors), 2 of which belong to the LFS tumor spectrum and the first of which occurred before age 46 years; OR
- A proband who is diagnosed with adrenocortical carcinoma or choroid plexus tumor, irrespective of family history.

Classic criteria for LFS have been estimated to have a positive predictive value of 56% and high specificity, although the sensitivity is low (≈40%). The Chompret criteria have an estimated positive predictive value of 20% to 35%, and when incorporated as part of *TP53* testing criteria in conjunction with classic LFS criteria, substantially improve the sensitivity of detecting LFS. When the Chompret criteria are added to the classic LFS criteria, the sensitivity for detected patients with *TP53* variants is approximately 95%.

The National Comprehensive Cancer Network also considers women with early-onset breast cancer (age of diagnosis <30 years), with or without a family history of the core tumor types found in LFS, as another group in whom *TP53* gene variant testing may be considered. If the LFS testing criteria are met, National Comprehensive Cancer Network guidelines recommend testing for the familial *TP53* variant if it is known to be present in the family. If it is not known to be present, comprehensive *TP53* testing is recommended, (ie, full sequencing of *TP53* and deletion/duplication analysis) of a patient with breast cancer. If the patient is unaffected, testing the family member with the highest likelihood of a *TP53* variant is recommended. If a variant is found, recommendations for management of LFS, include increased cancer surveillance and, at an earlier age, possible prophylactic surgical management, discussion of the risk of relatives, and

consideration of reproductive options. The National Comprehensive Cancer Network guidelines also state that in the situation where a person from a family with no known familial *TP53* variant undergoes testing and no variant is found, testing for other hereditary breast syndromes should be considered if testing criteria are met.

Cowden Syndrome
CS is a part of PHTS and is the only PHTS disorder associated with a documented predisposition to malignancies. Women with CS have a high risk of benign fibrocystic disease and a lifetime risk of breast cancer estimated at 25% to 50%, with an average age between 38 and 46 years at diagnosis. The *PTEN* variant frequency in people meeting International Cowden Consortium criteria for CS has been estimated to be approximately 80%. A presumptive diagnosis of PHTS is based on clinical findings; however, because of the phenotypic heterogeneity associated with the hamartoma syndromes, the diagnosis of PHTS is made only when a *PTEN* variant is identified. Clinical management of breast cancer risk in patients with CS includes screening at an earlier age and possible risk-reducing surgery.

Hereditary Ovarian Cancer
The single greatest risk factor for ovarian cancer is a family history of the disease. Breast and ovarian cancer are components of several autosomal dominant cancer syndromes. The syndromes most strongly associated with both cancers are the *BRCA1* or *BRCA2* variant syndromes. Ovarian cancer has been associated with Lynch syndrome, basal cell nevus (Gorlin) syndrome, and multiple endocrine neoplasia.

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.

The Single Hereditary Colon Cancer
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. 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. 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.

Identifying which patients should undergo genetic testing for an inherited colon cancer syndrome depends on family history and clinical manifestations. Clinical criteria are used to focus testing according to polyposis or nonpolyposis syndromes, and for adenomatous or hamartomatous type within the polyposis syndromes. If a patient presents with multiple adenomatous polyps, testing in most circumstances focuses on *APC* and *MUTYH* variants. Hamartomatous polyps could focus testing for variants in the *STK11*/*LKB1*, *SMAD4*, *BMPR1A*, and/or *PTEN* genes.

Genetic testing to confirm the diagnosis of Lynch syndrome is usually performed on the basis of family history in those families meeting the Amsterdam criteria who have tumor microsatellite instability by immunohistochemistry on tumor tissue. Immunohistochemical testing helps identify which of the 4 mismatch repair genes (*MLH1*, *MSH2*, *MSH6*, *PMS2*) most likely harbors a variant. The presence of tumor microsatellite instability in the tumor alone is not sufficient to diagnose Lynch because 10% to 15% of sporadic CRCs exhibit tumor microsatellite instability.

MLH1 and *MSH2* germline variants account for approximately 90% of variants in families with Lynch syndrome; *MSH6* variants in about 7% to 10%; and *PMS2* variants in fewer than 5%. Genetic testing for Lynch is ideally performed in a stepwise manner: testing for mismatch repair gene variants is often limited to *MLH1* and *MSH2* and, if negative, then *MSH6* and *PMS2* testing is performed.

