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***PTEN* Hamartoma Tumor Syndrome (PHTS)**

Includes: Bannayan-Riley-Ruvalcaba Syndrome (Bannayan-Ruvalcaba-Riley Syndrome, Bannayan-Zonana Syndrome, Riley-Smith Syndrome, Ruvalcaba-Myhre-Smith Syndrome), Cowden Syndrome, Proteus Syndrome, Proteus-Like Syndrome

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Summary

Disease characteristics. The *PTEN* hamartoma tumor syndrome (PHTS) includes Cowden syndrome (CS), Bannayan-Riley-Ruvalcaba syndrome (BRRS), Proteus syndrome (PS), and Proteus-like syndrome. 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 (usually follicular, rarely papillary, but never medullary thyroid cancer) is approximately 10%. The risk for endometrial cancer, although not well defined, may approach 5%-10%. 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 made only when a *PTEN* mutation is identified. Up to 85% of individuals who meet the diagnostic criteria for CS and 65% of individuals with a clinical diagnosis of BRRS have a detectable *PTEN* mutation. Preliminary data also suggest that up to 50% of individuals with a Proteus-like syndrome and up to 20% of individuals with Proteus syndrome have *PTEN* mutations. *PTEN* sequence analysis, deletion/duplication testing, and FISH testing are available on a clinical basis.

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

Surveillance: Because the most serious consequences of PHTS relate to the increased risk of breast, thyroid, endometrial, and renal cancers, the most important aspect of management of an individual with a *PTEN* mutation is increased cancer surveillance. Surveillance in general for individuals with *PTEN* mutations includes annual physical examination from age 18 years, annual urinalysis, and baseline colonoscopy at age 50 years. Specific surveillance for breast cancer in individuals with CS includes monthly self-examination beginning at age 18 years (for females and males), annual clinical breast examinations beginning at age 25 years, and annual mammography and breast MRI beginning at age 30-35 years, or five to ten years earlier than the youngest age at diagnosis of breast cancer in the family; surveillance for thyroid cancer includes baseline thyroid ultrasound examination at age 18 years and annual thyroid examination; surveillance for endometrial cancer includes annual suction biopsies beginning at age 35-40 years for premenopausal women and annual transvaginal ultrasound examination for postmenopausal women.

Testing of relatives at risk: When a *PTEN* mutation has been identified in a proband, molecular genetic testing of asymptomatic at-risk relatives can identify those who have the family-specific mutation 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 mutation and developing PHTS. Prenatal testing for pregnancies at increased risk is possible if the disease-causing mutation in the family is known.

Diagnosis

Clinical Diagnosis

A presumptive diagnosis of *PTEN* hamartoma tumor syndrome (PHTS) is based on clinical signs; by definition, however, the diagnosis of PHTS is made only when a *PTEN* mutation is identified.

Cowden syndrome (CS). Consensus diagnostic criteria for CS have been developed [Eng 2000] and are updated each year by the [National Comprehensive Cancer Network \[NCCN 2006\]](#). See [Guidelines](#). Clinical criteria have been divided into three categories: pathognomonic, major, and minor.

Pathognomonic criteria

- Adult Lhermitte-Duclos disease (LDD), defined as the presence of a cerebellar dysplastic gangliocytoma [Zhou et al 2003a]
- Mucocutaneous lesions (Figures 1, 2):
 - 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 ≥ 97 th percentile)
- Endometrial carcinoma

Minor criteria

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

An operational diagnosis of CS is made if an individual meets **any one** of the following criteria:

- Pathognomonic mucocutaneous lesions combined with one of the following:
 - Six or more facial papules, of which three or more must be trichilemmoma
 - Cutaneous facial papules and oral mucosal papillomatosis
 - Oral mucosal papillomatosis and acral keratoses
 - Six or more palmo-plantar 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 diagnosis of CS if they meet **any one** of the following criteria:

- The pathognomonic criteria
- 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, and pigmented macules of the glans penis [Gorlin et al 1992].

Proteus syndrome (PS) is highly variable and appears to affect individuals in a mosaic distribution (i.e., only some organs/tissues are affected). Thus, it is frequently misdiagnosed despite the development of consensus diagnostic criteria [Biesecker et al 1999]. Mandatory general criteria for diagnosis include mosaic distribution of lesions, progressive course, and sporadic occurrence.

Additional specific criteria for diagnosis include:

- Connective tissue nevi (pathognomonic)

OR two of the following:

- Epidermal nevus
- Disproportionate overgrowth (one or more)
 - Limbs: arms/legs; hands/feet/digits
 - Skull: hyperostoses
 - External auditory meatus: hyperostosis
 - Vertebrae: megalospondylodysplasia
 - Viscera: spleen/thymus
- Specific tumors before end of second decade (either one)
 - Bilateral ovarian cystadenomas
 - Parotid monomorphic adenoma

OR three of the following:

- Dysregulated adipose tissue (either one)
 - Lipomas
 - Regional absence of fat
- Vascular malformations (one or more)
 - Capillary malformation
 - Venous malformation
 - Lymphatic malformation
- Facial phenotype
 - Dolichocephaly
 - Long face
 - Minor downslanting of palpebral fissures and/or minor ptosis
 - Low nasal bridge

- Wide or anteverted nares
- Open mouth at rest

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

Testing

Pathologic review is essential in confirming the appropriate histopathology of the characteristic dermatologic, thyroid, breast, endometrial, and colonic lesions that can be seen with PHTS.

