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Cowden Syndrome: Recognizing and Managing a Not-So-Rare Hereditary Cancer Syndrome

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Cowden syndrome (CS) is an autosomal dominant hereditary cancer syndrome causing increased risk for breast, thyroid, renal, uterine, and other cancers as well as benign neoplasias and neurodevelopmental concerns. Timely diagnosis of affected patients is key, as early recognition allows for high-risk screening and other preventative measures prior to a patient enduring multiple cancer diagnoses. This review will highlight the cardinal features of CS and management recommendations for affected patients.
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INTRODUCTION

Cowden syndrome (CS) (OMIM #158350) is a dominantly inherited multi-system disorder causing increased risks for benign and malignant neoplasias. Initially considered a mainly dermatologic disease, over time, the phenotypic spectrum has broadened to include cancer risks as well as neurodevelopmental disorders. We also now understand the genetic mechanism causing disease in many patients, allowing for molecular diagnostic confirmation, predictive testing of at-risk relatives, and gene-informed high-risk management. This article will help the reader identify at-risk surgical patients who may benefit from referral for cancer genetics consultation and review management guidelines for affected patients.

FROM CLINICAL DIAGNOSIS TO GENE IDENTIFICATION

In 1962, Drs. Kenneth M. Lloyd and Macey Dennis published a case report about a 20-year-old woman named Rachel Cowden who presented to Youngstown Hospital with severe ulcerative, cystic breast disease. They noticed that both her medical history and physical exam revealed additional anomalies, including a large multinodular goiter, papillomatous overgrowths of her oral mucosa, central nervous system abnormalities, and dysmorphic characteristics, as well as a family history of similar findings. The authors believed that so many anomalies co-existing in one person was more likely due to an underlying syndrome than to chance alone. To honor the patient, Drs. Lloyd and Dennis decided to name the previously undescribed condition Cowden syndrome [1].

Additional patients with Cowden came to light in the following years, with the diagnosis resting on the presence of a combination of key mucocutaneous findings: facial papules, most often trichilemmomas, oral papillomas, acral keratoses, and fibromas [2]. An association with risk for breast cancer was quickly uncovered, and based on early case series an estimated breast cancer risk of 25–50% was quoted [2,3]. Among the first 100 cases of Cowden syndrome described in the literature, the most common features identified were thyroid goiter/adenoma (68%), fibrocystic breast disease (52%), GI polyps (35%), lipomas (31%), and macrocephaly (21%). Only 6% of patients had endometrial cancer, 3% thyroid cancer, and another 3% colorectal cancer [3]. Lhermitte–Duclos disease (LDD, dysplastic cerebellar gangliocytoma) was diagnosed in 2 CS patients; similar to Lloyd & Dennis, the authors surmised that it was unlikely for two rare occurrences in the same patients to be unrelated, and proposed that LDD become a part of the CS spectrum [4].

In the mid-1990s genetic linkage studies of 12 CS families identified a possible gene locus at chromosome sub-band 10q23 [5]. While no tumor suppressor genes had yet been identified in that region, loss of heterozygosity had been observed in follicular thyroid and uterine tumors [6,7]. A few years later, Li et al. identified a candidate tumor suppressor gene, *PTEN*, within this genomic region; somatic *PTEN* mutations had been identified in brain, breast, and prostate cancer cell lines [8]. *PTEN* sequencing within 5 CS kindreds identified a germline *PTEN* mutation in 4 families, confirming *PTEN* as the first gene known to cause CS [9].

