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# *PTEN* Hamartoma Tumor Syndrome

Synonym: PHTS

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## Summary

### Clinical characteristics

The *PTEN* hamartoma tumor syndrome (PHTS) includes Cowden syndrome (CS), Bannayan-Riley-Ruvalcaba syndrome (BRRS), *PTEN*-related Proteus syndrome (PS), and *PTEN*-related Proteus-like syndrome.

- CS is a multiple hamartoma syndrome with a high risk for benign and malignant tumors of the thyroid, breast, kidney, 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 85%, with an average age of diagnosis between 38 and 46 years. The lifetime risk for thyroid cancer (usually follicular, rarely papillary, but never medullary thyroid cancer) is approximately 35%. The lifetime risk for renal cell cancer (predominantly of papillary histology) is 34%. The risk for endometrial cancer may approach 28%.
- BRRS is a congenital disorder characterized by macrocephaly, intestinal hamartomatous polyposis, lipomas, and pigmented macules of the glans penis.
- 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.

### Diagnosis/testing

The diagnosis of PHTS is established in a proband by identification of a heterozygous germline *PTEN* pathogenic variant on molecular genetic testing.

### Management

*Treatment of manifestations:* Treatment for the benign and malignant manifestations of PHTS is the same as for their sporadic counterparts. Topical agents (e.g., 5-fluorouracil), curettage, cryosurgery, or laser ablation may

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alleviate the mucocutaneous manifestations of CS but are rarely utilized; cutaneous lesions should be excised only if malignancy is suspected or symptoms (e.g., pain, deformity, increased scarring) are significant.

*Surveillance:* To detect tumors at the earliest, most treatable stages:

- Children (age <18 years). Yearly thyroid ultrasound from the time of diagnosis (earliest reported at age 7 years) and skin check with physical examination
- Adults. Yearly thyroid ultrasound and dermatologic evaluation
- Women beginning at age 30 years. Monthly breast self-examination; annual breast screening (at minimum mammogram; MRI may also be incorporated). Starting by age 35 years, consider transvaginal ultrasound or endometrial biopsy.
- Men and women. Colonoscopy beginning at age 35 years with frequency dependent on degree of polyposis identified or family history of early-onset colon cancer (before age 40); biennial (every 2 years) renal imaging (CT or MRI preferred) beginning at age 40 years
- Those with a family history of a particular cancer type at an early age. Consider initiating screening 5 to 10 years prior to the youngest age of diagnosis in the family.

*Evaluation of relatives at risk:* When a *PTEN* pathogenic variant has been identified in a proband, molecular genetic testing of asymptomatic at-risk relatives can identify those who have the family-specific pathogenic variant and warrant ongoing surveillance.

### Genetic counseling

PHTS is 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. Perhaps 10%-50% of individuals with CS have an affected parent. Each child of an affected individual has a 50% chance of inheriting the pathogenic variant and developing PHTS. Once a *PTEN* pathogenic variant has been identified in an affected family member, prenatal testing for a pregnancy at increased risk is possible.

## *GeneReview* Scope

| *PTEN* Hamartoma Tumor Syndrome: Included Phenotypes [1] |
|---|
| • Cowden syndrome (CS)<br>• Bannayan-Riley-Ruvalcaba syndrome (BRRS)<br>• *PTEN*-related Proteus syndrome (PS)<br>• *PTEN*-related Proteus-like syndrome |

For synonyms and outdated names see Nomenclature.
*1.* For other genetic causes of these phenotypes see Differential Diagnosis.

## Diagnosis

### Suggestive Findings

The *PTEN* hamartoma tumor syndrome (PHTS) includes Cowden syndrome (CS), Bannayan-Riley-Ruvalcaba syndrome (BRRS), *PTEN*-related Proteus syndrome (PS), and *PTEN*-related Proteus-like syndrome.

*PTEN* hamartoma tumor syndrome (PHTS) **should be suspected** in individuals with the following clinical features.

## Cowden Syndrome (CS)

Based on more than 3,000 prospectively accrued cases of CS or Cowden-like syndrome (CLS) from the community, a scoring system (which can be found online) that takes into account phenotype and age at diagnosis has been developed. The scoring system allows input of clinical information on an individual suspected of having CS/CLS and subsequently generates the prior probability of finding a *PTEN* pathogenic variant.

- In adults, a clinical threshold score of ten or more leads to a recommendation for referral to a genetics professional to consider PHTS.
- In children, macrocephaly and one or more of the following leads to the consideration of PHTS:
  - Autism or developmental delay
  - Dermatologic features including lipomas, trichilemmomas, oral papillomas, or penile freckling
  - Vascular features, such as arteriovenous malformations or hemangiomas
  - Gastrointestinal polyps
  - Pediatric-onset thyroid cancer or germ cell tumors

Additionally, consensus clinical diagnostic criteria for CS have been developed [Eng 2000]. The National Comprehensive Cancer Network publishes updated clinical diagnostic criteria on a yearly basis. However, the CS scoring system discussed in this section has been shown to be more accurate than the NCCN diagnostic criteria [Tan et al 2011].

Consensus clinical diagnostic criteria have been divided into three categories: pathognomonic, major, and minor.

**Pathognomonic criteria**

- Adult Lhermitte-Duclos disease, defined as the presence of a cerebellar dysplastic gangliocytoma [Zhou et al 2003a]
- Mucocutaneous lesions:
  - Trichilemmomas (facial) (See Figure 1.)
  - Acral keratoses
  - Papillomatous lesions (See Figure 2.)
  - Mucosal lesions

**Major criteria**

- Breast cancer
- Epithelial thyroid cancer (non-medullary), especially follicular thyroid cancer
- Macrocephaly (occipital frontal circumference ≥97th percentile)
- Endometrial carcinoma

**Minor criteria**

- Other thyroid lesions (e.g., adenoma, multinodular goiter)
- Intellectual disability (IQ ≤75)
- Hamartomatous intestinal polyps
- Fibrocystic disease of the breast
- Lipomas
- Fibromas
- Genitourinary tumors (especially renal cell carcinoma)
- Genitourinary malformation
- Uterine fibroids

**A clinical diagnosis of CS** is established if an individual meets **any one** of the following criteria:

- Pathognomonic mucocutaneous lesions including one of the following:
  - Six or more facial papules, of which three or more must be trichilemmomas
  - Cutaneous facial papules and oral mucosal papillomatosis
  - Oral mucosal papillomatosis and acral keratoses
  - Six or more palmoplantar keratoses
- Two or more major criteria
- One major and three or more minor criteria
- Four or more minor criteria

In a family in which one individual meets the diagnostic criteria for CS listed above, other relatives are considered to have a clinical diagnosis of CS if they meet **any one** of the following criteria:

- A pathognomonic criterion
- Any one major criterion with or without minor criteria
- Two minor criteria
- History of Bannayan-Riley-Ruvalcaba syndrome

### Bannayan-Riley-Ruvalcaba Syndrome (BRRS)

Diagnostic criteria for BRRS have not been set but are based heavily on the presence of the cardinal features of macrocephaly, hamartomatous intestinal polyposis, lipomas, vascular malformations, and pigmented macules of the glans penis [Gorlin et al 1992].