Molecular Genetic Testing

Gene. *PTEN* is the only gene in which mutations are known to cause *PTEN* hamartoma tumor syndrome (PHTS).

Clinical testing

- **Sequence analysis.** Virtually all missense mutations in *PTEN* are believed to be deleterious [Eng 2003; Zbuk & Eng 2007; Eng, unpublished data].
 - Early studies suggest that up to 85% of individuals who meet the diagnostic criteria for CS [Marsh et al 1998, Zhou et al 2003b] and 65% of individuals with a clinical diagnosis of BRRS [Marsh et al 1999, Zhou et al 2003b] have a detectable *PTEN* mutation [Zbuk & Eng 2007]. More recently, it was found that approximately 25% of individuals who meet the strict diagnostic criteria for CS have a pathogenic *PTEN* mutation, including large deletions [Tan et al 2011]. Of note, Tan et al [2011] did not consider all variants of unknown significance; therefore, the estimate of 25% is very conservative.

Note: The discrepancy between the early studies and the more recent study of Tan et al [2011] is likely explained by the early studies analyzing CS that segregated in families and individuals with the most obvious phenotypes. The early series comprised part of the series that mapped and identified the gene.

- Data suggest that up to 50% of individuals with a Proteus-like syndrome and up to 20% of individuals with Proteus syndrome have *PTEN* mutations [Zhou et al 2001a, Smith et al 2002, Eng 2003, Loffeld et al 2006, Orloff & Eng 2008].

Note: In the Thiffault et al [2004] study, no *PTEN* mutations were detected in individuals with Proteus syndrome, potentially signaling the existence of other genes in this syndrome or the relative insensitivity of the mutation detection technique used.
- **Deletion/duplication analysis.** Southern blotting, real-time PCR, MLPA and other methods of detecting gene copy number variation can each be used to detect large *PTEN* deletions and rearrangements that are not detectable by PCR-based sequence analysis.
 - It was previously believed that individuals with CS do not harbor large deletions; however, individuals with CS who have such deletions have been reported [Zbuk & Eng 2007, Orloff & Eng 2008, Tan et al 2011].
 - Approximately 10% of individuals with BRRS who do not have a mutation detected in the *PTEN* coding sequence have large deletions within or encompassing *PTEN* [Zhou et al 2003b].

Research testing

- **Promoter analysis.** Direct sequencing of the promoter region detects mutations that alter the function of the gene in approximately 10% of those individuals with CS who do not have an identifiable mutation in the *PTEN* coding region [Zhou et al 2003b].

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

Gene Symbol	Test Method	Mutations Detected	Mutation Detection Frequency by Test Method and Phenotype ¹				Test Availability
			CS	BRRS	PLS	PS	
<i>PTEN</i>	Sequence analysis	Sequence variants ²	80%	60%	50%	20%	Clinical
	Deletion/ duplication analysis ³	Exonic or whole-gene deletions	See footnote 4	11% ⁵	Unknown	Unknown	Testing
	Promoter analysis	Promoter mutations	10% ^{5, 6}	See footnote 4	Unknown	Unknown	Research only

Test Availability refers to availability in the GeneTests Laboratory Directory. *GeneReviews* designates a molecular genetic test as clinically available only if the test is listed in the GeneTests Laboratory Directory by either a US CLIA-licensed laboratory or a non-US clinical laboratory. GeneTests does not verify laboratory-submitted information or warrant any aspect of a laboratory's licensure or performance. Clinicians must communicate directly with the laboratories to verify information.

CS= Cowden syndrome

BRRS= Bannayan-Riley-Ruvalcaba syndrome

PLS= Proteus-like syndrome

PS= Proteus syndrome

1. The ability of the test method used to detect a mutation that is present in the indicated gene

2. Examples of mutations detected by sequence analysis may include small intragenic deletions/insertions and missense, nonsense, and splice site mutations.

3. Testing that detects deletions/duplications not readily detectable by sequence analysis of genomic DNA; a variety of methods including quantitative PCR, real-time PCR, multiplex ligation-dependent probe amplification (MLPA), or array GH may be used.

4. Finite but unknown

5. Zhou et al [2003b]

6. 10% of individuals with CS phenotype who do not have an identifiable sequence variant

Interpretation of test results. Failure to detect a mutation does not exclude a clinical diagnosis of CS, BRRS, PS, or Proteus-like syndrome in an individual with significant signs associated with these disorders.

For issues to consider in interpretation of sequence analysis results, click [here](#).