About 60% of patients with Bannayan–Riley–Ruvalcaba syndrome (BRRS, OMIM #153480), also referred to as as Bannayan–Zonana, Riley–Smith, or Ruvalcaba–Myhre–Smith syndrome in the medical literature were also identified as having germline *PTEN* mutations [10–12]. BRRS was first described as a condition with pediatric onset, causing macrocephaly, lipomas, hamartomatous gastrointestinal polyps, vascular malformations, Hashimoto's thyroidits, and penile freckling [13]. Identical *PTEN* mutations were identified in families with differing clinical phenotypes, leading to the hypothesis that CS and BRRS should be considered as one condition, and that the increased cancer risks in CS should also apply to BRRS patients. Patients with a Proteus-Like syndrome as well as solely macrocephaly and autism were also identified with germline *PTEN* mutations, further expanding the clinical spectrum of this disease [14–18]. The term PTEN Hamartoma Tumor syndrome (PHTS) was coined to describe any patient with a germline *PTEN* mutation, regardless of clinical phenotype [19]. Clinical features associated with PHTS are listed in Table I [20].

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TABLE I. Clinical Characteristics of PTEN Hamartoma Tumor Syndrome

Benign neoplasias
Dermatologic
• Palmoplantar keratoses
• Trichilemmomas
• Lipomas
• Fibromas
• Freckling of the glans penis
Vascular anomalies/hemangiomas
Lhermitte-Duclos (dysplastic gangliocytoma of the cerebellum)
Genitourinary tumors/malformations
Colorectal polyposis
Mucosal lesions
Thyroid goiter/nodules
Proliferative breast changes
Malignancies
Breast cancer
Non-medullary thyroid cancer
Renal cancer
Endometrial cancer
Colorectal cancer
Melanoma
CNS
Macrocephaly
Autism/Developmental Delay
Dysmorphic Characteristics
Dolicocephaly
Postaxial polydactyly
Other
Autosomal dominant inheritance
10–44% caused by de novo mutation
Extreme intrafamilial variability common
Penetrance 100% by adulthood

TABLE II. Summary of Studies To Date Analyzing Lifetime Cancer Risks in Patients with Germline *PTEN* Mutations

	Tan et al. (2011)	Bubien et al. (2013)	Nieuwenhuis et al. (2013)
Number of patients	368	146	180
Median age (yrs)	39	36	32
Lifetime cancer risks*			
Female breast	85%	77%	67%
Thyroid	35%	38%	Women: 25% Men: 6%
Renal	34%	Elevated in women, N insufficient for further analysis	Women: 9%
Endometrial	28%	Elevated, N insufficient for further analysis	Women: 9% 21%
Colorectal	9%	Elevated in men, N insufficient for further analysis	Women: 17%
Women: 17%			
Melanoma	6%	Elevated, N insufficient for further analysis	Men: 2%

*Lifetime risks calculated to age 70 by Tan et al. and Bubien et al.; to age 60 by Nieuwenhuis et al.

CANCER RISKS AND PHTS/CS

In patients with germline *PTEN* mutations and thus PHTS, three studies to date have examined risks for malignancy (Table II) [21–23]. The largest, by Tan et al., identified greatly increased lifetime risks for breast, thyroid, renal, and endometrial cancers and slightly elevated risks for colorectal cancers and melanoma [21]. Attempts to identify clinically relevant genotype-phenotype correlations were unsuccessful, reinforcing the need for every PHTS patient to be offered high-risk management options for all associated cancers regardless of mutation type [21].

MANAGEMENT IN PHTS/CS

As noted previously, patients identified as having germline *PTEN* mutations have been proven to have greatly elevated cancer risks above those observed in the general population. Management guidelines for *PTEN*-mutation positive patients revolve around these high cancer risks, with the goal of cancer prevention through prophylactic surgery or identifying tumors at the earliest, most treatable stages (Table III).

