Medical Policy

Blue Cross Blue Shield Blue Care Network of Michigan

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***Current Policy Effective Date: 11/1/24**
(See policy history boxes for previous effective dates)

Title: Genetic Testing for PTEN Hamartoma Tumor Syndrome

Description/Background

The *PTEN* hamartoma tumor syndrome (PHTS) includes several syndromes with heterogeneous clinical symptoms, which may place individuals at an increased risk of the development of certain types of cancer. Genetic testing for *PTEN* can confirm a diagnosis of PHTS.

Background

PTEN HAMARTOMA TUMOR SYNDROMES

PTEN hamartoma tumor syndrome (PHTS) is characterized by hamartomatous tumors and *PTEN* germline disease-associated variants. Clinically, PHTS includes Cowden syndrome (CS), Bannayan-Riley-Ruvalcaba syndrome (BRRS), *PTEN*-related Proteus syndrome (PS), and Proteus-like syndrome (PLS).

CS is a multiple hamartoma syndrome with a high risk for benign and malignant tumors of the thyroid, breast, and endometrium. Affected individuals usually have macrocephaly, trichilemmomas, and papillomatous papules and present by the late 20s. The lifetime risk of developing breast cancer is 85%, with an average age of diagnosis between 38 and 46 years.(1) The lifetime risk for thyroid cancer, usually follicular carcinoma, is approximately 35%. The risk for endometrial cancer is not well defined, but may approach 28%.(1) A 2012 study included 3399 prospectively recruited individuals who met relaxed International Cowden Consortium PHTS criteria; 368 were found to have *PTEN* disease-associated variants.(2) Estimated lifetime cancer risks were, respectively, for breast 85.2% (95% confidence interval [CI], 71.4% to 99.1%), thyroid 35.2% (95% CI, 19.7% to 50.7%), endometrium 28.2% (95% CI, 17.1% to 39.3%), colorectal 9.0% (95% CI, 3.8% to 14.1%), kidney 33.6% (95% CI, 10.4% to 56.9%) and melanoma 6% (95% CI, 1.6% to 9.4%). A 2013 study of 154 individuals with a *PTEN* disease-associated variant were found to have cumulative cancer risks at age 70 of

85% for any cancer (95% CI, 70% to 95%), 77% for female breast cancer (95% CI, 59% to 91%), and 38% (95% CI, 25% to 56%) for thyroid cancer.(3)

BRRS is characterized by macrocephaly, intestinal hamartomatous polyposis, lipomas, and pigmented macules of the glans penis. Additional features include high birth weight, developmental delay and mental deficiency (50% of affected individuals), a myopathic process in proximal muscles (60%), joint hyperextensibility, pectus excavatum, and scoliosis (50%).

PS is a complex, highly variable disorder involving congenital malformations and hamartomatous overgrowth of multiple tissues, as well as connective tissue nevi, epidermal nevi, and hyperostoses.

PLS is undefined but refers to individuals with significant clinical features of PS who do not meet the diagnostic criteria for PS.

CS is the only PHTS disorder associated with a documented predisposition to cancer; however, it has been suggested that patients with other PHTS diagnoses associated with *PTEN* mutations should be assumed to have cancer risks similar to CS.

Clinical Diagnosis

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* disease-associated variant is identified.

Diagnostic Criteria for Cowden Syndrome

The International Cowden Consortium has developed criteria for diagnosing CS (see Table 1).(4)

Table 1. Diagnostic Criteria for Cowden Syndrome[a]

Diagnostic Criteria
Pathognomonic criteria
Lhermitte-Duclos disease adult defined as the presence of a cerebellar dysplastic gangliocytoma
Mucocutaneous lesions:
Trichilemmomas, facial
Acral keratoses
Papillomatous lesions
Major criteria
Breast cancer
Thyroid cancer (papillary or follicular)
Macrocephaly (occipital frontal circumference ≥97th percentile)
Endometrial cancer
Minor criteria
Other structural thyroid lesions (e.g., adenoma, multinodular goiter)
Mental retardation (i.e., IQ ≤75)
Gastrointestinal hamartomas
Fibrocystic disease of the breast
Lipomas
Fibromas
Genitourinary tumors (e.g., uterine fibroids, renal cell carcinoma) or
Genitourinary structural malformations
Operational diagnosis in an individual
Any of the following:
1. Mucocutaneous lesions alone if:

- There are 6 or more facial papules, of which 3 or more must be trichilemmoma, or
- Cutaneous facial papules and oral mucosal papillomatosis, or
- Oral mucosal papillomatosis and acral keratoses, or
- Palmoplantar keratoses, 6 or more

2. Two or more major criteria, but one must include macrocephaly or Lhermitte-Duclos disease; or
3. One major and 3 minor criteria; or
4. Four minor criteria.