### *PTEN*-Related Proteus Syndrome

*PTEN*-related Proteus syndrome (PS) is highly variable and typically characterized by a germline heterozygous *PTEN* pathogenic variant and potential acquired somatic *PTEN* pathogenic variants in affected organs in mosaic distribution [Zhou et al 2000]. Thus, it is frequently misdiagnosed despite the development of consensus diagnostic criteria [Biesecker et al 1999] (see Proteus Syndrome). This is why *PTEN* experts prefer the molecular diagnosis of PHTS.

### *PTEN*-Related Proteus-Like Syndrome

*PTEN*-related Proteus-like syndrome is undefined but describes individuals with significant clinical features of PS who do not meet the diagnostic criteria and who have a heterozygous germline *PTEN* pathogenic variant. Note: Using a molecular diagnosis of PHTS, without clinical attribution, would be the most accurate.

## Establishing the Diagnosis

The diagnosis of PHTS **is established** in a proband by identification of a heterozygous germline pathogenic variant in *PTEN* on molecular genetic testing (see Table 1).

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (single-gene testing, multigene panel) and **comprehensive genomic testing** (exome sequencing, genome sequencing) depending on the phenotype.

Gene-targeted testing requires that the clinician determine which gene(s) are likely involved, whereas genomic testing does not. Individuals with the distinctive findings described in Suggestive Findings are likely to be diagnosed using gene-targeted testing (see Option 1), whereas those with a phenotype indistinguishable from many other inherited disorders with macrocephaly, developmental delay, and/or early-onset tumors are more likely to be diagnosed using genomic testing (see Option 2).