Information on specific allelic variants may be available in Molecular Genetics (Table A and/or Pathologic allelic variants).

Testing Strategy

To confirm/establish the diagnosis in a proband requires *PTEN* molecular genetic testing.

Based on clinical and demographic features in 3042 probands with Cowden syndrome and Cowden-like syndrome, the *PTEN* Cleveland Clinic Risk Calculator provides the prior probability of finding a *PTEN* mutation in children and adults (www.lerner.ccf.org/gmi/ccscore/). It is recommended that clinical testing be considered for adults with a *PTEN* Cleveland Clinic Score of ≥ 10 . Of note, this is the first risk calculator designed specifically to assess children as well.

The order of testing to optimize yield would be:

1. Sequencing of *PTEN* exons 1-9 and flanking intronic regions
2. *PTEN* promoter analysis (research)
3. *PTEN* deletion/duplication analysis
4. *KLLN* promoter methylation analysis (research) [Bennett et al 2010] (see [Differential Diagnosis](#))
5. *SDHB-D* analysis (research) [Bennett et al 2010] (see [Differential Diagnosis](#))

Predictive testing for at-risk asymptomatic family members (including children) requires prior identification of the disease-causing mutation in the family.

Prenatal diagnosis and preimplantation genetic diagnosis (PGD) for at-risk pregnancies require prior identification of the disease-causing mutation in the family.

Note: It is the policy of *GeneReviews* to include clinical uses of testing available from laboratories listed in the GeneTests Laboratory Directory; inclusion does not necessarily reflect the endorsement of such uses by the author(s), editor(s), or reviewer(s).

Genetically Related (Allelic) Disorders

No phenotypes other than Cowden syndrome, Bannayan-Riley-Ruvalcaba syndrome, Proteus syndrome, and Proteus-like syndrome are known to be **consistently** caused by mutations in *PTEN*.

Phenotypes that can be associated with *PTEN* germline mutations:

- **Lhermitte-Duclos disease (LDD)**. Most, if not all, adult-onset Lhermitte-Duclos disease (dysplastic gangliocytoma of the cerebellum, a hamartomatous overgrowth known to be a feature of CS) can be attributed to mutations in *PTEN*, even in the absence of other clinical signs of CS/BRRS. However, germline *PTEN* mutations appear to be rare in individuals with childhood-onset LDD [Zhou et al 2003a].
- **Autism/pervasive developmental disorder and macrocephaly**. Germline *PTEN* mutations were identified in individuals with these findings, especially in the presence of other personal or family history consistent with CS/BRRS [Dasouki et al 2001, Goffin et al 2001]. Butler et al [2005] found that approximately 20% of individuals with autism spectrum disorders and macrocephaly have germline *PTEN* mutations. The 10%-20% prevalence of germline *PTEN* mutations in autism spectrum disorders with macrocephaly has now been confirmed by several independent groups [Herman et al 2007a, Herman et al 2007b, Orrico et al 2009, Varga et al 2009].

Clinical Description

Natural History

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

- CS is a multiple hamartoma syndrome with a high risk of benign and malignant tumors of the thyroid, breast, and endometrium.
- BRRS is a congenital disorder characterized by macrocephaly, intestinal polyposis, lipomas, 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 third 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 dolicocephaly.

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* mutation [Eng 2003, McGarrity et al 2003].

Tumor risk. Individuals with CS have a high risk of breast, thyroid, and endometrial cancers. As with other hereditary cancer syndromes, the risk of multifocal and bilateral (in paired organs such as the breasts) cancer is increased:

- **Breast disease**
 - Women with Cowden syndrome have as high as a 67% risk for benign breast disease.
 - The lifetime risk to females of developing breast cancer is 25%-50%, with an average age of diagnosis between 38 and 46 years [Brownstein et al 1978, Starink et al 1986]. Although breast cancer was described in males with a *PTEN* mutation [Fackenthal et al 2001], it was not observed in a recent study of more than 3000 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 thyroid cancer (usually follicular, rarely papillary, but never medullary thyroid cancer) is approximately 10% [Zbuk & Eng 2007]. It is not clear if the age of diagnosis of thyroid cancer is earlier than in the general population.
- **Endometrial disease**
 - Benign uterine fibroids are common.
 - Risk for endometrial cancer, although not well defined, may approach 5%-10%.
- **Other**
 - Skin cancers, renal cell carcinomas, and 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.
 - Although hamartomatous polyps may occur in the gastrointestinal tract, it is felt that the risk for colorectal cancer is not increased; unlike BRRS polyps, the polyps in CS are rarely symptomatic.

Bannayan-Riley-Ruvalcaba syndrome (BRRS). Common features of BRRS, in addition to those mentioned above, 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%) [Gorlin et al 1992, Zbuk & Eng 2007].

Although cancer was initially not believed to be a component of the syndrome, individuals with BRRS and *PTEN* mutations are currently thought to have the same cancer risks as individuals with CS [Marsh et al 1999]. It is not clear whether these risks apply to individuals with BRRS who do not have *PTEN* mutations.