Operational diagnosis in a family with a diagnosis of Cowden syndrome

1. One pathognomonic criterion; or
2. Any 1 major criterion with or without minor criteria; or
3. Two minor criteria; or
4. History of Bannayan-Riley-Ruvalcaba syndrome

Adapted from Blumenthal et al (2008).[4]

[a] These criteria for diagnosing Cowden syndrome have been adopted by the National Comprehensive Cancer Network.

In 2013, a systematic review was conducted related to the clinical features reported in individuals with a *PTEN* disease-associated variant, and revised diagnostic criteria were proposed.(5) 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 many of these clinical features are included in Cowden syndrome testing minor criteria in NCCN guidelines Genetic/Familial High-Risk Assessment: Breast and Ovarian.(6)

Bannayan-Riley-Ruvalcaba syndrome (BRRS)

Diagnostic criteria for BRRS have not been set but are based heavily on the presence of the cardinal features of macrocephaly, hamartomatous intestinal polyposis, lipomas, and pigmented macules of the glans penis.

Proteus syndrome

PS appears to affect individuals in a mosaic distribution (i.e., only some organs/tissues are affected). Thus, it is frequently misdiagnosed despite the development of consensus diagnostic criteria. Mandatory general criteria for diagnosis include mosaic distribution of lesions, progressive course, and sporadic occurrence. Additional specific criteria for diagnosis as listed in Table 2.(7)

Table 2. Diagnostic Criteria for Proteus Syndrome

Additional Diagnostic Criteria
Connective tissue nevi (pathognomonic) OR 2 of the following:
Epidermal nevus
Disproportionate overgrowth (1 or more): • Limbs: arms/legs; hands/feet/digits • Skull: hyperostoses • External auditory meatus: hyperostosis • Vertebrae: megaspondylodysplasia • Viscera: spleen/thymus
Specific tumors before end of second decade (either one): • Bilateral ovarian cystadenomas • Parotid monomorphic adenoma
OR 3 of the following:
Dysregulated adipose tissue (either one): • Lipomas • Regional absence of fat

Vascular malformations (1 or more): • Capillary malformation • Venous malformation • Lymphatic malformation
Facial phenotype: • Dolichocephaly • Long face • Minor down slanting of palpebral fissures and/or minor ptosis • Low nasal bridge • Wide or anteverted nares • Open mouth at rest

Adapted from Biesecker (2006).[7]

Proteus-Like Syndrome

PLS is undefined but describes individuals with significant clinical features of PS but who do not meet the diagnostic criteria.

Molecular Diagnosis

PTEN (phosphatase and tens in homologue on chromosome 10) is a tumor suppressor gene on chromosome 10q23 and is dual specificity phosphatase with multiple but incompletely understood roles in cellular regulation.(8) *PTEN* is the only gene in which disease-associated variants mutations are known to cause PHTS. *PTEN* disease-associated variants are inherited in an autosomal dominant manner.

Most CS cases are simplex. However, because CS is likely under diagnosed, the actual proportion of simplex cases (i.e., individuals with no obvious family history) and familial cases (i.e., ≥2 related affected individuals) cannot be determined. It is estimated that 50% to 90% of cases of CS are de novo and approximately 10% to 50% of individuals with CS have an affected parent.

Because of the phenotypic heterogeneity associated with the hamartoma syndromes, the diagnosis of PHTS is made only when a *PTEN* disease-associated variant is identified. Up to 85% of patients who meet the clinical criteria for a diagnosis of CS and 65% of patients with a clinical diagnosis of BRRS have a detectable *PTEN* disease-associated variant. Some data suggest that up to 20% of patients with PS and up to 50% of patients with a PLS have *PTEN* disease-associated variants.

Most of these disease-associated variants can be identified by sequence analysis of the coding and flanking intronic regions of genomic DNA. A smaller number of mutations are detected by deletion/duplication or promoter region analysis.

Penetrance

More than 90% of individuals with CS have some clinical manifestation of the disorder by the late 20s. By the third decade, 99% of affected individuals develop the mucocutaneous stigmata, primarily trichilemmomas and papillomatous papules, as well as acral and plantar keratoses.

Management

Treatment
Treatment of the benign and malignant manifestations of PHTS is the same as for their sporadic counterparts (i.e., chemotherapy, surgery, and/or radiotherapy as per usual guidelines and clinical practice).

