Clinical Implications for Germline *PTEN* Spectrum Disorders

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KEYWORDS

- *PTEN* • *PTEN* hamartoma tumor syndrome • Cowden syndrome

KEY POINTS

- Cowden syndrome 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 at birth, and skin features such as trichilemmomas and papillomatous papules present by the late 20s.
- The lifetime risk of developing breast cancer is 85%; the lifetime risk of thyroid cancer is approximately 35%; the lifetime risk of endometrial cancer may approach 28% and renal cancer 34%.
- The diagnosis of *PTEN* hamartoma tumor syndrome is established in a proband by identification of a heterozygous germline *PTEN* pathogenic variant on molecular genetic testing.
- When a proband is identified, genetic testing of asymptomatic at-risk relatives can identify those who have the family-specific pathogenic variant for high-risk cancer surveillance.

INTRODUCTION

PTEN-related disorders represent a group of autosomal-dominant heritable conditions associated with germline mutations in the tumor suppressor gene, *PTEN*, including Cowden syndrome (CS), Bannayan-Riley-Ruvalcaba syndrome, and Proteus-like

syndrome.[1,2] The first report of CS, the most well-documented clinical condition within this spectrum, was made in 1962 by Dr Macey Dennis and Dr Kenneth M. Lloyd describing a woman, Rachel Cowden, who presented with multiple anomalies including cystic breast disease, multinodular goiter, and oral papillomatosis.[3,4] Rachel Cowden died of metastatic breast cancer in her 30s.[3] The phenotypic spectrum of CS has expanded since its initial description as we longitudinally follow patients and their families. Increasingly, we are recognizing other manifestations associated with CS, such as autism spectrum disorders and other cancer types.[4–6]

The diagnostic criteria for CS were described initially by the International Cowden Consortium in 1995, and these criteria continue to evolve as researchers further delineate the clinical spectrum of CS (Box 1).[7] Several mucocutaneous findings are considered to be pathognomonic for CS, including trichilemmomas and other facial papules, acral keratoses, and oral papillomas.[2,4] Individuals with a diagnosis of CS were

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Box 1
National Comprehensive Cancer Network 2013 Cowden syndrome criteria

Major criteria

Breast cancer

Endometrial cancer (epithelial)

Thyroid cancer (follicular)

Gastrointestinal hamartomas (including ganglioneuromas but excluding hyperplastic polyps; >3)

Lhermitte-Duclos disease (adult)

Macrocephaly (>97th percentile: 58 cm for adult women, 60 cm for adult men)

Macular pigmentation of the glans penis

Multiple mucocutaneous lesions (any of the following):
　Multiple trihilemmomas (>3, ≥1 proven by biopsy)
　Acral keratoses (>3 palmoplantar keratotic pits and/or acral hyperkeratotic papules)
　Mucocutaneous neuromas (>3)
　Oral papillomas (particularly on tongue and gingival), multiple (>3) *or* biopsy proven *or* dermatologist diagnosed

Minor criteria

Autism spectrum disorder

Colon cancer

Esophageal glycogenic acanthosis (>3)

Lipomas (>3)

Intellectual disability (ie, intelligence quotient <75)

Renal cell carcinoma

Testicular lipomatosis

Thyroid cancer (papillary or follicular variant of papillary)

Thyroid structural lesions (eg, adenoma, multinodular goiter)

Vascular anomalies (including multiple intracranial developmental venous anomalies)

Data from Daly MB, Pilarski R, Axilbund JE, et al. Genetic/familial high-risk assessment: breast and ovarian, version 2.2015. J Natl Compr Canc Netw 2016;14(2):153–62.

traditionally thought to be at increased risk of developing benign and malignant tumors of the thyroid and breast.[5,6] Benign findings include lipomas, colonic polyps, and thyroiditis, which are commonly seen in the general population.[6,8] Other associated features such as Lhermitte-Duclos disease are less common, but are important for clinicians to know as possible "red flags" signaling a CS diagnosis. The overlap between the common benign features of CS and the presence of these features in the general population has caused difficulty in elucidating the true prevalence of CS.[2,9] Previous reports approximate an incidence of 1 in 200,000 for CS, although this is likely to be an underestimate.[2,9] In conjunction with the identification of germline *PTEN* mutations in individuals with CS,[4,10] more recent research has recognized additional cancer risks, including endometrial, colorectal, and renal carcinomas, and melanoma as well as an association between germline *PTEN* mutations and neurodevelopmental disorders such as autism spectrum disorder.[11–13]

