

MEDICAL POLICY

<p>SUBJECT: GENETIC TESTING FOR SUSCEPTIBILITY TO HEREDITARY CANCERS</p> <p>POLICY NUMBER: 2.02.44 CATEGORY: Laboratory Test</p>	<p>EFFECTIVE DATE: 06/19/14 REVISED DATE: 10/15/15, 10/20/16, 01/18/18, 10/18/18</p> <p>PAGE: 1 OF: 10</p>
<ul style="list-style-type: none"> • <i>If a product excludes coverage for a service, it is not covered, and medical policy criteria do not apply.</i> • <i>If a commercial product (including an Essential Plan product) or a Medicaid product covers a specific service, medical policy criteria apply to the benefit.</i> • <i>If a Medicare product covers a specific service, and there is no national or local Medicare coverage decision for the service, medical policy criteria apply to the benefit.</i> 	

POLICY STATEMENT:

- I. Based upon our criteria and assessment of the peer-reviewed literature, genetic testing for mutations in other high to moderate and low penetrance genes associated with breast and ovarian cancer (e.g., ATM, BARD1, BRIP1, CHEK2, NBN, PALB2, RAD50, RAD51C, and STK11) which are part of next generation sequencing panels (e.g., BRCAPlus, BreastNext™, CancerNext™, OvaNext™, Panexia®, Melaris®, OncoGene Dx, and myRisk™ Hereditary Cancer) is considered **medically appropriate** when:
- A. an individual meets criteria for genetic testing for BRCA1 and BRCA2 genetic testing for susceptibility to breast or ovarian cancer (Please refer to 2.02.06 Genetic Testing for Hereditary BRCA Mutations); or
 - B. the individual meets criteria for Cowden syndrome described in Policy Statements IIA; or
 - C. the individual meets criteria Li Fraumeni Syndrome described in Policy Statements IIB; or
 - D. the individual meets criteria for Hereditary Diffuse Gastric Cancer described in Policy Statement IIC; or
 - E. the individual meets criteria for any inherited colorectal cancer (Please refer to #2.02.11 Genetic Testing for Inherited Susceptibility to Colorectal Cancer).
- II. Based upon our criteria and assessment of the peer-reviewed literature, including National Comprehensive Cancer Network (NCCN) clinical guidelines genetic testing for hereditary breast and/or ovarian cancer has been medically proven to be effective and therefore **medically appropriate** in the following circumstances, when performed by a qualified laboratory and offered in a setting with adequately trained health care providers to provide appropriate pre-and post-test genetic counseling that will guide decisions regarding cancer prevention, surveillance, and treatment options.

Testing should be performed in the affected (personal history of cancer) family member first unless an unaffected individual has a family history of a known mutation; an affected individual has the highest likelihood for a positive test result (e.g., the family member with the youngest age at diagnosis, or bilateral disease, or multiple primary cancers, or other cancers associated with the syndrome, or most closely related to the proband). Testing of unaffected individuals (an individual who does not have cancer) should only be considered when an appropriate affected family member is unavailable for testing. A negative result for an unaffected individual with only a family history of cancer is considered indeterminate (or uninformative) and does not provide the same level of information as when there is a known deleterious mutation in the family. Testing of unaffected family members in the absence of having tested affected family members significantly limits the interpretation of the test results.

A. Cowden Syndrome (CS) (germline mutations of PTEN) (CPT: 81321, 81323):

1. An individual from a family with a known PTEN mutation (CPT: 81322); or
2. An individual with a personal history of Bannayan-Riley-Ruvalcaba syndrome (BRRS); or
3. An individual with a personal history of adult Lhermitte-Duclos disease (cerebellar tumors); or
4. An individual with a personal history of autism spectrum disorder and macrocephaly; or
5. An individual with a personal history of two or more biopsy-proven trichilemmomas; or
6. An individual meeting the clinical diagnostic criteria for CS/PTEN hemartoma tumor syndrome (PHTS); or
7. An individual with a personal history of:

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- a. Two or more major criteria (one must be macrocephaly); or
- b. Three major criteria, without macrocephaly; or
- c. One major and three or more minor criteria*; or
- d. Four or more minor criteria.