Surveillance
The most serious consequences of PHTS relate to the increased risk of cancers including breast, thyroid and endometrial, and to a lesser extent, renal. Therefore, the most important aspect of management of an individual with a *PTEN* disease-associated variant is increased cancer surveillance to detect tumors at the earliest, most treatable stages.

Regulatory Status

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

Medical Policy Statement

Genetic testing for *PTEN* is established to confirm the diagnosis when an individual displays clinical signs of a *PTEN* hamartoma tumor syndrome or in a first-degree relative of a proband with a known *PTEN* pathogenic variant. It may be considered a useful diagnostic option when indicated.

Genetic testing for *PTEN* is considered experimental/ investigational for all other indications, including, but not limited to, prenatal testing.

Inclusionary and Exclusionary Guidelines (Clinically based guidelines that may support individual consideration and pre-authorization decisions)

Inclusions:

- Genetic testing for *PTEN* to confirm the diagnosis of a *PTEN* hamartoma tumor syndrome when an individual displays clinical signs of any of the following suspected *PTEN* hamartoma tumor syndromes (see policy Background/Description section for detailed criteria):
  - Bannayan-Riley-Ruvalcaba syndrome (BRRS)
  - Cowden syndrome (CS)
  - *PTEN*-related Proteus syndrome (PS)
  - Proteus-like syndrome (PLS)

- Genetic testing for *PTEN* in a first-degree relative of a proband with a known *PTEN* pathogenic variant.

Exclusions:
- Prenatal genetic testing for a *PTEN* pathogenic variant
- All other indications not listed in the inclusion section

CPT/HCPCS Level II Codes *(Note: The inclusion of a code in this list is not a guarantee of coverage. Please refer to the medical policy statement to determine the status of a given procedure.)*

Established codes:

81321 81322 81323

Other codes (investigational, not medically necessary, etc.):

0235U*

**Proprietary tests, represented by Proprietary Laboratory Analyses (PLA) codes, are not separately payable. The laboratory should bill the appropriate representative CPT code.*

Note: The above code(s) may not be covered by all contracts or certificates. Please consult customer or provider inquiry resources at BCBSM or BCN to verify coverage.

Rationale

TESTING IN PATIENTS WITH SIGNS AND/OR SYMPTOMS OF *PTEN* HAMARTOMA TUMOR SYNDROME

Clinical Context and Test Purpose
The purpose of genetic testing of patients who have signs and/or symptoms of *PTEN* hamartoma tumor syndrome (PHTS) is to confirm a diagnosis and inform management decisions such as increased cancer surveillance.

The following PICOs were used to select literature to inform this review.

Populations
The relevant population of interest are individuals with clinical signs and/or symptoms of a PHTS.

Interventions
The test being considered is genetic testing for *PTEN.* Individuals may be referred from primary care to an oncologist or medical geneticist for investigation and management of PHTS. Referral for genetic counseling is important for explanation of genetic disease, heritability, genetic risk, test performance, and possible outcomes.

Comparators

The following practices are currently being used: standard clinical management without genetic testing for *PTEN*.

Outcomes
The potential beneficial outcomes of primary interest would be improvements in short-term and long-term OS and disease-specific survival and reductions in morbid events. Increased cancer surveillance in individuals with a *PTEN* pathogenic variant is initiated to detect the presence of cancer at earlier and more treatable stages.

Potential harmful outcomes are those resulting from a false-positive or false-negative test results. False-positive test results can lead to unnecessary cancer surveillance procedures such as invasive biopsies. False-negative test results can lead to lack of cancer surveillance that might detect cancer at earlier and more treatable stages.

Clinically Valid
A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Many reports on the prevalence of the features of Cowden syndrome (CS) and Bannayan-Riley-Ruvalcaba (BRRS) have been based upon data compiled from case reports and studies of small cohorts. Most of these reports were published before adoption of the International Cowden Consortium diagnostic criteria for CS in 1996, and the true frequencies of the clinical features in CS and BRRS are not known.(8)

According to a large reference laboratory, the clinical sensitivity of *PTEN*-related disorders sequencing is 80% for CS, 60% for BRRS, 20% for *PTEN*-related Proteus syndrome (PS) and 50% for Proteus-like syndrome (PSL). For *PTEN*-related deletion/duplication, it is up to 10% for BRRS and unknown for CS, Proteus syndrome, and Proteus-like syndrome.(9)