Bannayan-Riley-Ruvalcaba syndrome, also known as Bannayan-Zonana or Riley-Smith syndrome, was first described as a disorder of pediatric onset associated with macrocephaly, lipomas, thyroiditis, hamartomatous gastrointestinal polyps, penile freckling, and vascular malformations.[4,14–17] Previous literature reported that about 60% of individuals with a diagnosis of Bannayan-Riley-Ruvalcaba syndrome carry a germline *PTEN* mutation.[4,15–17] Bannayan-Riley-Ruvalcaba syndrome has been shown to be allelic to CS by the identification of identical *PTEN* mutations in families segregating both clinical disorders.[2,15–18] Proteus and Proteus-like syndromes are associated with the overgrowth of various tissues, and individuals with both conditions have been found to carry a detectable germline *PTEN* mutation, thus expanding the clinical spectrum of *PTEN*-related disorders.[2,4,15–18]

Owing to the phenotypic variability of the heritable conditions associated with germline *PTEN* mutations, the term *PTEN* hamartoma tumor syndrome (PHTS) is used to describe all individuals, irrespective of the clinical diagnosis or syndrome, with an identified germline *PTEN* mutation.[2] Early literature estimated that about 80% of individuals with a diagnosis of CS had a germline *PTEN* mutation.[10] A study by Tan and colleagues[19] looked at a diverse cohort of individuals with CS accrued from the community and found that germline *PTEN* mutations are present in about 25% of affected individuals. It is important for clinicians to be aware of the wide spectrum of clinical features of PHTS to help differentiate a diagnosis of PHTS from other hereditary cancer syndromes.[20,21]

MOLECULAR GENETICS

The spectrum of germline mutations seen in PHTS extends throughout the coding sequence of *PTEN*. Located on human chromosome subband 10q23.3, the 9-exon *PTEN* gene encodes a 403-amino acid phosphatase with 4 major domains.[12,22,23] *PTEN* is a tumor suppressor gene that participates in the PI3K/AKT/mTOR pathway and is increasingly shown to be involved in many different cellular pathways (Fig. 1). The main canonical function of *PTEN* is to antagonize AKT by dephosphorylating phosphatidylinositol 3,4,5-triphosphate (PIP3) to phosphatidylinositol 3,4,5-diphosphate (PIP2).[24–27] Germline mutations in *PTEN* cause an upregulation of the AKT pathway leading to decreased apoptosis and increased cell growth.[24,28,29] Within the N-terminal tail are several key motifs, including the phosphatidyl-inositol-bisphosphate (PIP$_2$) binding motif and both nuclear and cytoplasmic localization sequences. The protein phosphatase domain contains the catalytic core of the protein, stretching from amino acid 123 to 130. A C2 domain facilitates membrane binding, and the PDZ-binding motif within the C-terminal tail allows protein–protein
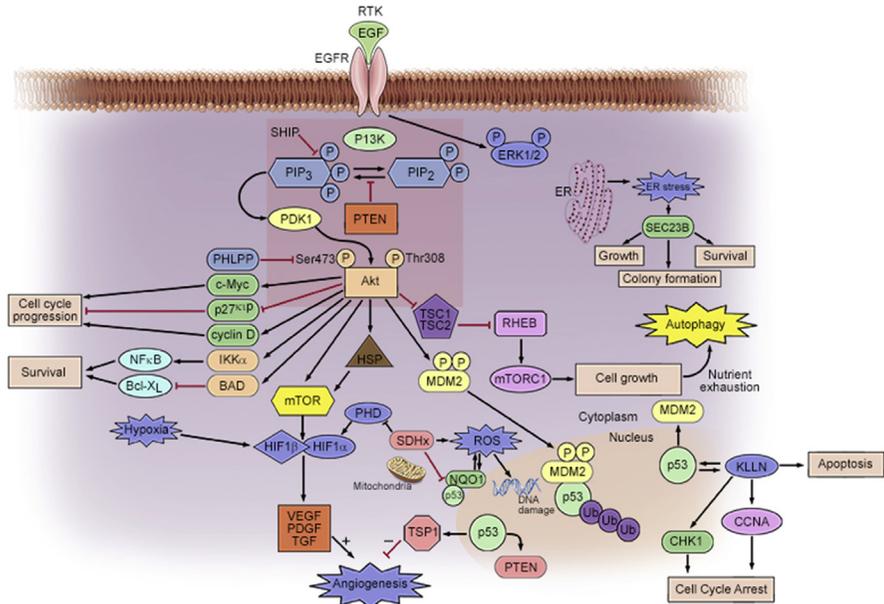
Fig. 1. *PTEN* cellular pathway involvement. Diagram depicts the canonical and non-canonical signaling involving Cowden syndrome (CS)/CS-like–related predisposition genes (*PTEN, AKT, PIK3CA, SDHx, KLLN,* and *SEC23B*). (*Adapted from* Figs. of Refs.[24–29])

