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Medical Policy Manual

Topic: Genetic Testing for PTEN Hamartoma Tumor Syndrome

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Section: Genetic Testing

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IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

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. PHTS can be diagnosed with the identification of a PTEN mutation.

Background

The *PTEN* (‘*p*hosphatase and *tensin* homologue on chromosome 10’) hamartoma tumor syndrome is characterized by hamartomatous tumors and PTEN germline mutations. 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 25-50%, with an average age of diagnosis between 38 and 46 years. The lifetime risk for thyroid cancer, which is usually follicular carcinoma, is approximately 10%. The risk for endometrial cancer is not well defined, but may approach 5-10%.

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 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 (see Policy Guidelines); however, because of the phenotypic heterogeneity associated with the hamartoma syndromes, the diagnosis of PHTS is made only when a PTEN mutation is identified.

Management

Treatment

Treatment of the benign and malignant manifestations of PHTS is the same as for their sporadic counterparts.

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 mutation is increased cancer surveillance to detect tumors at the earliest, most treatable stages.

Molecular Diagnosis

PTEN is a tumor suppressor gene on chromosome 10q23 and is dual specificity phosphatase with multiple but incompletely understood roles in cellular regulation.[1] PTEN mutations are inherited in an autosomal dominant manner.

Because CS is likely underdiagnosed, the actual proportion of simplex cases (defined as individuals with no obvious family history) and familial cases (defined as ≥2 related affected individuals) cannot be determined. The majority of CS cases are simplex. It is estimated that 50-90% of cases of CS are de novo and approximately 10-50% 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 mutation 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 mutation. Some data suggest the up to 20% of patients with Proteus syndrome and up to 50% of patients with a Proteus-like syndrome have PTEN mutations.

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.

PTEN is the only gene in which mutations are known to cause PHTS.

Regulatory Status

No U.S. Food and Drug Administration (FDA)-cleared molecular diagnostic tests were found. Thus, molecular evaluation is offered as a laboratory-developed test. Clinical laboratories may develop and validate tests in-house ("home-brew") and market them as a laboratory service; such tests must meet the general regulatory standards of the Clinical Laboratory Improvement Act (CLIA). The laboratory offering the service must be licensed by CLIA for high-complexity testing.

MEDICAL POLICY CRITERIA

I. Genetic testing for a PTEN mutation may be considered **medically necessary** to confirm the diagnosis when a patient has clinical signs of a PTEN hamartoma tumor syndrome. (See Policy Guidelines for clinical features.)

II. Genetic testing for a PTEN mutation may be considered **medically necessary** in a first -degree relative of a proband with a known PTEN mutation. (see Policy Guidelines)

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

POLICY GUIDELINES

National Comprehensive Cancer Network (NCCN) Cowden Syndrome/PTEN Hamartoma Tumor Syndrome Testing Criteria:[2]

- Individual from a family with a known *PTEN* mutation
- Individual meeting clinical diagnostic criteria for CS/PHTS
- Individual with a personal history of:
    - Bannayan-Riley-Ruvalcaba syndrome (BRRS), or
    - Adult Lhermitte-Duclos disease (cerebellar tumors) or
    - Autism spectrum disorder and macrocephaly or
    - Two or more biopsy-proven trichilemmomas or
    - Two or more major criteria (one must be macrocephaly) or
    - One major and ≥3 minor criteria or
    - ≥4 minor criteria

Major Criteria

- Breast cancer
- Endometrial cancer

- Follicular thyroid cancer
- Multiple gastrointestinal hamartomas or ganglioneuromas
- Macrocephaly (megalocephaly) (i.e. ≥97th percentile, 58 cam in adult woman, 60 cm in adult men)
- Macular pigmentation of glans penis
- Mucocutaneous lesions
    - One biopsy proven trichilemmoma
    - Multiple palmoplantar keratoses
    - Multifocal or extensive oral mucosal papillomatosis
    - Multiple cutaneous facial papules (often verrucous)

Minor Criteria

- Autism spectrum disorder
- Colon cancer
- ≥3 esophageal glycogenic acanthoses
- Lipomas
- Intellectual disability (i.e., IQ ≤75)
- Papillary or follicular variant of papillary thyroid cancer
- Thyroid structural lesions (e.g. adenoma, nodule (s), goiter)Fibrocystic disease of the breast
- Renal cell carcinoma
- Single GI hamartoma or ganglioneuroma
- Vascular anomalies (including multiple intracranial developmental venous anomalies)