Germline *PTEN* disease-associated variants have been identified in approximately 80% of patients meeting diagnostic criteria for CS and in 50 to 60% of patients with a diagnosis of BRRS, using sequencing analysis using polymerase chain reaction of the coding and flanking intronic regions of the gene.(10,11) Marsh et al (1998) screened DNA from 37 CS families and *PTEN* disease-associated variants were identified in 30 (81%) of 37 CS families, including single-nucleotide variations, insertions, and deletions.(10) Whether the remaining patients have undetected *PTEN* disease-associated variants or disease-associated variants in other, unidentified genes, is not known.(12)

A study by Pilarski et al (2011) determined the clinical features most predictive of a disease-associated variant in a cohort of patients undergoing *PTEN* testing.(8) Molecular and clinical data were reviewed for 802 patients referred for *PTEN* analysis by a single laboratory. All of the patients were classified as to whether they met revised International Cowden Consortium Diagnostic criteria. Two hundred and thirty of the 802 patients met diagnostic criteria for a diagnosis of CS. Of these, 79 had a *PTEN* disease-associated variant, for a detection rate of 34%. The authors commented that this disease-associated variant frequency was significantly lower than previously reported, possibly suggesting that the clinical diagnostic criteria for CS are not as robust at identifying patients with germline *PTEN* disease-associated variants as previously thought. In contrast, in their study, of the patients meeting diagnostic criteria for BRRS, 23 (55%) of 42 had a disease-associated variant, and 7 of 9 patients (78%) with

diagnostic criteria for both CS and BRRS had a disease-associated variant, consistent with the literature.

Section Summary: Clinically Valid

Evidence from several small studies indicated that the clinically sensitivity of genetic testing for *PTEN* may be highly variable. This may reflect the phenotypic heterogeneity of the syndromes and an inherent referral bias because patients with more clinical features of CS and BRRS are more likely to get tested. The true clinical specificity is uncertain because the syndrome is defined by the disease-associated variant.

Clinically Useful

A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

Direct Evidence

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from randomized controlled trials.

The clinical utility for patients with suspected PHTS depends on the ability of genetic testing to make a definitive diagnosis and for that diagnosis to lead to management changes that improve outcomes. There is no direct evidence for the clinical utility of genetic testing in these patients because no studies were identified describing how a molecular diagnosis of PHTS changed patient management.

Chain of Evidence

Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

For patients diagnosed with PHTS by identifying a *PTEN* disease-associated variant, the medical management focuses on increased cancer surveillance to detect tumors at the earlier, more treatable stages.

Section Summary: Clinical Utility

Direct evidence of the clinical utility of *PTEN* testing is lacking. However, the clinical utility of genetic testing for *PTEN* is that genetic testing can confirm the diagnosis in patients with clinical signs and/or symptoms of PHTS. Management changes include increased surveillance for the cancers associated with these syndromes.

FAMILIAL VARIANT TESTING OF ASYMPTOMATIC INDIVIDUALS

Clinical Context And Test Purpose

The purpose of familial variant testing of asymptomatic individuals with a first-degree relative with a PHTS is to screen for the family-specific pathogenic variant to inform management decisions (e.g., increased cancer surveillance) or to exclude asymptomatic individuals from increased cancer surveillance.

The following PICOs were used to select literature to inform this review.

Populations
The relevant population of interest are asymptomatic individuals with a first-degree relative who has a PHTS.

Interventions
Targeted genetic testing for a *PTEN* familial variant.

Comparators
The following practices are currently being used: standard clinical management without targeted genetic testing for a *PTEN* familial variant.

Outcomes
The potential beneficial outcomes of primary interest would be improvement in OS and disease-specific survival and decreased morbid events. Increased cancer surveillance in patients with a *PTEN* familial variant is initiated to detect the presence of cancer at earlier and more treatable stages. Asymptomatic individuals who test negative for a *PTEN* familial variant can be excluded from increased cancer surveillance.

The potential harmful outcomes are those resulting from a false-positive or false-negative test. False-positive test results can lead to unnecessary cancer surveillance procedures (e.g., invasive biopsies). False-negative test results can lead to lack of cancer surveillance that may detect cancer at earlier and more treatable stages.

Clinically Valid
A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

See the discussion in the previous section for patients with sign and/or symptoms of PHTS.

Clinically Useful
A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

Direct Evidence
Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from randomized controlled trials.

No randomized controlled trials were identified assessing the clinical usefulness of testing asymptomatic individuals with a first-degree relative who has a diagnosis of PHTS.

Chain of Evidence
Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

When a *PTEN* disease-associated variant has been identified in a proband, testing of first-degree relatives can identify those who also have the familial variant and have PHTS. These individuals require an initial evaluation and ongoing cancer surveillance. Alternatively, first-degree relatives who test negative for the familial variant would not require ongoing cancer surveillance.