interaction.[12,22–24] About one-half of the mutations in *PTEN* occur within the phosphatase domain, which is where the enzymatic activity of *PTEN* occurs. A catalytic core domain lies within the phosphatase domain, and many mutations are found within this area core motif, which disrupt its important enzymatic function.[12,22–24]

Pathogenic variants have been described in all 9 exons of *PTEN*, with various types of mutations identified, including missense, nonsense, splice site variants, intragenic deletions/insertions, and large deletions (**Fig. 2**).[23,30,31] Virtually all germline *PTEN* missense mutations within the coding region are pathogenic.[19,23] Common nonsense/frameshift mutations have been well-described in exons 5, 6, 7, and 8 of *PTEN* as well as specific truncation mutations in exons 5, 7, and 8, which are overrepresented in the *PTEN* mutation spectra[13,24] (see **Fig. 2**). The exon 5 hotspot includes the catalytic core of *PTEN*, and mutations within this 7-amino acid stretch affect probands with a wide variety of clinical presentations. Large deletions and duplications affecting *PTEN* are less common in PHTS than single base pair alterations, although they can be found over the entire coding sequence (see **Fig. 2**). Unfortunately, even the largest cohorts of patients with PHTS are insufficient to identify clear genotype–phenotype associations.

Over the last decade, it became obvious that there are individuals with classic CS without germline *PTEN* mutations. Recent research efforts have resulted in several other germline susceptibility genes for such individuals. Approximately 10% of individuals with classic CS or CS-like phenotypes carry germline heterozygous variants in the genes encoding 3 of the 4 subunits of succinate dehydrogenase or mitochondrial complex II.[32] Single-exon *KLLN*, on 10q23, encodes KILLIN, and shares a bidirectional promoter with *PTEN*. Up to 30% of individuals with CS/CS-like phenotypes, without germline *PTEN* or *SDHx* mutations, were recently found to have germline *KLLN*
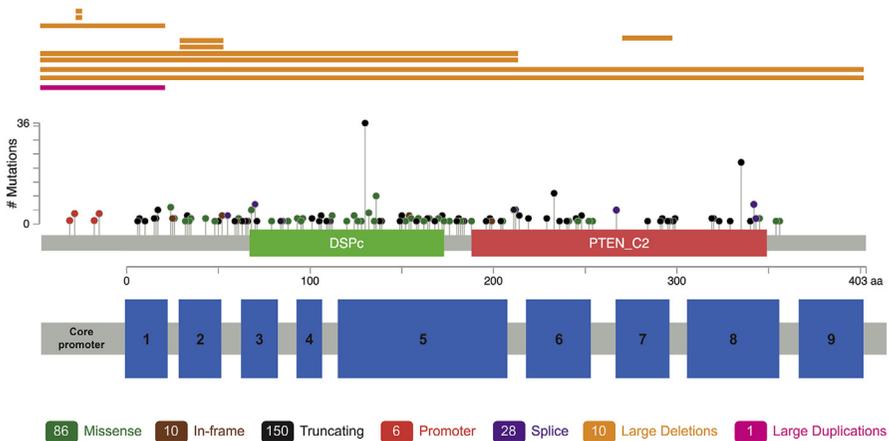
Fig. 2. *PTEN* germline mutational spectra in 291 probands. The domain structure of phosphatase and tensin homologue (PTEN). PTEN is a 403-amino acid protein that is composed of functional domains: a dual-specificity phosphatase, catalytic domain (DSPc), a C2 domain, a carboxy-terminal tail, and a PDZ-binding domain. PDZ domains are significant regions for protein-protein interactions that play a vital role in cellular signal transduction. The *N*-terminal domain contains the phosphatase domain (the enzymatic activity of PTEN) and it is, therefore, not surprising that the majority of PTEN mutations occur within this domain. The top solid bars represent large deletions and large duplications within the *PTEN* gene. Frequency of point mutations reported in probands is shown which correlates with the vertical height of the line (*middle*). Mutations have been identified in the promoter and all 9 exons of *PTEN* (*bottom*). A key at the bottom of the figure denotes the total number of unique alterations within each category of mutation identified in 291 probands. Missense mutations = green; in-frame mutations = brown; truncating mutations = black; promoter alterations = red; splice alterations = purple; large deletions = orange; large duplications = pink. (*From* Tan MH, Mester J, Peterson C, et al. A clinical scoring system for selection of patients for PTEN mutation testing is proposed on the basis of a prospective study of 3042 probands. Am J Hum Genet 2011;88(1):42–56; with permission.)