Breast

Women with *PTEN* mutations are at elevated risk for both primary as well as secondary breast cancer diagnoses. The highest risk estimate is 87% [21], a number comparable to that quoted for patients with Hereditary Breast and Ovarian Cancer (HBOC) syndrome, caused by the *BRCA1/2* genes [24]. It thus makes sense for women with *PTEN* mutations to have access to the same high-risk screening and surgical options as are offered to women with HBOC. This includes surveillance using a combination of clinical breast exams every 6 months along with imaging, alternating between mammography and MRI [25]. As demonstrated by the story of Rachel Cowden, some women with CS have so many benign breast lesions that their images are difficult to interpret, and they may be required to endure multiple call-backs and biopsies over the years [26]. For these reasons, some women may opt to pursue prophylactic mastectomy, which within the HBOC population has been shown to reduce breast cancer risk by 90% [27]. Women with *PTEN* mutations who have already had one breast cancer diagnosis are at 29% risk for another primary breast cancer within the next 10 years [28]; this reinforces a need for continued high-risk surveillance, consideration of mastectomy for surgical treatment of their first breast cancer, and consideration of contralateral prophylactic mastectomy.

Thyroid

Similar to the phenomenon observed in the realm of breast disease, most patients with *PTEN* mutations have thyroids with multiple nodules, some with a combination of goiter and Hashimoto's thyroiditis [29]. Among all the cancer types with highest risk, thyroid cancer can develop earliest in the *PTEN* mutation-positive patient population; the earliest diagnosis of thyroid cancer reported was at age 6 years, with other reports of children with thyroid cancer at *PTEN* mutations at age 7, 11, 14, and 17 [21,30]. Given that the risk begins in childhood and that thyroid ultrasound is a no-risk screening option, we recommend that all patients undergo baseline thyroid ultrasound at the age of clinical CS or molecular PHTS diagnosis (whichever occurs first), with follow-up on a yearly basis. If surgery becomes necessary – either due to a FNA positive for cancer or because the patient can no longer be followed safely by imaging alone – we recommend total thyroidectomy be performed, even if only one side of the thyroid appears affected, due to the high likelihood for additional disease and need for future surgery. Prophylactic thyroidectomy has also been proposed as an option for patients with autism or other cognitive defects who will not permit thyroid ultrasound without sedation [29].

Endometrial

PTEN mutation-positive women are at increased risk for endometrial cancer. To date, most diagnoses have occurred past the age of childbearing, but earlier diagnoses may occur; one case report details a

TABLE III. Cancer Screening/Management Recommendations for Patients with Germline *PTEN* Mutations

Cancer type	Screening recommendations	Surgical options
Female breast	Starting at age 30: annual mammogram; consider MRI for patients with dense breasts	Prophylactic mastectomy
Thyroid	Starting from age at diagnosis: annual ultrasound	
Renal	Starting at age 40: imaging every two years	
Endometrial	Starting at age 30: annual endometrial biopsy or transvaginal ultrasound	Prophylactic hysterectomy (oophorectomy unnecessary) once childbearing complete
Colorectal	Starting at age 35-40: Colonoscopy, with follow-up dependent on degree and type of polyps identified.	
Melanoma	Starting from age at diagnosis: annual dermatologic exam	

girl with PHTS and endometrial cancer diagnosed at age 14 [31]. For women who have completed childbearing, prophylactic hysterectomy could be considered. Interestingly, ovarian cancer has not been over-reported in patients with *PTEN* mutations, implicating that oophorectomy does not need to be performed simultaneously, and helping these women avoid the health risks and physical discomfort that come with surgically-induced menopause. For those women who do not wish to undergo hysterectomy, they may discuss surveillance options with a gynecologic oncologist. Transvaginal ultrasound and blind endometrial biopsy are suggested as surveillance options, but have not been proven in CS or other syndromes causing high endometrial cancer risk to reduce morbidity or mortality [21].

Renal

While small patient series and case reports described occasional patients with CS and renal cancer, it was not until a large series of patients was accrued that a true syndrome-associated increased risk for renal cancer was appreciated in this population, with maximum lifetime risk estimated at 34% [21]. On dedicated histologic review, most of the renal cancers in patients with germline *PTEN* mutations are either papillary or chromophobe in nature [32]. While bilateral disease has been reported, metastatic disease, to our knowledge, has not. Screening is recommended to begin at age 40 and continue every other year; in this manner, a kidney tumor can be detected and removed at the earliest point possible, allowing for nephron-sparing surgery in these patients who are then at risk for additional RCCs. The controversy, because of lack of data at this time, is the mode of surveillance. Typically, CT ably picks up small papillary RCC. However, larger papillary RCC are picked up by GU ultrasound. Given that we have yet to see metastatic disease, it is possible that renal ultrasounds may be adequate. This will require further study.