*If an individual has two or more major criteria, but does not have macrocephaly, one of the major criteria may be included as one of the three minor criteria to meet testing criteria.

- 8. An individual with a **first-degree** relative with a clinical diagnosis of CS or BRRS for whom testing has not been performed. The individual must meet the following diagnostic criteria:
 - a. Any one major criterion; or
 - b. Two minor criteria.

Major Criteria:

- a. Breast cancer; or
- b. Endometrial cancer; or
- c. Follicular thyroid cancer; or
- d. Multiple GI hamartomas or ganglioneuromas, excluding hyperplastic polyps (greater than or equal to 3)
- e. Macrocephaly (megalcephaly (i.e., greater than or equal to 97%, 58 cm in adult women, 60 cm in adult men); or
- f. Macular pigmentation of glans penis; or
- g. Mucocutaneous lesions
 - i. One biopsy proven trichilemmoma
 - ii. Multiple palmoplantar keratosis (palmoplantar keratotic pits/and or acral hyperkeratotic papules)
 - iii. Multifocal or extensive oral mucosal papillomatosis
 - iv. Multiple cutaneous facial papules (often verrucous)

Minor Criteria:

- a. Autism spectrum disorder; or
- b. Colon cancer; or
- c. Esophageal glycogenic acanthosis (greater than or equal to 3); or
- d. Lipomas; or
- e. Intellectual disability (i.e., IQ less than or equal to 75); or
- f. Papillary or follicular variant of papillary thyroid cancer; or
- g. Thyroid structural lesions (e.g., adenoma, nodules(s), goiter); or
- h. Renal cell carcinoma; or
- i. Single GI hamartoma or ganglioneuroma; or
- j. Testicular lipomatosis; or
- k. Vascular anomalies (including multiple intracranial developmental venous anomalies)

B. Li Fraumeni Syndrome (LFS) (germline mutations of TP53):

- 1. An individual from a family with a known TP53 mutation; or
- 2. Personal history of breast cancer diagnosed at age 31 years or younger; may be performed simultaneously with BRCA mutation testing or when BRCA1/BRCA2 is negative; or
- 3. Personal history of adrenocortical carcinoma, or choroid plexus carcinoma or rhabdomyosarcoma of embryonal anaplastic subtype diagnosed at any age regardless of the family history; or
- 4. Personal history of sarcoma diagnosed at age less than 45 years; AND (must have at least two 1st degree relatives or one 1st degree relative and one 2nd degree relative as described below)
 - a. Has one 1st degree relative diagnosed with cancer at age less than 45 years; AND
 - b. Has one additional 1st or 2nd degree relative on the same side of the family diagnosed with cancer at age less than 45 years, or a sarcoma at any age; or
- 5. Personal history of a tumor from the *LFS tumor spectrum diagnosed before age 46 years; AND
 - a. Has one or more 1st or 2nd degree relative with a tumor from the LFS tumor spectrum (other than breast cancer if the proband has breast cancer) diagnosed before age 56 years; or
 - b. Has one or more 1st or 2nd degree relative with multiple primaries diagnosed at any age; or

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*Tumors associated with LFS include but are not limited to: breast cancer, soft tissue sarcoma, osteosarcoma, CNS tumor, adrenocortical carcinoma.

6. Personal history of multiple tumors (except multiple breast tumors); AND
 - a. The *initial* tumor was diagnosed before age 46 years; AND
 - b. 2 of the tumors are from the *LFS tumor spectrum

*Tumors associated with LFS include but are not limited to: breast cancer, soft tissue sarcoma, osteosarcoma, CNS tumor, adrenocortical carcinoma.

