Title: Genetic Cancer Susceptibility Panels Using Next Generation Sequencing

DESCRIPTION
Numerous genetic mutations are associated with certain types of hereditary cancer. Genetic testing using next-generation sequencing (NGS) technology allows for the analysis of multiple genes at one time (panel testing), and these panels are commercially available. The utility of these genetic panels will be reviewed, in comparison with testing for individual mutations.

Background
Genetic testing for cancer susceptibility may be approached by a focused method that involves testing for well-characterized mutations based on a clinical suspicion of which
gene(s) may be the cause of the familial cancer. Panel testing involves testing for multiple mutations in multiple genes at one time.

Several companies, including Ambry Genetics and GeneDx, offer genetic testing panels that use NGS methods for hereditary cancers. NGS refers to 1 of several methods that use massively parallel platforms to allow the sequencing of large stretches of DNA. Panel testing is potentially associated with greater efficiencies in the evaluation of genetic diseases; however, it may provide information on genetic mutations 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 (i.e., 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 and 2, followed by a brief description of each gene.

**Table 1. Ambry Genetics Hereditary Cancer Panel Tests**

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Table 2. GeneDx Hereditary Cancer Panel Tests

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Mayo Clinic 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 offers the BROCA Cancer Risk Panel, which is an NGS panel that includes the following mutations: AKT1, APC, ATM, ATR, BAPI,
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 to be a comprehensive list of all genes included in all panels.

**BRCA1 and BRCA2 Mutations**

BRCA1 and BRCA2 germline mutations are associated with hereditary breast and ovarian cancer (HBOC) syndrome, which are 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 mutations are also associated with increased risk of other cancers, including prostate cancer, pancreatic cancer, gastrointestinal cancers, melanoma, and laryngeal cancer.

**APC Mutations**

APC germline mutations 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 Mutations**

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 conjunctiva, oculomotor apraxia, immune defects, and cancer predisposition, particularly leukemia and lymphoma.
BARD1, BRI1, MRE11A, NBN, RAD50, and RAD51C Mutations
BARD1, BRI1, MRE11A, NBN, RAD50, and RAD51C are genes in the Fanconi anemia/BRCA1 pathway. Mutations in these genes are estimated to confer up to a 4-fold increase in the risk for breast cancer.

BMPR1A and SMAD4 Mutations
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 Mutations
CHEK2 gene mutations 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 Mutations
CDH1 germline mutations are associated with lobular breast cancer in women and with hereditary diffuse gastric cancer. The estimated cumulative risk of gastric cancer for CDH1 mutation carriers by age 80 years is 67% for men and 83% for women. CDH1 mutations are associated with a lifetime risk of 39% to 52% of lobular breast cancer.

EPCAM, MLH1, MSH2, MSH6, and PMS2 Mutations
EPCAM, MLH1, MSH2, MSH6, and PMS2 are mismatch repair genes associated with LS (HNPCC). LS 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 Mutations
MUTYH germline mutations 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 mutations in the APC gene, have MUTYH mutations.

PALB2 Mutations
PALB2 germline mutations are associated with an increased risk of pancreatic and breast cancer. Familial pancreatic and/or breast cancer due to PALB2 mutations is inherited in an autosomal dominant pattern.
**PTEN Mutations**
PTEN mutations 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 Mutations**
STK11 germline mutations 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 Mutations**
TP53 are associated with LFS. People with TP53 mutations 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 Mutations**
Neurofibromin 1 (NF1) encodes a negative regulator in the ras signal transduction pathway. Mutations in the NF1 gene have been associated with neurofibromatosis type 1, juvenile myelomonocytic leukemia, and Watson syndrome.

**RAD51D Mutations**
RAD51D germline mutations are associated with familial breast and ovarian cancers.

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

**CDKN2A Mutations**
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. Mutations or deletions in CDKN2A are frequently found in multiple types of tumor cells. Germline mutations in CDKN2A have been associated with risk of melanoma, along with pancreatic and central nervous system cancers.