Section Summary: Clinical Useful
Direct evidence of the clinical utility of familial variant testing in asymptomatic individuals is lacking. However, for first-degree relatives of PHTS affected individuals, a positive test for a familial variant would confirm the diagnosis of PHTS and result in ongoing cancer surveillance. A negative test for a familial variant would reduce unnecessary cancer surveillance.

SUMMARY OF EVIDENCE
For individuals who have clinical signs and/or symptoms of a PHTS or who are asymptomatic with a first-degree relative with a PHTS and a known familial variant who receive genetic testing for a *PTEN* familial variant, the evidence includes case series and a large prospective study on the frequency of a *PTEN* variants in individuals meeting clinical criteria for a PTHS, and studies of cancer risk estimates in individuals with a *PTEN* disease-associated variant. Relevant outcomes are overall survival, disease-specific survival, test accuracy and validity, and morbid events. The published clinical validity of testing for *PTEN* is variable. The true clinical validity is difficult to ascertain because the syndrome is defined by the presence of a *PTEN* disease-associated variant. The sensitivity of tests for Cowden syndrome and Bannayan-Riley-Ruvalcaba syndrome has been reported to be up to 80% and 60%, respectively. Direct evidence of the clinical utility of genetic testing for *PTEN* is lacking; however, confirming a diagnosis in a patient with clinical signs of a PHTS will lead to changes in clinical management by increasing surveillance to detect cancers associated with PHTS at an early and treatable stage. Although most cases of a PHTS occur in individuals with no known family history of PHTS, testing of at-risk relatives will identify those who should also undergo increased cancer surveillance. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

Supplemental Information

PRACTICE GUIDELINES AND POSITION STATEMENTS

National Comprehensive Cancer Network
Current National Comprehensive Cancer Network guidelines (3.2024) on genetic/familial high-risk assessment for breast and ovarian cancer (6) include Testing Criteria for Cowden Syndrome (CS)/PTEN Hamartoma Tumor Syndrome (PHTS) that recommend testing for:

- Individual from a family with a known PTEN pathogenic/likely pathogenic variant
- Individual with a personal history of Bannayan-Riley-Ruvalcaba syndrome (BRRS)
- Individual meeting clinical diagnostic criteria for CS/PHTS
- Individual not meeting clinical diagnostic criteria for CS/PHTS with a personal history of: Adult Lhermitte-Duclos disease (cerebellar tumors); or autism spectrum disorder and macrocephaly; or 2 or more biopsy proven trichilemmomas; or 2 or more major criteria (1 must be macrocephaly); or 3 major criteria, without macrocephaly; or 1 major and ≥3 minor criteria; or ≥4 minor criteria.

- At-risk individual with a relative with a clinical diagnosis of CS/PHTS or BRRS for whom testing has not been performed. The at-risk individual must have the following: Any 1 major criterion or 2 minor criteria.
- PTEN pathogenic/likely pathogenic variant detected by tumor profiling on any tumor type in the absence of germline analysis.

Additionally, the following is recommended for Cowden syndrome management (see Table 3).

Table 3. NCCN Guidelines on Cowden Syndrome/ PTEN Hamartoma Tumor Syndrome Management

Populations	Recommendations
Women	• Breast awareness starting at age 18 years.
	• Clinical breast exam every 6 to 12 months, starting at age 25 years or 5 to 10 years before the earliest known breast cancer in the family (whichever comes first).
	• Breast screening:
	○ Annual mammography and breast MRI screening with and without contrast starting at age 30 years or 10 years before the earliest known breast cancer in the family (whichever comes first)
	○ Age >75, management should be considered on an individual basis.
	○ For individuals with a PTEN pathogenic/likely pathogenic variant who are treated for breast cancer, and have not had a bilateral mastectomy, screening with annual mammogram and breast MRI should continue as described above
	• Discuss option of risk-reducing mastectomy in individuals with pathogenic/likely pathogenic variants identified. For those with clinical CS/PHTS syndrome, consideration of risk-reducing surgery should be based on family history. Discuss risk-reducing mastectomy and hysterectomy and counsel regarding degree of protection, extent of cancer risk, and reconstructive options
	○ Counseling should include a discussion regarding degree of protection, reconstruction options, and risks. In addition, the family history and residual breast cancer risk with age and life expectancy should be considered during counseling.
	• For endometrial cancer screening, consider starting by age 35 years.
	○ Encourage patient education and prompt response to symptoms (e.g., abnormal bleeding). Patients are encouraged to keep a calendar in order to identify irregularities in their menstrual cycle.
	○ Because endometrial cancer can often be detected early based on symptoms, individuals should be educated regarding the importance of prompt reporting and evaluation of any abnormal uterine bleeding or postmenopausal bleeding. The evaluation of these symptoms should include endometrial biopsy.
	○ Endometrial cancer screening does not have proven benefit in individuals with CS/PHTS. However, endometrial biopsy is both highly sensitive and highly specific as a diagnostic procedure. Screening via endometrial biopsy every 1 to 2 years can be considered.
Men and women	• Annual comprehensive physical exam starting at age 18 years or 5 years before the youngest age of diagnosis of a component cancer in the family (whichever comes first), with particular attention to thyroid exam.
	• Annual thyroid ultrasound starting at age 7. This may also be considered for children at 50% risk of inheriting a known pathogenic/likely pathogenic mutation whose parents wish to delay genetic testing until age 18 years..
	• Colonoscopy, starting at age 35 years, unless symptomatic or a close relative with colon cancer under age 40 years. Colonoscopy should be done every 5 years or more frequently if patient is symptomatic or polyps found.
	• There may be an increased risk of melanoma, and the prevalence of other skin characteristics with CS/PTHS may independently make routine dermatology evaluations of value. Annual dermatology exams are recommended
	• Consider renal ultrasound starting at age 40 years, then every 1 to 2 years.
	• Consider psychomotor assessment in children at diagnosis and brain MRI if there are symptoms
	• Education regarding signs and symptoms of cancer

