PTEN-Related Disorders

Indications for Ordering

- Confirm clinical diagnosis of PTEN hamartoma tumor syndrome (PHTS)
- Determine if at-risk family members have a PTEN variant when a familial variant is unknown and affected relatives are unavailable for testing

Test Description

- Polymerase chain reaction and bidirectional sequencing of PTEN coding regions, intron/exon boundaries, and promoter (600 bp region745 bp upstream of translation start codon)
- Multiplex ligation-dependent probe amplification of PTEN coding regions

Tests to Consider

Primary tests

PTEN-Related Disorders (PTEN) Sequencing and Deletion/Duplication 2002470
- Preferred initial diagnostic and predictive test for PTEN-related disorders

PTEN-Related Disorders (PTEN) Sequencing 2002722
- Acceptable initial diagnostic and predictive test for PTEN-related disorders

Related test

Familial Mutation, Targeted Sequencing 2001961
- Useful when a pathogenic familial variant identifiable by sequencing is known

Disease Overview

Prevalence

- Cowden syndrome (CS) – at least 1/200,000
- Proteus syndrome (PS) – rare
  - ~120 reported cases
- Other PTEN-associated conditions – unknown

Symptoms

- Germline variants in PTEN gene cause several syndromes collectively referred to as PHTS
  - Associated disorders include
    - CS
    - Bannayan-Riley-Ruvalcaba syndrome (BRRS)
    - PS
    - Proteus-like syndrome (PLS)

For disease descriptions, see table below
- Established practice guidelines for tumor surveillance should be followed for individuals with an identified germline PTEN variant or suspected clinical diagnosis of a PTEN-related syndrome

Genetics

Gene – PTEN

Inheritance – autosomal dominant

Penetrance

CS – 99% by age 30

De novo variants – all cases of PS and 50-90% of CS

Variants

- Some variants may be associated with multiple phenotypes
- Type of variant detected may differ by phenotype
- Promoter variants
  - ~10% of individuals with CS do not have a PTEN sequence variant (Zhou, 2003)
  - Have not been identified in patients with BRRS
- Large deletions
  - 10% of individuals with BRRS do not have a PTEN sequence variant (Zhou, 2003)
  - Rare in CS
- Exon location
  - 65% of variants causing CS occur in exons 1-5 or the promoter
  - 60% of variants causing BRRS occur within exons 6-9
**Test Interpretation**

**Sensitivity/specificity**
- Clinical sensitivity
  - 25-85% for CS in individuals meeting strict diagnostic criteria (Marsh, 1998; Tan 2011)
  - 65% for BRRS (Marsh, 1998; Zhou, 2003)
  - 20% for PS (Zhou, 2001)
  - 50% for PSL (Zhou, 2001)
  - Up to 20% for autism spectrum disorder with significant macrocephaly (Butler, 2005)
- Analytical sensitivity/specificity
  - Sequencing – 99%
  - MLPA – 90% and 98% respectively

**Results**
- Positive – pathogenic variant in PTEN was identified
  - Confirms diagnosis of PHTS
- Negative – no variant detected
  - Decreases, but does not exclude, the probability of a PTEN-related disorder
- Sequence variants of unknown clinical significance may be detected

**Limitations**
- Deep intronic variants and some regulatory region variants are not detected
- Large deletions/duplications of exon 3 may not be detected
- Breakpoints for large deletions/duplications will not be determined
- Diagnostic errors can occur due to rare sequence variations