**RET Mutations**
RET encodes a receptor tyrosine kinase; mutations in this gene are associated with multiple endocrine neoplasia syndromes (types IIA and IIB) and medullary thyroid carcinoma.
**SDHA, SDHB, SDHC, SDHD, and SDHAF2 Mutations**

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

**TMEM127 Mutations**

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

**VHL Mutations**

VHL germline mutations 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 Mutations**

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

**FLCN Mutations**

Folliculin (FLCN) acts as a tumor suppressor gene; mutations 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 Mutations**

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

**MITF Mutations**

Microphthalmia-associated transcription factor (MITF) is a transcription factor involved in melanocyte differentiation. MITF mutations 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 Mutations**

Tuberous sclerosis 1 (TSC1) and tuberous sclerosis 2 (TSC2) encode the proteins hamartin and tuberin, which are involved in cell growth, differentiation, and proliferation. Mutations 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 Mutations**

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 Mutations**

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 Mutations**

AXIN2 mutations are associated with familial adenomatous polyposis syndrome, although the phenotypes associated with AXIN2 mutations 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 HBOC syndrome, most of which are due to mutations in the BRCA1 and BRCA2 genes. Other hereditary cancer syndromes such as LFS (associated with TP53 mutations), CS (associated with PTEN mutations), PJS (associated with STK11 mutations), hereditary diffuse gastric cancer, and, possibly, Lynch syndrome also predispose patients to varying degrees of risk for breast cancer. Other mutations and SNPs are associated with increased risk of breast cancer.

Mutations associated with breast cancer vary in their penetrance. Highly penetrant mutations 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, mutations in these genes may also confer a higher risk for other cancers.

Other mutations may be associated with intermediate penetrance and a lifetime breast cancer risk of 20% to 40% (e.g., CHEK2, APC, CDH1). Low-penetrance mutations discovered in genome-wide association studies (e.g., SNPs), are generally 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. 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 (e.g., benign skin tumors in CS).

Further discussion on the diagnostic criteria of HBOC 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 a high specificity, although the sensitivity is low at approximately 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 mutations is approximately 95%.

The National Comprehensive Cancer Network (NCCN) also considers women with early onset breast cancer (age of diagnosis younger than 30 years), with or without a family history of the core tumor types found in LFS, as another group in whom TP53 gene mutation testing may be considered. If the LFS testing criteria are met, NCCN guidelines recommend testing for the familial TP53 mutation if it is known to be present in the family. If it is not known to be present, comprehensive TP53 testing is recommended, i.e., 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 mutation is recommended. If a mutation is found, recommendations for management of LFS, include increased cancer surveillance and, at an earlier age, possible prophylactic surgical management, discussion of risk of relatives, and consideration of reproductive options. NCCN guidelines also state that in the situation where a person from a family with no known familial TP53 mutation undergoes testing and no mutation is found, testing for other hereditary breast syndromes should be considered if testing criteria are met.

**Cowden Syndrome**
CS is a part of the PTEN hamartoma tumor syndrome (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 of between 38 and 46 years at diagnosis. The PTEN mutation 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 mutation 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 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 mutation syndromes. Ovarian cancer has been associated with LS, basal cell nevus (Gorlin) syndrome, and multiple endocrine neoplasia.

**Hereditary Colon Cancer**
Hereditary colon cancer syndromes are thought to account for approximately 10% of all CRCs. Another 20% have a familial predilection for colorectal cancer 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.\(^7\) The polyposis syndromes can be further subdivided by polyp histology, which includes the adenomatous (\textit{FAP}, attenuated \textit{FAP}, \textit{MUTYH}-associated) and hamartomatous (\textit{JPS}, \textit{PJS}, \textit{PHTS}) polyposis syndromes. The nonpolyposis syndromes include Lynch.

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 \textit{APC} and \textit{MUTYH} mutations. Hamartomatous polyps could focus testing for mutations in the \textit{STK11/LKB1}, \textit{SMAD4}, \textit{BMPR1A}, and/or \textit{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 (MSI) by immunohistochemistry on tumor tissue.\(^8\) Immunohistochemical testing helps identify which of the 4 MMR genes (\textit{MLH1}, \textit{MSH2}, \textit{MSH6}, \textit{PMS2}) most likely harbors a mutation. The presence of MSI in the tumor alone is not sufficient to diagnose Lynch because 10% to 15% of sporadic CRCs exhibit MSI.