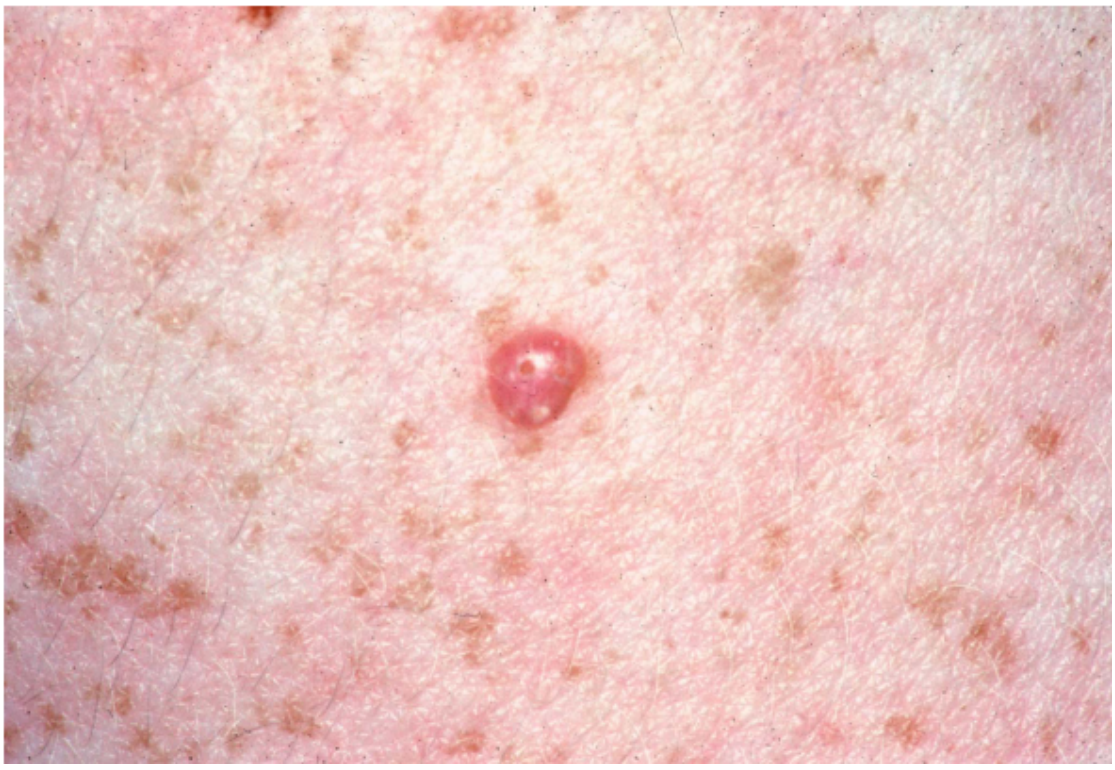

**Figure 1.** Trichilemmoma

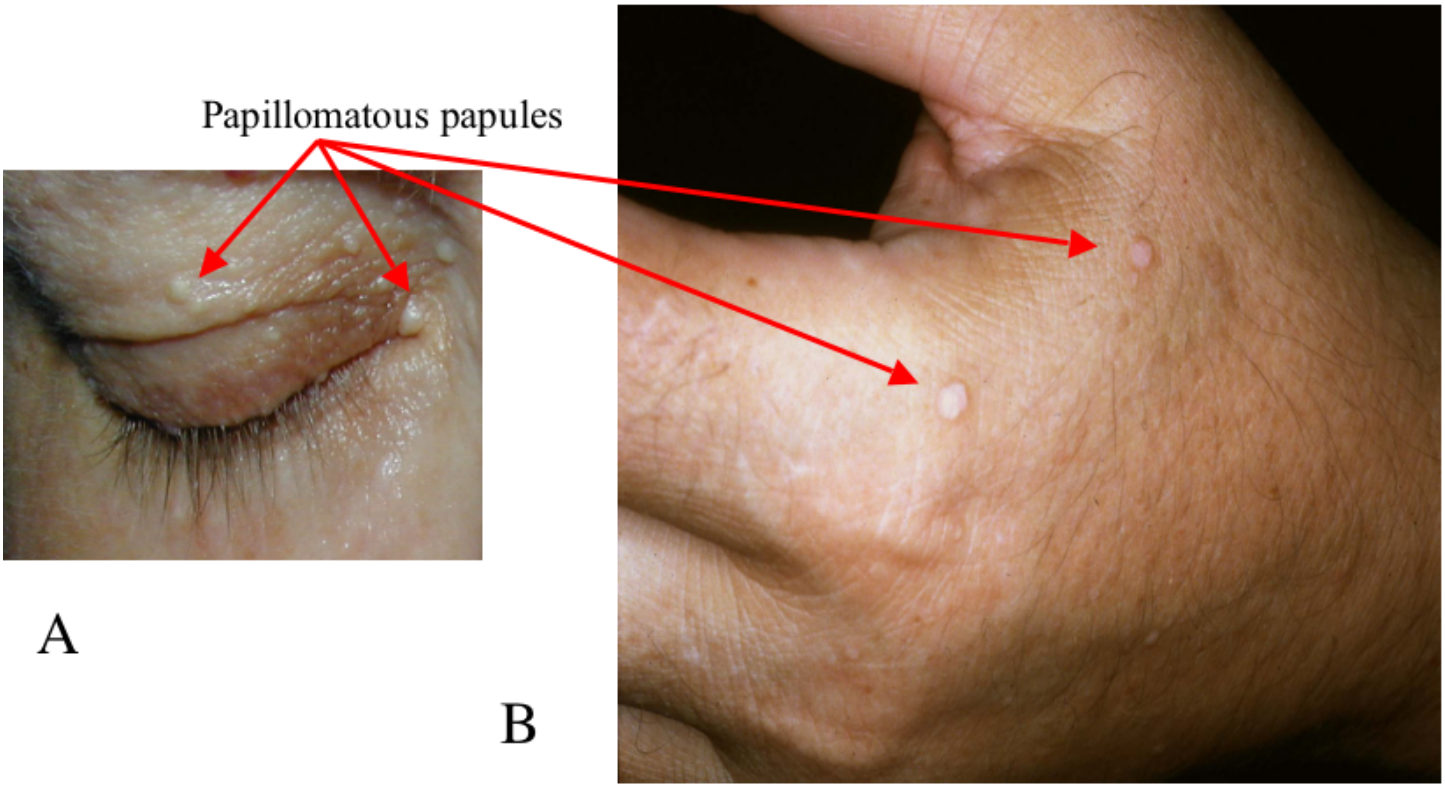


**Figure 2.** Papillomatous papules in the periocular region (A) and on the dorsum of the hand (B)

## Option 1

**Single-gene testing.** Sequence analysis of *PTEN* is performed first and followed by gene-targeted deletion/duplication analysis if no pathogenic variant is found. If a pathogenic variant is not identified with deletion/duplication analysis, perform sequence analysis of the *PTEN* promoter region for variants that decrease *PTEN* gene expression.

Note: In individuals with Cowden syndrome (CS) and Cowden-like syndrome (CLS), also consider a germline *KLLN* epimutation and *SDHB-D* analysis including *PIK3CA*, *AKT1* [Orloff et al 2013], *SEC23B* [Yehia et al 2015], and *WWP1* [Lee et al 2020] (see Differential Diagnosis, **Considerations in individuals with non-PHTS CS and CLS**).

**A multigene panel** that includes *PTEN* and other genes of interest (see Differential Diagnosis) may also be considered. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*; thus, clinicians need to determine which multigene panel is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

## Option 2

**Comprehensive genomic testing** does not require the clinician to determine which gene is likely involved. **Exome sequencing** is most commonly used; **genome sequencing** is also possible.

For an introduction to comprehensive genomic testing click here. More detailed information for clinicians ordering genomic testing can be found here.

**Table 1.** Molecular Genetic Testing Used in *PTEN* Hamartoma Tumor Syndrome

| Gene [1] | Method | Proportion of Probands by Phenotype with a Pathogenic Variant [2] Detectable by Method | | | |
|---|---|---|---|---|---|
| | | CS | BRRS | PLS | PS |
| *PTEN* | Sequence analysis of coding region [3] | 25%-80% | 60% | 50% [4] | 20% [4] |
| | Deletion/duplication analysis [5] | 3% [6] | 11% [7] | Unknown | Unknown |
| | Sequence analysis of promoter region [3] | 10% [7] | Rare [7] | Unknown | Unknown |

BRRS = Bannayan-Riley-Ruvalcaba syndrome; CS = Cowden syndrome; PLS = Proteus-like syndrome; PS = *PTEN*-related Proteus syndrome

*1.* See Table A. Genes and Databases for chromosome locus and protein.

*2.* See Molecular Genetics for information on variants detected in this gene.

*3.* Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.

*4.* Data suggest that up to 50% of individuals with a Proteus-like syndrome and 20% of individuals who meet the clinical diagnostic criteria of Proteus syndrome have *PTEN* pathogenic variants [Yehia & Eng 2018, Yehia et al 2019].

*5.* Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.

*6.* Individuals with CS who have large deletions have been reported [Tan et al 2011, Yehia et al 2019].

*7.* Zhou et al [2003b]

# Clinical Characteristics

## Clinical Description

*PTEN* hamartoma tumor syndrome (PHTS) is characterized by hamartomatous tumors and germline *PTEN* pathogenic variants. Clinically, PHTS includes Cowden syndrome (CS), Bannayan-Riley-Ruvalcaba syndrome (BRRS), *PTEN*-related Proteus syndrome (PS), and *PTEN*-related Proteus-like syndrome.

- CS is a multiple hamartoma syndrome with a high risk for benign and malignant tumors of the thyroid, breast, and endometrium. Renal cell carcinoma and colorectal carcinoma have also been shown to be in the PHTS spectrum.
- BRRS is a congenital disorder characterized by macrocephaly, intestinal polyposis, lipomas, vascular malformations, and pigmented macules of the glans penis.
- PS is a complex, highly variable disorder involving congenital malformations and overgrowth of multiple tissues.
- Proteus-like syndrome is undefined but refers to individuals with significant clinical features of PS who do not meet the diagnostic criteria for PS.

### Cowden Syndrome (CS)

More than 90% of individuals with CS have some clinical manifestation of the disorder by the late 20s [Nelen et al 1996, Eng 2000]. By the fourth decade, 99% of affected individuals develop the mucocutaneous stigmata (primarily trichilemmomas and papillomatous papules) as well as acral and plantar keratoses. In addition, individuals with Cowden syndrome usually have macrocephaly and dolichocephaly.

Hamartomatous and mixed gastrointestinal polyps, seen frequently in the majority of people with PHTS, do confer an increased risk for colorectal cancers [Heald et al 2010].

Based on anecdotal observations, glycogenic acanthosis in the presence of features of CS appears to be associated with a high likelihood of finding a *PTEN* pathogenic variant [McGarrity et al 2003].

**Tumor risk.** Individuals with CS are at high risk for breast, thyroid, renal, and endometrial cancers. As with other hereditary cancer syndromes, the risk for multifocal and bilateral (in paired organs such as the breasts) cancer is increased. Individuals with a germline *PTEN* pathogenic variant have a seven-fold increased risk of developing a second primary malignant neoplasm as compared to the general population [Ngeow et al 2014]:

- **Breast disease**
  - Women with Cowden syndrome are at as high as a 67% risk for benign breast disease.
  - An analysis of prospectively accrued and followed probands and family members with a *PTEN* pathogenic variant revealed an 85% lifetime risk for female breast cancer, with 50% penetrance by age 50 years [Tan et al 2012].
  - Although breast cancer has been described in males with a *PTEN* pathogenic variant [Fackenthal et al 2001], it was not observed in a study of more than 3,000 probands [Tan et al 2011].
- **Thyroid disease**
  - Benign multinodular goiter of the thyroid as well as adenomatous nodules and follicular adenomas are common, occurring in up to 75% of individuals with CS [Harach et al 1999].
  - The lifetime risk for epithelial thyroid cancer is approximately 35% [Tan et al 2012]. Median age of onset was 37 years; seven years was the youngest age at diagnosis [Ngeow et al 2011].
  - Note: (1) Follicular histology is overrepresented in adults compared to the general population in which papillary histology is overrepresented. (2) No medullary thyroid carcinoma was observed in the cohort with molecularly confirmed CS.
- **Endometrial disease**
  - Benign uterine fibroids are common.
  - Lifetime risk for endometrial cancer is estimated at 28%, with the starting age at risk in the late 30s to early 40s [Tan et al 2012].
- **Gastrointestinal neoplasias**
  - More than 90% of individuals with a *PTEN* pathogenic variant who underwent at least one upper or lower endoscopy were found to have polyps [Heald et al 2010]. Histologic findings varied, ranging from ganglioneuromatous polyps, hamartomatous polyps, and juvenile polyps to adenomatous polyps.
  - Lifetime risk for colorectal cancer is estimated at 9%, with the starting age at risk in the late 30s [Tan et al 2012].
- **Renal cell carcinoma (RCC).** Lifetime risk for RCC is estimated at 35%, with the starting age at risk in the 20s [Tan et al 2012, Kim et al 2020]. The predominant histology is papillary renal cell carcinoma [Mester et al 2012].
- **Cutaneous melanoma.** Lifetime risk for cutaneous melanoma is estimated at up to 6%. The earliest age at onset was age three years [Tan et al 2012]
- **Other**
  - Brain tumors as well as vascular malformations affecting any organ are occasionally seen in individuals with CS.
  - Note: Because meningioma is so common in the general population, it is not yet clear if meningioma is a true manifestation of CS.
  - A rare central nervous system tumor, cerebellar dysplastic gangliocytoma (Lhermitte-Duclos disease), is also found in CS and may be pathognomonic.

