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Cowden Syndrome and the *PTEN* Hamartoma Tumor Syndrome: Systematic Review and Revised Diagnostic Criteria

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Background *PTEN* hamartoma tumor syndrome (PHTS) refers to a spectrum of disorders caused by mutations in the phosphatase and tensin homolog (*PTEN)* gene. Diagnostic criteria for Cowden syndrome, the principal *PTEN*-related disorder, were first established in 1996 before the identification of the *PTEN* gene and the ability to molecularly confirm a clinical diagnosis. These consortium criteria were based on clinical experience and case reports in the existing literature, with their inherent selection biases. Although it was initially reported that approximately 80% of patients with Cowden syndrome had an identifiable germline *PTEN* mutation, more recent work has shown these diagnostic criteria to be far less specific. In addition, increasing evidence has documented the association of a broader spectrum of clinical features with *PTEN* mutations. Our goal was to develop revised, evidence-based diagnostic criteria and to include features of the broader spectrum of *PTEN*-related clinical syndromes.

Methods We performed a systematic search and review of the medical literature related to clinical features reported in individuals with a *PTEN* mutation and/or a related clinical diagnosis.

Results We found no sufficient evidence to support inclusion of benign breast disease, uterine fibroids, or genitourinary malformations as diagnostic criteria. There was evidence to include autism spectrum disorders, colon cancer, esophageal glycogenic acanthosis, penile macules, renal cell carcinoma, testicular lipomatosis, and vascular anomalies.

Conclusions We propose revised, evidence-based criteria covering the spectrum of *PTEN*-related clinical disorders. Additional research on clinical features associated with *PTEN* mutations is warranted.

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The term *PTEN* hamartoma tumor syndrome (PHTS) has been used to refer to a spectrum of disorders that have been linked to germline mutations in the phosphatase and tensin homolog *(PTEN)* gene, including Cowden syndrome (CS), Bannayan-Riley-Ruvalcaba

syndrome (BRRS), adult Lhermitte-Duclos disease (LDD), and autism spectrum disorders associated with macrocephaly. The bulk of the clinical data on these disorders comes from studies of patients with Cowden syndrome, and less commonly BRRS.

CS is a rare, multisystem disease that causes increased risks for malignancies (breast, thyroid, and endometrial) as well as benign hamartomatous overgrowth of tissues (skin, colon, thyroid, etc). CS was first described in one family in 1963 (1) and then extended by Weary et al. who added an additional set of 5 patients and expanded the spectrum of component features (2). Germline *PTEN* mutations were first reported in individuals with CS in 1997 (3,4).

BRRS is a rare congenital disorder whose primary clinical features include macrocephaly, hamartomatous intestinal polyps, lipomas, and pigmented macules on the penis. Other features include developmental delay, vascular anomalies, large birth weight, and joint hyperextensibility (5). Diagnoses are based on the presence of several of the primary clinical features. BRRS has been shown to be allelic to CS, with approximately 60% of patients with a clinical diagnosis of BRRS having *PTEN* mutations (6,7). There is relatively little data on the clinical features of BRRS patients with documented *PTEN* mutations, however, with only 30 published cases identified in a 2003 review (8).

Diagnostic criteria for CS were initially proposed by Salem and Steck in 1983 (9) and later revised by consensus of an international consortium of researchers in 1996 before identification of the CS gene (10). Clinical diagnoses since that time have been based on these consortium criteria, which were based upon early clinical experience and compilations of cases published in the literature, with their inherent selection biases, rather than on unselected series of patients. The single largest patient series in any of these reports until recently was 21 patients (11). Although the Cowden Consortium has not existed for some time, modifications to the original consortium diagnostic criteria have been proposed, including the addition of endometrial carcinoma as a major criterion and renal cell carcinoma as a minor criterion (12) and the reclassification of adult LDD as a pathognomonic criterion (13).

Although it has generally been reported that *PTEN* mutations are found in 80% of patients with CS, this was based on small early studies in which mutations were found in four of five (80%) (4) and 30 of 37 (81%) patients (14). In actuality mutation rates in other early studies ranged widely, from 11% to 61% (3,15,16) More recently, in much larger cohorts, *PTEN* mutations have been found in 30% to 35% of patients meeting consortium diagnostic criteria (7, 17) and in 23 of 42 (55%) patients with a clinical diagnosis of BRRS (7). Importantly, 63 of 172 (37%) patients with mutations in one of these studies did not meet diagnostic criteria for either CS or BRRS (7). Moreover, it appears that certain combinations of clinical features meeting consortium diagnostic criteria are nonspecific, particularly the combinations of macrocephaly and one cancer diagnosis (7).