C. Hereditary diffuse gastric cancer (HDGC) (germline mutations of CDH1)

1. Personal history of diffuse gastric cancer diagnosed before age 40 years with or without a family history; or
2. Personal history of lobular breast cancer and diffuse gastric cancer, one of which was diagnosed before age 50 years; or
3. An individual that has a 1st or 2nd degree relative diagnosed with lobular breast cancer and diffuse gastric cancer, one of which was diagnosed before age 50 years; or
4. Family history (may include individual with personal history) of one 1st or 2nd degree relative with lobular breast cancer and in another 1st or 2nd degree relative diffuse gastric cancer on the same side of the family, one of which was diagnosed before age 50 years; or
5. Family history (may include individual with personal history) of two cases of gastric cancer in 1st or 2nd degree relatives, one of which is a confirmed diffuse gastric cancer diagnosed before age 50 years; or
6. Family history (may include individual with personal history) of 3 or more 1st or 2nd degree relatives on the same side of the family with diffuse gastric cancer diagnosed at any age.

- III. Based upon our criteria and assessment of the peer-reviewed literature including National Comprehensive Cancer Network (NCCN) clinical guidelines, genetic testing in an individual from a family with a **known** mutation in the CHEK2, NBN, NF1, ATM or PALB2 gene, genetic testing for the known mutation is considered medically appropriate for individuals with these mutations as breast MRI would be recommended for screening due to an increased risk of breast cancer.
- IV. Based upon our criteria and assessment of the peer-reviewed literature including National Comprehensive Cancer Network (NCCN) clinical guidelines, genetic testing in an individual from a family with a **known** mutation in either the BRIP1, RAD51C, or RAD51D gene, genetic testing for the known mutation is considered medically appropriate when risk reducing salpingo-oophorectomy (RRSO) is being considered in individuals with these mutations due to an increased risk of ovarian cancer.
- V. Based upon our criteria and assessment of the peer-reviewed literature, genetic testing for mutations in other high to moderate and low penetrance genes associated with breast and ovarian cancer unless criteria in Policy Statement I are met (see above) (e.g., ATM, BARD1, BRIP1, CDH1, CHEK2, NBN, PALB2, RAD50, RAD51C, and STK11) which are part of next generation sequencing panels (e.g., BRCAPlus, BreastNext™, CancerNext™, OvaNext™, Panexia®, Melaris®, OncoGene Dx, and myRisk™ Hereditary Cancer) in a setting other than the above is considered **investigational**.

Refer to Corporate Medical Policy #2.02.03 regarding Genetic Testing for Specific Diseases.

Refer to Corporate Medical Policy 2.02.06 Genetic Testing for Hereditary BRCA Mutations.

Refer to Corporate Medical Policy #2.02.11 regarding Genetic Testing for Inherited Susceptibility to Colorectal Cancer.

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POLICY GUIDELINES:

- I. Supporting documentation required:
The purpose of genetic testing is to provide information that will guide decisions regarding cancer prevention, surveillance, and treatment options. Documentation which must be submitted for review includes:
 - A. Family history (pedigree) which includes first-, second-, and third-degree relatives, identifying family members affected with cancer; and
 - B. Type of cancer, age at diagnosis for each family member with a personal history of cancer (affected) and whether they are living or deceased;
 - C. Genetic testing results from any other family members. If family member(s) have not been testing (and are more appropriate to be tested first), clear and distinct rationale as to why the family member(s) cannot be tested (i.e., specific reason why testing was declined); and
 - D. Documentation of discussion between the physician and member of rationale for genetic testing and treatment options for the individual patient based on test results; and
 - E. Documentation of discussion between the physician and unaffected member of rationale for genetic testing when the affected family member cannot be tested including that a negative result for an unaffected individual with only a family history of cancer is considered indeterminate (or uninformative) and does not provide the same level of information as when there is a known deleterious mutation in the family. Testing of unaffected family members in the absence of having tested affected family members significantly limits the interpretation of the test results.