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.

Juvenile polyposis of infancy (JPI), in this rare condition, caused by germline deletion of *BMPR1A* and *PTEN*, juvenile polyposis is diagnosed before age six years [Delnatte et al 2006]. Often the gastrointestinal manifestations of bleeding, diarrhea, and protein-losing enteropathy are severe. External stigmata may mimic BRRS.

Proteus syndrome (PS) is a complex disorder comprising malformations and hamartomatous overgrowth of multiple tissues, connective tissue nevi, epidermal nevi, and hyperostoses. The manifestations are commonly present at birth and persist or progress postnatally. Tumors or malignancies are not frequently reported in PS. However, certain unusual tumor types, such as cystadenoma of the ovary, various types of testicular tumors, central nervous system tumors, and parotid monomorphic adenomas, are occasionally associated with PS and therefore can be of diagnostic value when present. PS is uncommon; approximately 120 affected individuals have been reported [Cohen 1999].

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

Genotype-Phenotype Correlations

For purposes of 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* mutation are more likely to develop malignant breast disease than are families who do not have a *PTEN* mutation [Marsh et al 1998]. In addition, missense mutations and mutations 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].

The mutational spectra of BRRS and CS have been shown to overlap, thus lending formal proof that CS and BRRS are allelic [Marsh et al 1999]. No difference in mutation frequencies was observed between BRRS occurring in a single individual in a family and BRRS occurring in multiple family members. More than 90% of families with CS-BRRS overlap were found to have germline *PTEN* mutations. In addition, the presence of *PTEN* mutations in BRRS was associated with the development of lipomas and tumors of the breast [Marsh et al 1999]. Therefore, individuals with BRRS and *PTEN* mutations may have increased cancer risks (despite the fact that this syndrome was previously not believed to be associated with malignancy).

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.Arg335X *PTEN* mutation and the same somatic mutation (p.Arg130X) in three separate tissues, possibly representing germline mosaicism [Zhou et al 2000]. Both mutations have been previously described in classic CS and BRRS.

Two of nine individuals with Proteus syndrome and three of six with Proteus-like syndrome were found to have germline *PTEN* mutations [Zhou et al 2001a]. Since then multiple single cases of germline *PTEN* mutations in Proteus and Proteus-like syndrome have been reported [Smith et al 2002, Loffeld et al 2006].

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, Zbuk & Eng 2007]. By the third decade, 99% of affected individuals develop the mucocutaneous stigmata, primarily trichilemmomas and papillomatous papules, as well as acral and plantar keratoses.

Anticipation

Anticipation is not observed.

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* mutation 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* mutation, was termed SOLAMEN (segmental overgrowth, lipomatosis, arteriovenous malformation and epidermal nevus) syndrome [Caux et al 2007]. This is not useful, especially in the molecular era, as any phenotype associated with a *PTEN* mutation should be termed PHTS with all its implications for clinical management [Zbuk & Eng 2007, Orloff & Eng 2008].

Prevalence

Because the diagnosis of CS is difficult to establish, the true prevalence is unknown. The prevalence has been estimated at one in 200,000 [Nelen et al 1999]; this is likely an underestimate. Because of the variable and often subtle external manifestations of CS/BRRS, many individuals remain undiagnosed [Haibach et al 1992; Schragger et al 1998; Zbuk & Eng 2007; Eng, unpublished].

Differential Diagnosis

For current information on availability of genetic testing for disorders included in this section, see GeneTests Laboratory Directory. —ED.

Germline *KLLN* epimutation. Bennett et al [2010] determined that approximately 30% of individuals with Cowden syndrome (CS) and Cowden-like syndrome who do not have a *PTEN* germline mutation have a germline *KLLN* epimutation, which resulted in down-regulation of expression of *KLLN*, but not *PTEN*. Of note, *KLLN* shares a bidirectional promoter with *PTEN*. Pilot data suggest that individuals with CS and Cowden-like syndrome with a germline *KLLN* epimutation have a greater prevalence of breast and renal cell carcinomas than do those with germline *PTEN* mutations. Thus, individuals with Cowden-like syndrome (especially breast and/or renal carcinomas in the individual and/or family) should be offered *KLLN* methylation analysis first because it accounts for 30% of such individuals, whereas *PTEN* germline mutations account for 5%-10%.

New susceptibility genes in individuals with non-PHTS CS and a CS-like disorder. A pilot study found that individuals with CS and a CS-like disorder without germline *PTEN* mutations, but with increased levels of manganese superoxide dismutase, harbored germline variants in *SDHB* and *SDHD* [Ni et al 2008].

The primary differential diagnoses to consider are other hamartoma syndromes, including juvenile polyposis syndrome (JPS) and Peutz-Jeghers syndrome (PJS), both inherited in an autosomal dominant manner.