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

**Management of Polyposis Syndromes**

\textit{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 \textit{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.\(^9\) For \textit{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 LS have lifetime risks for cancer as follows: 52% to 82% for colorectal cancer (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 LS-related cancers is lower, although substantially increased over that of the general population. For HNPCC or LS, colonoscopic screening should start at age 20 to 25 years. Prophylactic colectomy is based on aggressive colorectal cancer penetrance in the family. Screening and treatment for the extracolonic malignancies in HNPCC also are established.\textsuperscript{10}

**Regulatory Status**

Clinical laboratories may develop and validate tests in-house ("home-brew") and market them as a laboratory service; such tests must meet the general regulatory standards of the Clinical Laboratory Improvement Act (CLIA). The laboratory offering the service must be licensed by CLIA for high-complexity testing. Ambry Genetics is CLIA licensed.
POLICY
Genetic cancer susceptibility panels using next generation sequencing are considered experimental / investigational.

Policy Guidelines
Although genetic cancer susceptibility panels using next generation sequencing are considered investigational, there may be individual components of the panel that are medically necessary.

RATIONALE
Updated literature reviews were conducted most recently through April 14, 2016.

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

According to Ambry Genetics, the analytical sensitivity for the 22 genes analyzed on their cancer susceptibility panels by next generation sequencing is 96% to 99%. According to the GeneDx website, their comprehensive cancer susceptibility panel has greater than 99% sensitivity in detecting mutations identifiable by sequencing or array comparative genomic hybridization.11 This analytic sensitivity approaches that of direct sequencing of individual genes.

In 2015, Lincoln et al reported on a comparison of traditional and multigene panel testing for hereditary and ovarian cancer genes.12 They tested over a 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 mutations (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 mutations. 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 variant of unknown significance (VOUS) among the 29 genes, with 11.4% having 2 or more VOUS.

To determine whether NGS would enable accurate identification of inherited mutations for breast and ovarian cancer, Walsh et al developed a genomic assay to capture, sequence, and detect all mutations in 21 genes (which included 19 of the genes on the BreastNext and OvaNext panels).13 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 mutation 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, a panel that detects mutations in the 6 high-risk breast cancer susceptibility genes (BRCA1, BRCA2, CDH1, PTEN, TP53, STK11) using NGS and aCGH.14 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%.

**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 next generation sequencing, and the usual approach to establishing the clinical validity for 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 next generation sequencing for cancer susceptibility panels, which include mutations associated with an unknown or variable cancer risk, are of uncertain clinical validity.

For genetic susceptibility to cancer, clinical validity can be considered on 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?

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

In 2015, 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. Genes included in the panels were grouped into 3 risk categories based on penetrance data available in 2012, as follows: high risk: APC, BMPR1A, BRCA1, BRCA2, CDH1, CDKN2A, EPCAM, MLH1, MSH2, MSH6, MUTYH, PMS2, PTEN, SMAD4, STK11, TP53, and VHL; moderate risk: ATM, CHEK2, and PALB2; and increased but less well-defined risk: AXIN2, BARD1, BRIP1, CDK4, FANCC, NBN, RAD51C, RAD51D, and XRCC2. Genetic variants were classified as pathogenic, likely pathogenic, VOUS, likely benign, or benign/polymorphism according to the 2007 guidelines from the American College of Medical Genetic and Genomics.