Colon

While a slight increased risk for early-onset colorectal cancer is appreciated in patients with *PTEN* mutations (9% lifetime risk) [21], gastrointestinal polyposis is by far a more common occurrence. In a series of patients who had undergone endoscopy, 93% had polyps [33]. The number and type of polyps varied dramatically from patient to patients with a subset having only a few hyperplastic polyps; others had thousands of polyps, with several adenomas in the mix. At this time, we do not advocate prophylactic colectomy be considered unless a patient has several adenomas seen on subsequent scopes, and there is such a large number of other polyps that the surgeon is concerned that adenomas may be missed among the field of hamartomatous, hyperplastic, and other polyp types. It is recommended that if a patient remains asymptomatic, the first colonoscopy occurs at age 35–40, with follow-up interval determined by the number and type of polyps seen on previous scoping [21,33,34].

Skin

A slight increase in risk for melanoma (6% compared to 2% in the general population) has also been reported for patients with *PTEN* mutations, with one young patient diagnosed at age 3 [21]. Yearly dermatologic examination is recommended.

KEYS TO RECOGNIZING PATIENTS WITH POSSIBLE PHTS/CS FOR GENETICS REFERRAL

CS can be difficult to recognize due to diverse clinical presentations. Patients with multiple primary cancer diagnoses are most easily recognized and will likely be referred based on that history; however, the task becomes more difficult for patients with mostly benign features. Ironically, these patients, who can take advantage of high-risk screening protocols, are those for whom a diagnosis would have the greatest direct benefit.

There are several characteristics which should raise strong clinical suspicion for PHTS given their rarity in the general population or in other genetic syndromes which are easily identifiable through either quick pathology/history review or brief physical examination:

- Lhermitte-Duclos disease (dysplastic cerebellar gangliocytoma),
- Extreme macrocephaly (children, +5 standard deviations above the mean or higher; adult women > 60 cm, adult men > 63 cm),
- Oral mucosal papillomatosis (Fig. 1a-b),
- Penile freckling,
- Hamartomatous/ganglioneuromatous gastrointestinal polyps,
- Glycogenic acanthosis,
- Pediatric non-medullary thyroid carcinoma, and
- Endometrial cancer diagnosed prior to age 30.

These findings were among the highest-scoring components on the Cleveland Clinic PTEN Risk Calculation tool, which calculates a patient's *a priori PTEN* mutation risk [35]. This tool, freely available online at http://www.lerner.ccf.org/gmi/ccscore/ awarded a weighted score for each characteristic after comparing age-related prevalence within mutation positive and negative research participants to expected community frequencies as derived from published literature and the Surveillance Epidemiology and End Results database. The calculation provides a percentage risk for *PTEN* mutation in adults and recommendation whether or not to pursue *PTEN* testing/genetics referral for both pediatric and adult patients.

The generic "red flags" for cancer genetics referral can also be useful in identifying patients at risk for PHTS/CS. These include:

- Early-onset diagnosis for the cancer type,
- Multiple primary tumors,
- Multifocal/bilateral tumors,

