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Clinical UM Guideline

Subject:	**Genetic Testing for PTEN Hamartoma Tumor Syndrome**		
Guideline #:	**CG-GENE-08**	**Publish Date:**	**05/09/2019**
Status:	**New**	**Last Review Date:**	**03/21/2019**

Description

This document addresses mutation testing of the phosphatase and tensin homolog (PTEN) gene.

The phosphatase and tensin homolog on chromosome 10 (PTEN) is a tumor suppressor gene on chromosome 10q23. The PTEN protein assists with the regulation of cell migration, the adhesion of cells to surrounding tissues, and angiogenesis. Loss of function of this gene contributes to oncogenesis.

Germline mutations in PTEN have been associated with a variety of rare conditions collectively known as PTEN hamartoma tumor syndrome (PHTS). The hallmark clinical feature of PHTS is the presence of hamartomatous tumors, which are benign tumors resulting from an overgrowth of normal tissue. PHTS includes Cowden syndrome (CS), Bannayan-Riley-Ruvalcaba syndrome (BRRS) and Adult Lhermitte-Duclos disease (ALDD). Proteus syndrome (PS) was previously considered part of the PHTS spectrum; however, it is now known to be its own entity caused by mutations in the AKT1 gene. Although CS is the only PHTS disorder associated with a documented predisposition to multiple malignancies, including breast, thyroid, colon and endometrium, it has been suggested that individuals with other PHTS syndromes associated with PTEN mutations should be assumed to have cancer risks similar to CS. When characteristic features of CS are present, in particular the cancers associated with this condition, but do not meet the strict criteria for a diagnosis of Cowden syndrome, the term "Cowden-like syndrome" (CS-like) is used.

Clinical Indications

Medically Necessary:

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Genetic testing for a PTEN mutation is considered medically necessary when any one of criteria A-D and all of E are met:

A. The individual has a first- or second-degree relative with a known PTEN mutation;
or

B. The individual has a personal history of:
1. **BRRS (macrocephaly, intestinal polyposis, lipomas, pigmented macules of the glans penis); or**
2. **ALDD (cerebellar dysplastic gangliocytoma); or**
3. **Autism spectrum disorder and macrocephaly.**

or

C. The individual meets any of the following testing criteria for Cowden/PHTS syndrome:
1. **Two or more biopsy proven trichilemmomas; or**
2. **Macrocephaly and one or more of the other *major criteria* listed below; or**
3. **Three or more of the *major criteria* listed below (without macrocephaly); or**
4. **Two *major* and two or more of the *minor criteria* listed below; or**
5. **One *major* and three or more of the *minor criteria* listed below; or**
6. **Four or more of the *minor criteria* listed below.**

or

D. The individual has:
1. **A first-degree relative with a clinical diagnosis of CS/PHTS or BRRS who is not available for testing; and**
2. **One of the *major criteria* or two of the *minor criteria* listed below.**

and

E. Genetic counseling, which encompasses all of the following components, has been performed:
1. **Interpretation of family and medical histories to assess the probability of disease occurrence or recurrence; and**

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2. **Education about inheritance, genetic testing, disease management, prevention and resources; and**
3. **Counseling to promote informed choices and adaptation to the risk or presence of a genetic condition; and**
4. **Counseling for the psychological aspects of genetic testing.**

Major Criteria

A. **Breast cancer; or**
B. **Endometrial cancer; or**
C. **Follicular thyroid cancer; or**
D. **Multiple GI hamartomas or ganglioneuromas; or**
E. **Macrocephaly (greater than or equal to the 97%th percentile; 58cm in adult women, 60 cm in adult men); or**
F. **Macular pigmentation of glan penis; or**
G. **Mucocutaneous lesions:**
   1. **One biopsy proven trichelemmoma; or**
   2. **Multiple palmoplantar keratoses; or**
   3. **Multiple or extensive oral mucosal papillomatosis; or**
   4. **Multiple cutaneous facial papules (often verrucous); or**
   5. **Three or more mucocutaneous neuromas.**

Minor Criteria

A. **Autism spectrum disorder (without macrocephaly); or**
B. **Colon cancer; or**
C. **Esophageal glycogenic acanthoses (greater than or equal to 3); or**
D. **Lipomas; or**
E. **Intellectual developmental disorder (that is, an IQ less than or equal to 75); or**
F. **Papillary or follicular variant of papillary thyroid cancer; or**
G. **Thyroid structural lesions (eg, adenoma, nodule[s], goiter); or**
H. **Renal cell carcinoma; or**

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I. **Single GI hamartoma or ganglioneuroma; or**
J. **Testicular lipomatosis; or**
K. **Vascular anomalies (including multiple intracranial developmental venous anomalies).**

Note: If two criteria involve the same structure, organ, or tissue, both may be counted as criteria met.