### Bannayan-Riley-Ruvalcaba Syndrome (BRRS)

Common features of BRRS, in addition to those mentioned above, include high birth weight, developmental delay, and intellectual disability (50% of affected individuals), a myopathic process in proximal muscles (60%), joint hyperextensibility, pectus excavatum, and scoliosis (50%) [Gorlin et al 1992].

Individuals with BRRS and a *PTEN* pathogenic variant are thought to have the same cancer risks as individuals with CS but formal study has not been performed. Note: It is not clear whether these risks apply to individuals with BRRS who do not have a *PTEN* pathogenic variant.

The gastrointestinal hamartomatous polyps in BRRS (seen in 45% of affected individuals) may occasionally be associated with intussusception, but rectal bleeding and oozing of "serum" is more common. These polyps are not believed to increase the risk for colorectal cancer. PHTS hamartomatous polyps are different in histomorphology from the polyps seen in Peutz-Jeghers syndrome.

### *PTEN*-Related Proteus Syndrome (PS)

PS is characterized by progressive segmental or patchy overgrowth of diverse tissues of all germ layers, most commonly affecting the skeleton, skin, adipose tissue, and central nervous system. In most individuals, Proteus syndrome has minimal or no manifestations at birth, develops and progresses rapidly beginning in the toddler period, and relentlessly progresses through childhood, causing severe overgrowth and disfigurement. It is associated with a range of tumors, pulmonary complications, and a striking predisposition to deep vein thrombosis and pulmonary embolism. See Proteus Syndrome.

### *PTEN*-Related Proteus-Like Syndrome

Proteus-like syndrome is undefined but describes individuals with significant clinical features of PS who do not meet the PS diagnostic criteria.

## Clinical Implications of All PHTS Phenotypes

The two most serious clinical manifestations in individuals with germline *PTEN* pathogenic variants are organ-specific cancers and neurodevelopmental disorders, including autism spectrum disorder (ASD).

***PTEN*-related lifetime neoplasia risks.** Regardless of clinical diagnosis, individuals with a germline *PTEN* pathogenic variant are thought to have the same cancer risks as individuals with CS [Tan et al 2012].

**Neurodevelopmental disorders.** Neurodevelopmental phenotypes such as megalencephaly, ASD, and developmental delay have been reported in individuals with PHTS [Goffin et al 2001, Butler et al 2005, Hansen-Kiss et al 2017]. Germline *PTEN* pathogenic variants have been identified in 10%-20% of individuals with ASD and macrocephaly [Yehia et al 2020]. The extent of macrocephaly observed in *PTEN*-related ASD is often more severe than in individuals with macrocephalic ASD unrelated to *PTEN* [Mester et al 2011]. Individuals with *PTEN*-related ASD show increases in cortical white matter and a distinctive neurocognitive and behavioral phenotype including delayed language development, poor working memory and processing speed, and adaptive and sensory abnormalities [Frazier et al 2015, Busch et al 2019].

## Genotype-Phenotype Correlations

For purposes of *PTEN* genotype-phenotype analyses, a series of 37 unrelated probands with CS were ascertained by the operational diagnostic criteria of the International Cowden Consortium, 1995 version [Nelen et al 1996, Eng 2000]. Association analyses revealed that families with CS and a germline *PTEN* pathogenic variant are more likely to develop malignant breast disease than are families who do not have a *PTEN* pathogenic variant [Marsh et al 1998]. In addition, pathogenic missense variants and others 5' to or within the phosphatase core

motif appeared to be associated with involvement of five or more organs, a surrogate phenotype for severity of disease [Marsh et al 1998].

More than 90% of families that included individuals with CS and also individuals with BRRS were found to have a germline *PTEN* pathogenic variant. The mutational spectra of BRRS and CS have been shown to overlap. No difference in mutation frequencies was observed between BRRS occurring in a single individual in a family and BRRS occurring in multiple family members.

An individual presenting as a simplex case (i.e., one with no known family history) of Proteus-like syndrome comprising hemihypertrophy, macrocephaly, lipomas, connective tissue nevi, and multiple arteriovenous malformations was found to have a germline p.Arg335Ter *PTEN* pathogenic variant and the same somatic pathogenic variant (p.Arg130Ter) in three separate tissues, possibly representing germline mosaicism [Zhou et al 2000]. Both pathogenic variants have been previously described in individuals with clinical features of CS and BRRS.

Two of nine individuals who met the clinical diagnostic criteria of Proteus syndrome and three of six with Proteus-like syndrome were found to have germline *PTEN* pathogenic variants. Subsequently multiple individuals with germline *PTEN* pathogenic variants who met the clinical diagnostic criteria of Proteus syndrome have been reported [Yehia & Eng 2018].

### Penetrance

More than 90% of individuals with CS have some clinical manifestation of the disorder by the late 20s [Nelen et al 1996, Eng 2000, Yehia et al 2020]. By the fourth decade, 99% of affected individuals develop the mucocutaneous stigmata, primarily trichilemmomas and papillomatous papules, as well as acral and plantar keratoses. (See also Clinical Description, Cowden Syndrome for the age at which specific manifestations are likely to become evident.)

### Nomenclature

Cowden syndrome, Cowden disease, and multiple hamartoma syndrome have been used interchangeably.

Bannayan-Riley-Ruvalcaba syndrome, Bannayan-Ruvalcaba-Riley syndrome, Bannayan-Zonana syndrome, and Myhre-Riley-Smith syndrome refer to a similar constellation of signs that comprise what the authors refer to as BRRS. When a *PTEN* pathogenic variant is found, the gene-related name, PHTS, should be used.

One form of Proteus-like syndrome, with a clinical presentation similar to that first described by Zhou et al [2000] and with a germline *PTEN* pathogenic variant, was termed SOLAMEN (*s*egmental *o*vergrowth, *l*ipomatosis, *a*rteriovenous *m*alformation, and *e*pidermal *n*evus) syndrome [Caux et al 2007]. This is not useful, especially in the molecular era, as any phenotype associated with a *PTEN* pathogenic variant should be termed PHTS with all its implications for clinical management [Yehia et al 2020].