NCCN Revised PTEN Hamartoma Tumor Syndrome Clinical Diagnostic Criteria

Major Criteria

- Breast Cancer
- Endometrial cancer (epithelial)
- Thyroid Cancer (follicular)
- Gastrointestinal hamartomas (including ganglioneuromas, but excluding hyperplastic polyps; ≥3)
- Lhermitte-Duclos disease (adult)
- Macrocephaly (megalocephaly) (i.e. ≥97th percentile, 58 cam in adult woman, 60 cm in adult men)
- Macular pigmentation of glans penis
- 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)
    - 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)

Operational Diagnosis in an Individual

Any of the following:

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

Operational Diagnosis in a Family Where One Individual Meets Revised PTEN Hamartoma Tumor Syndrome Clinical Diagnostic Criteria or Has a PTEN Mutation:

1. Any two major criteria with our without minor criteria; or
2. One major and two minor criteria; or
3. Three minor criteria.

Testing Strategy for Confirming the Diagnosis in a Proband

The order of testing to optimize yield would be:

1. Sequencing of PTEN exons 1-9 and flanking intron regions.

2. If no mutation is identified, perform deletion/duplication analysis.

3. If no mutation is identified, consider promoter analysis, which detects mutations in ~10% of individuals with CS who do not have an identifiable mutation in the *PTEN* coding region.

Testing in a First-Degree Relative

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

SCIENTIFIC EVIDENCE

Literature Appraisal

Validation of the clinical use of any genetic test focuses on 3 main principles:

1. Analytic validity, which refers to the technical accuracy of the test in detecting a mutation that is present or in excluding a mutation that is absent;

2. Clinical validity, which refers to the diagnostic performance of the test (sensitivity, specificity, positive and negative predictive values) in detecting clinical disease; and
3. Clinical utility, i.e., how the results of the diagnostic test will be used to change management of the patient and whether these changes in management lead to clinically important improvements in health outcomes.

The focus of this review is on evidence from well designed, studies related to the ability of test results to:

- Guide decisions in the clinical setting related to either treatment, management, or prevention, and
- Improve health outcomes as a result of those decisions.

Analytic Validity

According to a large reference laboratory, analytical sensitivity and specificity for polymerase chain reaction (PCR) sequencing PTEN-related disorders is 99%, and analytical sensitivity and specificity of testing for deletions/duplications by MLPA (multiplex ligation-dependent probe amplification) is 90% and 98%, respectively.[3]

Clinical Validity

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.[1]

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, PS, and PSL.[3]

Germline PTEN mutations have been identified in ~80% of patients meeting diagnostic criteria for CS and in 50-60% of patients with a diagnosis of BRRS, using PCR-based mutation analysis of the coding and flanking intronic regions of the gene.[4,5] Marsh et al. screened DNA from 37 CS families and PTEN mutations were identified in 30 of 37 CS families (81%), including point mutations, insertions, and deletions.[4]

Whether the remaining patients have undetected PTEN mutations or mutations in other, unidentified genes, is not known.[6]

A 2011 study by Pilarski et al. determined the clinical features most predictive of a mutation in a cohort of patients tested for PTEN mutations.[1] 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 mutation, for a detection rate of 34%. The authors commented that this mutation 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 mutations as previously thought. In contrast, in their study, of

the patients meeting diagnostic criteria for BRRS, 23 of 42 (55%) had a mutation, and 7 of 9 patients (78%) with diagnostic criteria for both CS and BRRS had a mutation, consistent with the literature.

Conclusions

Evidence from several small studies indicated that the clinical sensitivity of genetic testing for PTEN mutations may be highly variable. This may be a reflection of the phenotypic heterogeneity of the syndromes and an inherent referral bias as patients with more clinical features of CS/BRRS are more likely to get tested. The true clinical specificity is uncertain because the syndrome is defined by the mutation.

Clinical Utility

The clinical utility of genetic testing can be considered in the following clinical situations:

1. Individuals with suspected PTEN hamartoma tumor syndrome (PHTS
2. Family members of individuals with PHTS, and
3. Prenatal testing.