Juvenile polyposis syndrome (JPS) is characterized by predisposition for hamartomatous polyps in the gastrointestinal tract, specifically in the stomach, small intestine, colon, and rectum. The term "juvenile" refers to the type of polyp, not the age of onset of polyps. Juvenile polyps are hamartomas that show a normal epithelium with a dense stroma, an inflammatory infiltrate, and a smooth surface with dilated, mucus-filled cystic glands in the lamina propria.

Most individuals with JPS have some polyps by age 20 years. Some individuals may have only four or five polyps over a lifetime, whereas others in the same family may have more than one hundred. If the polyps are left untreated, they may cause bleeding and anemia. Most juvenile polyps are benign; however, malignant transformation can occur.

Approximately 20% of individuals with JPS have mutations in *MADH4*; another approximately 20% have mutations in *BMPR1A* [Howe et al 1998, Howe et al 2001]:

- Prior case reports have claimed that germline *PTEN* mutations can occur in individuals with JPS [Olschwang et al 1998, Huang et al 2000]. However, closer

inspection of these probands revealed that one likely had CS, another was too young for CS to be clinically excluded, and for the third it is suspected that thorough examination would have revealed signs of PHTS, since little clinical information was provided. Indeed, in a systematic study of individuals with the diagnosis of JPS examined for germline *PTEN* mutations, one individual with JPS was found to have a germline *PTEN* mutation [Kurose et al 1999]. Upon re-examination of this individual, clinical features of CS were identified [Kurose et al 1999].

- Conversely, a germline *BMPR1A* mutation was identified in an individual with only colonic polyposis but a family history suggestive of Cowden syndrome. Although this could suggest that *BMPR1A* may be responsible for a small proportion of CS/BRRS-like cases, the authors felt that on the basis of the mutation status this individual should be classified as having JPS [Zhou et al 2001b].

Peutz-Jeghers syndrome (PJS) is characterized by the association of gastrointestinal polyposis and mucocutaneous pigmentation. PJS-type hamartomatous polyps are most prevalent in the small intestine, but also occur in the stomach and large bowel in the majority of affected individuals. The Peutz-Jeghers polyp has a diagnostic appearance and is quite different from the hamartomatous polyps seen in CS or JPS. Clinically, Peutz-Jeghers polyps are often symptomatic (intussusception, rectal bleeding), whereas CS polyps are rarely so.

The pigmentation of the perioral region is pathognomonic, particularly if it crosses the vermilion border. Hyperpigmented macules on the fingers are also common.

Molecular genetic testing of *STK11* reveals disease-causing mutations in approximately 70% of individuals who have a positive family history and 20%-70% of individuals who have no family history of PJS.

Other, less likely, differential diagnoses to consider for PHTS:

- **Birt-Hogg-Dubé syndrome (BHD)** is characterized by cutaneous findings (fibrofolliculomas, trichodiscomas, and acrochordons), pulmonary cysts/history of pneumothorax, and renal tumors (most commonly renal oncocytoma, chromophobe renal cell carcinoma, or a hybrid of oncocytoma and chromophobe histologic cell types). Disease severity can vary significantly. Skin lesions typically appear during the third or fourth decade of life and increase in size and number with age. Lung cysts are mostly bilateral and multifocal; most individuals are asymptomatic but have a high risk for spontaneous pneumothorax. Approximately 15% of individuals with BHD syndrome have renal tumors; median age of tumor diagnosis is 48 years. *FLCN*, the gene encoding folliculin, is the only gene known to be associated with BHD. Inheritance is autosomal dominant.
- **Neurofibromatosis type 1 (NF1)**. The only two features seen in both NF1 and CS/BRRS are café-au-lait macules and fibromatous tumors of the skin. The diagnosis of NF1 is sometimes mistakenly given to individuals with CS/BRRS because of the presence of ganglioneuromas in the gastrointestinal tract.
- **Nevoid basal cell carcinoma (Gorlin) syndrome** is characterized by basal cell nevi, basal cell carcinoma, and diverse developmental abnormalities. Affected individuals can also develop other tumors and cancers including fibromas, hamartomatous gastric polyps, and medulloblastomas. However, the dermatologic findings and developmental features in CS and nevoid basal cell carcinoma (Gorlin) syndrome are quite different.

Note to clinicians: For a patient-specific 'simultaneous consult' related to this disorder, go to [SimulConsult®](#), an interactive diagnostic decision support software tool that provides differential diagnoses based on patient findings (registration or institutional access required).

- [Bannayan-Riley-Ruvalcaba syndrome](#)
- [Cowden syndrome](#)
- [Proteus syndrome](#)

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease in an individual diagnosed with *PTEN* hamartoma tumor syndrome (PHTS), the following evaluations are recommended:

- Complete history, especially family history
- Physical examination with **particular** attention to:
 - Skin
 - Mucous membranes
 - Thyroid
 - Breasts
- Urinalysis with cytospin
- Baseline thyroid ultrasound examination at age 18 years or five years younger than the earliest age at thyroid cancer diagnosis in the family
- Genetics consultation

Treatment of Manifestations

The mucocutaneous manifestations of Cowden syndrome are rarely life threatening:

- If asymptomatic, observation alone is prudent.
- When symptomatic, 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 cheloid formation and recurrence (often rapid) of the lesions [Eng, unpublished data].