- II. A first-degree relative is a blood relative with whom an individual shares approximately 50% of her/his genes (parents, full siblings, and children). A second-degree relative is a blood relative with whom an individual shares approximately 25% of her/his genes (grandparents, grandchildren, aunts, uncles, nephews, nieces and half-siblings). A third-degree relative is a blood relative with whom an individual shares approximately 12.5% of her/his genes (great-grandparents, great-grandchildren, great-aunts, great-uncles, first cousin, and grand-niece or nephew.)

- III. For the majority of families in whom mutation status is unknown, it is best to consider testing an affected family member first, especially a family member with early-onset disease, bilateral disease, or multiple primaries, because that individual is most likely to test positive. The testing of unaffected family members may be considered when no affected member is available.

- IV. It is recommended that unaffected individuals with a strong family history who do not meet criteria for BRCA testing or who test negative be referred to an adequately trained health care professional (genetic counselor) to provide appropriate genetic risk assessment to determine the individual's risk for developing cancer.

- V. Genetic testing in the absence of a personal or family history of breast cancer is not medically appropriate due to the low probability of detecting a mutation and the considerable psychological impact that may be involved. Widespread screening of specific sub-populations is not endorsed.

- VI. If the genetic test is being done for knowledge only and that knowledge will not alter management or treatment of the patient or family member then the testing is not medically appropriate.

- VI. The Health Plan and its employees adhere to all state and federal laws concerning the confidentiality of genetic testing and the results of genetic testing. All records, findings and results of any genetic test performed on any person shall be deemed confidential and shall not be disclosed without the written informed consent of the person to whom such genetic test relates. This information shall not be released to any person or organization not specifically authorized by the individual subject of the test.

- VII. Laboratories performing clinical tests must be certified under the Clinical Laboratory Improvement Amendments of 1988 (CLIA).

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DESCRIPTION:

Cowden Syndrome

Cowden syndrome is an autosomal dominant disorder associated with germline mutations in the PTEN (phosphatase and tensin homolog) tumor suppressor gene. It is considered to be part of the spectrum of PTEN hamartoma tumor syndromes (PHTS) which also includes Bannayan-Riley-Ruvalcaba syndrome (BRRS), PTEN-related Proteus syndromes (PS), and Proteus-like syndrome (PLS). Additional clinical syndromes related to germline mutations in PTEN include Lermite-Duclos disease and autism spectrum disorders with macrocephaly, both of which have been associated with Cowden syndrome. Cowden syndrome has been conservatively estimated to occur in 1 in 200,000, with an estimated penetrance of 80%. CS is associated with multiple hamartomas and/or cancerous lesions in various organs and tissues, including the skin, mucous membranes, breast, thyroid, endometrium and brain. Women diagnosed with CS have a high risk of benign fibrocystic breast disease and their lifetime risk of breast cancer has been estimated at 25-50% with an average age of diagnosis of 38-46 years.

LiFraumeni Syndrome

Li Fraumeni syndrome (LFS) is a rare hereditary cancer syndrome associated with germline TP53 gene mutations. It has been estimated to be involved in only 1% hereditary breast cancer cases, but results from recent studies show that it may be more common than previously believed. Germline mutations in the TP53 gene have been observed in over 50% of families meeting the classical definition of LFS. LFS is a highly penetrant cancer syndrome and is characterized by a wide spectrum of neoplasms occurring at a young age. It is associated with soft tissue sarcomas, osteosarcomas (Ewing's sarcoma less likely in cases of LFS), premenopausal breast cancer, acute leukemia, colon cancer, adrenal cortex and brain tumors. The "core" LFS tumors are noted to be sarcoma, breast cancer, adrenocortical tumors, and certain brain tumors because they are the more predominant cancers in this syndrome. Individuals with LFS often present with certain cancers in early childhood and have an increased risk of developing multiple cancers in their lifetime.

Hereditary Diffuse Gastric Cancer Syndrome

Hereditary diffuse gastric cancer (HDGC) is an autosomal dominant syndrome characterized by the development of diffuse (signet ring cell) gastric cancer at a young age. Truncating mutations in CDH1, the gene encoding the cell adhesion molecular E-cadherin, are found in 30% to 50% of cases. The lifetime risk for gastric cancer by age 80 years is estimated to be at 67% for men and 83% for women. Average age at diagnosis of gastric cancer is 37 years. Women with CDH1 mutations are at higher risk of developing lobular carcinoma of the breast with a cumulative lifetime risk for breast cancer of 39% to 52%.