Management of Polyposis Syndromes
FAP has a 100% penetrance, with polyps developing on average around the time of puberty, and the average CRC diagnosis before age 40. Endoscopic screening should begin around age 10 to 12 years, and operative intervention (colectomy) remains the definitive treatment. For attenuated *FAP*, colonoscopic surveillance is recommended to begin between ages 20 and 30 years, or 10 years sooner than the first polyp diagnosis in the family. For *MUTYH*-associated polyposis, colonoscopic surveillance is recommended to start between ages 20 and 30 years.

Colonic surveillance in the hamartomatous polyposis syndromes includes a colonoscopy every 2 to 3 years, starting in the teens.

Management of Nonpolyposis Syndromes
People with Lynch syndrome have lifetime risks for cancer as follows: 52% to 82% for CRC (mean age at diagnosis, 44-61 years); 25% to 60% for endometrial cancer in women (mean age at diagnosis, 48-62 years); 6% to 13% for gastric cancer (mean age at diagnosis, 56 years); and 4% to 12% for ovarian cancer (mean age at diagnosis, 42.5 years; approximately one-third are diagnosed before age 40 years). The risk for other Lynch-related cancers is lower, although substantially increased over that of the general population. For hereditary nonpolyposis colorectal cancer or Lynch, colonoscopic screening should start between ages 20 and 25 years. Prophylactic colectomy is based on aggressive CRC penetrance in the family. Screening and treatment for the extracolonic malignancies in hereditary nonpolyposis colorectal cancer also are established.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

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

Centers for Medicare and Medicaid Services (CMS)

There is no national coverage determination (NCD). In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers.

Rationale/Source

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 (ie, demonstration that the diagnostic information can be used to improve patient outcomes).

CANCER SUSCEPTIBILITY PANELS

Clinical Context and Test Purpose

Cancer susceptibility panels may be either diagnostic or prognostic.

The purpose of diagnostic testing in patients for genetic or heritable pathogenic variants in a symptomatic individual is to establish a molecular diagnosis defined by the presence of known pathologic variant(s). For genetic testing, a symptomatic individual is defined as an individual with a clinical phenotype that correlates with a known pathologic variant. 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 or to predict the natural disease course (eg, aggressiveness, risk of recurrence, death) in an affected individual. 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 who are diagnosed with heritable cancer (diagnostic testing) or have a family member who has been diagnosed with heritable cancer (prognostic testing).

Intervention
The intervention of interest is a cancer susceptibility panel.

Comparator
The comparator of interest is 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
The time of interest varies by whether testing is diagnostic or prognostic.

Setting
These tests are offered commercially through various manufacturers and institutions.

Analytic Validity
Analytic validity is the technical accuracy of the test in detecting a variant that is present or in excluding a variant that is absent.

According to the GeneDx website, its comprehensive cancer susceptibility panel has greater than 99% sensitivity in detecting variants identifiable by sequencing or array comparative genomic hybridization (aCGH). This analytic sensitivity approaches that of direct sequencing of individual genes.

In a 2016 report by Mu et al (Ambry Genetics), 7845 pathogenic, likely pathogenic, and variants of uncertain significance (VUS) identified with panels of 47 genes in 20,000 samples underwent Sanger sequencing. Of these, 98.7% were concordant between NGS and Sanger sequencing, and 1.3% were identified as false positives. These genes were located mainly in complex genomic regions (A/T-rich, G/C-rich, and pseudogene regions as well as homopolymer stretches). Adjusting the variant-calling threshold decreased

sensitivity to 97.8%, with a missed detection of 176 Sanger-confirmed variants. The study concluded that Sanger sequencing would be needed in complex genomic regions to maintain the highest sensitivity.

In 2015, Lincoln et al reported on a comparison of traditional and multigene panel testing for hereditary and ovarian cancer genes. They tested over 1000 individuals using a 29-gene NGS panel. The population consisted of patients referred for hereditary breast and ovarian cancer counseling and/or testing (n=735), patients referred for known familial variants (n=118) and patients referred for high-risk personal and family features (n=209). Of the total patients, 92% had previously undergone traditional *BRCA1* and/or *BRCA2* testing, and a small subset (4%) had undergone testing for other genetic variants. Analytic concordance was 100% when the 29-gene panel results were compared with previous traditional and reference data. In 4.5% of cases considered previously to be *BRCA*-negative, panel testing identified pathogenic variants in other genes considered to be clinically relevant. Forty-one percent of cases had at least 1 VUS among the 29 genes, with 11.4% having 2 or more VUS.

