Corporate Medical Policy

Genetic Testing for PTEN Hamartoma Tumor Syndrome AHS – M2087

File Name: genetic_testing_for_PTEN_hamartoma_tumor_syndrome
Origination: 01/01/2019
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Description of Procedure or Service

Phosphatase and tensin homolog (PTEN) hamartoma tumor syndromes (PHTS) are primarily characterized by hamartomatous tumors (disorganized growths of native cells in native tissues) caused by PTEN germline mutations. PHTS include Cowden syndrome (CS), Bannayan-Riley-Ruvalcaba syndrome (BRRS), *PTEN*-related Proteus syndrome (PS), and Proteus-like syndrome (PLS)(Eng, 2016; Stanich & Lindor, 2017).

******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

1. Genetic testing for a *PTEN* mutation is considered medically necessary to confirm the diagnosis when a patient has clinical signs of Cowden Syndrome/PTEN hamartoma tumor syndrome.
    A. Three or more major criteria, but one must include macrocephaly, Lhermitte-Duclos disease, or gastrointestinal hamartomas; OR
    B. Two major and three minor criteria

Major Criteria:

i. Breast Cancer
ii. Endometrial cancer (epithelial)
iii. Thyroid Cancer (follicular)
iv. Gastrointestinal hamartomas (including ganglioneuromas, adenomas, hyperplastic polyps; ≥3)
v. Lhermitte-Duclos disease (adult)

vi. Macrocephaly (megalocephaly) (i.e. ≥97th percentile, 58 cm in adult woman, 60 cm in adult men)
vii. Macular pigmentation of glans penis
viii. Multiple mucocutaneous lesions (any of the following):
- Multiple trichilemmomas (≥3, at least one biopsy proven)
- Acral keratoses (≥3 palmoplantar keratotic pits and/or acral hyperkeratotic papules) 4 – GT63
- Mucocutaneous neuromas (≥3)
- Oral papillomas (particularly on tongue and gingiva), multiple (≥3) OR biopsy proven OR dermatologist diagnosed

Minor Criteria:
i. Autism spectrum disorder
ii. Colon cancer
iii. ≥3 esophageal glycogenic acanthoses
iv. Lipomas (≥3)
v. Intellectual disability (i.e., IQ ≤75)
vi. Renal cell carcinoma
vii. Testicular lipomatosis
viii. Thyroid cancer (papillary or follicular variant of papillary)
ix. Thyroid structural lesions (e.g. adenoma, multinodular goiter)
x. Vascular anomalies (including multiple intracranial developmental venous anomalies)

2. Genetic testing for a *PTEN* mutation is considered medically necessary in individuals not meeting the clinical diagnostic criteria for Cowden Syndrome/PTEN hamartoma tumor syndrome with a personal history of any one of the following:
   A. Adult Lhermitte-Duclos disease (cerebellar tumors)
   B. Autism spectrum disorder and macrocephaly
   C. Two or more biopsy-proven trichilemmomas
   D. Two or more major criteria (one must be macrocephaly)
   E. Three major criteria without macrocephaly
   F. One major and ≥3 minor criteria
   G. ≥4 minor criteria

3. Genetic testing for a *PTEN* mutation is considered medically necessary in individuals with a personal history of Bannayan-Riley-Ruvalcaba syndrome (BRRS)

4. Genetic Testing for a PTEN mutation is considered medically necessary in at-risk individuals with a relative with a clinical diagnosis of Cowden Syndrome/PTEN Hamartoma Tumor syndrome for whom testing has not been performed AND with either one of the following criteria:
   A. Any one major criterion, OR
   B. Two minor criteria

5. Genetic testing for a PTEN mutation is considered medically necessary in a first-degree relative of a proband with a known PTEN mutation.

When is not covered

Genetic testing for a PTEN mutation is considered investigational for all other indications.

Policy Guidelines

Background

The tumor suppressor (Sansal & Sellers, 2004) phosphatase and tensin homolog (PTEN) is an important phosphatase regulator of the phosphatidylinositol 3-kinase (PI3K)/AKT and the mechanistic target of rapamycin (mTOR) signaling pathways (Krymskaya & Goncharova, 2009), critical for cell proliferation, cell cycle progression, and apoptosis (Stambolic et al., 1998). Loss of function of this gene contributes to an increased risk of both benign and malignant tumors and is implicated in increased lifetime risks of breast, thyroid, uterine, renal and other cancers(Eng, 2016). The resulting spectrum of autosomal dominant disorders are known as phosphatase and tensin homolog (PTEN) hamartoma tumor syndrome (PHTS), which include Cowden syndrome (CS), Bannayan-Riley-Ruvalcaba syndrome (BRRS), *PTEN*-related Proteus syndrome (PS), and Proteus-like syndrome (PLS).

