Medical Policy

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Title: Genetic Cancer Susceptibility Panels Using Next Generation Sequencing

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DESCRIPTION

Numerous genetic mutations are associated with certain types of hereditary cancer. Genetic testing using next-generation sequencing 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 to ordering individual tests.

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.

Ambry Genetics offers 4 different genetic testing panels for hereditary cancers. These panels do not include all genes associated with hereditary cancer syndromes. The use of these panels is intended for patients who have tested negative for *BRCA1* and *BRAC2* mutations. 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.

A list of the genes that are included in these panels is given in Table 1, followed by a brief description of each gene.

Table 1

Gene Tested	BreastNext	OvaNext	ColoNext	CancerNext
ATM	X	X		X
BARD1	X	X		X
BRIP1	X	X		X
MRE11A	X	X		X
NBN	X	X		X
RAD50	X	X		X
RAD51C	X	X		X
PALB2	X	X		X
STK11	X	X	X	X
CHEK2	X	X	X	X
PTEN	X	X	X	X
TP53	X	X	X	X
CDH1	X	X	X	X
MUTYH	X	X	X	X
MLH1		X	X	X
MSH2		X	X	X
MSH6		X	X	X
EPCAM		X	X	X
PMS2		X	X	X
APC			X	X
BMPR1A			X	X
SMAD4			X	X

Genes:

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

ATM is associated with the autosomal recessive condition ataxia-telangiectasia. This condition is characterized by progressive cerebellar ataxia with onset between the ages of one 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 are genes in the Fanconi anemia-*BRCA* pathway. Mutations in these genes are estimated to confer up to a 4-fold increase in the risk for breast cancer.

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

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

CDH1 germline mutations have been 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 39-52% of lobular breast cancer.

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

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

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

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

Mayo Clinic also offers a hereditary colon cancer multi-gene panel analysis, which includes the genes in the Ambry Genetics ColoNext, with the addition of two other low-risk genes (*MLH3* and *AXIN2*).

Hereditary Cancer and Cancer Syndromes

Hereditary breast cancer

Breast cancer can be classified as sporadic, familial or hereditary. Sporadic breast cancer accounts for 70-75% 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 15-25% of cases. Hereditary breast accounts for 5-10% of cases and is characterized by well-known susceptibility genes with apparently autosomal dominant transmission.

The "classic" inherited breast cancer syndrome is the hereditary breast and ovarian cancer [HBOC] syndrome, the vast majority of which are due to mutations in the *BRCA1* and *BRCA2* genes. Other hereditary cancer syndromes such as Li-Fraumeni syndrome (associated with *TP53* mutations), Cowden syndrome (CS, associated with *PTEN* mutations), Peutz-Jeghers syndrome, hereditary diffuse gastric cancer, and, possibly, Lynch syndrome also predispose patients, to varying degrees of risk for breast cancer. Other mutations and SNPs have also been 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 40-85%. Only about 5-10% 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. (1)

Other mutations may be associated with intermediate penetrance and a lifetime breast cancer risk of 20-40% (e.g., *CHEK2*, *APC*, *CDH-1*). 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 individuals 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 the individuals with malignancies and also 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, as some inherited cancer syndromes are also associated with other nonmalignant physical characteristics (e.g., benign skin tumors in Cowden syndrome).

Further discussion on the diagnostic criteria of HBOC will not be addressed in this policy. Criteria for a presumptive clinical diagnosis of Li-Fraumeni and Cowden syndromes have been established.

Li-Fraumeni Syndrome (LFS)

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. Individuals with LFS often present with certain cancers (soft-tissue sarcomas, brain tumors, and 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, pre-menopausal 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), two 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%. (2) The Chompret criteria have an estimated positive predictive value (PPV) of 20-35%, 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 an individual 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)

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 25-50%, with an average age of 38-46 years at diagnosis. The *PTEN* mutation frequency in individuals meeting International Cowden Consortium criteria (3) 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 Lynch syndrome, 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 colorectal cancers. Another 20% have a familial predilection for colorectal cancer without a clear hereditary syndrome identified. (4) The hereditary colorectal cancer 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. (5) The polyposis syndromes can be further subdivided by polyp histology, which includes the adenomatous (*FAP*, *aFAP* and *MUTYH*-associated) and hamartomatous (*JPS*, *PJS*, *PTEN* hamaratoma tumor syndrome) 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* testing. Hamartomatous polyps could focus testing for mutations in the genes *STK11*/*LKB1*, *SMAD4*, *BMPR1A*, and/or *PTEN*.