Also in 2015, Judkins et al reported on the development and analytic validity of a 25-gene NGS panel to assess genes associated with hereditary cancer syndromes. The panel of genes were selected for their association with hereditary cancer syndromes, some of which are associated with clinical management changes; genes included were *BRCA1*, *BRCA2*, *MLH1*, *MSH2*, *MSH6*, *PMS2*, *EPCAM* (for large rearrangements of the last 2 exons only), *APC*, *MUTYH*, *CDKN2A*, *PALB2*, *ATM*, *STK11*, *PTEN*, *TP53*, *CDH1*, *BMPR1A*, *SMAD4*, *BARD1*, *CHEK2*, *CDK4*, *NBN*, *RAD51C*, *BRIP1*, and *RAD51D*. The test's analytic characteristics were compared with Sanger sequencing for *BRCA1* and *BRCA2,* using 1864 anonymized samples, with an estimated analytical sensitivity for NGS greater than 99.96% (lower limit of the 95% confidence interval) and an estimated analytic specificity greater than 99.99% (lower limit 95% confidence interval). The panel was validated by Sanger sequencing in 100 anonymized samples, with 100% concordance for variants. The estimated analytical sensitivity of the NGS assay was greater than 99.92% (lower limit of 95% confidence interval) and the estimated analytical specificity was greater than 99.99% (lower limit of 95% confidence interval), with good reproducibility.

To determine whether NGS would enable accurate identification of inherited variants for breast and ovarian cancer, Walsh et al (2010) developed a genomic assay to capture, sequence, and detect all variants in 21 genes (which included 19 of the genes on the BreastNext and OvaNext panels). Constitutional genomic DNA from persons with known inherited mutations was hybridized to custom oligonucleotides and then sequenced. The analysis was carried out blindly as to the variant in each sample. All single-nucleotide substitutions, small insertions and deletions, and large duplications and deletions were detected. There were no false-positive results.

Chong et al reported the design and validation of BRCAplus (Ambry, Aliso Viejo, CA), a panel that detects variants in the 6 high-risk breast cancer susceptibility genes (*BRCA1*, *BRCA2*, *CDH1*, *PTEN*, *TP53*, *STK11*) using NGS and aCGH. NGS analysis was confirmed by Sanger sequencing, and aCGH analysis (for duplications and deletions) was confirmed by multiplex ligation-dependent probe amplification analysis. The analyses were conducted on 250 previously characterized, archived genomic DNA samples, which

harbored a total of 3025 previously defined germline variants in the 6 targeted genes. The BRCAplus test correctly identified all variants, resulting in 100% sensitivity. There were 30 false positives from 5,788,250 base pairs interrogated, resulting in an analytic specificity for NGS of 99.99%

In 2017, Cheng et al reported on the analytic validity of the MSK-IMPACT test to detect genetic alterations in 76 genes implicated in cancer predisposition. They examined 233 samples variants in cancer predisposition genes that had been previously confirmed using Sanger sequencing, aCGH, or multiplex ligation-dependent probe amplification analysis. A majority of the variants (168/228 [74%]) were positive for variants in *BRCA1*, *BRCA2*, *MSH2*, *MLH1*, and *APC*. The MSK-IMPACT algorithm (filter of 50 times coverage and 25% allele frequency) identified 96% of single-nucleotide variants (SNVs) and 90% of insertions and deletions (indels). Copy number variants (CNVs) were detected in all 43 samples with a previously identified CNV. Also, 16 pathogenic or likely pathogenic variants were identified incidentally. Reproducibility was confirmed with inter- and intrarun replicates of samples with previously confirmed SNVs, indels, and large deletions. The number of exonic variants was identical across replicates, but variants in the noncoding regions varied across replicates.

Vysotkaia et al reported the analytic validity of the 36-gene Counsyl Reliant™‡ Cancer Screen (Counsyl, San Francisco, CA) in 2017. The validation study evaluated 111 cell lines from the 1000 Genomes Projects and included samples with SNVs and indel in the 36 genes. Also, 223 patient samples from the Counsyl library were selected that had CNVs, larger indels, or Alu insertions confirmed by Sanger or multiplex ligation-dependent probe amplification analysis. Sensitivity and specificity were reported to be 100% for the detection of SNVs, indels, CNVs, and Alu insertions, although the authors noted that the low prevalence of CNVs made it difficult to assess CNV calling sensitivity with precision. Intrarun and interrun repeatability were reported to be greater than 99.99%.