~~Investigational and~~ Not Medically Necessary:

Genetic testing for a PTEN mutation is considered ~~investigational and~~ not medically necessary when the criteria above are not met and for all other indications not addressed above.

Coding

The following codes for treatments and procedures applicable to this guideline are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

~~**When services may be Medically Necessary when criteria are met:**~~

CPT	
81321	***PTEN (phosphatase and tensin homolog)* (eg, Cowden syndrome, PTEN hamartoma tumor syndrome) gene analysis; full sequence analysis**
81322	***PTEN (phosphatase and tensin homolog)* (eg, Cowden syndrome, PTEN hamartoma tumor syndrome) gene analysis; known familial variant**
81323	***PTEN (phosphatase and tensin homolog)* (eg, Cowden syndrome, PTEN hamartoma tumor syndrome) gene analysis; duplication/deletion variant**

ICD-10 Diagnosis

All diagnoses

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~~**When services are Investigational and Not Medically Necessary:**~~
~~**For the procedure codes listed above when criteria are not met or when the code describes a procedure indicated in the Position Statement section as investigational and not medically necessary.**~~

Discussion/General Information

Germline mutations in PTEN have been identified in a variety of rare syndromic manifestations that are collectively known as PTEN hamartoma tumor syndrome (PHTS). The defining clinical feature of PHTS is the presence of hamartomatous tumors, benign tumors resulting from an overgrowth of normal tissue. The phenotypic spectrum of PHTS includes CS, BRRS, and ALDD. Notably, germline mutations in PTEN are also associated with Lhermitte-Dulcos disease, autism spectrum disorders with macrocephaly, and possibly intellectual disability/developmental delay with macrocephaly. The estimated penetrance of PTEN mutation is approximately 80%, although risk estimates vary.

CS is characterized by multiple hamartomas and/or an increased risk of developing cancerous lesions in various tissues and organs, including the skin, mucous membranes, breast, thyroid, endometrium and brain. Other cancers associated with CS include colorectal cancer, kidney cancer, and possibly melanoma. Additional conditions associated with CS include macrocephaly and Lhermitte-Duclos disease. A small percentage of affected individuals have delayed development or intellectual disability. The features of CS overlap with those of BRRS.

BRRS is characterized by macrocephaly, hamartomas, lipomas and pigmented macules of the glans penis. The signs of BRRS that may be present at birth include macrocephaly and macrosomia. Developmental delays may present in early childhood. Individuals with BRRS frequently develop intestinal hamartomas, lipomas, angiolipomas and hemangiomas. Other signs associated with BRRS include pectus excavatum, hypotonia, hyperextensibility of joints, thyroid disorders, seizures and scoliosis.

Adult Lhermitte-Dulcos disease (ALDD, also known as dysplastic gangliocytoma of the cerebellum) is characterized by the development of hamartomatous outgrowths of the cerebellum. The lesions typically arise in the cerebellar hemispheres, most frequently in the left hemisphere. This condition is most frequently

seen in adults, with the average age at diagnosis of 34 years. Developmental abnormalities including macrocephaly and intellectual developmental disorder are common.

A presumptive diagnosis of PHTS may be made based on clinical findings; however, a definitive diagnosis of PHTS is made when genetic testing identifies a germline mutation.

PTEN mutation testing is available from numerous clinical laboratories. The specific method of testing may include testing for sequence variants in the PTEN gene using polymerase chain reaction (PCR) followed by direct sequencing using automated dideoxy methods. Deletion and duplication analysis may be performed by multiplex ligation-dependent probe amplification (MLPA) or comparative genomic hybridization (CGH).