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 (6) who have tumor microsatellite instability (MSI) by immunohistochemistry on tumor tissue. Immunohistochemical testing helps identify which of the 4 *MMR* genes *(MLH1*, *MSH2*, *MSH6*, and *PMS2)* most likely harbors a mutation. The presence of MSI in the tumor alone is not sufficient to diagnose Lynch syndrome because 10-15% of sporadic colorectal cancers exhibit MSI.

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

Management of Polyposis Syndromes

FAP has a 100% penetrance, with polyps developing on average around the time of puberty, and the average colorectal cancer diagnosis before age 40. Endoscopic screening should begin around age 10-12 years, and operative intervention (colectomy) remains the definitive treatment. For attenuated *FAP*, colonoscopic surveillance is recommended to begin at age 20-30 years, or 10

years sooner than the first polyp diagnosis in the family. (7) For *MUTYH*-associated polyposis, colonoscopic surveillance is recommended to start at age 20-30 years.

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

Management of Nonpolyposis Syndromes
Individuals with Lynch syndrome have lifetime risks for cancer as follows: 52-82% for colorectal cancer (mean age at diagnosis 44-61 years); 25-60% for endometrial cancer in women (mean age at diagnosis 48-62 years); 6-13% for gastric cancer (mean age at diagnosis 56 years); and 4-12% for ovarian cancer (mean age at diagnosis 42.5 years; approximately one third are diagnosed before age 40 years). The risk for other Lynch syndrome-related cancers is lower, although substantially increased over that of the general population. For HNPCC or Lynch syndrome, colonoscopic screening should start at age 20-25 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. (8)

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.**

RATIONALE

Literature Review

This policy was created with a review of the literature through MEDLINE as of March 30, 2013.

Analytic validity (refers to 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 96-99%. This analytic sensitivity approaches that of direct sequencing of individual genes.

In order to determine whether next generation sequencing would enable accurate identification of inherited mutations for breast and ovarian cancer, Walsh and colleagues 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). (9) Constitutional genomic DNA from individuals 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.

Clinical validity (refers to 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.

Clinical utility (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 to 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 an individual 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.

Genetic cancer susceptibility panels using next generation sequencing for breast cancer, ovarian cancer, colon cancer or multiple cancer types (e.g., BreastNext, OvaNext, ColoNext and CancerNext, respectively) include mutations associated with varying risk of developing cancer. Therefore, these panels are of limited utility in that they may identify a clinically actionable mutation/syndrome, but could also identify a mutation for which there are no well-established guidelines or actionable level of risk associated with it.

In addition, high rates of variants of uncertain significance have been reported with the use of these panels. (10)

Summary

The use of next generation sequencing has made it possible to simultaneously test for multiple mutations. Cancer susceptibility mutation panels address three specific types of cancer that may be inherited (breast, ovarian and colon) and one panel that includes all of the mutations addressed in the three separate panels. The mutations included in these panels are associated with varying levels of risk of developing cancer, and only some of the mutations are associated with well-defined cancer syndromes which have established clinical management guidelines.

Management guidelines for syndromes with high penetrance in appropriate patient populations 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 variants of uncertain significance have been reported with the use of these panels.

Therefore, the use of genetic cancer susceptibility panels using next generation sequencing for breast, ovarian, colon and multiple cancer types is considered investigational.

Practice Guidelines and Position Statements

In a 2010 policy statement update on genetic and genomic testing for cancer susceptibility, the American Society of Clinical Oncology (ASCO) stated that testing for high-penetrance mutations in appropriate populations has clinical utility in that they inform clinical decision making and facilitate the prevention or amelioration of adverse health outcomes, but that genetic testing for intermediate-penetrance mutations are of uncertain clinical utility because the cancer risk associated with the mutation is generally too small to form an appropriate basis for clinical decision making. (11) ASCO recommends that genetic tests with uncertain clinical utility (low-to-moderate penetrance mutations) be administered in the context of clinical trials.

National Comprehensive Cancer Network (NCCN) guidelines on genetic/familial high-risk assessment for breast and ovarian cancer (v1.2013) state that next generation sequencing gene

panels for hereditary breast, ovarian and other cancers have limitations including an unknown percentage of variants of unknown significance, uncertainty of level of risk associated with most of the genes on the panel, and lack clear guidelines on the risk management of carriers of some of the mutations on the panel.