Although analytic validity for the detection of variants in cancer panels has been reported to be high, interpretation of the clinical significance of the variants varies between laboratories. In 2016, Balmana et al reported on variant interpretations for 518 participants (603 variants) who participated in the PROMPT (Prospective Registry of Multiplex Testing) registry. Each participant in this study had a non-*BRCA* result from a gene panel that was interpreted by more than one laboratory. Based on the clinical interpretation in ClinVar, results were consistently classified as VUS in 220 (36%), pathogenic/likely pathogenic in 191 (32%), and benign or likely benign in 34 (6%). However, for 155 (26%) of variants, the interpretation was conflicting. Differing interpretations were most frequent for *CHEK2* and *ATM*, followed by *RAD51C*, *PALB2*, *BARD1*, *NBN*, and *BRIP1* genes. Among the 518 participants, 56 (11%) had a variant with different interpretations that ranged from pathogenic or likely pathogenic to VUS, potentially altering medical management.

Section Summary: Analytic Validity
Published data on analytic validity panel testing has been reported to be high, approaching that of direct sequencing of individual genes. However, the accuracy of NGS may be reduced in complex genomic regions, such as A/T-rich, G/C-rich, and pseudogene regions, as well as in homopolymer stretches. Also,

the interpretation and reporting of the significance of the variant (pathogenic, benign, or VUS) have been shown to differ between laboratories.

Clinical Validity
Clinical validity is the diagnostic performance of the test—sensitivity, specificity, positive and negative predictive values.

The published literature provides no guidance for the assessment of the clinical validity of panel testing for cancer susceptibility with 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?

General Cancer Gene 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.

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 a hereditary cancer panel between August 2013 and October 2014. 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, VUS, likely benign, or benign or polymorphism according to the 2007 guidelines from the American College of Medical Genetics and Genomics.

Genes included in the panels were grouped into 3 risk categories based on penetrance data available in 2012, as follows:
- high risk: *APC*, *BMPR1A*, *BRCA1*, *BRCA2*, *CDH1*, *CDKN2A*, *EPCAM*, *MLH1*, *MSH2*, *MSH6*, *MUTYH*, *PMS2*, *PTEN*, *SMAD4*, *STK11*, *TP53*, and *VHL*
- moderate risk: *ATM*, *CHEK2*, and *PALB2*

- increased but less well-defined risk: *AXIN2*, *BARD1*, *BRIP1*, *CDK4*, *FANCC*, *NBN*, *RAD51C*, *RAD51D*, and *XRCC2*.

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 panel (GeneDx, Gaithersburg, MD), 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 colorectal cancer 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 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*) 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 reported 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 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 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, OvaNext, ColoNext, or CancerNext (Ambry Genetics). 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

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

Gene	Odds Ratio	95% Confidence Interval	Risk Category
ATM	2.78	2.22 to 3.62	Moderate
BARD1	2.16	1.31 to 3.63	Moderate

CHEK2	1.48	1.31 to 1.67	Moderate
PALB2	7.46	5.12 to 11.19	High
RAD51D	3.07	1.21 to 7.88	Moderate

Other studies have assessed the prevalence of pathogenic variants among patients with breast cancer who were referred for genetic testing, using a panel of 25 genes associated with inherited cancer predisposition (Myriad Genetics). 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). Variants were identified in 16 genes, with the most frequent being *BRCA1*, *BRCA2*, *CHEK2*, *ATM,* and *PALB2.* A 2017 study by Buys et al included over 35,000 women with breast cancer who were assessed with the Myriad 25-gene panel. 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 genes related to breast cancer, 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. 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.

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. 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.

Colorectal Cancer
In 2014, in an industry-sponsored study, Cragun et al reported the prevalence of clinically significant variants and VUS among patients who underwent ColoNext panel testing. 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 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 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."

Section Summary: Clinical Validity
Clinical validity studies have reported the results of the frequency with which variants are identified using large panels, and occasionally have reported the VUS rate. VUS rates increase in proportion with panel size, reaching nearly 50% for large gene panels.

Clinical Utility
Clinical utility is how the results of the diagnostic test will be used to change management of the patient and whether these changes in management lead to clinically important improvements in health outcomes.