promoter hypermethylation.[33] Another 9% of unrelated CS individuals without germline *PTEN* mutations were found to have germline *PIK3CA* mutations and 2% harbored germline *AKT1* mutations.[34] Functionally, we saw a significant increase of phosphorylated-AKT1 levels in these patients' lymphoblastoid cell lines supporting their potential role as novel CS susceptibility genes.[34] More recently, germline heterozygous gain-of-function mutations in *SEC23B* have been identified in approximately 5% of CS patients and enriched in apparently sporadic thyroid cancer patients.[35] Gain-of-function germline mutations in *EGFR* have been seen in a unique CS family presenting with Lhermitte-Duclos disease.[36]

CANCER CLINICAL FEATURES

Before the association of germline *PTEN* mutations with CS, it was recognized that individuals with CS were at an increased risk of developing thyroid and breast cancers.[6] Additional research performed over recent years has expanded the spectra of cancers associated with germline *PTEN* mutations to include cancers of the endometrium, kidney, and colon, and melanoma as well as benign findings such as GI polyposis.[2,6,8,13] To date, 3 studies have reexamined the lifetime risks for malignancy and germline

PTEN mutations, with the largest study by Tan and colleagues[13] identifying significantly increased risks for endometrial, renal, thyroid, and breast cancers[1,37] (Fig. 3).

Breast

Many CS patients may first present to breast surgeons and oncologists because of both benign and malignant breast pathology. Early estimates of breast cancer risk for females with histories consistent with CS were traditionally reported to be around 25% to 50%.[6] Three more recent studies have reexamined the lifetime risks for malignancy in CS patients with germline *PTEN* mutations and have found that early risk figures may have been underestimates, especially before the identification of *PTEN*.[1,4,13,37] The largest of the 3 most recent cohort studies, by Tan and colleagues,[13] identified increased risks for several types of cancer, with the highest risk estimate increase for female breast cancer. Tan and colleagues[13] identified an 85% lifetime risk, beginning around age 30 years, for female breast cancer, with 50% penetrance by age 50 years. This risk figure is comparable to that quoted for patients with Hereditary Breast and Ovarian Cancer syndrome.[4] A similar study by

Lifetime Risks of Cancer for Patients with PHTS

Thyroid, 1%
(35%)

Melanoma, 2%
(6%)

Breast, 12%
(85%)

Renal cell, 1.6%
(34%)

Colon, 5.5%
(9%)

Endometrial, 2.6%
(28%)