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

81200	ASPA (aspartoacylase) (eg, Canavan disease) gene analysis, common variants (eg, E285A, Y231X)
81201	APC (adenomatous polyposis coli) (eg, familial adenomatosis polyposis [FAP], attenuated FAP) gene analysis; full gene sequence
81202	APC (adenomatous polyposis coli) (eg, familial adenomatosis polyposis [FAP], attenuated FAP) gene analysis; known familial variants
81203	APC (adenomatous polyposis coli) (eg, familial adenomatosis polyposis [FAP], attenuated FAP) gene analysis; duplication/deletion variants
81205	BCKDHB (branched-chain keto acid dehydrogenase E1, beta polypeptide) (eg, Maple syrup urine disease) gene analysis, common variants (eg, R183P, G278S, E422X)
81206	BCR/ABL1 (t(9;22)) (eg, chronic myelogenous leukemia) translocation analysis; major breakpoint, qualitative or quantitative
81207	BCR/ABL1 (t(9;22)) (eg, chronic myelogenous leukemia) translocation analysis; minor breakpoint, qualitative or quantitative
81208	BCR/ABL1 (t(9;22)) (eg, chronic myelogenous leukemia) translocation analysis; other breakpoint, qualitative or quantitative
81209	BLM (Bloom syndrome, RecQ helicase-like) (eg, Bloom syndrome) gene analysis, 2281del6ins7 variant
81210	BRAF (v-raf murine sarcoma viral oncogene homolog B1) (eg, colon cancer), gene analysis, V600E variant
81211	BRCA1, BRCA2 (breast cancer 1 and 2) (eg, hereditary breast and ovarian cancer) gene analysis; full sequence analysis and common duplication/deletion variants in BRCA1 (ie, exon 13 del 3.835kb, exon 13 dup 6kb, exon 14-20 del 26kb, exon 22 del 510bp, exon
81212	BRCA1, BRCA2 (breast cancer 1 and 2) (eg, hereditary breast and ovarian cancer) gene analysis; 185delAG, 5385insC, 6174delT variants
81213	BRCA1, BRCA2 (breast cancer 1 and 2) (eg, hereditary breast and ovarian cancer) gene analysis; uncommon duplication/deletion variants
81214	BRCA1 (breast cancer 1) (eg, hereditary breast and ovarian cancer) gene analysis; full sequence analysis and common duplication/deletion variants (ie, exon 13 del 3.835kb, exon 13 dup 6kb, exon 14-20 del 26kb, exon 22 del 510bp, exon 8-9 del 7.1kb)
81215	BRCA1 (breast cancer 1) (eg, hereditary breast and ovarian cancer) gene analysis; known familial variant