The available peer-reviewed evidence from several small studies suggests that the clinical sensitivity of genetic testing for PTEN mutations may be highly variable. This may be due to the phenotypic heterogeneity of the syndromes and an inherent referral bias as the individuals with more clinical features of CS/BRRS are more likely to be tested. The true clinical specificity is not certain because the syndrome is defined by the mutation.

According to Marsh and colleagues (1998 and 1999), PCR-based mutation analysis of the coding and flanking intronic regions of the gene resulted in PTEN germline mutations being identified in approximately 80% of individuals meeting the diagnostic criteria for CS and in approximately 50-60% of individuals with a diagnosis of BRRS. However these estimates were compared against the diagnostic criteria at that time, which have since been updated.

The ARUP (Associated Regional and University Pathologists, Inc.) Laboratories' Laboratory Test Directory reports the clinical sensitivity of sequencing for PTEN-related disorders to be 80% and 60% for CS and BRRS respectively. The analytical sensitivity and specificity for polymerase chain reaction (PCR) sequencing PTEN-related disorders is 99%. The analytical sensitivity and specificity of testing for deletions/duplications by multiplex ligation-dependent probe amplification (MLPA) is 99%. By age 30, CS is 99% penetrant (ARUP, 2017).

According to the National Comprehensive Cancer Network (NCCN), the criteria for genetic testing for individuals at risk for CS are divided into three categories. The first category includes individuals meeting the diagnostic criteria for CS, or a personal history of BRRS, Adult LDD, autism spectrum disorder with macrocephaly, or two or more biopsy proven trichelemmomas. Any person presenting with one or more of these diagnoses warrants genetic testing for the PTEN mutation. Another criterion considered to be sufficient to warrant PTEN gene mutation testing is a family history positive for the presence of a known deleterious PTEN mutation. The next category represents "major" features which have been associated with CS. The major criteria include the presence of breast cancer, macrocephaly (megalocephaly), follicular thyroid cancer, endometrial cancer, multiple gastrointestinal hamartomas or ganglioneuromas, macular pigmentation of the glans penis, and other mucocutaneous lesions that are frequently observed in individuals with CS (for example, one biopsy proven trichelemmoma, multiple palmoplantar keratoses, multiple or extensive oral mucosal papilomatosis, multiple cutaneous facial papules). With respect to the presence of mucocutaneous lesions, the NCCN panel did not consider the published evidence sufficient to specify an exact number or extent of these lesions required for the condition to be defined as a major criterion for Cowden syndrome. An individual exhibiting at least two of the major criteria where one of these is macrocephaly meets the threshold for genetic testing. An individual with at least three of the major criteria (without macrocephaly) is also considered to have met the threshold for genetic testing. In addition, individuals exhibiting one major criterion and at least three minor criteria are considered to have met the threshold for genetic testing (NCCN, 2019).

The final category for testing represents conditions with a "minor" association with CS. These include autism spectrum disorder (without macrocephaly), colon cancer, esophageal glycogenic acanthoses (three or more), lipomas, intellectual developmental disorder, papillary or follicular variant of papillary thyroid cancer, thyroid structural lesions other than follicular thyroid cancer (for example, adenoma, nodules, goiter), renal cell carcinoma, a gastrointestinal hamartoma or ganglioneuroma, testicular lipomatosis, or vascular anomalies (including multiple intracranial developmental venous anomalies). The NCCN panel felt that evidence from the literature was not sufficient to include fibrocystic breast disease, uterine fibroids or fibromas as part of the testing criteria. An individual would need to demonstrate at least four of the minor criteria or at least three of the minor criteria and one major criterion to meet the testing criteria (NCCN, 2019).

Last, but not least, an at-risk individual (first-degree relative of an affected individual) with one or more major criterion or two or more minor criteria, along with a relative diagnosed with CS or BBRS (for whom testing has not been performed), would also meet the threshold for PTEN gene mutation testing (NCCN, 2019).

When these conditions are met, it is recommended that the individual undergo pre-genetic testing counseling and then testing for PTEN mutation. If there is no known familial PTEN mutation, consideration should be given to initially testing the family member most likely to have a PTEN mutation based upon the clinical presentation.