■ (PHTS Lifetime Risk)
■ General Population Lifetime Risk
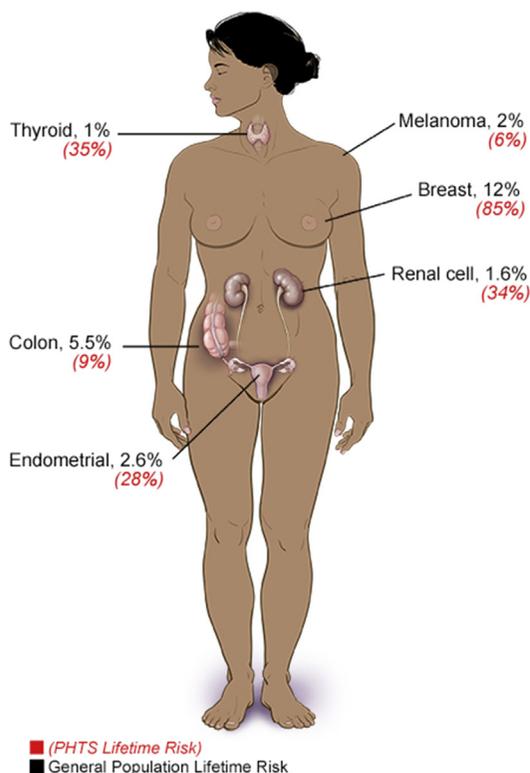
Fig. 3. Lifetime cancer risks for individuals with germline *PTEN* mutations. Lifetime cancer risks for *PTEN* hamartoma tumor syndrome are shown in black; organ-specific lifetime risk for cancer in the general population is shown in brackets in gray. (*From* Tan MH, Mester JL, Ngeow J, et al. Lifetime cancer risks in individuals with germline PTEN mutations. Clin Cancer Res 2012;18(2):400–7; with permission.)

Bubien and colleagues[1] found a cumulative 77% risk for female breast cancer at age 70 years for women with *PTEN* mutations. In addition, Nieuwenhuis and colleagues[37] identified a 67% risk for females with germline *PTEN* mutations developing breast cancer by age 60 years.

Several studies have also considered *PTEN* mutation status related to primary and second primary breast cancer diagnoses, and found that women with *PTEN* mutations are at increased risk for both.[4,38] These studies also identified that women with *PTEN* mutations who have had a diagnosis of breast cancer have a 29% risk of developing a secondary breast cancer within 10 years.[4,38] Women may choose to pursue prophylactic mastectomy for these reasons, particularly if the patients have associated benign breast lesions, making breast cancer surveillance difficult. Breast cancer has been described in males with *PTEN* mutations, but an overall increased risk for male breast cancer was not established in a recent study of more than 3000 patients, although the adults in the cohort were mostly female patients.[19,39]

Thyroid

The only population-based clinical epidemiologic study, performed before the discovery of *PTEN*, suggested that two-thirds of CS patients have benign thyroid disease, and 10% have malignant thyroid neoplasias.[6] However, a systematic study of thyroid neoplasms from a prospectively accrued series of individuals with CS and CS-like features have revised the lifetime thyroid cancer risk for individuals with germline *PTEN* mutations upwards to be around 34%, with the earliest age at diagnosis of 7 years.[1,13,37] Thyroid pathology in PHTS typically affects follicular cells,[40,41] with follicular thyroid carcinoma (FTC) considered a major diagnostic criterion and an important feature in PHTS. Benign thyroid lesions, such as thyroid nodules, multinodular goiter, and Hashimoto's thyroiditis, are also common in individuals with germline *PTEN* mutations.[4] An individual's risk of developing epithelial thyroid cancer was increased by 70-fold when compared with the general population.[19] FTC was overrepresented in a cohort of germline *PTEN* mutation positive individuals, the ratio of FTC to the more common papillary thyroid cancer was 1 in 2 among PHTS patients as compared with approximately 1 in 14 in the general population.[42] Several reports of thyroid cancer in children with germline *PTEN* mutations[43] have been described, emphasizing the need to begin thyroid screening annually at the time of PHTS diagnosis.[4,44]

The prevalence of germline *PTEN* mutations in unselected differentiated thyroid cancer is low (<1%).[45,46] A pediatric onset of thyroid cancer, male gender, history of thyroid nodules and/or thyroiditis, and FTC histology were factors that were found to be predictive of PHTS in a cohort of patients with CS and CS-like disease and with thyroid cancer.[42] These "red flags" and/or a family history of cancers, and physical signs such as macrocephaly and mucocutaneous features should alert the clinician to the possibility of CS.