81216 BRCA2 (breast cancer 2) (eg, hereditary breast and ovarian cancer) gene analysis; full sequence analysis
81217 BRCA2 (breast cancer 2) (eg, hereditary breast and ovarian cancer) gene analysis; known familial variant
81220 CFTR (cystic fibrosis transmembrane conductance regulator) (eg, cystic fibrosis) gene analysis; common variants (eg, ACMG/ACOG guidelines)
81221 CFTR (cystic fibrosis transmembrane conductance regulator) (eg, cystic fibrosis) gene analysis; known familial variants
81222 CFTR (cystic fibrosis transmembrane conductance regulator) (eg, cystic fibrosis) gene analysis; duplication/deletion variants
81223 CFTR (cystic fibrosis transmembrane conductance regulator) (eg, cystic fibrosis) gene analysis; full gene sequence
81224 CFTR (cystic fibrosis transmembrane conductance regulator) (eg, cystic fibrosis) gene analysis; intron 8 poly-T analysis (eg, male infertility)
81225 CYP2C19 (cytochrome P450, family 2, subfamily C, polypeptide 19) (eg, drug metabolism), gene analysis, common variants (eg, *2, *3, *4, *8, *17)
81226 CYP2D6 (cytochrome P450, family 2, subfamily D, polypeptide 6) (eg, drug metabolism), gene analysis, common variants (eg, *2, *3, *4, *5, *6, *9, *10, *17, *19, *29, *35, *41, *1XN, *2XN, *4XN)
81227 CYP2C9 (cytochrome P450, family 2, subfamily C, polypeptide 9) (eg, drug metabolism), gene analysis, common variants (eg, *2, *3, *5, *6)
81228 Cytogenomic constitutional (genome-wide) microarray analysis; interrogation of genomic regions for copy number variants (eg, Bacterial Artificial Chromosome [BAC] or oligo-based comparative genomic hybridization [CGH] microarray analysis)
81229 Cytogenomic constitutional (genome-wide) microarray analysis; interrogation of genomic regions for copy number and single nucleotide polymorphism (SNP) variants for chromosomal abnormalities
81235 EGFR (epidermal growth factor receptor) (eg, non-small cell lung cancer) gene analysis, common variants (eg, exon 19 LREA deletion, L858R, T790M, G719A, G719S, L861Q)
81240 F2 (prothrombin, coagulation factor II) (eg, hereditary hypercoagulability) gene analysis, 20210G>A variant
81241 F5 (coagulation Factor V) (eg, hereditary hypercoagulability) gene analysis, Leiden variant
81242 FANCC (Fanconi anemia, complementation group C) (eg, Fanconi anemia, type C) gene analysis, common variant (eg, IVS4+4A>T)
81243 FMR1 (Fragile X mental retardation 1) (eg, fragile X mental retardation) gene analysis; evaluation to detect abnormal (eg, expanded) alleles
81244 FMR1 (Fragile X mental retardation 1) (eg, fragile X mental retardation) gene analysis; characterization of alleles (eg, expanded size and methylation status)
81245 FLT3 (fms-related tyrosine kinase 3) (eg, acute myeloid leukemia), gene analysis, internal tandem duplication (ITD) variants (ie, exons 14, 15)
81250 G6PC (glucose-6-phosphatase, catalytic subunit) (eg, Glycogen storage disease, Type 1a, von Gierke disease) gene analysis, common variants (eg, R83C, Q347X)
81251 GBA (glucosidase, beta, acid) (eg, Gaucher disease) gene analysis, common variants (eg, N370S, 84GG, L444P, IVS2+1G>A)
81252 GJB2 (gap junction protein, beta 2, 26kDa, connexin 26) (eg, nonsyndromic hearing loss) gene analysis; full gene sequence

81253 GJB2 (gap junction protein, beta 2, 26kDa; connexin 26) (eg, nonsyndromic hearing loss) gene analysis; known familial variants

81254 GJB6 (gap junction protein, beta 6, 30kDa, connexin 30) (eg, nonsyndromic hearing loss) gene analysis, common variants (eg, 309kb [del(GJB6-D13S1830)] and 232kb [del(GJB6-D13S1854)])

81255 HEXA (hexosaminidase A [alpha polypeptide]) (eg, Tay-Sachs disease) gene analysis, common variants (eg, 1278insTATC, 1421+1G>C, G269S)

81256 HFE (hemochromatosis) (eg, hereditary hemochromatosis) gene analysis, common variants (eg, C282Y, H63D)

81257 HBA1/HBA2 (alpha globin 1 and alpha globin 2) (eg, alpha thalassemia, Hb Bart hydrops fetalis syndrome, HbH disease), gene analysis, for common deletions or variant (eg, Southeast Asian, Thai, Filipino, Mediterranean, alpha3.7, alpha4.2, alpha20.5, and Co

81260 IKBKAP (inhibitor of kappa light polypeptide gene enhancer in B-cells, kinase complex-associated protein) (eg, familial dysautonomia) gene analysis, common variants (eg, 2507+6T>C, R696P)

81261 IGH@ (Immunoglobulin heavy chain locus) (eg, leukemias and lymphomas, B-cell), gene rearrangement analysis to detect abnormal clonal population(s); amplified methodology (eg, polymerase chain reaction)

81262 IGH@ (Immunoglobulin heavy chain locus) (eg, leukemias and lymphomas, B-cell), gene rearrangement analysis to detect abnormal clonal population(s); direct probe methodology (eg, Southern blot)

81263 IGH@ (Immunoglobulin heavy chain locus) (eg, leukemia and lymphoma, B-cell), variable region somatic mutation analysis

81264 IGK@ (Immunoglobulin kappa light chain locus) (eg, leukemia and lymphoma, B-cell), gene rearrangement analysis, evaluation to detect abnormal clonal population(s)

81265 Comparative analysis using Short Tandem Repeat (STR) markers; patient and comparative specimen (eg, pre-transplant recipient and donor germline testing, post-transplant non-hematopoietic recipient germline [eg, buccal swab or other germline tissue sample]