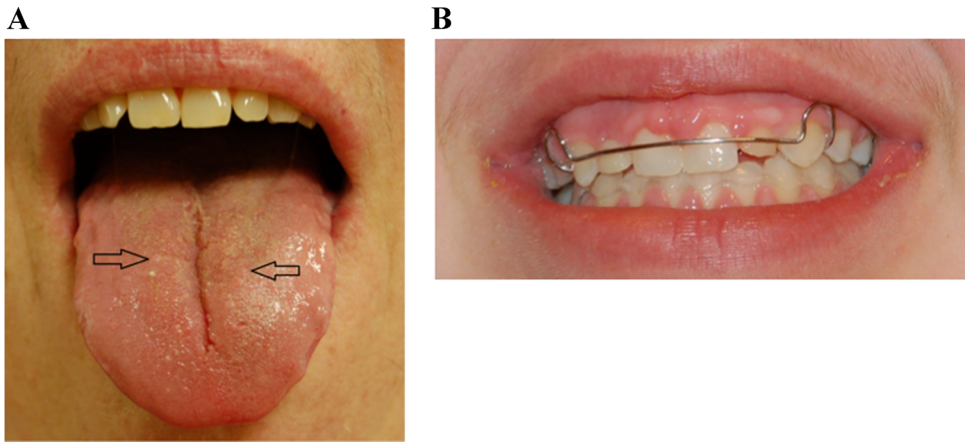

Fig. 1. **a–b: Oral mucosa papillomatosis a:** Arrows pointing to papillomas of the tongue on a 57-year-old woman with PHTS. **b:** Gingival papillomas on a teenaged young lady with PHTS; easily spotted when the overgrowth crosses the tooth border.

- Rare histologies, and
- Family history of similarly affected relatives.

Additionally, any individual who reports a family member previously diagnosed with Cowden syndrome, PHTS, or any other hereditary cancer predisposition syndrome should always be referred to cancer genetics for further evaluation and testing.

FAMILY MATTERS

CS is inherited in an autosomal dominant manner; this means that the children of an affected person have a 50% chance to share the condition, and other relatives (siblings, parents, aunts/uncles, cousins, etc.) are all at increased risk as well. In up to 44% of cases of persons with *PTEN* mutations, the mutation occurred de novo, meaning that it occurred sporadically in the affected patient and is not shared by either of their parents [36]. However, the only way to understand with certainty whether a person has PHTS is through genetic testing. Once a mutation is identified within one patient, all of their at-risk relatives can then pursue testing for that known familial mutation and receive a "yes or no" answer regarding whether they share the mutation and with it, increased cancer risk. Patients testing negative for a familial mutation would then be at general population risk for cancer barring other factors, and patients testing positive would then share the same cancer and other risks as previously discussed and then be able to take advantage of increased surveillance and other available management options.

Genetic counseling is an important component of the genetic testing process and is recommended by the American Society of Clinical Oncology [37]. During pre-test counseling, the genetic counselor reviews the syndrome in question with the patient and helps them understand whether the decision to pursue testing is right for them at this point in their life. Some patients may have preconceptions about risk for genetic discrimination; genetic counselors are equipped to explain the risks and benefits of testing and protective laws such as the Genetic Information and Nondiscrimination Act, which makes it illegal for most employers and health insurance companies to discriminate against a patient or treat them differently based on genetic testing or family history information (http://www.genome.gov/Pages/PolicyEthics/GeneticDiscrimination/GINAInfoDoc.pdf).

After a positive genetic test result, the genetic counselor can take time to explain testing results to the patient, help the patient understand their screening and management options, and help guide them to appropriate specialists for this purpose. Collaboration among the patient, their primary care provider, and the genetics team can be extremely helpful for patient care and referral management. In addition to genetics, patients with PHTS/CS frequently benefit from care from subspecialists in the following areas: endocrinology, gastroenterology, dermatology, high-risk breast management, gynecologic oncology, neurology, and developmental pediatrics.

Receiving a diagnosis of PHTS/CS or any other genetic condition can cause a strong emotional reaction in patients as well, and genetic counseling can help them understand how to accept this new genetic diagnosis and use this information about their health risks in a positive manner. Patient support groups can be a source of comfort and empowerment, and can help patients with rare genetic syndromes feel less isolated and alone. After a genetic diagnosis is made, a genetic counselor will research available support resources such as disease-specific support groups that the patient might find helpful. If your medical center does not have a genetic counselor on staff, one close to you may be located by visiting the National Society of Genetic Counselors website: www.nsgc.org.