Relatives	• Advise about possible inherited cancer risk to relatives, options for risk assessment, and management
	• Recommend genetic counseling and consideration of genetic testing for family members
Reproductive options	• For women of reproductive age, advise about options for prenatal diagnosis and assisted reproduction including preimplantation genetic diagnosis. Discussion should include known risks, limitations, and benefits of these technologies

CS: Cowden Syndrome; MRI: magnetic resonance imaging; PHTS: *PTEN* hamartoma tumor syndrome.

U.S. PREVENTIVE SERVICES TASK FORCE RECOMMENDATIONS

No U.S. Preventive Services Task Force recommendations for genetic testing for *PTEN* hamartoma tumor syndrome have been identified.

Government Regulations

National:

NCD for Next Generation Sequencing (NGS) for Patients with Somatic (Acquired) and Germline (inherited) Cancer; Publication 100-3, Manual Section 90.2; Effective date: 1/27/20; Implemented: 11/13/20.

General

Clinical laboratory diagnostic tests can include tests that, for example, predict the risk associated with one or more genetic variations. In addition, in vitro companion diagnostic laboratory tests provide a report of test results of genetic variations and are essential for the safe and effective use of a corresponding therapeutic product. Next Generation Sequencing (NGS) is one technique that can measure one or more genetic variations as a laboratory diagnostic test, such as when used as a companion in vitro diagnostic test.

This National Coverage Determination (NCD) is only applicable to diagnostic lab tests using NGS for somatic (acquired) and germline (inherited) cancer. Medicare Administrative Contractors (MACs) may determine coverage of diagnostic lab tests using NGS for RNA sequencing and protein analysis.

Indications and Limitations of Coverage

Nationally Covered Indications

Germline (Inherited) Cancer

Effective for services performed on or after January 27, 2020, the Centers for Medicare & Medicaid Services (CMS) has determined that Next Generation Sequencing (NGS) as a diagnostic laboratory test is reasonable and necessary and covered nationally for patients with germline (inherited) cancer, when performed in a Clinical Laboratory Improvement Amendments (CLIA)-certified laboratory, when ordered by a treating physician, and when all of the following requirements are met:

- Patient has:
  - ovarian or breast cancer; and,
  - a clinical indication for germline (inherited) testing for hereditary breast or ovarian cancer; and,
  - a risk factor for germline (inherited) breast or ovarian cancer; and
  - not been previously tested with the same germline test using NGS for the same germline genetic content.

- The diagnostic laboratory test using NGS must have all of the following:
  - Food & Drug Administration (FDA) approval or clearance; and,
  - results provided to the treating physician for management of the patient using a report template to specify treatment options.

Other

Germline (Inherited) Cancer

Effective for services performed on or after January 27, 2020, MACs may determine coverage of NGS as a diagnostic laboratory test for patients with germline (inherited) cancer only when the test is performed in a CLIA-certified laboratory, when ordered by a treating physician, when results are provided to the treating physician for management of the patient and when the patient has:

- any cancer diagnosis; and,
- a clinical indication for germline (inherited) testing of hereditary cancers; and,
- a risk factor for germline (inherited) cancer; and,
- not been previously tested with the same germline test using NGS for the same germline genetic content.

See determination for complete guidance as the information listed above has been condensed.