81266 Comparative analysis using Short Tandem Repeat (STR) markers; each additional specimen (eg, additional cord blood donor, additional fetal samples from different cultures, or additional zygosity in multiple birth pregnancies) (List separately in addition to code for primary procedure)

81267 Chimerism (engraftment) analysis, post transplantation specimen (eg, hematopoietic stem cell), includes comparison to previously performed baseline analyses; without cell selection

81268 Chimerism (engraftment) analysis, post transplantation specimen (eg, hematopoietic stem cell), includes comparison to previously performed baseline analyses; with cell selection (eg, CD3, CD33), each cell type

81270 JAK2 (Janus kinase 2) (eg, myeloproliferative disorder) gene analysis, p.Val617Phe (V617F) variant

81275 KRAS (v-Ki-ras2 Kirsten rat sarcoma viral oncogene) (eg, carcinoma) gene analysis, variants in codons 12 and 13

81280 Long QT syndrome gene analyses (eg, KCNQ1, KCNH2, SCN5A, KCNE1, KCNE2, KCNJ2, CACNA1C, CAV3, SCN4B, AKAP, SNTA1, and ANK2); full sequence analysis

81281 Long QT syndrome gene analyses (eg, KCNQ1, KCNH2, SCN5A, KCNE1, KCNE2, KCNJ2, CACNA1C, CAV3, SCN4B, AKAP, SNTA1, and ANK2); known familial sequence variant

81282 Long QT syndrome gene analyses (eg, KCNQ1, KCNH2, SCN5A, KCNE1, KCNE2, KCNJ2, CACNA1C, CAV3, SCN4B, AKAP, SNTA1, and ANK2); duplication/deletion variants

81290 MCOLN1 (mucolipin 1) (eg, Mucolipidosis, type IV) gene analysis, common variants (eg, IVS3-2A>G, del6.4kb)

81291 MTHFR (5,10-methylenetetrahydrofolate reductase) (eg, hereditary hypercoagulability) gene analysis, common variants (eg, 677T, 1298C)

81292 MLH1 (mutL homolog 1, colon cancer, nonpolyposis type 2) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis

81293 MLH1 (mutL homolog 1, colon cancer, nonpolyposis type 2) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; known familial variants

81294 MLH1 (mutL homolog 1, colon cancer, nonpolyposis type 2) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; duplication/deletion variants

81295 MSH2 (mutS homolog 2, colon cancer, nonpolyposis type 1) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis

81296 MSH2 (mutS homolog 2, colon cancer, nonpolyposis type 1) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; known familial variants

81297 MSH2 (mutS homolog 2, colon cancer, nonpolyposis type 1) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; duplication/deletion variants

81298 MSH6 (mutS homolog 6 [E. coli]) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis

81299 MSH6 (mutS homolog 6 [E. coli]) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; known familial variants

81300 MSH6 (mutS homolog 6 [E. coli]) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; duplication/deletion variants

81301 Microsatellite instability analysis (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) of markers for mismatch repair deficiency (eg, BAT25, BAT26), includes comparison of neoplastic and normal tissue, if performed

81302 MECP2 (methyl CpG binding protein 2) (eg, Rett syndrome) gene analysis; full sequence analysis

81303 MECP2 (methyl CpG binding protein 2) (eg, Rett syndrome) gene analysis; known familial variant

81304 MECP2 (methyl CpG binding protein 2) (eg, Rett syndrome) gene analysis; duplication/deletion variants

81310 NPM1 (nucleophosmin) (eg, acute myeloid leukemia) gene analysis, exon 12 variants

81315 PML/RARalpha, (t(15;17)), (promyelocytic leukemia/retinoic acid receptor alpha) (eg, promyelocytic leukemia) translocation analysis; common breakpoints (eg, intron 3 and intron 6), qualitative or quantitative

81316 PML/RARalpha, (t(15;17)), (promyelocytic leukemia/retinoic acid receptor alpha) (eg, promyelocytic leukemia) translocation analysis; single breakpoint (eg, intron 3, intron 6 or exon 6), qualitative or quantitative

81317 PMS2 (postmeiotic segregation increased 2 [S. cerevisiae]) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis

81318 PMS2 (postmeiotic segregation increased 2 [S. cerevisiae]) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; known familial variants

81319 PMS2 (postmeiotic segregation increased 2 [S. cerevisiae]) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; duplication/deletion variants

81321 PTEN (phosphatase and tensin homolog) (eg, Cowden syndrome, PTEN hamartoma tumor syndrome) gene analysis; full sequence analysis

