Genetic Testing for PTEN Hamartoma Tumor Syndrome

Description of Procedure or Service

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. 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%.

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.

Proteus-like syndrome (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 variants 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.

International Cowden Consortium Diagnostic Criteria for the Diagnosis of Cowden Syndrome

Pathognomonic Criteria

- Lhermitte-Duclos disease (LDD)–adult defined as the presence of a cerebellar dysplastic gangliocytoma
- Mucocutaneous lesions:
  - Trichilemmomas, facial
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- 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:
   a. There are 6 or more facial papules, of which 3 or more must be trichilemmoma, or
   b. Cutaneous facial papules and oral mucosal papillomatosis, or
   c. Oral mucosal papillomatosis and acral keratoses, or
   d. Palmoplantar keratoses, 6 or more
2. Two or more major criteria, but one must include macrocephaly or LDD; or
3. One major and 3 minor criteria; or
4. Four minor criteria.

**Operational Diagnosis in a Family Where 1 Individual Is Diagnostic for 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

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. 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 CS testing minor criteria in NCCN guidelines genetic/familial high risk assessment of breast and ovarian cancers. (v1.2018).

**Bannayan-Riley-Ruvalcaba Syndrome**
Diagnostic criteria for BRRS have not been established. Current diagnostic practices 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 is highly variable and 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
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diagnostic criteria. Mandatory general criteria for diagnosis include mosaic distribution of lesions, progressive course, and sporadic occurrence. Additional specific criteria for diagnosis include:

- 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
  - Vertebral column: megaspondylodyplasia
  - 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 downslanting of palpebral fissures and/or minor ptosis
  - Low nasal bridge
  - Wide or anteverted nares
  - Open mouth at rest

Proteus-Like Syndrome

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

Management

Treatment

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

Surveillance

The most serious consequences of PHTS relates 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.

Molecular Diagnosis

PTEN (phosphatase and tensin homolog deleted on chromosome 10) is a tumor suppressor gene on chromosome 10q23 and is dual- specificity phosphatase with multiple but incompletely understood
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roles in cellular regulation. PTEN is the only gene in which disease-associated variants 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 underdiagnosed, the actual proportion of simplex cases (ie, individuals with no obvious family history) and familial cases (ie, ≥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.

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.

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 Amendments (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.

***Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.

Policy
BCBSNC will provide coverage for Genetic Testing for PTEN Hamartoma Tumor Syndrome when it is determined to be medically necessary because the medical criteria and guidelines shown below are met.

Benefits Application
This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this medical policy.

When Genetic Testing for PTEN Hamartoma Tumor Syndrome is covered

Genetic testing for PTEN may be considered medically necessary to confirm the diagnosis when a patient has clinical signs of a PTEN hamartoma tumor syndrome.

Targeted genetic testing for a PTEN familial variant may be considered medically necessary in a first-degree relative of a proband with a known PTEN pathogenic variant.

When Genetic Testing for PTEN Hamartoma Tumor Syndrome is not covered

Genetic testing for PTEN is considered investigational for all other indications not listed above.
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Policy Guidelines
The evidence for genetic testing for a PTEN familial variant in individuals who have clinical signs and/or symptoms of a PTEN hamartoma tumor syndrome (PHTS) or in individuals who are asymptomatic with a first-degree relative with a PHTS includes case series and 1 large prospective study on the frequency of a PTEN variant in individuals meeting clinical criteria for a PHTS, 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 the PTEN gene is variable, and 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 have been reported to be up to 80% and 60%, respectively. Direct evidence of the clinical utility of genetic testing for a 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 known to be 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.

Billing/Coding/Physician Documentation Information
This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at www.bcbsnc.com. They are listed in the Category Search on the Medical Policy search page.

Applicable service codes: 81321, 81322, 81323

BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

Scientific Background and Reference Sources
Medical Director review 3/2013


Specialty Matched Consultant Advisory Panel review 8/2014
Medical Director review 8/2014

Specialty Matched Consultant Advisory Panel review 8/2015
Medical Director review 8/2015
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Medical Director review 7/2016

Medical Director review 2/2017
Specialty Matched Consultant Advisory Panel review 7/2017
Medical Director review 7/2017

Medical Director review 2/2018
Specialty Matched Consultant Advisory Panel review 7/2018
Medical Director review 7/2018

Policy Implementation/Update Information

4/1/13 New Evidence Based Guideline developed. Genetic testing for a PTEN mutation is recommended to confirm the diagnosis when a patient has clinical signs of a PTEN hamartoma tumor syndrome. Genetic testing for a PTEN mutation is recommended in a first -degree relative of a proband with a known PTEN mutation. Genetic testing for a PTEN mutation is not recommended for all other indications, including, but not limited to, prenatal testing. Medical Director review 3/2013. (mco)

4/1/14 “When not Recommended” section updated. Statement revised from “Genetic testing for a PTEN mutation is not recommended for all other indications, including, but not limited to, prenatal testing” to “Genetic testing for a PTEN mutation is not recommended for all other indications.” References updated. (mco)


3/31/15 References updated. Policy Statement unchanged. (td)


4/1/16 Description section updated. Policy Guidelines section updated. References updated. (td)

8/30/16 Specialty Matched Consultant Advisory Panel review 7/2016. Medical Director review 7/2016. (jd)
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3/31/17 Description section, policy statement and policy guidelines updated with current genetic terminology. References updated. Medical Director review 2/2017. (jd)


3/9/17 Minor revision to Description section and Policy Guidelines. References updated. Medical Director review 2/2018. (jd)


Medical policy is not an authorization, certification, explanation of benefits or a contract. Benefits and eligibility are determined before medical guidelines and payment guidelines are applied. Benefits are determined by the group contract and subscriber certificate that is in effect at the time services are rendered. This document is solely provided for informational purposes only and is based on research of current medical literature and review of common medical practices in the treatment and diagnosis of disease. Medical practices and knowledge are constantly changing and BCBSNC reserves the right to review and revise its medical policies periodically.