### Prevalence

Because the diagnosis of CS is difficult to establish, the true prevalence is unknown. The prevalence estimate of 1:200,000 [Nelen et al 1999] is likely low. Because of the variable and often subtle external manifestations of CS and BRRS, many individuals remain undiagnosed [Yehia et al 2020].

## Genetically Related (Allelic) Disorders

Other phenotypes that can be associated with *PTEN* germline pathogenic variants are summarized in Table 2.

**Table 2.** *PTEN* Allelic Disorders

| Disorder | Clinical Characteristics | Comment |
|---|---|---|
| Apparently isolated Lhermitte-Duclos disease (LDD) | Apparently isolated dysplastic gangliocytoma of the cerebellum | Most (if not all) adult-onset LDD can be attributed to *PTEN* path vars, even if no other clinical signs of CS/BRRS. Note: Germline *PTEN* path vars appear rare in persons w/childhood-onset LDD. [1] Evaluated all persons w/apparently isolated LDD for other manifestations of CS/BRRS. |
| Autism/pervasive developmental disorder & macrocephaly (OMIM 605309) | ASD & macrocephaly | ~10%-20% of persons w/ASD & macrocephaly have germline *PTEN* path vars. [2] |
| Juvenile polyposis of infancy (JPI) (OMIM 612242) | Juvenile polyposis diagnosed before age 6 yrs; GI manifestations (bleeding, diarrhea, & protein-losing enteropathy) are often severe. | Rare condition caused by germline deletion of *BMPR1A* & *PTEN*; external stigmata of JPI may mimic BRRS. |

ASD = autism spectrum disorder; BRRS = Bannayan-Riley-Ruvalcaba syndrome; CS = Cowden syndrome; GI = gastrointestinal; path var = pathogenic variant
*1.* Zhou et al [2003a]
*2.* Butler et al [2005], Hansen-Kiss et al [2017], Yehia et al [2020]

**Sporadic tumors** (including endometrial cancer, prostate cancer, glioblastoma) occurring as single tumors in the absence of any other findings of PHTS frequently harbor somatic variants in *PTEN* that are **not** present in the germline. In these circumstances predisposition to these tumors is not heritable. For more information, see Cancer and Benign Tumors.

# Differential Diagnosis

**Table 3.** Disorders to Consider in the Differential Diagnosis of *PTEN* Hamartoma Tumor Syndrome

| Gene(s) | Disorder | Clinical Characteristics | Comment |
|---|---|---|---|
| *AKT1* | *AKT1*-related Proteus syndrome [1, 2] | Progressive segmental or patchy overgrowth most commonly affecting skeleton, skin, adipose tissue, & CNS; development of a range of tumors, pulmonary complications, & a striking predisposition to DVT & pulmonary embolism | PHTS is assoc w/growth abnormalities w/linear nevi & vascular malformations that are clinically & molecularly distinct from those of *AKT1*-related Proteus syndrome. |
| *BMPR1A* *SMAD4* | Juvenile polyposis syndrome (JPS) | Predisposition to hamartomatous polyps in GI tract (specifically stomach, small intestine, colon, & rectum). Untreated polyps may cause bleeding & anemia. Most juvenile polyps are benign, but malignant transformation can occur. | Unlike PHTS, polyps usually present by age 20 & can reach up to 100 during a lifetime. JPS polyps are juvenile polyps by histology. PHTS polyps carry diverse histology incl epithelial overgrowth, hamartomatous, neuromatous, juvenile, adenomatous. |
| *FLCN* | Birt-Hogg-Dubé syndrome [1] | Cutaneous manifestations (fibrofolliculomas, acrochordons, angiofibromas, oral papules, cutaneous collagenomas, & epidermal cysts), pulmonary cysts / history of pneumothorax, & various types of renal tumors | Cutaneous lesions can be mistaken for trichilemmomas characteristic of PHTS. Unlike the predominant papillary renal cancers in PHTS, BHD renal cancers have a mixed chromophobe/oncocytic histology. |

*Table 3. continued from previous page.*

| Gene(s) | Disorder | Clinical Characteristics | Comment |
|---|---|---|---|
| *NF1* | Neurofibromatosis type 1 (NF1) [1] | The only features seen in both NF1 & CS/BRRS are café au lait macules & fibromatous tumors of the skin. | NF1 may be mistakenly diagnosed in persons w/CS/BRRS due to presence of ganglioneuromas in GI tract. |
| *PTCH1*<br>*SUFU* | Nevoid basal cell carcinoma syndrome (NBCCS) [1] | Multiple jaw keratocysts &/or basal cell carcinomas; skeletal anomalies; ectopic calcification; & in ~60% of persons, a recognizable appearance w/macrocephaly, frontal bossing, coarse facial features, & facial milia | Dermatologic findings & developmental features in CS & NBCCS are quite different. |
| *STK11* | Peutz-Jeghers syndrome | GI polyposis, mucocutaneous pigmentation, & cancer predisposition | The P-J polyp has a diagnostic appearance & is quite different from CS or JPS hamartomatous polyps. P-J polyps are often symptomatic (intussusception, rectal bleeding); CS polyps are rarely so. |

BRRS = Bannayan-Riley-Ruvalcaba syndrome; CS = Cowden syndrome; DVT = deep vein thrombosis; GI = gastrointestinal; PHTS = *PTEN* hamartoma tumor syndrome; P-J = Peutz-Jeghers

*1.* Birt-Hogg-Dubé syndrome, neurofibromatosis type 1, and nevoid basal cell carcinoma (Gorlin) syndrome are inherited in an autosomal dominant manner. All individuals with clinically confirmed Proteus syndrome (known to authors of the Proteus Syndrome *GeneReview*) have been simplex cases caused by somatic mosaicism for the specific *de novo AKT1* pathogenic variant c.49G>A (p.Glu17Lys).

*2.* Since *PTEN* downregulates AKT1 activation by decreasing phosphorylation, the finding of an activating *AKT1* pathogenic variant in Proteus syndrome confirms that Proteus syndrome is a "PTEN-pathway-opathy."