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.

Mauer et al (2014) reported on the experience of a single academic center's genetics program with NGS panels for cancer susceptibility. The authors retrospectively reviewed the outcomes and clinical indications for the ordering of Ambry's NGS panels (BreastNext, OvaNext, ColoNext, CancerNext) for patients seen for cancer genetics counseling from April 2012 to January 2013. Of 1521 new patients seen for cancer genetics counseling, 1233 (81.1%) had genetic testing. Sixty (4.9% of total) of these patients had an NGS panel ordered, 54 of which were ordered as a second-tier test after single-gene testing was performed. Ten tests were canceled due to out-of-pocket costs or previously identified variants. Of the 50 tests obtained, 5 had a deleterious result (10%; vs 131 [10.6%] of the 1233 single-gene tests ordered at the same center during the study time frame). The authors reported that of the 50 completed tests, 30 (60%) did not affect management decisions, 15 (30%) introduced uncertainty regarding the patients' cancer risks, and 5 (10%) directly influenced management decisions.

In 2014, Kurian et al evaluated the information from an NGS panel of 42 cancer-associated genes in women who had been previously referred for clinical *BRCA1* and *BRCA2* testing after clinical evaluation of hereditary breast and ovarian cancer from 2002 to 2012. 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, 1 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 a *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).

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. From this sample, 129 patients had a personal history of cancer (11 with a pathogenic or likely pathogenic variant, 14 with a VUS, 104 with normal test results) and 103 had a family history of cancer (14 with a pathogenic or likely pathogenic variant, 20 with a VUS, 69 with normal test results). The greatest impact of test results was for the 14 patients with a family history of breast or ovarian cancer who received a positive (pathogenic or likely pathogenic) test result, leading to greater distress and more frequent screening in 13 patients and prophylactic surgery in 1. Positive test results for the 11 patients with a personal history of cancer influenced their decision about the type of surgery for 4 (36.4%) patients. For the 20 patients with a family history of cancer and a VUS result, distress increased to an intermediate level, and 7 (35%) patients reported that their test result would impact the decision to have additional screening. The authors of this study noted that the VUS rate would increase with the number of genes in a panel, further noting 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. 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.

Desmond et al (2015) evaluated the prevalence of cancer risk genes and potential to take clinical action in 1046 individuals without a pathogenic variant in *BRCA1* or *BRCA2* who had been referred for genetic evaluation; 83% had a personal history of breast cancer and/or ovarian cancer. Pathogenic variants in cancer predisposition genes were identified in 40 (3.8%) patients. Eight (0.8%) pathogenic variants were identified in genes associated with Lynch syndrome, and 3 (0.3%) pathogenic variants were found in high-risk breast cancer genes (*CDH1*) other than *BRCA1* or *BRCA2*. Most variants were in genes associated with low or moderately increased breast cancer risk, and management changes would be recommended in a minority of these cases. The authors reported that the utility of identifying the low- and moderate-risk

HBOC genes was greatest for first-degree relatives of test recipients (n=42), who would then receive recommendations for familial testing.

Section Summary: Clinical Utility

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 rates of VUS 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 next-generation sequencing panels, the evidence includes reports describing the frequency of detecting variants in patients referred for panel testing. Relevant outcomes are overall survival, disease-specific survival, test accuracy, and test validity. Published data on the analytic validity of next-generation sequencing has been reported to be high, approaching that of direct sequencing of individual genes. However, 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 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. Also, 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.

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Policy History

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09/05/2013	Medical Policy Committee review
09/18/2013	Medical Policy Implementation Committee approval. New policy.
09/04/2014	Medical Policy Committee review
09/17/2014	Medical Policy Implementation Committee approval. No change to coverage.
01/01/2015	Coding Update
09/03/2015	Medical Policy Committee review
09/23/2015	Medical Policy Implementation Committee approval. No change to coverage.
09/08/2016	Medical Policy Committee review
09/21/2016	Medical Policy Implementation Committee approval. No change to coverage.
01/01/2017	Coding update: Removing ICD-9 Diagnosis Codes
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12/20/2017	Medical Policy Implementation Committee approval. No change to coverage.
04/01/2018	Coding update
07/01/2018	Coding update

Next Scheduled Review Date: 12/2018

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Genetic Cancer Susceptibility Panels Using Next Generation Sequencing

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