The identification of a PTEN mutation can have an impact on patient management. When a PTEN mutation is identified, medical management of the affected individual focuses on increased cancer surveillance to detect tumors at the earliest and most treatable stages. Women are encouraged to begin breast self-examinations as early as age 18 years and clinical breast exam every 6-12 months beginning at age 25 years, or 5-10 years before the earliest known case of breast cancer in the family. Annual mammography and annual breast MRI screening is started at age 30-35 years or individualized based on the earliest age of onset in the family. It is also recommended that women are educated on endometrial cancer and the importance of a prompt response to symptoms. Any individual (both male and female) with a positive PTEN mutation should have annual comprehensive physical examinations beginning at age 18 years, or 5 years before the earliest age of diagnosis in the family (whichever comes first) with particular attention being paid to the skin, breast and thyroid. It is also recommended that these individuals undergo an annual thyroid ultrasound beginning at the time of CS/PHTS diagnosis. Dermatologic examinations should be considered annually. Colonoscopy should begin at age 35 years, and then every 5-10 years thereafter or more frequently if the individual is symptomatic or when polyps are found. When a PTEN mutation is identified in a proband, testing of at-risk relatives can identify those who also have the mutation and are in need of an initial evaluation and ongoing surveillance (NCCN, 2019).

In summary, genetic testing in individuals believed to be at increased risk for a PTEN mutation is generally accepted by the medical community. Genetic testing can confirm the diagnosis in individuals with clinical

signs and symptoms of PHTS. Changes in medical management of individuals found to have the PTEN mutation includes increased surveillance for the cancers that are associated with these syndromes.

Definitions

Hamartoma: A tumor-like growth.

Oncogenesis: A process leading to the formation of a cancer or tumor (carcinogenesis).

References

Peer Reviewed Publications:

1. **Heald B, Mester J, Rybicki L, et al. Frequent gastrointestinal polyps and colorectal adenocarcinomas in a prospective series of PTEN mutation carriers. Gastroenterology. 2010; 139(6):1927-1933.**
2. **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.**
3. **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):1461-1472.**
4. **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):1607-1616.**
5. **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):323-326.**
6. **Riegert-Johnson DL, Gleeson FC, Roberts M, et al. Cancer and Lhermitte-Duclos disease are common in Cowden syndrome patients. Hered Cancer Clin Pract. 2010; 8(1):6.**
7. **Tan MH, Mester JL, Ngeow J, et al. Lifetime cancer risks in individuals with germline PTEN mutations. Clin Cancer Res. 2012; 18(2):400-407.**

Government Agency, Medical Society, and Other Authoritative Publications:

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1. **National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology™. © 2019 National Comprehensive Cancer Network, Inc. For additional information visit the NCCN website at: http://www.nccn.org. Accessed on January 21, 2019.**
   - **Genetic/familial high-risk assessment: breast and ovarian. V.3.2019. Revised January 18, 2019.**

Websites for Additional Information

1. **ARUP Laboratories. ARUP's Laboratory Test Directory: PTEN-Related Disorders (PTEN) Sequencing: 2002722. Updated 2017. Available at: http://www.aruplab.com/guides/ug/tests/2002722.jsp. Accessed January 21, 2019.**
2. **National Library of Medicine (NLM). Genetics Home Reference. Bannayan-Riley-Ruvalcaba syndrome. Reviewed September 2012. Published January 15, 2019. Available at: https://ghr.nlm.nih.gov/condition/bannayan-riley-ruvalcaba-syndrome. Accessed on January 21, 2019.**
3. **National Library of Medicine (NLM). Genetics Home Reference. Cowden Syndrome. Reviewed October 2012. Published January 15, 2019. Available at: https://ghr.nlm.nih.gov/condition/cowden-syndrome. Accessed on January 21, 2019.**
4. **National Library of Medicine (NLM). Genetics Home Reference. PTEN gene. Reviewed May 2015. Published January 15, 2019. Available at: https://ghr.nlm.nih.gov/gene/PTEN. Accessed on January 21, 2019.**

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The use of specific product names is illustrative only. It is not intended to be a recommendation of one product over another, and is not intended to represent a complete listing of all products available.

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History

Status	Date	Action
New	03/21/2019	Medical Policy & Technology Assessment Committee (MPTAC) review.
New	03/20/2019	Hematology/Oncology Subcommittee review. Initial document development. Moved content of GENE.00031 Genetic Testing for PTEN Hamartoma Tumor Syndrome to new clinical utilization management guideline document with the same title.

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