Gastrointestinal Tract

Whether GI neoplasias, especially malignancies, are true component phenotypes of CS was not certain owing to the lack of systematic studies. In the largest study to date, Heald and colleagues[8] demonstrated almost all (>90%) *PTEN* mutation carriers who had a colonoscopy performed as part of clinical care, had colorectal polyps typically with a mix of histologic subtypes. Patients who developed colorectal carcinomas also tended to have multiple, and mixed, polyps. A small increase in the lifetime risk for colorectal cancer has been associated with PHTS (9%).[13] These findings led to a change in clinical practice; colorectal surveillance should now be offered to any

PTEN mutation carrier, especially those with multiple lower GI polyps. In *PTEN* mutation carriers, upper GI polyps do occur with some frequency, and, for a subset of patients, they do experience symptoms. Notably, a significant proportion (approximately 20%) of those with upper GI examinations had glycogenic acanthosis.[8,47,48]

Endometrial

Individuals with germline *PTEN* mutations have a 28% lifetime risk of developing endometrial cancer.[13] A recent study showed that age less than 50 years at presentation of endometrial carcinoma, macrocephaly, and/or prevalent or synchronous renal cell carcinoma in these women could predict for germline *PTEN* mutation.[42] The mean age of endometrial cancer diagnosis in those with *PTEN* mutations was 44 years, with three-quarters diagnosed at less than 50 years of age. This observation may guide the age range for consideration of surveillance or prophylactic surgery. Individuals with germline *PTEN* mutations are also additionally at increased risk of developing benign findings of the endometrium, such as uterine fibroids.[13]

Renal

Patients with PHTS have a 34% lifetime risk of developing renal cell carcinoma (RCC).[13] The reported histology of each mutation positive patient's RCC was variable. However, on central pathology re-review of 8 patients, 6 examined lesions were determined to be of papillary subhistology, with the other 2 patients' tumors consistent with the initial report of chromophobe RCC. Immunohistochemistry demonstrated complete loss of PTEN protein in all *PTEN* mutation positive patients' papillary RCCs and patchy positivity in 1 chromophome RCC. Physicians caring for PHTS patients should have a low threshold for investigating possible RCC in patients with relevant complaints. Renal ultrasound examination is not sensitive for detecting papillary RCC, especially if small, and so PHTS patients should have alternate renal imaging (computed tomography san or MRI).[49] Recent research has also identified a small increase in the estimated lifetime risk for melanoma (6%) for individuals with germline *PTEN* mutations.[4,13]

NONCANCER CLINICAL FEATURES
Neurologic

The first case study of a child with a *PTEN* mutation and autism described a boy who inherited a nonsense mutation from his mother, who herself was diagnosed with CS but did not have social or intellectual disabilities.[12] After this report, which recommended *PTEN* mutation scanning in cases of macrocephaly with pervasive developmental delay, came the first estimate of mutation frequency in a prospective series of patients with macrocephaly and autism. In 2005, Butler and colleagues[11] reported 3 *PTEN* mutations in a series of 18 children with macrocephaly and autism spectrum disorder. This benchmark prevalence of 17% remains near the weighted average reported across nearly 10 subsequent studies.[50] Together, these results provide a strong case for the association of germline *PTEN* mutation in children with autism spectrum disorder and macrocephaly. These data form the basis for the recommendation of genetic testing in this subset of autism spectrum disorder patients. The degree of macrocephaly observed in patients with autism spectrum disorder and *PTEN* mutations is often more severe than that seen in those with wild-type *PTEN*. A 2011 study examined OFCs in a cohort of 181 *PTEN* mutation carriers, finding their average head size to be +3.5 standard deviations (SDs) from average in adults and +5 SDs in the pediatric subset.[21] Recently, a series of case reports demonstrated epileptic seizures

in *PTEN* mutation-positive patients, often linked to underlying cortical dysplasia.[51] Further studies are needed to fully understand the full neurologic sequelae of *PTEN* mutation carriers including cognitive profile.

