Medical Policy
Genetic Cancer Susceptibility Panels Using Next Generation Sequencing

Table of Contents
- Policy: Commercial
- Policy: Medicare
- Authorization Information
- Coding Information
- Description
- Policy History
- Information Pertaining to All Policies
- References

Policy Number: 574
BCBSA Reference Number: 2.04.93
NCD/LCD: NA

Related Policies
- Genetic Testing for Lynch Syndrome and Other Inherited Intestinal Polyposis Syndromes, #226
- Use of Common Genetic Variants to Predict Risk of Nonfamilial Breast Cancer, #252
- Genetic Testing for PTEN Hamartoma Tumor Syndrome, #615

Policy
Commercial Members: Managed Care (HMO and POS), PPO, and Indemnity
Medicare HMO BlueSM and Medicare PPO BlueSM Members

Genetic cancer susceptibility panels using next generation sequencing are considered INVESTIGATIONAL.

Prior Authorization Information
Pre-service approval is required for all inpatient services for all products.
See below for situations where prior authorization may be required or may not be required for outpatient services.
Yes indicates that prior authorization is required.
No indicates that prior authorization is not required.
N/A indicates that this service is primarily performed in an inpatient setting.

<table>
<thead>
<tr>
<th>Outpatient</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Commercial Managed Care (HMO and POS)</td>
<td>This is not a covered service.</td>
</tr>
<tr>
<td>Commercial PPO and Indemnity</td>
<td>This is not a covered service.</td>
</tr>
<tr>
<td>Medicare HMO BlueSM</td>
<td>This is not a covered service.</td>
</tr>
<tr>
<td>Medicare PPO BlueSM</td>
<td>This is not a covered service.</td>
</tr>
</tbody>
</table>
CPT Codes / HCPCS Codes / ICD-9 Codes

The following codes are included below for informational purposes. Inclusion or exclusion of a code 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 as it applies to an individual member.

Providers should report all services using the most up-to-date industry-standard procedure, revenue, and diagnosis codes, including modifiers where applicable.

There are no specific codes for this procedure.

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.

<table>
<thead>
<tr>
<th>Gene Tested</th>
<th>BreastNext</th>
<th>OvaNext</th>
<th>ColoNext</th>
<th>CancerNext</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATM</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BARD1</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BRIP1</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MRE11A</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NBN</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>RAD50</td>
<td>X</td>
<td>X</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>RAD51C</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>PALB2</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>STK11</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>CHEK2</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>PTEN</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>TP53</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>CDH1</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>MUTYH</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>MLH1</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>MSH2</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>MSH6</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>EPCAM</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>PMS2</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>APC</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMPR1A</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Ambry Genetics offers 4 different genetic testing panels for hereditary cancers. These panels do not include all genes associated with hereditary cancer syndromes. For example, \textit{BRCA1} and \textit{BRCA2} mutations are not included in the panels, and the use of these panels are intended for patients who have tested negative for \textit{BRCA1} and \textit{BRCA2} 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.

\begin{table}[h]
\centering
\begin{tabular}{|l|c|c|}
\hline
\textbf{Genes} & \textbf{SMAD4} & \textbf{X} \\
\hline
\end{tabular}
\caption{Table 1}
\end{table}

\textbf{Table 1}
\textbf{Genes:}
\textit{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.

\textit{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.

\textit{BARD1, BRIP1, MRE11A, NBN, RAD50, and RAD51C} are genes in the Fanconi anemia-\textit{BRCA} pathway. Mutations in these genes are estimated to confer up to a 4-fold increase in the risk for breast cancer.

\textit{BMPR1A} and \textit{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%.

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

\textit{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.

\textit{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/endorometrial 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.

\textit{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 \textit{APC} gene, have \textit{MUTYH} mutations.

\textit{PALB2} germline mutations have been associated with an increased risk of pancreatic and breast cancer. Familial pancreatic and/or breast cancer due to \textit{PALB2} mutations is inherited in an autosomal dominant pattern.

\textit{PTEN} mutations have been associated with \textit{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.

Other mutations may be associated with intermediate penetrance and a lifetime breast cancer risk of 20-40% (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 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, 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), 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%. 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 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. 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. The polyposis syndromes can be further subdivided by polyp histology, which includes the adenomatous (FAP, aFAP and MUTYH-associated) and hamartomatous (JPS, PJS, PTEN hamarotoma 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 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. 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.

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.

### Policy History

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>11/2017</td>
<td>New references added from BCBSA National medical policy.</td>
</tr>
<tr>
<td>6/2015</td>
<td>New references added from BCBSA National medical policy.</td>
</tr>
<tr>
<td>9/2014</td>
<td>New references added from BCBSA National medical policy.</td>
</tr>
</tbody>
</table>

### Information Pertaining to All Blue Cross Blue Shield Medical Policies

Click on any of the following terms to access the relevant information:

- Medical Policy Terms of Use
- Managed Care Guidelines
- Indemnity/PPO Guidelines
- Clinical Exception Process
- Medical Technology Assessment Guidelines

### References