The National Comprehensive Cancer Network has established testing criteria to indicate when *PTEN* testing is indicated, based on the clinical features present in a patient (18). They have also established management and screening recommendations for individuals who are found to have a *PTEN* mutation. However, in clinical practice it is often necessary to provide management for a patient based on their clinical diagnosis alone, either because testing is not possible or because it was done but no mutation was found. Thus accurate clinical diagnostic criteria are a necessary adjunct to genetic testing. Our goal was to review the literature addressing each of the consortium diagnostic criteria, as well as several more recent clinical features seen in PHTS to determine which current clinical features are supported by scientific evidence. Using this evidence-based approach, we propose revised, more stringent diagnostic criteria encompassing not only CS but also the spectrum of *PTEN*-related disorders.

Methods

A systematic review of the English language medical literature was performed by the authors using Medline (through http://www.ncbi.nlm.nih.gov/pubmed/). The search strategy included the combinations of *PTEN* OR Cowden OR Bannayan-Riley-Ruvalcaba syndrome AND each of the relevant clinical features reviewed. The reference sections of identified manuscripts were also searched for relevant reports, which were then also reviewed. Attention was paid to whether studies were published before or after adoption of the consortium diagnostic criteria and whether or not subjects had documented *PTEN* mutations. Findings were reviewed by all authors, and consensus was reached on the strength of the data and the appropriateness of including or excluding each clinical feature.

To assess the effectiveness of the resulting criteria, we tested them against the clinical features of patients with *PTEN* mutations who were evaluated at several of our institutions. With approval of the appropriate institutional review board at each institution, the medical records were reviewed on all patients with known *PTEN* mutations and adequate clinical information available. A total of 48 patients met these eligibility criteria.

Results

Brain Lesions

A wide range of brain tumors has been purportedly linked to *PTEN* mutations. The true spectrum and frequency of brain lesions in PHTS is difficult to estimate, however, because brain imaging is rarely done on asymptomatic individuals. There has been only one report of brain magnetic resonance imaging done on 20 asymptomatic CS patients (mean age = 42 years) (19). Brain abnormalities were identified in seven patients, including three with LDD, six with venous and cavernous angiomas, and one with a meningioma. Although at least seven cases of meningioma have now been reported in CS [reviewed in (19)], there are insufficient data to determine whether they are truly associated. The high frequency (30%) of hamartomatous vascular malformations seen by Lok et al. (19) has not been otherwise reported.

LDD (dysplastic gangliocytoma of the cerebellum) is a rare, benign, slow-growing hamartoma that is usually diagnosed in a patient's twenties or thirties. Although a 2007 review identified 54 cases of LDD associated with CS, the frequency of LDD in patients with CS is unknown (20). A prevalence of 1.8% (n = 3 of 172) was found in patients undergoing clinical *PTEN* testing (7), a prevalence of 6% (n = 18 of 290) was found in patients in a research

cohort (17), and a prevalence of 15% was found in cases reported in the literature (21). Adult-onset LDD has been reported to be more indicative of a *PTEN* mutation than childhood onset, based on an analysis of LDD tumors in which mutations were identified in the tumors from all 15 adults but in none of the 3 children (22). Germline confirmation was only possible on six of the adult patients, however. In a literature review of 14 patients with LDD diagnosed when they were aged less than 18 years, three had clinical diagnoses of CS, eight had no signs of the disease, and three had insufficient information to determine a diagnosis (23). Thus, although adult-onset LDD appears to have a stronger association with *PTEN* mutations than pediatric onset, there is insufficient evidence to consider it a pathognomonic criterion.

Although developmental delay and mental retardation have been reported to be associated with *PTEN* mutations in BRRS and CS, there is limited data on this. Mental retardation/developmental delay was reported in 12% of cases in the literature in one report (24) and in 15% to 20% in another (25). It was seen in 17% of 110 mutation-positive patients who underwent clinical testing (7). Reportedly 15% to 20% of patients with BRRS have mental retardation, and an additional 50% may have motor and speech delays but normal adult intelligence (25). Because the rate of mental retardation in the general population is approximately 3%, it appears that this should remain a criterion despite the need for additional data.