Local:

MolDX: Lab-Developed Tests for Inherited Cancer Syndromes in Patients with Cancer (L39040). Original effective date: 7/3/22; Revision effective date: 4/18/24

Coverage Indications, Limitations, and/or Medical Necessity

This policy describes and clarifies coverage for Lab-Developed Tests (LDTs), Federal Drug Administration (FDA)-cleared, and FDA-approved clinical laboratory tests in hereditary cancer tests including Next-Generation Sequencing (NGS) tests as allowable under the National Coverage Determination (NCD) 90.2, under section D describing Medicare Administrative Contractor (MAC) discretion for coverage. This policy's scope is specific for hereditary germline testing, and is exclusive of polygenic risk scores, solid tumor, hematologic malignancies, circulating tumor deoxyribonucleic acid (DNA) testing (ctDNA), and other acquired cancer-related tests.

Criteria for Coverage

All the following must be present for coverage eligibility:

- The patient must have:
  - Any cancer diagnosis
  - AND a clinical indication for germline (inherited) testing for hereditary cancer
  - AND a risk factor for germline (inherited) cancer
  - AND has not been previously tested for the same germline genetic content.
- The test has satisfactorily completed a Technical Assessment (TA) by Molecular Diagnostic Services Program (MolDX®) for the stated indications of the test.
- The test performed includes **at least** the minimum genetic content (genes or genetic variants) with definitive or well-established guidelines-based evidence required for clinical decision making for its intended use that can be reasonably detected by the test.

    - Because these genes and variants will change as the literature and drug indications evolve, they are listed separately in associated documents, such as the MolDX® TA forms.
    - A single gene or variant may be tested if it is the only gene or variant considered to be reasonable and necessary for a cancer type.
- If a previous test was performed with a similar/duplicative intended use, a subsequent test is only reasonable and necessary if the non-duplicative genetic content of the second test is reasonable and necessary.
- If the test is an NGS test, it must abide by all conditions listed in the NCD 90.2.

Situations in which a test should not be used or coverage is denied:
The test in question will be non-covered if:

- It is an NGS test and does not fulfill all the criteria set forth in the NCD 90.2
- A previous test was performed for the same genetic content
- It is a panel or single gene test used to identify a known familial variant(s) that could be identified with a test targeted to that specific variant(s)
- It is a panel or single gene test used to confirm a variant(s) detected by somatic tumor testing that can be confirmed by a test targeted to that specific variant(s)
- A satisfactory TA is not completed
- For tests that are currently covered but a TA submission has not been made, providers must submit complete TA materials by the original effective date of the policy or coverage will be denied.

(The above Medicare information is current as of the review date for this policy. However, the coverage issues and policies maintained by the Centers for Medicare & Medicare Services [CMS, formerly HCFA] are updated and/or revised periodically. Therefore, the most current CMS information may not be contained in this document. For the most current information, the reader should contact an official Medicare source.)

Related Policies

Genetic Testing and Counseling

References

1. Eng C. PTEN Hamartoma Tumor Syndrome (PHTS). In: Pagon RA, Adam MP, Ardinger HH, et al., eds.
2. Tan MH, Mester JL, Ngeow J, et al. Lifetime cancer risks in individuals with germline PTEN mutations. Clin Cancer Res. Jan 15 2012;18(2):400-407. PMID 22252256
3. Bubien V, Bonnet F, Brouste V, et al. High cumulative risks of cancer in patients with PTEN hamartoma tumour syndrome. J Med Genet. Apr 2013;50(4):255-263. PMID 23335809
4. Blumenthal GM, Dennis PA. PTEN hamartoma tumor syndromes. Eur J Hum Genet. Nov 2008;16(11):1289-1300. PMID 18781191
5. Pilarski R, Burt R, Kohlman W et al. Cowden syndrome and the PTEN hamartoma tumor syndrome: systematic review and revised diagnostic criteria. J Natl Cancer Inst 2013; 105(21):1607-16.
6. National Comprehensive Cancer Network (NCCN). NCCN guidelines Genetic/Familial High-Risk Assessment: Breast and Ovarian (v.3.2024);