CS is defined by multiple hamartomas with a high risk for benign and malignant tumors of the thyroid, breast, and endometrium. Besides multiple hamartomas in a variety of tissues, patients have macrocephaly as well as characteristic dermatologic manifestations such as trichilemmomas and papillomatous papules. The lifetime risk of developing breast cancer is 25 percent to 50 percent; for thyroid cancer, which is usually follicular carcinoma, is approximately 10 percent; for endometrial cancer is 5 to 10 percent(Eng, 2016). The estimated prevalence of CS is 1 in 200,000 to 250,000(Nelen et al., 1999), though is likely underreported(Stanich & Lindor, 2017).

BRRS is characterized by hamartomas along with macrocephaly, lipomas, and pigmented penile macules. It is also associated with high birth weight, developmental delay or deficiency, proximal muscle myopathy, joint hypermobility, high palate and scoliosis(Stanich & Lindor, 2017).

Similar mutations in the *PTEN* gene are found in both CS and BRRS, which are now considered phenotypically distinct presentations of a similar genetic abnormality (Lachlan, Lucassen, Bunyan, & Temple, 2007; Marsh et al., 1999).

PS is characterized by hamartomatous overgrowth of multiple tissues, with hyperostoses, vascular malformations, dysregulation of fatty tissues connective tissue nevi, epidermal nevi (Eng, 2016).

PLS is undefined but refers to individuals with significant clinical features of PS who do not meet the diagnostic criteria for PS(Eng, 2016).

Only CS has been documented to confer a predisposition to cancer, however, it has been suggested that any patients with *PTEN* mutations should be assumed to have cancer risks similar to CS(Stanich & Lindor, 2017).

All types of mutations have been reported including missense, nonsense, splice site, insertions, and deletions therefore *PTEN* mutation testing usually includes sequence analysis of the entire coding region and deletion/duplication analysis (Eng, 2016; Marsh et al., 1999). Mutations have also been reported in the *PTEN* promoter, and a test for mutations in this region of the gene has become clinically available(Stanich & Lindor, 2017). Germline *PTEN* mutations are found in approximately 20 to 34 percent of individuals who meet clinical criteria for Cowden syndrome or who meet criteria for genetic testing (Pilarski, Stephens, Noss, Fisher, & Prior, 2011; Tan et al., 2011).

Mingo et al (2018)recently found that “the frequent occurrence of PTEN gene mutations targeting PTEN N-terminus whose pathogenicity may be related, at least in part, with the

retention of PTEN in the nucleus. This could be important for the implementation of precision therapies for patients with alterations in the PTEN pathway."

Yehia et al (2018) conducted "a 4-year multicenter prospective study of incident patients with features of Cowden/Cowden-like (CS/CS-like) and Bannayan-Riley-Ruvalcaba syndromes (BRRS) without PTEN mutations. Exome sequencing and targeted analysis were performed including 59 clinically actionable genes from the American College of Medical Genetics and Genomics (ACMG) and 24 additional genes associated with inherited cancer syndromes. Pathogenic or likely pathogenic cancer susceptibility gene alterations were found in 7 of the 87 (8%) CS/CS-like and BRRS patients and included MUTYH, RET, TSC2, BRCA1, BRCA2, ERCC2 and HRAS.

Applicable Federal Regulations

This test is considered a laboratory developed test (LDT); developed, validated and performed by individual laboratories.

LDTs are regulated by the Centers for Medicare and Medicaid (CMS) as high-complexity tests under the Clinical Laboratory Improvement Amendments of 1988 (CLIA'88).

As an LDT, the U. S. Food and Drug Administration has not approved or cleared this test; however, FDA clearance or approval is not currently required for clinical use.

Guidelines and Recommendations

The International Cowden Consortium operational criteria for the diagnosis of Cowden Syndrome *Ver 2000* recommended the following (Pilarski & Eng, 2004):

Pathognomonic criteria

Mucocutaneous lesions

- Trichilemmomas, facial
- Acral keratoses
- Papillomatous papules
- Mucosal lesions

Major criteria

- Breast carcinoma
- Thyroid carcinoma (non-medullary), especially follicular thyroid carcinoma
- Macrocephaly (megalencephaly) (say, ≥97th centile)
- Lhermitte-Duclos disease (LDD)
- Endometrial carcinoma

Minor criteria

- Other thyroid lesions (eg, adenoma or multinodular goitre)
- Mental retardation (say, IQ
- GI hamartomas
- Fibrocystic disease of the breast
- Lipomas
- Fibromas