Other Gene Mutations

Mutations in genes other than the BRCA1 and BRCA2 have been reported to be associated with an increased risk of breast cancer. It is now possible to test for multiple breast and/or ovarian cancer susceptibility genes in parallel using multigene or multiplex panels. High-penetrance gene mutations such as TP53 and PTEN are thought to account for a large proportion of familial breast cancers while gene mutations in CDH1 and STK11 have been associated with hereditary diffuse gastric cancer, which includes an increased risk for lobular breast cancer and Peutz-Jeghers syndrome, respectively (refer to Corporate Medical Policy #2.02.11 regarding Genetic Testing for Inherited Susceptibility to Colorectal Cancer). Mutations in genes such as CHEK2, BRIP1, RAD51C, and PALB2, among other mutations have been confirmed to be associated with increased risk and at this time are considered to be genes with low- or moderate-penetrance. Those high penetrance and low-and moderate penetrance genes listed above are examples of the mutations included in the multiplex panels. These panels may be resource efficient in terms of time and costs, but currently there is no consensus on recommendations for optimal management or surveillance approaches for carrier of these lower or moderate penetrance genes and there is no data available to address cancer risk assessments in individuals who are found to carry multiple gene mutations with moderate penetrance. Additional genetic counseling approaches must be vetted and developed in order to adequately address the limitations and implications associated with interpretation of multiplex testing results. Consequently these multiplex panels are not yet considered part of standard clinical practice. Examples of panels include the BreastNext™, CancerNext™, and OvaNext™ panels offered by Ambry Genetics while Myriad Genetics offers the myRisk™ Hereditary Cancer panel as well as, Prolaris®, Melaris®, and Panexia® panels.

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RATIONALE:

A systematic review by Pilarski et al., was conducted related to the clinical features reported in individuals with a *PTEN* mutation, and revised diagnostic criteria were proposed. The authors concluded that there was insufficient evidence to support inclusion of benign breast disease, uterine fibroids, or genitourinary malformations as diagnostic criteria. There was sufficient evidence to include autism spectrum disorders, colon cancer, esophageal glycogenic acanthosis, penile macules, renal cell carcinoma, testicular lipomatosis and vascular anomalies, and these clinical features are included in Cowden syndrome testing minor criteria in National Comprehensive Cancer Network (NCCN) guidelines.

The International Cowden Consortium criteria for Cowden syndrome have been updated several times since 1996 and is the basis for the National Comprehensive Cancer Network (NCCN) (2018) criteria for *PTEN* mutation testing. The criteria have been divided into 3 categories depending on diagnostic features, major and minor features associated with Cowden’s syndrome. In addition, a first-degree relative of an affected individual with one or more major, or two or more minor criteria, along with a relative diagnosed with Cowden syndrome or Bannayan-Riley-Ruvalcaba syndrome (who has not been tested) would also meet the threshold for *PTEN* testing.

The National Comprehensive Cancer Network (NCCN) (2018) for Genetic/familial high-risk assessment: breast and ovarian utilizes both the classic Li Fraumeni clinical criteria and the Chompret criteria when recommending genetic testing for a mutation in the *TP53* gene. The NCCN panel also included lung bronchoalveolar cancer and leukemia as one of the core tumor types. Testing individuals with choroid plexus carcinoma diagnosed at any age and regardless of family history based upon high incidence of *TP53* mutations found in patients with this rare form of brain tumor has also been recommended. Women with early-onset breast cancer (age of diagnosis 31 years or younger) with or without core history of tumor types are another group for whom *TP53* mutation testing may be considered. A member of a family with a known *TP53* mutation is considered to be at sufficient risk to warrant gene mutation testing, even in the absence of any other risk factors.