https://www.nccn.org/professionals/physician_gls/pdf/genetics_bop.pdf. Accessed June 16, 2023.
7. Biesecker L. The challenges of Proteus syndrome: diagnosis and management. Eur J Hum Genet. Nov 2006;14(11):1151-1157. PMID 16883308
8. Pilarski R, Stephens JA, Noss R et al. Predicting PTEN mutations: an evaluation of Cowden syndrome and Bannayan-Riley-Ruvalcaba syndrome clinical features. J Med Genet 2011; 48(8):505-12.
9. ARUP Laboratory Test Directory. PTEN-Related Disorder (PTEN Sequencing); http://ltd.aruplab.com/tests/pub/2002722. Accessed June 15, 2023
10. Marsh DJ, Coulon V, Lunetta KL et al. Mutation spectrum and genotype-phenotype analyses in Cowden disease and Bannayan-Zonana syndrome, two hamartoma syndromes with germline PTEN mutation. Hum Mol Genet 1998; 7(3):507-515.
11. Marsh DJ, Kum JB, Lunetta KL et al. PTEN mutation spectrum and genotype-phenotype correlations in Bannayan-Riley-Ruvalcaba syndrome suggest a single entity with Cowden syndrome. Hum Mol Genet 1999; 8(8):1461-72.
12. Pilarski R, Eng C. Will the real Cowden syndrome please stand up (again)? Expanding mutational and clinical spectra of the PTEN hamartoma tumour syndrome. J Med Genet 2004; 41(5):323-6.
13. Centers for Medicare & Medicaid Services. “Next Generation Sequencing (NGS) for Patients with Somatic (Acquired) and Germline (inherited) Cancer.” 100-3:90.2; v2. 2020. https://www.cms.gov/medicare-coverage-database/view/ncd.aspx?ncdid=372&ncdver=2&keyword=next%20generation%20sequencing&keywordType=starts&areaId=s27&docType=NCA,CAL,NCD,MEDCAC,TA,MCD,6,3,5,1,F,P&contractOption=all&sortBy=relevance&bc=1. Accessed May 24, 2024.
14. Centers for Medicare & Medicaid Services. “Lab-Developed Tests for Inherited Cancer Syndromes in Patients with Cancer.” L39040. 2022. https://www.cms.gov/medicare-coverage-database/view/lcd.aspx?lcdid=39040&ver=6&keyword=Lab-Developed%20Tests%20for%20Inherited%20Cancer%20Syndromes%20in%20Patients%20with%20Cancer&keywordType=all&areaId=s27&docType=NCA,CAL,NCD,MEDCAC,TA,MCD,6,3,5,1,F,P&contractOption=all&sortBy=relevance&bc=1. Accessed May 24, 2024.

The articles reviewed in this research include those obtained in an Internet based literature search for relevant medical references through 5/24/24, the date the research was completed.

Joint BCBSM/BCN Medical Policy History

Policy Effective Date	BCBSM Signature Date	BCN Signature Date	Comments
1/1/14	101513	10/25/13	Joint policy established
7/1/15	4/24/15	5/8/15	Routine maintenance
7/1/16	4/19/16	4/19/16	Routine maintenance
11/1/16	8/16/16	8/16/16	Routine maintenance
11/1/17	8/15/17	8/15/17	Routine maintenance
11/1/18	8/21/18	8/21/18	Routine maintenance
11/1/19	8/20/19		Routine maintenance New NCD added
11/1/20	8/18/20		Routine maintenance
11/1/21	8/17/21		Routine maintenance 0235U added to policy (EI)
11/1/22	8/16/22		Routine maintenance
11/1/23	8/15/23		• Routine maintenance (slp) • Vendor managed: N/A
11/1/24	8/20/24		• Routine maintenance (slp) • Vendor managed: N/A

Next Review Date: 3rd Qtr, 2025

Pre-Consolidation Medical Policy History

Original Policy Date	Comments
BCN: N/A	Revised: N/A
BCBSM: N/A	Revised: N/A

BLUE CARE NETWORK BENEFIT COVERAGE
POLICY: GENETIC TESTING FOR PTEN HAMARTOMA TUMOR SYNDROME

I. Coverage Determination:

Commercial HMO (includes Self-Funded groups unless otherwise specified)	Covered, criteria apply
BCNA (Medicare Advantage)	Refer to the Medicare information under the Government Regulations section of this policy.
BCN65 (Medicare Complementary)	Coinsurance covered if primary Medicare covers the service.

II. Administrative Guidelines:

- The member's contract must be active at the time the service is rendered.
- Coverage is based on each member's certificate and is not guaranteed. Please consult the individual member's certificate for details. Additional information regarding coverage or benefits may also be obtained through customer or provider inquiry services at BCN.
- The service must be authorized by the member's PCP except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Services must be performed by a BCN-contracted provider, if available, except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Payment is based on BCN payment rules, individual certificate and certificate riders.
- Appropriate copayments will apply. Refer to certificate and applicable riders for detailed information.
- CPT - HCPCS codes are used for descriptive purposes only and are not a guarantee of coverage.