### Considerations in individuals with non-PHTS Cowden syndrome (CS) and Cowden-like syndrome (CLS):

- **Germline *KLLN* epimutation.** Approximately 30% of individuals with CS (OMIM 615107) or CLS who do not have a *PTEN* germline pathogenic variant have a germline *KLLN* methylation epimutation [Yehia & Eng 2020], which resulted in downregulation of expression of *KLLN* but not of *PTEN*. Of note, *KLLN* shares a bidirectional promoter with *PTEN*. Pilot data suggest that individuals with CS and CLS with a germline *KLLN* epimutation have a greater prevalence of breast and renal cell carcinomas than do those with a germline *PTEN* pathogenic variant. Note: To date, *KLLN* methylation is not offered clinically because of the technical challenges.
- **Susceptibility genes in individuals with non-PHTS CS and CLS.** A pilot study found that individuals with CS and CLS without germline *PTEN* pathogenic variants (but with increased levels of manganese superoxide dismutase) harbored germline variants in *SDHB* and *SDHD* [Ni et al 2008]. That germline variants in *SDHB*, *SDHC*, and *SDHD* occur in approximately 10% of persons with CS or CLS who do not have a *PTEN* pathogenic variant has been validated in an independent series of 608 research participants [Yehia & Eng 2020]. These variants were associated with stabilization of HIF1a, destabilization of p53 secondary to decreased NQ01 interaction, and increased reactive oxygen species with consequent apoptosis resistance. Approximately 10% of individuals with CS and CLS without germline *PTEN* or *SDHx* pathogenic variants have been found to harbor germline *PIK3CA* (see *PIK3CA*-Related Segmental Overgrowth) or *AKT1* pathogenic variants [Orloff et al 2013]. Another 3%-6% of individuals with CS and CLS without pathogenic variants in the above known genes have germline heterozygous SEC23B pathogenic variants, which are particularly associated with thyroid carcinoma and enhanced ribosome biogenesis [Yehia et al 2015, Yehia & Eng 2018]. Germline heterozygous *WWP1* gain-of-function variants have been identified in a subset of individuals with CS and CLS characterized by oligopolyposis and/or colorectal cancer [Lee et al 2020]. Activating *WWP1* pathogenic variants resulted in aberrant enzymatic activation, with consequent *PTEN* inactivation, thereby triggering hyperactive growth-promoting PI3K signaling to mimic PTEN loss of function. Other gene discoveries are detailed in Yehia & Eng [2020].

# Management

## Evaluations and Surveillance Guidelines Following Initial Diagnosis

To establish the extent of disease and needs of an individual diagnosed with *PTEN* hamartoma tumor syndrome (PHTS), the evaluations summarized in Table 4 (if not performed as part of the evaluation that led to the diagnosis) are recommended. The most serious consequences of PHTS relate to the increased risk of cancers including breast, thyroid, endometrial, renal, and to a lesser extent, colon. In this regard, the most important aspect of management of **any** individual with a *PTEN* pathogenic variant is increased cancer surveillance to detect any tumors at the earliest, most treatable stages. Current suggested screening and surveillance by age are detailed in Table 4.

**Table 4.** Recommended Evaluations and Surveillance Following Initial Diagnosis in Individuals with *PTEN* Hamartoma Tumor Syndrome

| System/Concern | Evaluation & Surveillance [1] |
|---|---|
| **General** | • Complete medical history & family history for features of PHTS<br>• Annual comprehensive physical exam starting at age 18 yrs, or 5 yrs before youngest age of diagnosis of a component cancer in family (whichever comes 1st), w/particular attention to thyroid exam<br>• Encourage education re signs & symptoms of cancer. |
| **Breast (female)** | • Starting at age 18 yrs: consistent breast awareness & self-exam; report changes to health care provider.<br>• Starting at age 25 yrs [2]: clinical breast exam every 6-12 mos<br>• Starting at ages 30-35 yrs [2]: annual mammogram w/consideration of tomosynthesis & breast MRI w/contrast<br>• Discuss mastectomy as needed. |
| **Thyroid** | Starting at age of diagnosis (youngest thyroid cancer reported: age 7 yrs): annual thyroid US |
| **Kidney** | • Starting at age 40 yrs: consider renal US every 1-2 yrs<br>• Renal imaging (CT or MRI preferred) |
| **Endometrium** | • Consider endometrial cancer screening by age 35 yrs.<br>• Encourage education & prompt response to symptoms (e.g., abnormal bleeding).<br>• Consider endometrial biopsy screening every 1-2 yrs.<br>• Transvaginal US in postmenopausal women at clinician's discretion & as needed<br>• Discuss hysterectomy on completion of childbearing & as needed. |
| **Colon** | Starting at age 35 yrs [2]: colonoscopy every 5 yrs; more frequently if person is symptomatic or polyps are found |
| **Dermatologic** | Annual dermatologic exams are recommended (incl for cutaneous melanoma). |
| **Developmental** | • Starting at age of diagnosis: at clinician's recommendation, consider psychomotor assessment in children; brain MRI if symptomatic<br>• Eval for early intervention / special education where indicated |

*Table 4. continued from previous page.*

| System/Concern | Evaluation & Surveillance [1] |
|---|---|
| **Genetic counseling** | • By genetics professionals [3]<br>• To inform affected persons & their families re nature, MOI, & implications of PHTS to facilitate medical & personal decision making<br>• Refer to psychosocial support as needed (e.g., to address the diagnosis, family planning, risk-reducing mastectomy). |

MOI = mode of inheritance; PHTS = *PTEN* hamartoma tumor syndrome; US = ultrasound

*1.* Adapted with permission from the NCCN Guidelines® for **Genetic/Familial High-Risk Assessment: Breast and Ovarian V.1.2021**. © 2021 National Comprehensive Cancer Network, Inc. All rights reserved. The NCCN Guidelines and illustrations herein may not be reproduced in any form for any purpose without the express written permission of the NCCN. Accessed December 27, 2020. To view the most recent and complete version of the guideline, go online to NCCN.org (no-fee registration and login required). NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.

*2.* For individuals with a family history of a particular cancer type at an early age, screening should be considered five to ten years prior to the youngest diagnosis in the family.

*3.* Medical geneticist, certified genetic counselor, or certified advanced genetic nurse

### Bannayan-Riley-Ruvalcaba Syndrome (BRRS)

Note: Screening recommendations have not been established for BRRS. Given recent molecular epidemiologic studies, however, individuals with BRRS and a germline *PTEN* pathogenic variant should undergo the same surveillance as individuals with CS (see Table 4). Individuals with BRRS should especially be monitored for complications related to gastrointestinal hamartomatous polyposis (which can be more severe than in individuals with CS) and musculoskeletal features such as hypotonia and scoliosis.

### Proteus Syndrome / Proteus-Like Syndrome

Note: Although the observation of germline *PTEN* pathogenic variants in a minority of individuals who meet the clinical diagnostic criteria for Proteus syndrome and Proteus-like syndrome is relatively new, clinicians should consider instituting the above surveillance recommendations for individuals with these disorders who have germline *PTEN* pathogenic variants.

## Treatment of Manifestations

**Table 5.** Treatment of Manifestations in Individuals with Cowden Syndrome and Bannayan-Riley-Ruvalcaba Syndrome

| Manifestation/Concern | Treatment | Considerations/Other |
|---|---|---|
| **Mucocutaneous lesions** | Asymptomatic lesions: observation alone is prudent. | Cutaneous lesions should be excised only if malignancy is suspected or symptoms (e.g., pain, deformity, ↑ scarring) are significant. |
| | Symptomatic lesions: topical agents (e.g., 5-fluorouracil), curettage, cryosurgery, or laser ablation may provide only temporary relief [Hildenbrand et al 2001]. | Surgical excision is sometimes complicated by keloid formation & recurrence (often rapid) of the lesions [Eng, unpublished data]. |
| **Developmental delay** | As needed:<br>• Developmental support services<br>• Early intervention &/or special education services | |
| **Breast disease / neoplasia** | Treatment per breast cancer specialist | |

*Table 5. continued from previous page.*

| Manifestation/Concern | Treatment | Considerations/Other |
|---|---|---|
| **Thyroid disease** | • Thyroid US to monitor for ↑ in size of nodules, or multinodular goiter<br>• If results of fine needle aspirate are suspicious for malignancy, perform total thyroidectomy. | Sub-total thyroidectomies will → regrowth of thyroid w/similar cancer risks. |
| **Endometrial disease** | Multiple fibroids are treated w/total abdominal hysterectomy. | Single fibroid removals → dramatic recurrences. |
| **Gastrointestinal neoplasias** | Endoscopy w/removal of polyps per gastroenterologist | |
| **Renal cell carcinoma** | Standard treatment | |

US = ultrasound

### Treatment of Manifestations in Individuals with Proteus Syndrome / Proteus-Like Syndrome

Individuals with a germline *PTEN* pathogenic variant should follow management recommendations for CS and BRRS (see Table 5). Also see Proteus Syndrome, Management.