The National Comprehensive Cancer Network (NCCN) (2018) Gastric Cancer Guidelines recognizes that women with *CDH1* mutations are at an increased risk for breast cancer and screening with breast MRI, and the option of risk-reducing mastectomy should be discussed.

The National Comprehensive Cancer Network (NCCN) (201) include new genetic testing panels using next generation sequencing for hereditary breast, ovarian and other cancers in the Genetic/familial High-Risk Assessment: Breast and Ovarian (2018) guidelines. The guidelines state that these panels are intended for individuals who have tested negative for high penetrance genes (*BRCA1/2*) and for those whose family history is suggestive of more than one syndrome. Limitations of these panels include unknown percentage of variants of unknown significance, uncertainty of the level of risk associated with most of these genes, and lack of clear guidelines on risk management of carriers of some of these mutations. NCCN recommends that these multigene hereditary cancer panels should only be ordered in consultation with a cancer genetics professional.

CODES: Number Description

Eligibility for reimbursement is based upon the benefits set forth in the member’s subscriber contract.

CODES MAY NOT BE COVERED UNDER ALL CIRCUMSTANCES. PLEASE READ THE POLICY AND GUIDELINES STATEMENTS CAREFULLY.

Codes may not be all inclusive as the AMA and CMS code updates may occur more frequently than policy updates.

<u>CPT:</u>	81162	BRCA1, BRCA2 (breast cancer 1 and 2) (eg, hereditary BRCA1, BRCA2 (breast cancer 1 and 2) (eg, hereditary breast and ovarian cancer) gene analysis; full sequence analysis and full duplication/deletion
	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

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- 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
- 81432 Hereditary breast cancer-related disorders (eg, hereditary breast cancer, hereditary ovarian cancer, hereditary endometrial cancer); genomic sequence analysis panel, must include sequencing of at least 10 genes, always including BRCA1, BRCA2, CDH1, MLH1, MSH2, MSH6, PALB2, PTEN, STK11, and TP53
- 81433 Hereditary breast cancer-related disorders (eg, hereditary breast cancer, hereditary ovarian cancer, hereditary endometrial cancer) duplication/deletion analysis panel, must include analyses for BRCA1, BRCA2, MLH1, MSH2, and STK11

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HCPCS: No specific code(s)

- ICD10:** C50.011-C50.929 Malignant neoplasm of breast (code range)
C56.1-C56.9 Malignant neoplasm of ovary (code range)
C79.60-C79.62 Secondary malignant neoplasm of ovary (code range)
C79.81 Secondary malignant neoplasm of breast
D05.00-D05.02 Lobular carcinoma in situ of breast (code range)
D05.10-D05.12 Intraductal carcinoma in situ of breast (code range)
D05.80-D05.92 Carcinoma in situ of breast, specified, unspecified (code range)
D07.30-D07.39 Carcinoma in situ of other and unspecified female genital organs (code range)
Z15.01 Genetic susceptibility to malignant neoplasm of breast
Z80.3 Family history of malignant neoplasm of breast
Z80.41 Family history of malignant neoplasm of ovary
Z85.3 Personal history of malignant neoplasm of breast
Z85.43 Personal history of malignant neoplasm of ovary

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* key article

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SUBJECT: GENETIC TESTING FOR SUSCEPTIBILITY TO HEREDITARY CANCERS	EFFECTIVE DATE: 06/19/14 REVISED DATE: 10/15/15, 10/20/16, 01/18/18, 10/18/18
POLICY NUMBER: 2.02.44 CATEGORY: Laboratory Test	PAGE: 10 OF: 10

CMS COVERAGE FOR MEDICARE PRODUCT MEMBERS

There is currently a Local Coverage Determination (LCD) for Molecular Pathology Procedures. Please refer to the following LCD website for Medicare Members: https://www.cms.gov/medicare-coverage-database/details/lcd-details.aspx?LCDId=35000&ver=113&CntrctrSelected=298*1&Cntrctr=298&s=41&DocType=Active&bc=AAgAAAQBAAAA&