Macrocephaly was initially reported to affect approximately 40% of CS patients, based on cases reported in the early literature. However, at that time it was not routinely assessed, and in more recent studies, macrocephaly (defined as a head circumference greater than the 97th percentile) has been found in 80% to 100% of patients with *PTEN* mutations (7,17,20,26,27). Macrocephaly is also seen in the majority of BRRS patients (25).

Germline mutations in *PTEN* also cause a subset of patients with both autism spectrum disorders and macrocephaly, with patients with largest head sizes being more likely to have a mutation (28–32). A recent review found 24 cases reported in the literature (33). Mutations have been found in patients even in the absence of other personal or family history consistent with PHTS.

Breast Disease

Breast cancer is recognized as the most common malignancy associated with CS, with a lifetime risk typically quoted to be 25% to 50% (7,17,24,34,35). The age of onset of breast cancer is believed to be young (age 38–50 years). Three more recent reports on series of women with CS projected the lifetime risk of breast cancer to be 77% in a cohort with clinical testing (36), 81% (37) based primarily on cases reported in the literature, and 85% (38) based on a research cohort. Although each of these approaches suffers from selection biases and there remains debate as to the degree of increased risk, it is clear that female breast cancer is indeed an important part of the tumor spectrum associated with CS. Two males with *PTEN* mutations and breast cancer have been reported (39,40), but male breast cancer was not seen in the two largest cohorts of patients with *PTEN* testing reported to date (17,41).

Benign Breast Disease. Benign breast disease was first noted to be associated with CS in the original case series of Brownstein (34) and has historically been reported to affect approximately 75% of women with the disease (42). Although the term benign breast disease includes all nonmalignant conditions of the breast, fibrocystic breast disease, intraductal papillomas, and fibroadenomas are specifically associated with CS.

Fibrocystic breast disease technically describes pathologic changes seen under the microscope (43) but is often used to clinically describe painful, lumpy breasts. Clinical fibrocystic breast disease affects 30% to 60% of women overall and at least 50% of women of childbearing age (44). Fibroadenomas are the most common benign tumor of the breast, accounting for 50% of all breast biopsies (45). The reported frequencies of these lesions in women with CS (32%–64%) (9,17,24,35,41,46) are nearly identical to that reported in the general population and do not support their inclusion as diagnostic criteria.

Solitary intraductal papillomas, which have an incidence of 2% to 3% in the general population (47), have a high rate of coexistent carcinoma (22%–67%) if atypia is present (48–52). Only one series of CS patients assessed the presence of intraductal papilloma and found a prevalence of seven of 51 (14%) (46) in cases reported before adoption of the consortium diagnostic criteria. Further research is needed in unselected case series to determine if patients with CS are at increased risk for intraductal papillomas or if intraductal papillomas are simply a surrogate marker for a breast cancer.

Gastrointestinal Disease

Recent studies demonstrate that colonic polyps in CS are found in up to 95% of those undergoing colonoscopy (53,54). Polyps may occur at a young age, although their natural history requires more study. Polyps are multiple, may be numerous, even in the hundreds, and are distributed throughout the colon. The most common type of polyp is hamartomatous [29% in one study (53)]; these are usually juvenile polyps, although small hamartomas may not be distinguishable into subtypes. Other reported polyp types include ganglioneuromas, adenomatous, and inflammatory polyps [26%, 27%, and 18%, respectively, in one study (53)] and less commonly leiomyomatous, lipomatous, and lymphoid polyps (42). Hyperplastic polyps have been reported as an association, but this is less certain because hyperplastic polyps are so common in the general population and have not been observed in all studies. That said, hyperplastic polyps were the most common histologic polyp type in one study, and the definition of hyperplastic polyposis (now serrated polyposis) was met in a number of patients with *PTEN*-associated disease (53,55). The majority of CS patients have multiple synchronous histologic types at colonoscopy.