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 \textit{BRCA1} and \textit{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 \textit{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: \textit{MLH1}, \textit{MSH2}, \textit{MSH6}, \textit{PMS2}, \textit{EPCAM}, \textit{MUTYH}, \textit{APC}, \textit{PTEN}, and \textit{STK11}. However, 28.2\% (35/124) were observed in genes not considered classical for gastrointestinal cancers: \textit{BRCA1}, \textit{BRCA2}, \textit{CHEK2}, \textit{ATM}, \textit{PALB2}, \textit{BRIPI}, and \textit{RAD51D}. \textit{BRCA1} and \textit{BRCA2} accounted for 9.7\% (12/124) of positive variants identified in individuals diagnosed with colon cancer. The Lynch syndrome/colorectal cancer panel, containing \textit{MLH1}, \textit{MSH2}, \textit{MSH6}, \textit{PMS2}, \textit{EPCAM}, \textit{APC}, and \textit{MUTYH}, had the highest yield (13.7\% overall; 17.6\% among affected individuals), 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 \textit{BRCA1}, \textit{BRCA2}, \textit{CDH1}, \textit{PTEN}, \textit{STK11}, and \textit{TPS3} had the lowest yield (3.8\% overall, 4.2\% among individuals with breast cancer). The highest VOUS frequency was observed with the largest panel (29 genes), and the lowest VOUS 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 \textit{BRCA1} and \textit{BRCA2} testing were found to carry a pathogenic or likely pathogenic variant, of which \textit{BRCA1} and \textit{BRCA2} accounted for 39.1\%, other high-risk genes (including \textit{TP53}, \textit{PTEN}, and \textit{CDH1}) 5.8\% (19/330), and 5.2\% (17/330) in the Lynch syndrome genes. Moderate and less well-defined risk genes accounted for 50.0\% (165/330) of all positive results among women with breast cancer. Of women with ovarian cancer without reported previous \textit{BRCA1} and \textit{BRCA2} testing, 13.4\% (89/663) had mutations, of which \textit{BRCA1} and \textit{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 mutation was 11.9\% (n=54); 7.3\% (n=33) of these were within a Lynch gene, most commonly \textit{MSH6}, \textit{CHEK2} was positive in 7\%, with an overall frequency of 1.5\%, and 6 positive results were identified in \textit{BRCA1} and \textit{BRCA2}; 10.9\% (6/55) of all positive variants identified. Among 190 pancreatic cancer patients, the yield for identifying a mutation was 10.5\% (n=20), most commonly identified in \textit{ATM} (40.0\% [8/20]), \textit{BRCA2} (25.0\% [5/20]), and \textit{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 \textit{TPS3} did not meet classic Li-Fraumeni syndrome, Li-Fraumeni-like, 2009 Chompret, or National Comprehensive Cancer Network guideline criteria for \textit{TPS3} testing, resulting in a frequency of 0.06\% (6/9605) unanticipated positive results. Four patients had a positive \textit{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 \textit{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 \textit{BRCA1} and \textit{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.

In 2015, Tung et al assessed the frequency of pathogenic mutations among patients with breast cancer who were referred for BRCA1 and BRCA2 testing, using a panel of 25 genes associated with inherited cancer predisposition (Myriad Genetics). The study included 2 cohorts: 1781 patients referred for commercial testing for BRCA1 and BRCA2 mutations 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). Mutations were identified in 16 genes, with the most frequent being BRCA1/2, CHEK2, ATM, and PALB2. In cohort 1, a total of 241 (13.5%) individuals had a mutation in at least one of the genes tested, 162 (67%) in BRCA1 and BRCA2 and 76 (32%) in at least 1 of the other 23 genes. Three (1%) individuals had a mutation in both BRCA2 and another gene (ATM, CHEK2, or NBN). When BRCA1 and BRCA2 mutation carriers were excluded from cohort 1, a mutation was detected with a frequency of 4.7%. In cohort 2, the frequency of mutations in breast- and ovarian-associated genes (other than BRCA1 and BRCA2) was 2.9%; 0.8% had an incidental mutation. In both cohorts, CHEK2 mutations were the most common non-BRCA1 and -BRCA2 mutations identified, in approximately 33%.

In 2014, in an industry-sponsored study, Cragun et al reported the prevalence of clinically significant mutations and variants of uncertain significance (VUSs) 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 mutation; (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 mutations or likely pathogenic variants; after 8 patients with only CHEK2 or 1 MUTYH mutation were removed, 42 (7.2%) patients were considered to have actionable mutations. One hundred eighteen (20.1%) patients had at least 1 VOUS, including 14 patients who had at least 1 VOUS in addition to a pathologic mutation. Of the 42 patients with a pathologic mutation, most (30 [71%] patients) clearly met National Comprehensive Cancer Network guidelines for syndrome-based testing, screening, or diagnosis, based on the available clinical and family history. The authors noted that, "The reality remains that syndrome based testing would have been sufficient to identify the majority of patients with deleterious mutations. 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.”