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

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 of endometrial cancer associated with tamoxifen use in a population already at increased risk for endometrial cancer.

Surveillance

The most serious consequences of PHTS relate to the increased risk of cancers including breast, thyroid, endometrial, and to a lesser extent, renal. In this regard, the most important aspect of management of **any** individual with a *PTEN* mutation is increased cancer surveillance.

Cowden Syndrome

General. Annual comprehensive physical examination starting at age 18 years (or five years before the youngest component cancer diagnosis in the family), with attention paid to skin changes and the neck region:

- Consider annual dermatologic examination
- Annual urinalysis. Consider annual cytology and renal ultrasound examination if the family history is positive for renal cell carcinoma
- Baseline colonoscopy at age 50 years (unless symptoms arise earlier). If only hamartomas are found, the American Cancer Society guidelines for colon cancer screening (i.e., annual fecal occult blood testing and sigmoidoscopy every five years or colonoscopy every ten years) should be followed.

Breast cancer

- **Women** [Eng 2000, NCCN 2006]:
 - Monthly breast self-examination beginning at age 18 years
 - Annual clinical breast examinations beginning at age 25 years or five to ten years younger than earliest known breast cancer diagnosis in the family (whichever is earliest)
 - Annual mammography and breast MRI beginning at age 30-35 years or five to ten years younger than the earliest known breast cancer diagnosis in the family (whichever is earliest)
- **Men** should perform monthly breast self-examination.

Thyroid cancer

- Baseline thyroid ultrasound examination at age 18 years or five years younger than earliest age at thyroid cancer diagnosis in family
- Consider annual thyroid ultrasound examination thereafter (although annual neck examination may be sufficient)

Endometrial cancer

- **Premenopausal women.** Annual blind resect (suction) biopsies beginning at age 35-40 years (or 5 years younger than the youngest endometrial cancer diagnosis in the family)
- **Postmenopausal women.** Annual transvaginal ultrasound examination with biopsy of suspicious areas

Note: Although the NCCN Guidelines removed endometrial surveillance after 2007 (without expert PHTS input), it is prudent to ensure the minimal surveillance for endometrial cancer as detailed if family history is positive for endometrial cancer.

Bannayan-Riley-Ruvalcaba Syndrome

Screening recommendations have not been established for BRRS. Given recent molecular epidemiologic studies, however, individuals with BRRS and a germline *PTEN* mutation should undergo the same surveillance as individuals with CS.

Individuals with BRRS should also be monitored for complications related to gastrointestinal hamartomatous polyposis, which can be more severe than in CS.

Proteus Syndrome/Proteus-Like Syndrome

Although the observation of germline *PTEN* mutations in Proteus and Proteus-like syndromes is relatively new, clinicians should consider instituting the CS surveillance recommendations for individuals with these disorders who have germline *PTEN* mutations.

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.

Testing of Relatives at Risk

When a *PTEN* mutation has been identified in a proband, testing of asymptomatic at-risk relatives can identify those who have the family-specific mutation and, therefore, have PHTS. These individuals are in need of 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 Proteus syndrome. In individuals with PHTS, the earliest documented breast cancer and thyroid cancer are at age 17 years and before age nine years, respectively.

Relatives who have not inherited the *PTEN* mutation found in an affected relative do not have PHTS or its associated cancer risks.

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* mutation, use should be limited to clinical trials. At this time, one clinical trial is specifically directed at PHTS.

Search ClinicalTrials.gov for access to information on clinical studies for a wide range of diseases and conditions.

Other

Genetics clinics, staffed by genetics professionals, provide information for individuals and families regarding the natural history, treatment, mode of inheritance, and genetic risks to other family members as well as information about available consumer-oriented resources. See the GeneTests Clinic Directory.

See Consumer Resources for disease-specific and/or umbrella support organizations for this disorder. These organizations have been established for individuals and families to provide information, support, and contact with other affected individuals.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, 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. This section is not meant to address all personal, cultural, or ethical issues that individuals may face or to substitute for consultation with a genetics professional. To find a genetics or prenatal diagnosis clinic, see the GeneTests Clinic Directory.

Mode of Inheritance

PTEN hamartoma tumor syndrome (PHTS) is inherited in an autosomal dominant manner.