The risk of colon cancer in CS has historically been said not to be elevated (56). Recent reports, however, have indeed shown increased risk. A study from Japan found a 9% prevalence of colon cancer, which is remarkable in view of that country's lower than expected overall risk of this malignancy (57). One multicenter study found 13% of *PTEN* mutation carriers to have colon cancer, all aged less than 50 years (53). A later publication from the same group predicted a 9% (95% confidence interval (CI) = 3.8% to 14.1%) lifetime risk (58). A separate investigation projected a 16% (95% CI = 8% to 24%) lifetime risk of colon cancer, based primarily on review of published cases (21). A recent series from the Mayo Clinic found two of 13 CS patients affected (54). It remains uncertain

whether colonic malignancy arises from adenomatous polyps or if it can also arise from the hamartomatous polyps. Together, the literature now indicates that there is a well-documented increased risk of young-age colon cancer associated with CS.

The esophagus in PHTS is characterized by glycogenic acanthosis (59). One or several such lesions may occasionally be observed in unaffected individuals, but diffuse (ie, dozens to scores or more of them) lesions are observed in 80% or more of those with CS who undergo evaluation (55). The exact frequency of glycogenic acanthosis in CS remains to be determined. It has been suggested that diffuse esophageal glycogenic acanthosis combined with colonic polyposis should be considered pathognomonic for CS (60).

Three studies with reviews report the frequent finding of multiple hamartomatous polyps in the stomach, duodenum, and small bowel (53,56,59). Polyp histologies included hamartomas, hyperplastic polyps (different from colonic hyperplastic polyps), ganglioneuromas, adenomas, and inflammatory polyps. In a recent endoscopic study of 10 *PTEN* mutation–positive CS patients, all 10 had multiple hyperplastic and three had hamartomatous gastric polyps (55). One had a single hamartomatous polyp, and three had adenomatous polyps in the duodenum. There are two reports of gastric cancer in CS patients—one aged 67 years and one aged 73 years (56,61). In the 67-year-old patient, the tumor was found to lack *PTEN* protein. A possible gastric cancer association awaits further study. Further systematic study is also needed of the upper gastrointenstinal and small bowel phenotype in general.

Genitourinary Problems

Women with CS have an elevated risk of endometrial cancer, which has been demonstrated consistently across multiple studies. In two large research series, endometrial cancer occurred in 14.1% and 7.6% of female *PTEN* mutation carriers (7,17), whereas in a cohort of clinically tested patients, 17% of adult women had been diagnosed (7). The relative risk was increased most dramatically for endometrial cancer occurring in women aged less than 50 years. The lifetime risk of endometrial cancer in *PTEN* mutation carriers has been estimated at 19% to 28% at age 70 years (21,36,58). Because these studies did not censor endometrial cancer incidence rates for previous hysterectomy, these rates could be somewhat of an underestimation in women with an intact uterus. Conversely, these studies all suffer from ascertainment biases, which may lead to an overestimate of cancer risk. The proportion of all endometrial cancers attributable to inherited *PTEN* mutations is quite small (62).

Uterine leiomyomata (fibroids) have been frequently espoused as a clinical feature of CS. However, uterine leiomyomata are extremely common in the healthy adult population, where rates depend on age, diagnostic criteria, and whether symptomatic or asymptomatic fibroids are reported. Symptomatic fibroids are generally reported to occur in approximately 20% to 35% of adult women but may be incidentally diagnosed in as many as 60% to 80% of adult women (63,64). Because reports on uterine fibroids in women with a CS diagnosis or with *PTEN* mutations have not described diagnostic criteria, it is not clear whether the rate (21%–38%) (7,17) is increased, but it seems unlikely to be dramatically elevated.

Genitourinary anomalies have also been used as a diagnostic criterion, based on early case reports. Genitourinary anomalies were reported in 5.7% and 1.3% of patients in two research cohorts (17) and 0.6% of a clinically tested cohort (7). The difference in genitourinary anomaly rates between these series is likely attributable to differences in ascertainment and definitions. Presumably, these anomalies were self-reported, and verification is not described. Genitourinary anomalies are some of the most common congenital anomalies that occur in otherwise healthy individuals; the incidence of uterine malformations alone is approximately 5.5% in the general population, and hypospadius and congenital anomalies of the kidneys and urinary tract are also common (65–67) Therefore there is no evidence to demonstrate an increased rate of genitourinary anomalies in subjects with CS or *PTEN* mutations.