Individuals with Suspected PHTS

The clinical utility for these patients 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 as no studies were identified that described how a molecular diagnosis of PHTS changed patient management.

However, for patients who are diagnosed with PHTS by identifying a PTEN mutation, the medical management focuses on increased cancer surveillance to detect tumors at the earliest, most treatable stages.

- Family members.

  When a PTEN mutation has been identified in a proband, testing of at-risk relatives can identify those who also have the mutation and have PTEN hamartoma tumor syndrome (PHTS). These individuals need initial evaluation and ongoing surveillance.

- Prenatal screening.

  Prenatal diagnosis is possible for pregnancies at increased risk, by amniocentesis or chorionic villus sampling; the disease-causing allele of an affected family member must be identified before prenatal testing can be performed.

Recent studies reporting on the clinical features of individuals with a *PTEN* mutation have indicated there is insufficient evidence to support the inclusion of benign breast disease, uterine fibroids, or genitourinary malformations as diagnostic criteria. However, there was sufficient evidence identified to include autism spectrum disorders, colon cancer, esophageal glycogenic acanthosis, penile macules, renal cell carcinoma, testicular lipomatosis and vascular anomalies. These identified clinical features are included in CS testing minor criteria in National Comprehensive Cancer Network guidelines (v1.2014) (see Description section above) and described in a recent systematic review.[2,7]

Conclusions

Evidence that supports the clinical utility of genetic testing for PTEN mutations, or how management changes as a result of genetic testing, remains insufficient.

Clinical Practice Guidelines

National Comprehensive Cancer Network (NCCN)

The 2014 NCCN guidelines on Genetic/Familial High-Risk Assessment: Breast and Ovarian recommend the following for CS/PHTS management:[2]

For Women:

- Breast self-exam training and education starting at age 18 years
- Clinical breast exam every 6-12 months, starting at age 25 years or 5-10 years before the earliest known breast cancer in the family
- Annual mammography and breast MRI [magnetic resonance imaging] screening starting at age 30-35 years or individualized based on earliest age of onset in family.
- For endometrial cancer screening, encourage patient education and prompt response to symptoms and participation in a clinical trial to determine the effectiveness and necessity of screening modalities
- Discuss option of risk-reducing mastectomy and hysterectomy on case-by-case basis and counsel regarding degree of protection, extent of cancer risk, and reconstructive options
- Address psychosocial, social, and quality-of-life aspects of undergoing risk-reducing mastectomy and/or hysterectomy

For 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, with particular attention to breast and thyroid exam
- Baseline thyroid ultrasound at age 18 years, and consider annual thereafter
- Consider colonoscopy, starting at age 35 years, then every 5-10 years or more frequently if patient is symptomatic or polyps found
- Consider renal ultrasound starting at age 40 years, then every 1-2 years
- Consider annual dermatologic exam
- Consider psychomotor assessment in children at diagnosis and brain MRI if there are symptoms
- Education regarding the signs and symptoms of cancer

For Relatives:

- Advise about possible inherited cancer risk to relatives, options for risk assessment, and management
- Recommend genetic counseling and consideration of genetic testing for at-risk relatives

Summary

The published clinical validity of testing for PTEN mutations is variable, and the true clinical validity is difficult to ascertain, as the syndrome is defined by the presence of a PTEN mutation. The clinical utility of genetic testing for a PTEN mutation is high, in that confirming a diagnosis in a patient with clinical signs of a PTEN hamartoma tumor syndrome (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. Therefore, genetic testing for a PTEN mutation may be considered medically necessary when a presumptive diagnosis of a PTEN hamartoma tumor syndrome has been made, based on clinical signs and also in first-degree relatives of a probands with a known PTEN mutation. Genetic testing for a PTEN mutation is considered investigational for all other indications

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CROSS REFERENCES

Genetic and Molecular Diagnostic Testing, Genetic Testing, Policy No. 20

CODES	NUMBER	DESCRIPTION
CPT	81321	*PTEN (phosphatase and tensin homolog)* (e.g., Cowden syndrome, PTEN hamartoma tumor syndrome) gene analysis; full sequence analysis

CODES	NUMBER	DESCRIPTION
	81322	; known familial variant
	81323	; duplication/deletion variant
HCPCS	None	