Protocol

Genetic Testing for PTEN Hamartoma Tumor Syndrome

(20488)

Medical Benefit		**Effective Date**: 07/01/14	**Next Review Date**: 05/19
Preauthorization	Yes	**Review Dates**: 05/13, 05/14, 05/15, 05/16, 05/17, 05/18	

Preauthorization is required.

The following protocol contains medical necessity criteria that apply for this service. The criteria are also applicable to services provided in the local Medicare Advantage operating area for those members, unless separate Medicare Advantage criteria are indicated. If the criteria are not met, reimbursement will be denied and the patient cannot be billed. Please note that payment for covered services is subject to eligibility and the limitations noted in the patient's contract at the time the services are rendered.

Populations	Interventions	Comparators	Outcomes
Individuals: • With clinical signs of a *PTEN* hamartoma tumor syndrome	Interventions of interest are: • Genetic testing for *PTEN*	Comparators of interest are: • Standard clinical management without genetic testing	Relevant outcomes include: • Overall survival • Disease-specific survival • Test accuracy • Test validity • Morbid events
Individuals: • Who are asymptomatic with a first-degree relative with a *PTEN* hamartoma tumor syndrome and a known familial variant	Interventions of interest are: • Targeted genetic testing for a *PTEN* familial variant	Comparators of interest are: • Standard clinical management without genetic testing	Relevant outcomes include: • Overall survival • Disease-specific survival • Test accuracy • Test validity • Morbid events

DESCRIPTION

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

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 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. 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 (CS) and Bannayan-Riley-Ruvalcaba syndrome (BRRS) 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.

POLICY

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.

Genetic testing for PTEN is considered **investigational** for all other indications.

POLICY GUIDELINES

TESTING STRATEGY TO CONFIRM THE DIAGNOSIS IN A PROBAND

The order of testing to optimize yield would be: (1) sequencing of PTEN exons one through nine and flanking intronic regions. If no disease-associated variant is identified, perform (2) deletion/duplication analysis. If no disease-associated variant is identified, consider, (3) promoter analysis, which detects disease-associated variants in approximately 10% of individuals with CS who do not have an identifiable disease-associated variant in the PTEN coding region.

TESTING A FIRST DEGREE RELATIVE

When a PTEN disease-associated variant has been identified in the proband, testing of asymptomatic at-risk relatives can identify those family members who have the familial variant, for whom an initial evaluation and ongoing surveillance should be performed.

GENETICS NOMENCLATURE UPDATE

Human Genome Variation Society (HGVS) nomenclature is used to report information on variants found in DNA and serves as an international standard in DNA diagnostics. It is being implemented for genetic testing protocols starting in 2017 (see Table PG1). HGVS nomenclature is recommended by HGVS, the Human Variome Project, and the HUman Genome Organization (HUGO).

The American College of Medical Genetics and Genomics (ACMG) and Association for Molecular Pathology (AMP) standards and guidelines for interpretation of sequence variants represent expert opinion from ACMG, AMP, and the College of American Pathologists. These recommendations primarily apply to genetic tests used in clinical laboratories, including genotyping, single genes, panels, exomes, and genomes. Table PG2 shows the recommended standard terminology—"pathogenic," "likely pathogenic," "uncertain significance," "likely benign," and "benign"—to describe variants identified that cause Mendelian disorders.

Table PG1. Nomenclature to Report on Variants in DNA

Previous	Updated	Definition
Mutation	Disease-associated variant	Disease-associated change in the DNA sequence
	Variant	Change in the DNA sequence
	Familial variant	Disease-associated variant identified in a proband for use in subsequent targeted genetic testing in first-degree relatives

Table PG2. ACMG-AMP Standards and Guidelines for Variant Classification

Variant Classification	Definition
Pathogenic	Disease-causing change in the DNA sequence
Likely pathogenic	Likely disease-causing change in the DNA sequence
Variant of uncertain significance	Change in DNA sequence with uncertain effects on disease
Likely benign	Likely benign change in the DNA sequence
Benign	Benign change in the DNA sequence

ACMG: American College of Medical Genetics and Genomics; AMP: Association for Molecular Pathology.