The risk for renal cell carcinoma was initially suggested to be increased in CS based on a few case reports (68,69). In the recent large case series of patients with *PTEN* mutations, renal cell carcinoma was reported in 5% of 107 clinically tested adults and 3% to 6.7% of adults who had research testing (7,17). Lifetime risks for renal cell carcinoma were recently projected to be approximately 34% in two studies, although these were based on small numbers of cases and may be an overestimate reflecting ascertainment bias (36,58).

Skin Lesions

CS was initially felt to be primarily a dermatological disease until increased risks were eventually shown for breast cancer (34) and other features. The classic feature of multiple trichilemmomas is well documented throughout early and current studies. In the initial case series, genetic testing was not available, but clinicians commonly observed multiple trichilemmomas on the face, especially on the central portions, including the eyes, mouth, nose, and forehead (9,35,70–73) Other published cases reported other sites of involvement such as the neck, axillae, and hand (74,75). In more recent literature, trichilemmomas were observed in families where genetic testing confirmed a *PTEN* mutation, with prevalences ranging from 6% to 25% in large case series and five of five in a small research cohort (7,17,53,76). In two of these recent cohorts, fewer patients aged less than 18 years compared with patients aged greater than 18 years were noted to have trichilemmomas, suggesting that although they may have a childhood onset, the majority of lesions are clinically evident by adulthood (7,17). It is unclear whether these lesions were only clinically ascertained or whether a skin biopsy was obtained for a proper histopathologic diagnosis. Trichilemmomas are clinically indistinguishable from trichoepitheliomas, fibrofolliculomas, trichodiscomas, or other benign lesions involving the pilosebaceous unit. Additionally, some experts have described trichilemmomas as having either a papular or verruca-like outer appearance, with the latter often leading to a mistaken clinical diagnosis of a common facial wart if there is no confirmatory histopathology (71,72,77,78). A trichilemmoma is rarely a sporadic feature, and the CS literature often reports numerous lesions at presentation in individuals with a clinical and/or genetic diagnosis. Therefore, trichilemmoma is a clinically significant sign of CS when seen in multiplicity (at least ≥3), but at least one lesion should be biopsy proven given the difficulty with clinical diagnosis.

Oral papillomas, especially on the lips, are a major criterion and can be seen in abundance on the tongue, buccal mucosa, and gingivae (9,24,35,70,74,75,78–82). In the original families clinically diagnosed with CS, Starink and colleagues reported that 100% of patients developed oral papillomas by the second decade (35). However, diagnoses in these patients were typically based strongly on dermatological features. Other studies later confirmed this age of onset in both clinically diagnosed patients and *PTEN* mutation carriers (70,74,75,83,84). Oral papillomas are typically asymptomatic and thus can be distinguished from mucocutaneous neuromas in the same location (83,85). However, a mucosal biopsy should be obtained in clinically ambiguous lesions.

Mucocutaneous neuromas (hamartoma of the peripheral nerve sheath) have been reported in older and recent literature (9,83,85). Neuromas may represent an inadvertently unreported and therefore less-defined entity because of clinical misclassification in absence of a biopsy (85). Starink and colleagues reported that more than half of their clinically diagnosed patients had developed mucocutaneous neuromas before age 18 years (35). Selected case studies observed neuromas on the face and at sites including the hands, palms, shins, and back (83,85). Based on the current evidence, at least three mucocutaneous neuromas present on the face or elsewhere on the body, with or without a skin biopsy, should count as a major diagnostic feature of PHTS. Further studies are needed to more precisely define relevant characteristics and locations of these neuromas.

Acral keratoses are located on the palmoplantar surfaces and dorsal hands/feet and are hyperkeratotic or palpable, wart-like appearing lesions (9,24,35,74,80,84,86). Acral keratoses have been noted in both pediatric and adult populations of *PTEN* mutation carriers, but further studies are needed to define the age of onset and penetrance (17,53,84,87). Some case reports observed keratoses appearing on nonacral sites, such as the face and trunk, but skin biopsies were not mentioned (9,35). Further studies are needed to determine if keratoses are a common feature in nonacral sites in the *PTEN* hamartoma tumor syndrome.