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:

1. Does panel testing offer substantial advantages in efficiency compared with sequential analysis of individual genes?
2. 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?
3. 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 mutation that confers a high risk of developing cancer could lead to changes in clinical management and improved health outcomes. There are well-defined clinical guidelines on the management of patients who are identified as having a high-risk hereditary cancer syndrome. Changes in clinical management could include modifications in cancer surveillance, specific risk-reducing measures (e.g., prophylactic surgery), and treatment guidance (e.g., avoidance of certain exposures). In addition, other at-risk family members could be identified.

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

Mauer et al reported a single academic center’s genetics program’s experience with next generation sequencing panels for cancer susceptibility. The authors conducted a retrospective review of the outcomes and clinical indications for the ordering of Ambry’s next generation sequencing 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 of these patients (4.9% of total) had a next generation sequencing panel ordered, 54 of which were ordered as a second-tier test after single-gene testing was performed. Ten tests were cancelled due to out-of-pocket costs or previously identified mutations. Of the 50 tests obtained, 5 were found to have a deleterious result (10%; compared with 131 [10.6%] of the 1233 single-gene tests ordered at the same center during the study time frame). The authors report 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 a NGS panel of 42 cancer associated genes in women who had been previously referred for clinical BRCA1/2 testing after clinical evaluation of hereditary breast and ovarian cancer from 2002 to 2012. 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 BRCA1/2 mutations. Testing with the panel confirmed 57 of 59 of the pathogenic BRCA1/2 mutations; 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 BRCA1/2 mutations (n=141), 16 had pathogenic mutations 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. 80% of the women with pathogenic mutations in the non BRCA1/2 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 mutations in ATM, BLM, CDH1, NBN, and SLX4 were advised to consider annual breast magnetic resonance imagings because of an estimated doubling of breast cancer risk, and 6 with mutations 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 mutation consistent with LS underwent risk-reducing salpingooophorectomy and early colonoscopy which identified a tubular adenoma that was excised (she had previously undergone hysterectomy for endometrial carcinoma).

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-intermediate penetrance are not standardized, and the clinical utility of genetic testing for these mutations is uncertain and could potentially lead to harm. In addition, high rates of VUSs have been reported with the use of these panels.

Ongoing and Unpublished Clinical Trials
Some currently unpublished trials that might influence this policy are listed in Table 3.

<table>
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<th>NCT No.</th>
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<th>Planned Enrollment</th>
<th>Completion Date</th>
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<td>Ohio Colorectal Cancer Prevention Initiative: Universal Screening for Lynch Syndrome</td>
<td>5000</td>
<td>Sep 2018</td>
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</tbody>
</table>

NCT: national clinical trial.
**Summary of Evidence**

For individuals who have a personal and/or family history suggesting an inherited cancer syndrome who receive testing with a next-generation sequencing panel, the evidence includes mainly reports describing the frequency of detecting mutations in patients referred for panel testing. Relevant outcomes are overall survival, disease-specific survival, test accuracy, and test validity. Published data on analytic validity is lacking, but it has been reported to be high, approaching that of direct sequencing of individual genes. Clinical validity studies have generally reported the results of the frequency with which mutations are identified using large panels, and occasionally have reported the variant of unknown significance rate. Published data on clinical utility is lacking, and it is unknown whether use of these panels improves health outcomes. Many panels include mutations that are considered to be of moderate or low penetrance, and management guidelines are not well-defined in these patients, leading to the potential for harm in identifying one of these non-highly penetrant mutations. The evidence is insufficient to determine the effects of the technology on health outcomes.