81322 PTEN (phosphatase and tensin homolog) (eg, Cowden syndrome, PTEN hamartoma tumor syndrome) gene analysis; known familial variant

81323 PTEN (phosphatase and tensin homolog) (eg, Cowden syndrome, PTEN hamartoma tumor syndrome) gene analysis; duplication/deletion variant

81324 PMP22 (peripheral myelin protein 22) (eg, Charcot-Marie-Tooth, hereditary neuropathy with liability to pressure palsies) gene analysis; duplication/deletion analysis

81325 PMP22 (peripheral myelin protein 22) (eg, Charcot-Marie-Tooth, hereditary neuropathy with liability to pressure palsies) gene analysis; full sequence analysis

81326 PMP22 (peripheral myelin protein 22) (eg, Charcot-Marie-Tooth, hereditary neuropathy with liability to pressure palsies) gene analysis; known familial variant

81330 SMPD1(sphingomyelin phosphodiesterase 1, acid lysosomal) (eg, Niemann-Pick disease, Type A) gene analysis, common variants (eg, R496L, L302P, fsP330)

81331 SNRPN/UBE3A (small nuclear ribonucleoprotein polypeptide N and ubiquitin protein ligase E3A) (eg, Prader-Willi syndrome and/or Angelman syndrome), methylation analysis

81332 SERPINA1 (serpin peptidase inhibitor, clade A, alpha-1 antiproteinase, antitrypsin, member 1) (eg, alpha-1-antitrypsin deficiency), gene analysis, common variants (eg, *S and *Z)

81340 TRB@ (T cell antigen receptor, beta) (eg, leukemia and lymphoma), gene rearrangement analysis to detect abnormal clonal population(s); using amplification methodology (eg, polymerase chain reaction)

81341 TRB@ (T cell antigen receptor, beta) (eg, leukemia and lymphoma), gene rearrangement analysis to detect abnormal clonal population(s); using direct probe methodology (eg, Southern blot)

81342 TRG@ (T cell antigen receptor, gamma) (eg, leukemia and lymphoma), gene rearrangement analysis, evaluation to detect abnormal clonal population(s)

81350 UGT1A1 (UDP glucuronosyltransferase 1 family, polypeptide A1) (eg, irinotecan metabolism), gene analysis, common variants (eg, *28, *36, *37)

81355 VKORC1 (vitamin K epoxide reductase complex, subunit 1) (eg, warfarin metabolism), gene analysis, common variants (eg, -1639/3673)

81400 Molecular pathology procedure, Level 1(eg, identification of single germline variant [eg, SNP] by techniques such as restriction enzyme digestion or melt curve analysis)

81401 Molecular pathology procedure, Level 2 (eg, 2-10 SNPs, 1 methylated variant, or 1 somatic variant [typically using nonsequencing target variant analysis], or detection of a dynamic mutation disorder/triplet repeat)

81402 Molecular pathology procedure, Level 3 (eg, >10 SNPs, 2-10 methylated variants, or 2-10 somatic variants [typically using non-sequencing target variant analysis], immunoglobulin and T-cell receptor gene rearrangements, duplication/deletion variants of 1 exon, loss of heterozygosity [LOH], uniparental disomy [UPD])

81403 Molecular pathology procedure, Level 4 (eg, analysis of single exon by DNA sequence analysis, analysis of >10 amplicons using multiplex PCR in 2 or more independent reactions, mutation scanning or duplication/deletion variants of 2-5 exons)
81404 Molecular pathology procedure, Level 5 (eg, analysis of 2-5 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 6-10 exons, or characterization of a dynamic mutation disorder/triplet repeat by Southern blot analysis)
81405 Molecular pathology procedure, Level 6 (eg, analysis of 6-10 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 11-25 exons), regionally targeted cytogenomic array analysis
81406 Molecular pathology procedure, Level 7 (eg, analysis of 11-25 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 26-50 exons, cytogenomic array analysis for neoplasia)
81407 Molecular pathology procedure, Level 8 (eg, analysis of 26-50 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of >50 exons, sequence analysis of multiple genes on one platform)
81408 Molecular pathology procedure, Level 9 (eg, analysis of >50 exons in a single gene by DNA sequence analysis)
81479 Unlisted molecular pathology procedure

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

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

REVISIONS

02-07-2014	Policy added to the bcbsks.com web site on 01-08-2014 for an effective date of 02-07-2014.

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