- Genito-urinary tumours (eg, renal cell carcinoma, uterine fibroids) or malformation

According to the International Cowden Consortium, an operational diagnosis of Cowden Syndrome is made if the individual meets any of the following (Pilarski and Eng, 2004):

(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) 2 major criteria but one must include macrocephaly or LDD

(3) 1 major and 3 minor criteria

(4) 4 minor criteria

According to the International Cowden Consortium, an operational diagnosis of Cowden Syndrome in a family where one person is diagnostic for Cowden syndrome is made if any of the following criteria are met (Pilarski and Eng, 2004:

(1) The pathognomonic mucocutaneous lesion

(2) Any one major criterion with or without minor criteria

(3) Two minor criteria

In 2013, Pilarski et al published revised evidence-based criteria covering the spectrum of PTEN-related clinical disorders. The revised guidelines define the operational diagnosis of PTEN Hamartoma Tumor syndrome in an individual who meets either one of the following:

- Three or more major criteria, but one must include macrocephaly, Lhermitte-Duclos disease, or gastrointestinal hamartomas; or
- Two major and three minor criteria

The operational diagnosis in a family where one individual meets the revised PTEN Hamartoma Tumor syndrome clinical diagnostic criteria or has a PTEN mutation is as follows (Pilarski et al., 2013):

- Any two major criteria with our without minor criteria; or
- One major and two minor criteria; or
- Three minor criteria

Pilarski et al (2013) defined the major and minor criteria as follows:

Major Criteria:

- Breast Cancer
- Endometrial cancer (epithelial)
- Thyroid Cancer (follicular)

- Gastrointestinal hamartomas (including ganglioneuromas, adenomas, hyperplastic polyps; ≥3)
- Lhermitte-Duclos disease (adult)
- Macrocephaly (megalocephaly) (i.e. ≥97th percentile, 58 cm in adult woman, 60 cm in adult men)
- Macular pigmentation of glans penis
- Multiple mucocutaneous lesions (any of the following):
  - Multiple trichilemmomas (≥3, at least one biopsy proven)
  - Acral keratoses (≥3 palmoplantar keratotic pits and/or acral hyperkeratotic papules) 4 – GT63
  - Mucocutaneous neuromas (≥3)
  - Oral papillomas (particularly on tongue and gingiva), multiple (≥3) OR biopsy proven OR dermatologist diagnosed

Minor Criteria:

- Autism spectrum disorder
- Colon cancer
- ≥3 esophageal glycogenic acanthoses
- Lipomas (≥3)
- Intellectual disability (i.e., IQ ≤75)
- Renal cell carcinoma
- Testicular lipomatosis
- Thyroid cancer (papillary or follicular variant of papillary)
- Thyroid structural lesions (e.g. adenoma, multinodular goiter)
- Vascular anomalies (including multiple intracranial developmental venous anomalies)

Practice Guidelines and Position Statements

The **National Comprehensive Cancer Network** (NCCN, 2017) guidelines for Cowden Syndrome/PTEN Hamartoma Tumor syndrome recommends testing in individuals who meet any of the following criteria:

- Individual from a family with a known PTEN mutation
- Individuals with a personal history of Bannayan-Riley-Ruvalcaba syndrome (BRRS)
- Individuals meeting the clinical diagnostic criteria for CS/PHTS
- Individuals not meeting the clinical diagnostic criteria for Cowden Syndrome/PTEN hamartoma tumor syndrome with a personal history of any one of the following:
  - Adult Lhermitte-Duclos disease (cerebellar tumors)
  - Autism spectrum disorder and macrocephaly
  - Two or more biopsy-proven trichilemmomas
  - Two or more major criteria (one must be macrocephaly)
  - Three major criteria without macrocephaly
  - One major and ≥3 minor criteria
  - ≥4 minor criteria
- At-risk individuals with a relative with a clinical diagnosis of Cowden Syndrome/PTEN Hamartoma Tumor syndrome for whom testing has not been performed. The at-risk individual must have the following:

- Any one major criterion, OR
- Two minor criteria

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, 81445

Code Number	PA Required	PA Not Required	Not Covered
81321	X		
81322	X		
81323	X		
81445	X		

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

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Policy Implementation/Update Information

1/1/2019	BCBSNC will provide coverage for genetic testing for PTEN hamartoma tumor syndrome when it is determined to be medically necessary because criteria and guidelines are met. Medical Director review 1/1/2019. Policy noticed 1/1/2019 for effective date 4/1/2019. (jd)