**Practice Guidelines and Position Statements**

**American Society of Clinical Oncology**

A 2015 update of a policy statement on genetic and genomic testing for cancer susceptibility from the American Society of Clinical Oncology (ASCO) addresses the application of next-generation sequencing. ASCO recognizes that concurrent multigene testing (i.e., panel testing) may be efficient in circumstances that require evaluation of multiple high-penetrance genes of established clinical utility as possible explanations for a patient’s personal or family history of cancer. Depending on the specific genes included on the panel employed, panel testing may also identify mutations in genes associated with moderate or low cancer risks and mutations in high-penetrance genes that would not have been evaluated on the basis of the presenting personal or family history. Multigene panel testing will also identify variants of uncertain significance (VOUS) in a substantial proportion of patient cases. ASCO affirms that it is sufficient for cancer risk assessment to evaluate genes of established clinical utility that are suggested by the patient’s personal and/or family history. Because of the current uncertainties and knowledge gaps, providers with particular expertise in cancer risk assessment should be involved in the ordering and interpretation of multigene panels that include genes of uncertain clinical utility and genes not suggested by the patient’s personal and/or family history. This type of testing may be particularly useful in situations where there are multiple high-penetrance genes associated with a specific cancer, the prevalence of actionable mutations in one of several genes is high, and it is difficult to predict which gene may be mutated on the basis of phenotype or family history. So far, there is little consensus as to which genes should be included on panels offered for cancer susceptibility testing—this heterogeneity presents a number of challenges. All panels include high-penetrance genes that are known to cause autosomal dominant predisposition syndromes, but often include genes not necessarily linked to the disease for which the testing is being offered. There is uncertainty regarding the appropriate risk estimates and management strategies for families with unexpected mutations in high-penetrance genes when there is no evidence of the associated syndrome. Clinical utility remains the fundamental issue with respect to testing for mutations in moderate-penetrance genes. It is not yet clear whether clinical management should change based on the presence or absence of a mutation. There is insufficient evidence at present to conclusively demonstrate the clinical utility of testing for moderate-penetrance mutations, and no guidelines exist to assist oncology providers. Early experience with panel-based testing indicates
that a substantial proportion of tests identify a VOUS in 1 or more genes, and VOUS are more common in broad-panel testing both because of the number of genes tested and because of the limited understanding of the range of normal variation in some of these genes.

**National Comprehensive Cancer Network**
National Comprehensive Cancer Network (NCCN) guidelines on genetic/familial high-risk assessment for breast and ovarian cancer (v.2.2016) state that, regarding 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 1 gene can explain an inherited cancer syndrome, then multigene testing may be more efficient and/or cost effective.

- "There is also a role for multigene 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.

- "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.

- "Multigene 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 multigene 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 VUSs 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 posttest counseling.

NCCN guidelines on genetic/familial high risk assessment for colorectal cancer (v.2.2015) state that “if abnormal results are found for IHC [immunohistochemical] and/or MSI [microsatellite instability], then germline testing may include testing of the genes that are indicated by the abnormal tumor test results, or instead, multi-gene testing that includes MLH1, MSH2, MSH6, PMS2, and EPCAM concurrently may be performed.

**U.S. Preventive Services Task Force Recommendations**
The U.S. Preventive Services Task Force recommends that primary care providers screen women who have family members with breast, ovarian, tubal, or peritoneal cancer with 1 of several screening tools designed to identify a family history that may be associated with an increased risk for potentially harmful mutations in breast cancer and susceptibility genes (BRCA1 or BRCA2). Women with a positive screening results should receive genetic counseling and, if indicated after counseling, BRCA testing (grade B recommendation, 2013). The use of genetic cancer susceptibility panels is not specifically mentioned.
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 (e.g., hereditary breast cancer, hereditary ovarian cancer, hereditary endometrial cancer); genomic sequence analysis panel, must include sequencing of at least 14 genes, including ATM, BRCA1, BRCA2, BRIP1, CDH1, MLH1, MSH2, MSH6, NBN, PALB2, PTEN, RAD51C, STK11, and TP53

81433  Hereditary breast cancer-related disorders (e.g., hereditary breast cancer, hereditary ovarian cancer, hereditary endometrial cancer); duplication/deletion analysis panel, must include analyses for BRCA1, BRCA2, MLH1, MSH2, and STK11