DIAGNOSING COWDEN SYNDROME WHEN PTEN TESTING IS NEGATIVE

Despite initial impressions, CS is genetically heterogeneous. Early studies of patients with strong phenotype in both their personal and family history accrued from tertiary referral centers identified mutations in 80% of CS patients [9]. More recently, prospective accrual from the community to include broad and more relaxed phenotypic criteria resulted in 25% of patients meeting CS diagnostic criteria (Table IV) [38] without a family history being *PTEN* mutation positive [35]. Mutations in other genes, *SDHB/C/D*, *PIK3CA*, and *AKT1*, as well as hypermethylation of *KLLN* have been identified in a subset of mutation-negative cases, but the clinical relevance of these other genetic alterations continues to be studied in a research setting [39–42].

Before assuming a patient is truly mutation-negative, it is important to review the patient's genetic testing results to determine whether the most up-to-date testing methodologies were utilized. Techniques such as array (CGH) or multiplex ligation probe amplification (MLPA) are used to detect larger deletions or duplications not picked up by PCR-based sequencing technology and are now incorporated into the *PTEN* testing protocol by most clinical laboratories. Review of the fine print within the patient's original genetic testing report is needed to understand whether the analysis performed included a methodology that would detect large rearrangements. More importantly, the MLPA probe sets can change without notification. It would likely be helpful to refer the patient to a cancer genetics specialist, who will review the patient's previous genetic

TABLE IV. Cowden Syndrome Clinical Diagnostic Criteria

Pathognomonic criteria	Major criteria	Minor criteria
Mucocutaneous lesions: • Facial trichilemmomas • Acral keratoses • Papillomatous papules • Mucosal lesions	Breast cancer Non-medullary thyroid cancer Macrocephaly Endometrial cancer Lhermitte-Duclos disease	Benign thyroid lesions (goiter/nodules) Mental retardation Hamartomatous intestinal polyps Lipomas Fibrocystic breast disease Fibromas Genitourinary tumors or malformations
Operational clinical diagnostic criteria for an individual:		
Pathognomonic mucocutaneous lesions alone if:		
• Six or more facial papules, at least three of which are biopsy-confirmed trichilemmomas, or		
• Cutaneous facial papules plus oral mucosal papillomatosis, or		
• Oral mucosal papillomatosis plus acral keratoses, or		
• Six or more palmoplantar keratoses		
Two or more major criteria, one of which must be macrocephaly or Lhermitte-Duclos		
One major plus three minor criteria		
Four minor criteria		

testing and order additional testing if they determine this is indicated. The cancer genetics specialist might also need to rule out other diagnoses whose phenotypic spectra overlap with CS via further testing before being able to grant a clinical diagnosis of CS.

For those patients in whom thorough *PTEN* and other indicated genetic analyses have been performed with negative results, it is necessary to understand whether the patient meets criteria for a clinical diagnosis of CS. These criteria (Table IV) were developed by the International Cowden Consortium and are based upon the criteria developed during the gene identification process. For mutation-negative patients meeting CS diagnostic criteria, based on the case series reviewed prior to the identification of PTEN, a breast cancer risk of 25–50% and thyroid cancer risk of up to 10% are proposed [43] plus other screening as dictated based on the patient's family history of cancer.

CONCLUSIONS

It is important for surgeons to recognize the patient with potential Cowden syndrome and refer them for cancer genetics consultation. Patients with early-onset or multiple primary cancer diagnoses should be referred to genetics, as well as those with characteristics which create high suspicion for PHTS/CS: Lhermitte–Duclos disease, oral papillomatosis, extreme macrocephaly, hamartomatous polyps, and in males penile freckling. The Cleveland Clinic PTEN risk calculator: www.lerner.ccf.org/gmi/ccscore can be a helpful tool in the assessment process. Diagnosing PHTS/CS can lead to changes in management, including surgical, for both the patient as well as their family members, leading to decreased morbidity and mortality through cancer prevention and early detection.

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