Metabolic, Immunologic, and Others

Pal and colleagues[52] studied the impact of *PTEN* haploinsufficiency in a cohort of patients and identified that it is a monogenic cause of profound constitutive insulin sensitization. Fasting insulin levels were significantly lower in the *PTEN* mutation carriers than in controls; because the liver is the principal insulin-responsive tissue, the fasting insulin level predominantly reflects insulin resistance in the liver. The authors observed a significant association between *PTEN* haploinsufficiency and increased insulin sensitivity of muscle tissue and that PTEN deficiency enhances insulin signaling in both muscle and liver tissue in humans, possibly by way of its action on the PI3K–AKT pathway. The *PTEN* mutation carriers were obese as compared with population-based controls. This increased body mass in the patients was owing to augmented adiposity without corresponding changes in fat distribution. The authors demonstrated an apparently divergent effect of *PTEN* mutations: increased risks of obesity and cancer but a decreased risk of type 2 diabetes owing to enhanced insulin sensitivity. These data support a large body of studies linking PTEN with the insulin receptor substrate 1/2 (IRS1/2) pathways.[43,53]

Clinicians have observed that PHTS patients commonly suffer from a range of immune-related disorders such as thyroiditis[42] and eosinophilic esophagitis.[54] Indeed, a recent study showed that autoimmunity and peripheral lymphoid hyperplasia was found in 43% of 79 PHTS patients. In a recent study, we reported that immune dysregulation in PHTS patients included lymphopenia, CD4$^+$ T-cell reduction and changes in T- and B-cell subsets.[36]

IDENTIFYING PATIENTS FOR GENETICS RISK ASSESSMENT

CS can be differentiated from other hereditary cancer syndromes including hereditary breast ovarian cancer syndrome, Lynch syndrome, and other hamartomatous polyposis syndromes based on personal as well as family history but, given the protean nature of CS and lack of general awareness among clinicians, this differentiation can be challenging.[20] Additionally, because of the high frequency of de novo *PTEN* germline mutations,[55] a family history of associated cancers may not be apparent. Furthermore, many of the benign features of CS are common in the general population making the diagnosis of CS a challenge for most clinicians. An occipitofrontal head circumference in adults of greater than 2 SDs is seen in the majority of adult PHTS patients; this is one useful clinical feature that can help to flag which cancer patients are at risk of PHTS. Any cancer patient with a large occipitofrontal head circumference should be assessed for personal/family history of other CS-related features (eg thyroiditis, polyps, developmental delay/autism and other malignancies) and be referred for genetic risk assessment.[20,21,56]

To aid in the clinical diagnosis, a clinical predictor (Cleveland Clinic *PTEN* Risk Calculator) was developed based on clinical features derived from a prospective study of more than 3000 patients suspected of having CS.[19] The questionnaire-based clinical decision tool is available online (http://www.lerner.ccf.org/gmi/ccscore/) to assist clinicians at the point of patient care. Based on a patient's presentation, a score (CC score) will be derived that corresponds with an estimated risk for germline *PTEN* mutation to guide clinicians for referral to genetics professionals. A CC score at a threshold of 15 (CC15) corresponds with a 10% a priori risk of a germline *PTEN*

mutation detection, which is the lowest among different strategies tested. At a cost-effectiveness threshold of $100,000 per quality-adjusted life-year, CC15 is the optimal strategy for female patients older than 50 years, and CC10 is the optimal strategy for female patients younger than 50 years of age and male patients of all ages.[57] Thus, patients with a CC score of greater than 10 should be considered for genetic risk assessment referral. Additionally, the American College of Medical Genetics published a practical guide for which patients should be referred for genetic assessment for CS. They recommend referral for anyone meeting any 3 criteria from the major or minor diagnostic criteria (see Box 1). Referral should be considered for any individual with a personal history of or first-degree relative with (1) Lhermitte–Duclos disease diagnosed after age 18 or (2) any 3 criteria from the major or minor diagnostic criteria list in the same person.[58]

For pediatric cases, we recommend that the presence of macrocephaly (occipito-frontal head circumference > 2 SD over the population mean, or 97.5th percentile) was a necessary criterion for diagnosis, based on 100% prevalence at the point of diagnosis.[19] Neurologic (autism and developmental delay) and dermatologic (lipomas, oral papillomas) features represented extremely common secondary features; either or both systems were involved in 100% of patients with germline *PTEN* mutation. However, given that dermatologic features may often be overlooked, less prevalent features in patients at first presentation in the pediatric setting are likely to be at least as important, such as vascular (such as arteriovenous) malformations, gastrointestinal polyps, thyroid goiter, and early onset cancers (thyroid and germ cell), and warrant consideration for *PTEN* testing (Table 1).