## Prevention of Primary Manifestations

Some women at increased risk for breast cancer consider prophylactic mastectomy, especially if breast tissue is dense or if repeated breast biopsies have been necessary. Prophylactic mastectomy reduces the risk of breast cancer by 90% in women at high risk [Hartmann et al 1999]. Note: The recommendation of prophylactic mastectomy is a generalization for women at increased risk for breast cancer from a variety of causes, not just from PHTS.

No **direct** evidence supports the routine use of agents such as tamoxifen or raloxifene in individuals with PHTS to reduce the risk of developing breast cancer. Physicians should discuss the limitations of the evidence and the risks and benefits of chemoprophylaxis with each individual. In addition, the clinician must discuss the increased risk for endometrial cancer associated with tamoxifen use in a population already at increased risk for endometrial cancer.

## Agents/Circumstances to Avoid

Because of the propensity for rapid tissue regrowth and the propensity to form keloid tissue, it is recommended that cutaneous lesions be excised only if malignancy is suspected or symptoms (e.g., pain, deformity) are significant.

## Evaluation of Relatives at Risk

It is appropriate to clarify the genetic status of at-risk relatives of an affected individual by molecular genetic testing for the *PTEN* pathogenic variant identified in the proband. Family members who have the familial *PTEN* pathogenic variant (and therefore have PHTS) are in need of initial evaluation and ongoing surveillance.

Molecular testing is appropriate for at-risk individuals younger than age 18 years, given the possible early disease presentation in individuals with BRRS and *PTEN*-related Proteus syndrome. In individuals with PHTS, the earliest documented breast cancer and thyroid cancer are at age 17 years and at age seven years, respectively.

Family members who have not inherited the *PTEN* pathogenic variant and their subsequent offspring have cancer risks similar to the general population.

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

## Therapies Under Investigation

Although mTOR inhibitors show promise for treatment of malignancies in individuals who have a germline *PTEN* pathogenic variant, use should be limited to clinical trials. A Phase II open-label clinical trial (NCT00971789) utilized the mTOR inhibitor sirolimus in adults with PHTS and showed evidence of improvement of symptoms throughout the duration of the trial [Komiya et al 2019]. Another double-blind drug-placebo cross-over clinical trial with the mTOR inhibitor everolimus is completing accrual of pediatric, adolescent, and young adults with germline *PTEN* pathogenic variants and autism spectrum disorder (NCT02461446).

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for access to information on clinical studies for a wide range of diseases and conditions.

# Genetic Counseling

*Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional.* —ED.

## Mode of Inheritance

Cowden syndrome and Bannayan-Riley-Ruvalcaba syndrome are autosomal dominant disorders caused by either an inherited or a *de novo PTEN* pathogenic variant.

*PTEN*-related Proteus syndrome and Proteus-like syndrome are also autosomal dominant disorders but are almost always caused by a *de novo* pathogenic variant.

## Risk to Family Members

**Parents of a proband**

- **Cowden syndrome (CS).** 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. Based on practical experience, about 50% of individuals diagnosed with CS have an affected relative [Author, unpublished data]. *De novo PTEN* pathogenic variants occur in 10%-44% of PHTS probands [Mester & Eng 2012].
- **Bannayan-Riley-Ruvalcaba syndrome (BRRS).** The majority of evidence suggests that *PTEN* pathogenic variants occur in both simplex and familial occurrences of BRRS [Mester & Eng 2012, Yehia & Eng 2018].
- ***PTEN*-related Proteus syndrome and Proteus-like syndrome.** Virtually all individuals have a *de novo* pathogenic variant.
- If the proband appears to be the only affected family member, molecular genetic testing is recommended for the parents of the proband to confirm their genetic status and to allow reliable recurrence risk counseling.
- If the pathogenic variant identified in the proband is not identified in either parent, the following possibilities should be considered:

- The proband has a *de novo* pathogenic variant. Note: A pathogenic variant is reported as "*de novo*" if: (1) the pathogenic variant found in the proband is not detected in parental DNA; and (2) parental identity testing has confirmed biological maternity and paternity. If parental identity testing is not performed, the variant is reported as "assumed *de novo*" [Richards et al 2015].
- The proband inherited a pathogenic variant from a parent with germline (or somatic and germline) mosaicism.* Note: Testing of parental leukocyte DNA may not detect all instances of somatic mosaicism.

  * A parent with somatic and germline mosaicism for a *PTEN* pathogenic variant may be mildly/minimally affected.

- The family history of many individuals diagnosed with *PTEN* hamartoma tumor syndrome (PHTS) may appear to be negative because of failure to recognize the disorder in family members, early death of the parent before the onset of symptoms, or late onset of the disorder in a heterozygous parent. Therefore, an apparently negative family history cannot be confirmed unless molecular genetic testing has demonstrated that neither parent is heterozygous for the pathogenic variant identified in the proband.

**Sibs of a proband.** The risk to the sibs of the proband depends on the genetic status of the parents:

- If a parent of the proband has the *PTEN* pathogenic variant identified in the proband, the risk to the sibs of inheriting the variant is 50%. The penetrance of PHTS is close to 99% by the 30s in individuals with a *PTEN* pathogenic variant.
- If the *PTEN* pathogenic variant identified in the proband cannot be detected in the leukocyte DNA of either parent, the recurrence risk to sibs is slightly greater than that of the general population because of the possibility of parental germline mosaicism [Pritchard et al 2013].
- If the parents have not been tested for the *PTEN* pathogenic variant but are clinically unaffected and are in their thirties, the risk to the sibs of a proband appears to be low. However, sibs of a proband with clinically unaffected parents are still presumed to be at increased risk for PHTS because of the possibility of age-related penetrance in a heterozygous parent or parental germline mosaicism.

**Offspring of a proband.** Each child of an individual with PHTS has a 50% chance of inheriting the *PTEN* pathogenic variant.

**Other family members.** The risk to other family members depends on the status of the proband's parents: if a parent has the *PTEN* pathogenic variant, his or her family members may be at risk.

## Related Genetic Counseling Issues

See Management, Evaluation of Relatives at Risk for information on evaluating at-risk relatives for the purpose of early diagnosis and treatment.

**Predictive testing** for at-risk asymptomatic family members requires prior identification of the germline *PTEN* pathogenic variant in the family.

**Genetic cancer risk assessment and counseling.** For a comprehensive description of the medical, psychosocial, and ethical ramifications of identifying at-risk individuals through cancer risk assessment with or without molecular genetic testing, see Cancer Genetics Risk Assessment and Counseling – for health professionals (part of PDQ®, National Cancer Institute).

**Family planning**

- The optimal time for determination of genetic risk and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.

- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected or at risk.

## Prenatal Testing and Preimplantation Genetic Testing

Once the *PTEN* pathogenic variant has been identified in an affected family member, prenatal and preimplantation genetic testing are possible.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful.

# Resources

*GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.*

- **MedlinePlus**

  Cowden syndrome

- **PTEN Hamartoma Tumor Syndrome Foundation**

  *The PTEN Hamartoma Tumor Syndrome Foundation was founded with a mission to educate about PTEN syndromes, provide financial support to patients, support research, and to promote awareness.*

  **Email:** ptensyndromefoundation@gmail.com

  www.ptenfoundation.org

- **PTEN Italia**

  Via San Giuseppe Cottolegno, 36

  20143 Milano

  Italy

  **Email:** info@ptenitalia.org

  www.ptenitalia.org

- **PTEN Research**

  3rd Floor, Paternoster House

  London EC4M 8AB

  United Kingdom

  **Email:** contact@ptenresearch.org

  www.ptenresearch.org

- **American Cancer Society**

  **Phone:** 800-227-2345

  www.cancer.org

- **CancerCare**

  **Phone:** 800-813-4673

**Email:** info@cancercare.org

www.cancercare.org

- **International Society for Gastrointestinal Hereditary Tumours (InSiGHT)**

  www.insight-group.org

- **National Breast Cancer Coalition (NBCC)**

  **Phone:** 800-622-2838

  **Fax:** 202-314-3458

  **Email:** info@stopbreastcancer.org

  www.stopbreastcancer.org

- **National Coalition for Cancer Survivorship (NCCS)**

  **Phone:** 877-NCCS-YES

  **Email:** info@canceradvocacy.org

  www.canceradvocacy.org

- **Susan G. Komen Breast Cancer Foundation**

  **Phone:** 877 GO KOMEN

  **Email:** helpline@komen.org

  www.komen.org

# Molecular Genetics

*Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information.* —ED.

**Table A.** PTEN Hamartoma Tumor Syndrome: Genes and Databases

| Gene | Chromosome Locus | Protein | Locus-Specific Databases | HGMD | ClinVar |
|---|---|---|---|---|---|
| *PTEN* | 10q23.31 | Phosphatidylinositol 3,4,5-trisphosphate 3-phosphatase and dual-specificity protein phosphatase PTEN | PTEN database | PTEN | PTEN |

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.

**Table B.** OMIM Entries for PTEN Hamartoma Tumor Syndrome (View All in OMIM)

| | |
|---|---|
| 158350 | COWDEN SYNDROME 1; CWS1 |
| 601728 | PHOSPHATASE AND TENSIN HOMOLOG; PTEN |

## Molecular Pathogenesis

While much functional research has been accomplished, complete function of PTEN is not yet fully understood. PTEN belongs to a subclass of phosphatases called dual-specificity phosphatases that remove phosphate groups from tyrosine as well as serine and threonine. In addition, PTEN is the major phosphatase for phosphoinositide-3,4,5-triphosphate, and thus downregulates the PI3K/AKT pathway [Yehia et al 2019].

The PTEN protein localizes to specific nuclear and cytoplasmic components. The wild type protein is a major lipid phosphatase that downregulates the PI3K/AKT pathway to cause G1 cell cycle arrest and apoptosis. In addition, the protein phosphatase appears to play an important role in inhibition of cell migration and spreading, as well as downregulating several cell cyclins. It appears that nuclear PTEN mediates cell cycle arrest, while cytoplasmic PTEN is required for apoptosis [Yehia & Eng 2018, Yehia et al 2019].

Germline pathogenic variants have been found throughout *PTEN* and include missense, nonsense, and splice site variants, small deletions, insertions, and large deletions. More than 150 unique pathogenic variants are currently listed in the Human Gene Mutation Database (see Table A). Nearly 40% of pathogenic variants are found in exon 5, which encodes the phosphate core motif [Yehia et al 2019]. Most pathogenic variants are unique, although a number of recurrent pathogenic variants have been reported, particularly those in Table 6.

**Mechanism of disease causation.** The majority (76%) of germline pathogenic variants in *PTEN* predict either truncated PTEN protein, lack of protein (haploinsufficiency), or dysfunctional protein. Many missense variants are functionally null and several act as dominant negatives [Papa et al 2014]. When PTEN is absent, decreased, or dysfunctional, phosphorylation of AKT1 is uninhibited, leading to the inability to activate cell cycle arrest and/or to undergo apoptosis. In addition, through lack of protein phosphatase activity, the mitogen-activated protein kinase (MAPK) pathway is dysregulated, leading to abnormal cell survival [Yehia et al 2019].

***PTEN*-specific laboratory technical considerations.** *PTEN* has a highly homologous pseudogene (*PTENP1)* on chromosome 9 [Dahia et al 1998]. Special consideration should be taken when designing *PTEN*-specific primers to ensure specificity and to avoid cross-amplification of this pseudogene [Ngeow & Eng 2016].

**Table 6.** Notable *PTEN* Pathogenic Variants

| Reference Sequences | DNA Nucleotide Change | Predicted Protein Change | Comment [Reference] |
|---|---|---|---|
| NM_000314.8<br>NP_000305.3 | c.388C>T | p.Arg130Ter | Recurrent pathogenic variants [Yehia et al 2019] |
| | c.697C>T | p.Arg233Ter | |
| | c.1003C>T | p.Arg335Ter | |

Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.
*GeneReviews* follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.

## Cancer and Benign Tumors

**Sporadic cancers** (including endometrial cancer, prostate cancer, glioblastoma) occurring as single tumors in the absence of any other findings of PHTS frequently harbor somatic variants in *PTEN* that are **not** present in the germline. Somatic *PTEN* variants and loss of gene expression are frequently found in both endometrioid endometrial adenocarcinoma and precancerous endometrial lesions (intraepithelial neoplasia) [Mutter et al 2000]. In these circumstances predisposition to these tumors is not heritable.

# Chapter Notes

## Author Notes

Dr Eng is the chair and coordinator of the International Cowden Syndrome Consortium, founding Chairwoman of the Cleveland Clinic Genomic Medicine Institute, and a primary researcher in the field of *PTEN*-related disorders. Dr Yehia is an Ambrose Monell Foundation Cancer Genomic Medicine Fellow at the Cleveland Clinic Genomic Medicine Institute. The Cleveland Clinic Genomic Medicine Institute program features the only

multidisciplinary Cowden Syndrome center in the US, with ongoing clinical and molecular research protocols in PHTS.

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- 11 February 2021 (sw) Comprehensive update posted live
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- 23 January 2014 (me) Comprehensive update posted live
- 19 April 2012 (ce) Somatic *AKT1* pathogenic variants reported to result in Proteus syndrome [Lindhurst et al 2011]
- 21 July 2011 (me) Comprehensive update posted live
- 5 May 2009 (me) Comprehensive update posted live
- 10 January 2006 (me) Comprehensive update posted live
- 19 May 2004 (ce) Revision: Genetic Counseling
- 17 December 2003 (me) Comprehensive update posted live
- 23 May 2003 (ce) Revision: Differential Diagnosis
- 29 November 2001 (me) Review posted live
- 10 July 2001 (ce) Original submission

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