Risk to Family Members

Parents of a proband. Because Cowden syndrome (CS) is likely underdiagnosed, the actual proportion of simplex cases (defined as individuals with no obvious family history) and familial cases (defined as two or more related affected individuals) cannot be determined:

- From the literature and the experience of both major CS centers in the US, the majority of individuals with CS have no obvious family history. As a broad estimate, perhaps 10%-50% of individuals with CS have an affected parent [Marsh et al 1999].
- The majority of evidence suggests that *PTEN* mutations occur in both simplex and familial occurrences of Bannayan-Riley-Ruvalcaba syndrome (BRRS) [Eng 2003, Zbuk & Eng 2007].
- If a *PTEN* mutation is identified in the proband, the parents should be offered molecular genetic testing to determine if one of them has previously unidentified PHTS. If no mutation is identified in the proband, both parents should undergo thorough clinical examination to help determine if either parent has signs of PHTS.

Note: Although some individuals diagnosed with PHTS have an affected parent, the family history 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 disease in the affected parent.

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 PHTS, the risk to sibs is 50%.
- If it has been shown that neither parent has the *PTEN* mutation found in the proband, the risk to sibs is probably negligible, as germline mosaicism has not been reported in PHTS.
- If a mutation cannot be identified in the proband, PHTS can be excluded on clinical grounds. Normal clinical examinations in parents in their thirties done looking specifically for signs of CS/BRRS would make the risk to sibs of the proband minimal, since an estimated 99% of affected individuals have signs by that age.

Offspring of a proband. Each child of an affected individual has a 50% chance of inheriting the mutation and developing PHTS.

Other family members of a proband. The risk to other family members depends on the genetic status of the proband's parents. If a parent is affected, his or her family members are at risk.

Related Genetic Counseling Issues

See Management, [Testing Relatives at Risk](#) for information on testing at-risk relatives for the purpose of early diagnosis and treatment.

Testing of at-risk relatives. When a mutation has been identified in a proband, testing of asymptomatic at-risk relatives can identify those who also have the mutation and have PHTS. These individuals are in need of 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 Proteus syndrome.

Considerations in families with an apparent *de novo* mutation. When neither parent of a proband with an autosomal dominant condition has the disease-causing mutation or clinical evidence of the disorder, it is likely that the proband has a *de novo* mutation. However, possible non-medical explanations, including alternate paternity or maternity (e.g., with assisted reproduction) or undisclosed adoption could also be explored.

Genetic cancer risk assessment and counseling. For comprehensive descriptions of the medical, psychosocial, and ethical ramifications of identifying at-risk individuals through cancer risk assessment with or without molecular genetic testing, see [Elements of Cancer Genetics Risk Assessment and Counseling](#) (part of PDQ®, National Cancer Institute).

Family planning

- The optimal time for determination of genetic risk and discussion of the availability of prenatal 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.

DNA banking is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methodology and our understanding of genes, mutations, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals. See [Testing](#) for a list of laboratories offering DNA banking.

Prenatal Testing

Prenatal diagnosis for pregnancies at increased risk is possible by analysis of DNA extracted from fetal cells obtained by amniocentesis usually performed at approximately 15 to 18 weeks' gestation or chorionic villus sampling (CVS) at approximately ten to 12 weeks' gestation. The disease-causing allele of an affected family member must be identified before prenatal testing can be performed.

Note: Gestational age is expressed as menstrual weeks calculated either from the first day of the last normal menstrual period or by ultrasound measurements.

Preimplantation genetic diagnosis (PGD) may be available for families in which the disease-causing mutation has been identified. For laboratories offering PGD, see [Testing](#).

Note: It is the policy of *GeneReviews* to include clinical uses of testing available from laboratories listed in the GeneTests Laboratory Directory; inclusion does not necessarily reflect the endorsement of such uses by the author(s), editor(s), or reviewer(s).

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 Symbol	Chromosomal Locus	Protein Name	Locus Specific	HGMD
PTEN	10q23 .3	Phosphatidylinositol-3,4,5-trisphosphate 3-phosphatase and dual-specificity protein phosphatase PTEN	Catalogue of Somatic Mutations in Cancer (COSMIC)	PTEN

Data are compiled from the following standard references: gene symbol from HGNC; chromosomal locus, locus name, critical region, complementation group from OMIM; protein name from UniProt. For a description of databases (Locus Specific, HGMD) linked to, click [here](#).

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

153480	BANNAYAN-RILEY-RUVALCABA SYNDROME; BRRS
158350	COWDEN DISEASE; CD
176920	PROTEUS SYNDROME

Molecular Genetic Pathogenesis

While much functional research has been accomplished, complete function of PTEN is not yet fully understood. PTEN belongs to a sub-class 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. In vitro and human immunohistochemical data suggest that PTEN trafficks in and out of the nucleus [Ginn-Pease & Eng 2003, Chung et al 2005, Minaguchi et al 2006]. When PTEN is in the nucleus, it predominantly signals down the protein phosphatase and MAPK pathway to elicit cell cycle arrest [Chung & Eng 2005]. One of the nuclear functions of PTEN is to stabilize the genome [Shen et al 2007]. When in the cytoplasm, its lipid phosphatase predominantly signals down the AKT pathway to illicit apoptosis.

Somatic *PTEN* mutations and loss of gene expression are frequently found in both endometrioid endometrial adenocarcinoma and precancerous endometrial lesions (intraepithelial neoplasia), confirming the critical role that *PTEN* must play in endometrial tissues [Mutter et al 2000].