SURVEILLANCE AND MANAGEMENT OF COWDEN SYNDROME

The mucocutaneous manifestations of CS are rarely life threatening. If asymptomatic, observation alone is prudent. When symptomatic, topical agents (eg, 5-fluorouracil), curettage, cryosurgery, or laser ablation may provide only temporary relief.[59] Treatment for the benign and malignant manifestations of PHTS is similar to their sporadic counterparts. Some women at increased risk for breast cancer consider prophylactic mastectomy, especially if complicated by existing benign breast disease and/or if repeated breast biopsies have been necessary. 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 and is best managed by breast surgeons with a specialty interest in high-risk breast cancer patients.

Table 1	
Pediatric criteria for consideration of *PTEN* hamartoma tumor syndrome	
Required Criteria	**Secondary Criteria**
Macrocephaly (≥2 SD)	At least 1 of the following should be present: • Autism or developmental delay • Dermatologic features (lipomas, oral papillomas, trichilemmomas, penile freckling) • Vascular features (arteriovenous malformations or hemangiomas) • Gastrointestinal polyps • Pediatric-onset thyroid cancer or germ cell tumors

Data from Tan MH, Mester J, Peterson C, et al. A clinical scoring system for selection of patients for PTEN mutation testing is proposed on the basis of a prospective study of 3042 probands. Am J Hum Genet 2011;88(1):42–56.

The most serious consequences of PHTS relate to the increased risk of cancers, including breast, thyroid, endometrial, and, to a lesser extent, renal cancers. In this regard, the most important aspect of management of any individual with a *PTEN* mutation is increased cancer surveillance to detect any tumors at the earliest, most treatable stages. Current surveillance and management guidelines for adults can be found in **Table 2**. Management of the malignant and benign manifestations of PHTS varies depending on the age of the individual.[13] For adults, current recommendations include annual a comprehensive physical examination and dermatologic examination beginning at the age of 18 years.[13] Screening for additional cancer types may begin at the ages listed in **Table 1**, or 5 to 10 years before the youngest diagnosis of that particular type of cancer in the family if this is earlier.[4,13] For children, it is currently recommended to perform an annual dermatologic examination and annual thyroid ultrasound examination at the age of PHTS diagnosis.[13] Earlier screening may be advisable because thyroiditis and nodules are seen by the time patients reach adolescence, and cancer diagnosis occurs on average 14 years earlier than expected. Furthermore, the thyroid cancer risks observed may justify prophylactic total thyroidectomy in select PHTS patients undergoing surgery for benign thyroid disease.[44]

FUTURE CONSIDERATIONS AND SUMMARY

Patients with PHTS may present to a variety of different subspecialties with benign and malignant clinical features. They have increased lifetime risks of breast, endometrial, thyroid, renal, and colon cancers as well as neurodevelopmental disorders such autism spectrum disorder. Patients and affected family members can be offered

Table 2
Cancer risks and screening recommendations for *PTEN* hamartoma tumor syndrome

Cancer	General Population Risk (%)	Lifetime Risk with *PTEN* Hamartoma Tumor Syndrome (%)	Age at Presentation	Screening Recommendations
Breast	12	~85	40s	Starting at age 30 Annual mammogram Consider MRI for patients with dense breasts
Thyroid	1	35	30s–40s	Baseline ultrasound examination at diagnosis Annual ultrasound and clinical examination
Endometrial	2.6	28	40s–50s	Starting at age 30 Annual endometrial biopsy or transvaginal ultrasound examination
Renal cell	1.6	34	50s	Starting at age 40 Renal imaging every 2 y
Colon	5	9	40s	Starting at age 40 Colonoscopy every 2 y
Melanoma	2	6	40s	Annual dermatologic examination

Data from Tan MH, Mester JL, Ngeow J, et al. Lifetime cancer risks in individuals with germline PTEN mutations. Clin Cancer Res 2012;18(2):400–7.

gene-directed surveillance and management. Patients who are unaffected can be spared unnecessary investigations. With longitudinal follow-up, we are likely to identify other noncancer manifestations associated with PHTS such as metabolic, immunologic, and neurologic features.

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