GENETIC COUNSELING

Experts recommend formal genetic counseling for patients who are at risk for inherited disorders and who wish to undergo genetic testing. Interpreting the results of genetic tests and understanding risk factors can be difficult for some patients; genetic counseling helps individuals understand the impact of genetic testing, including the possible effects the test results could have on the individual or their family members. It should be noted that genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing; further, genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.

BACKGROUND

PTEN HAMARTOMA TUMOR SYNDROMES

PHTS is characterized by hamartomatous tumors and PTEN germline disease-associated variants. Clinically, PHTS includes CS, 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 age 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: 85.2% for breast (95% confidence interval [CI], 71.4% to 99.1%); 35.2% for thyroid; (95% CI, 19.7% to 50.7%); 28.2% for endometrium (95% CI, 17.1% to 39.3%); 9.0% for colorectal (95% CI, 3.8% to 14.1%); 33.6% for kidney (95% CI, 10.4% to 56.9%); and 6% for melanoma (95% CI, 1.6% to 9.4%). A 2013 study of 154 individuals with a PTEN disease-associated variant found cumulative cancer risks at age 70 of 85% (95% CI, 70% to 95%) for any cancer, 77% (95% CI, 59% to 91%) for female breast cancer, 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 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.

Diagnostic Criteria for CS

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 six or more facial papules, of which three or more must be trichilemmoma, or
Cutaneous facial papules and oral mucosal papillomatosis, or
Oral mucosal papillomatosis and acral keratoses, or
Palmoplantar keratoses, six or more
2. Two or more major criteria, but one must include macrocephaly or Lhermitte-Duclos disease; or
3. One major and three 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 one 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 assessed the clinical features reported in individuals with a PTEN disease-associated variant, and proposed revised diagnostic criteria.[5] Reviewers 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 glyco-

genic acanthosis, penile macules, renal cell carcinoma, testicular lipomatosis, and vascular anomalies, and these clinical features are included in CS testing minor criteria in the National Comprehensive Cancer Network guidelines on genetic/familial high-risk assessment of breast and ovarian (v.1.2018).[6]

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 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 two of the following:
Epidermal nevus
Disproportionate overgrowth (one 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 three of the following:
Dysregulated adipose tissue (either one): • Lipomas • Regional absence of fat
Vascular malformations (one 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

Adapted from Biesecker (2006).[7]

Proteus-Like Syndrome

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

Molecular Diagnosis

PTEN (phosphatase and tensin homolog deleted on chromosome 10) is a tumor suppressor gene on chromosome 10q23 and is a dual-specificity phosphatase with multiple but incompletely understood roles in cellular

regulation.[8] PTEN is the only gene for 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 (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 have suggested 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 variants 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 a diagnosis 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.

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 the CLIA. Laboratories that offer LDTs must be licensed by the 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.

Services that are the subject of a clinical trial do not meet our Technology Assessment Protocol criteria and are considered investigational. *For explanation of experimental and investigational, please refer to the Technology Assessment Protocol.*

It is expected that only appropriate and medically necessary services will be rendered. We reserve the right to conduct prepayment and postpayment reviews to assess the medical appropriateness of the above-referenced

procedures. **Some of this protocol may not pertain to the patients you provide care to, as it may relate to products that are not available in your geographic area.**

REFERENCES

We are not responsible for the continuing viability of web site addresses that may be listed in any references below.

1. Eng C. PTEN Hamartoma Tumor Syndrome. In: Adam MP, Ardinger HH, Pagon RA, et al., eds. GeneReviews. Seattle, WA: University of Washington; 2016.
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. Nov 6 2013;105(21):1607-1616. PMID 24136893
6. National Comprehensive Cancer Network (NCCN). NCCN clinical practice guidelines in oncology: Genetic/ familial high risk assessment: breast and ovarian. Version 1.2018. http://www.nccn.org/professionals/physician_gls/pdf/genetics_screening.pdf. Accessed January 29, 2018.
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. Aug 2011;48(8):505-512. PMID 21659347
9. ARUP Laboratories. Laboratory Test Directory: PTEN-Related Disorder (PTEN) Sequencing. n.d.; http://ltd.aruplab.com/tests/pub/2002722. Accessed January 29, 2018.
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. Mar 1998;7(3):507-515. PMID 9467011
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. Aug 1999;8(8):1461-1472. PMID 10400993
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 [commentary]. J Med Genet. May 2004;41(5):323-326. PMID 15121767