Normal allelic variants. The gene comprises nine exons and likely spans a genomic distance of more than 120 kb. The 1209-bp coding sequence is predicted to encode a 403-amino acid protein.

Pathologic allelic variants. Germline mutations have been found throughout *PTEN* (with the exception of exon 9) and include missense and nonsense mutations, splice site mutations, small deletions, insertions, and several large deletions. More than 150 unique mutations are currently listed in the Human Gene Mutation Database (see Table A). Nearly 40% of mutations are found in exon 5, which encodes the phosphate core motif [Eng 2003]. Most mutations are unique, although a number of recurrent mutations (particularly p.Arg130X, p.Arg233X, and p.Arg335X) have been reported (see Table 2) [Bonneau & Longy 2000, Zbuk & Eng 2007, Orloff & Eng 2008].

Table 2. Selected *PTEN* Pathologic Allelic Variants

DNA Nucleotide Change	Protein Amino Acid Change	Reference Sequences
c.388C>T	p.Arg130X	NM_000314 .4 NP_000305 .3
c.697C>T	p.Arg233X	
c.1003C>T	p.Arg335X	

See Quick Reference for an explanation of nomenclature. *GeneReviews* follows the standard naming conventions of the Human Genome Variation Society (www.hgvs.org).

Approximately 10% of individuals with CS who do not have a mutation detected in the *PTEN* coding sequence have heterozygous germline mutations in the *PTEN* promoter [Zhou et al 2003b]. In contrast, 10% of individuals with BRRS who do not have an identifiable *PTEN* mutation on sequence analysis have large deletions within or encompassing *PTEN* [Zhou et al 2003b].

Normal gene product. *PTEN* encodes an almost ubiquitously expressed dual specificity phosphatase. 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 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 [Eng 2003]. It appears that nuclear PTEN mediates cell cycle arrest, while cytoplasmic PTEN is required for apoptosis [Chung & Eng 2005].

Abnormal gene product. The majority (76%) of germline mutations in *PTEN* result in either truncated protein, lack of protein (haploinsufficiency), or dysfunctional protein. Many missense mutations are functionally null and several act as dominant negatives. When PTEN is absent, decreased, or dysfunctional, phosphorylation of Akt 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 [Eng 2003].

Resources

See *Consumer Resources for disease-specific and/or umbrella support organizations for this disorder. These organizations have been established for individuals and families to provide information, support, and contact with other affected individuals. GeneTests provides information about selected organizations and resources for the benefit of the reader; GeneTests is not responsible for information provided by other organizations.*—ED.

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Medical Genetic Searches: A specialized PubMed search designed for clinicians that is located on the PubMed Clinical Queries page [PubMed](#)

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Chapter Notes

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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. The Cleveland Clinic Genomic Medicine Institute program features the only Cowden Syndrome center in the US, with ongoing clinical and molecular research protocols in PHTS.

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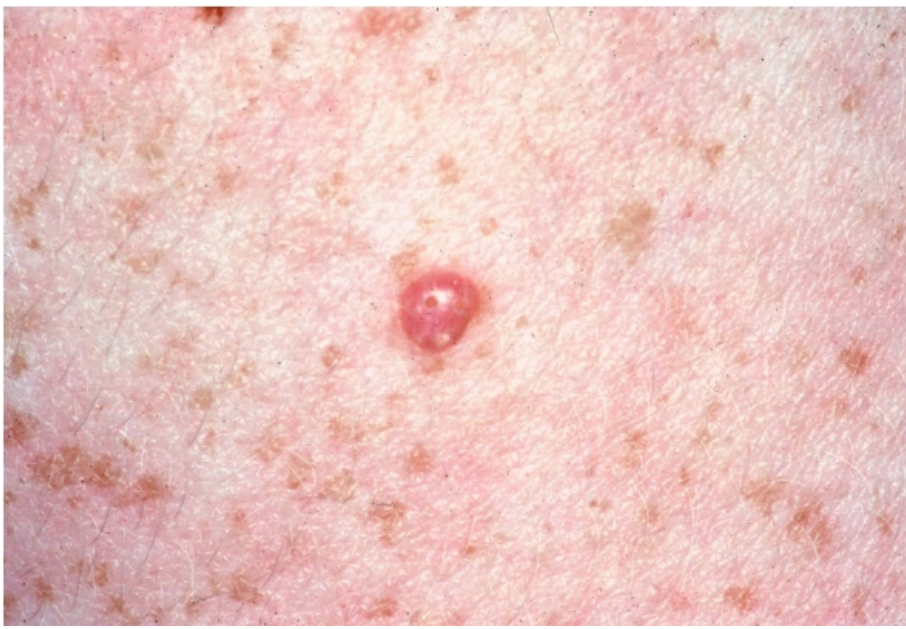


Figure 1. Trichilemmoma

Papillomatous papules



A



B

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

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