81434  Hereditary colon cancer disorders (e.g., Lynch syndrome, PTEN hamartoma syndrome, Cowden syndrome, familial adenomatosis polyposis); genomic sequence analysis panel, must include sequencing of at least 10 genes, including APC, BMPR1A, CDH1, MLH1, MSH2, MSH6, MUTYH, PTEN, SMAD4, and STK11

81435  Hereditary colon cancer disorders (e.g., Lynch syndrome, PTEN hamartoma syndrome, Cowden syndrome, familial adenomatosis polyposis); duplication/deletion analysis panel, must include analysis of at least 5 genes, including MLH1, MSH2, EPCAM, SMAD4, and STK11

81436  Hereditary neuroendocrine tumor disorders (e.g., medullary thyroid carcinoma, parathyroid carcinoma, malignant pheochromocytoma or paraganglioma); genomic sequence analysis panel, must include sequencing of at least 6 genes, including MAX, SDHB, SDHC, SDHD, TMEM127, and VHL

81437  Hereditary neuroendocrine tumor disorders (e.g., medullary thyroid carcinoma, parathyroid carcinoma, malignant pheochromocytoma or paraganglioma); duplication/deletion analysis panel, must include analyses for SDHB, SDHC, SDHD, and VHL

81445  Targeted genomic sequence analysis panel, solid organ neoplasm, DNA analysis, and RNA analysis when performed, 5-50 genes (e.g., ALK, BRAF, CDKN2A, EGFR, ERBB2, KIT, KRAS, NRAS, MET, PDGFR, PDGFRB, PGR, PI3CA, 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 (e.g., 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 (e.g., ALK, BRAF, CDKN2A, CEBPA, DNMT3A, EGFR, ERBB2, EZH2, FLT3, IDH1, IDH2, JAK2, KIT, KRAS, MLL, NPM1, NRAS, MET, NOTCH1, PDGFR, PDGFRB, PGR, PI3CA, PTEN, RET), interrogation for sequence variants and copy number variants or rearrangements, if performed

81479  Unlisted molecular pathology procedure
Effective in 2015, there are CPT codes for genomic sequencing procedures (or "next-generation sequencing" panels). If the panel meets the requirements listed in the code descriptor, the following codes may be used: 81435, 81436, 81445, 81450, 81455.

Prior to 2015, there were no specific codes for molecular pathology testing by panels. During that time and currently if the panel does not meet the criteria in the specific code descriptors, if the specific analyte if not listed in the more specific CPT codes, unlisted code 81479 should be reported. The unlisted code would be reported once to represent all of the unlisted analytes in the panel.

**Diagnoses**

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

**REVISED**

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<th>Date</th>
<th>Event Description</th>
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<td>02-07-2014</td>
<td>Policy added to the bcbsks.com web site on 01-08-2014 for an effective date of 02-07-2014.</td>
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<tr>
<td>10-28-2014</td>
<td>Updated Description section.</td>
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<td>Added Policy Guideline section.</td>
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<td>In Revisions section, removed &quot;Updated Summary section&quot; from 10-28-2014.</td>
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<td>01-01-2016</td>
<td>In Coding section:</td>
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<td>• Added CPT codes: 81432, 81433, 81435, 81436, 81437, 81438, 81445, 81450, 81455.</td>
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<td>• Removed CPT codes: 81200, 81201, 81202, 81203, 81205, 81206, 81207, 81208,</td>
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**REFERENCES**


**Other References:**
1. Blue Cross and Blue Shield of Kansas Surgery Liaison Committee, August 2014; August 2015.
2. Blue Cross and Blue Shield of Kansas Ad Hoc Committee on Genetic Panel Testing, October 2014.
3. Blue Cross and Blue Shield of Kansas Pathology Liaison Committee, May 2015.
4. Blue Cross and Blue Shield of Kansas Oncology Liaison Committee, February 2014; February 2015.
5. Blue Cross and Blue Shield of Kansas Internal Medicine Liaison Committee, August 2015.