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### PHTS

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Age of onset</th>
<th>Pathognomonic</th>
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<tbody>
<tr>
<td>CS</td>
<td>By late 20s</td>
<td>Adult-onset lhermitte-Duclos disease (cerebellar tumors)</td>
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<td></td>
<td></td>
<td>Mucocutaneous lesions</td>
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<td></td>
<td></td>
<td>Facial trichilemmomas</td>
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<td></td>
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<td>Palmoplantar keratoses</td>
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<td></td>
<td></td>
<td>Oral mucosal papillomatosis in combination with trichilemmomas/keratoses</td>
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<tr>
<td></td>
<td></td>
<td>Major</td>
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<tr>
<td></td>
<td></td>
<td>Macrocephaly</td>
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<tr>
<td></td>
<td></td>
<td>Breast cancer</td>
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<td></td>
<td></td>
<td>Nonmedullary thyroid cancer</td>
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<td>Endometrial cancer</td>
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<td>Minor</td>
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<td></td>
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<td>Thyroid lesions</td>
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<td>Intellectual disability</td>
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<td></td>
<td></td>
<td>Fibrocystic breast disease</td>
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<td></td>
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<td>GI hamartomas</td>
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<td></td>
<td></td>
<td>Uterine fibroids</td>
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<td></td>
<td></td>
<td>GU malformations/tumors</td>
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<tr>
<th>Tumor Risks</th>
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<tbody>
<tr>
<td>Breast disease</td>
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<tr>
<td>- Benign disease – up to 67%</td>
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<tr>
<td>- Breast cancer</td>
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<tr>
<td>- Lifetime risk – 25-85%</td>
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<tr>
<td>- Average age at diagnosis – 38-46 years</td>
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<tr>
<td>Thyroid disease</td>
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<tr>
<td>- Benign – thyroid nodules, adenomas, goiter in up to 75%</td>
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<tr>
<td>- Nonmedullary thyroid cancer</td>
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<tr>
<td>- Lifetime risk – ~35%</td>
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<tr>
<td>- Childhood onset has been reported</td>
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<tr>
<td>Endometrial disease</td>
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<tr>
<td>- Benign disease – uterine fibroids common</td>
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<tr>
<td>- Endometrial cancer – lifetime risk of ~25%</td>
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<tr>
<td>Gastrointestinal disease</td>
</tr>
<tr>
<td>- Benign – &gt;90% with polyps</td>
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<tr>
<td>- Colorectal cancer – lifetime risk of ~9%</td>
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<tr>
<td>Renal disease</td>
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<tr>
<td>- Renal cell carcinoma – ~35%</td>
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<tr>
<td>Other</td>
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<td>- Melanoma – lifetime risk of &gt;5%</td>
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<td>- Brain tumors – occasional</td>
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**References**

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<thead>
<tr>
<th>Syndrome</th>
<th>Age of onset</th>
<th>Diagnostic Criteria</th>
<th>Tumor Risks</th>
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</table>
| BRRS     | Birth to early childhood | • Diagnostic criteria not set but heavily based on the following  
  o Macrocephaly  
  o Intestinal hamartomas  
  o Polyposis  
  o Lipomas  
  o Hemangiomas  
  o Pigmented lesions of the glans penis | • Same cancer risks as CS if PTEN variant present |
| BRRS     | Birth to early childhood | • Additional  
  o High birth weight  
  o Developmental delay  
  o Intellectual disability  
  o Proximal myopathy  
  o Joint hyperextensibility  
  o Pectus excavatum  
  o Scoliosis | |
| PS       | Infancy     | • Major  
  o Mosaic distribution of lesions  
  o Progressive course  
  o Sporadic occurrence  
  • Additional  
  o Connective tissue nevi  
  o Epidermal nevus  
  o Disproportionate overgrowth in limbs, skull, vertebrae, viscera  
  o Specific tumors before end of second decade  
    ▪ Bilateral ovarian cystadenoma  
    ▪ Parotid monomorphic adenoma  
  o Dysregulated adipose tissue  
  o Vascular malformations – capillary, venous and/or lymphatic  
  o Facial phenotype  
    ▪ Dolichocephaly  
    ▪ Long face  
    ▪ Low nasal bridge  
    ▪ Wide or anteverted nares  
    ▪ Open mouth at rest  
    ▪ Minor downslanting of palpebral fissures | • Tumors and malignancies are not common  
  • Reported  
    o Cystadenoma of the ovary  
    o Testicular tumors  
    o Central nervous system tumors  
    o Parotid monomorphic adenomas |
| PLS      | Infancy     | Clinical features of PS which do not meet diagnostic criteria for PS | |