Penile pigmentation (macular pigmentation of the glans penis) is a major criterion in male subjects. Genital benign melanocytic neoplasms (or melanosis) are reported in up to 15% of both male and female persons in the general population (88). The first identification of pigmented macules on the penis were reported in 1996 in two unrelated families with a clinical diagnosis of BRRS, well after the original description of the syndrome in 1971 (78,89). In the most recent literature, two large cohort studies reported that 48% of all males with either a clinical diagnosis or a *PTEN* mutation and a combined 53% of male *PTEN* mutation carriers were reported to have clinically significant penile freckling (7,17). Based on the cumulative evidence, multiple genital lentigenes appear to be highly predictive of having a *PTEN* mutation compared with solitary genital brown macules.

Both lipomas and vascular (venous or arterial) anomalies are common in BRRS and CS. In a prospective cohort of 43 clinically and/or genetically diagnosed unrelated BRRS cases compared with 37 unrelated CS families, the features of lipomas and vascular abnormalities were more commonly observed in BRRS or BRRS/CS overlap families (90). Other selected case reports confirm the association of arteriovenous malformations in clinically diagnosed BRRS individuals (2,91–93) The arteriovenous malformations have been reported on the retina, buttocks, back, and groin, as well as visceral organs. Smaller case series have reported hemangiomas (considered a vascular neoplasm with many subtypes) and cavernous hemangiomas (considered a venous malformation) present in both pediatric and adult cases of *PTEN* carriers (83,86,94). However, because these cases do not specify the hemangioma subtype, their association with PHTS is uncertain. In the general population, certain subtypes of hemangioma are sporadic and common in children or adults. The presence of multiple lipomas in an individual in the general population is rare, but this has been reported in several small and large case series of individuals with a *PTEN* mutation (7,9,35,53,68,74,78,81,83,84,94–96)

Fibromas, including sclerotic fibroma of the skin and oral fibromas, have been reported in patients with CS. Sclerotic fibroma of the skin is rare in the general population as reported by Rapini and colleagues, and there are several case series representing CS patients who consistently show both solitary and multiple lesions with histopathological confirmation from skin biopsies (35,97–99). However, it still remains unclear whether sclerotic fibroma is a true component feature of PHTS because these case series represent individuals with a clinical diagnosis of CS without genetic testing. Oral fibroma is more common in the general population than sclerotic fibroma, but the incidence of sporadic oral fibromas is not well defined. Multiple oral fibromas in CS families are reported to range between 14% and 76%, but again these individuals did not undergo genetic testing (24,35). Although studies are needed in individuals with *PTEN* mutations, because sclerotic fibromas and multiple oral fibromas are rare in the general population and given the multiplicity of these fibromas observed in patients with CS, these features have been included in the clinical diagnostic criteria.

Although cutaneous melanoma has not been included in past diagnostic criteria, there have been case reports suggesting that it may be associated with CS (9,100–102). Melanoma was reported in only two of 172 patients with mutations detected through clinical testing in one recent cohort (7), but the mean age of the cohort was only 29.8 years. More recently, two groups have projected a lifetime risk for melanoma of 6% (based on nine cases of melanoma reported among 368 patients with mutations) and standardized incidence ratios (of 28.3 in women and 39.4 in men (based on nine cases among 154 mutation-positive patients) (36,58). Although there is increasing evidence of some association, we believe that more studies are necessary before adding melanoma as a diagnostic criterion.

Testicular lipomas were not included in the consortium diagnostic criteria for CS. They were first reported in 2003 in a 39-year-old male with CS who presented with multiple fat-containing hamartomas of the testicles (103). Woodhouse et al. next reported a series of eight males (aged 16–58 years) with documented *PTEN* mutations in whom testicular ultrasounds identified distinctive, multiple (>40 per patient), bilateral hyperechoic lesions in all but the youngest patient (104,105). Four patients had biopsies, which confirmed they were lipomas. Subsequently, several other cases of testicular lipomas in males with CS or BRRS have been reported (106,107) Testicular lipomas are very rare in the general population in absence of testicular neoplasia (105), with Harper et al. finding only one case in a Medline search from 1970 to 2001 (108). Thus,

although the literature is limited and the frequency in males with *PTEN* mutations is unknown, the finding of multiple testicular lipomas appears to be a clinically significant indicator of the presence of an underlying *PTEN* mutation.

Thyroid Disease

CS and BRRS have both been associated with both benign and malignant thyroid disease. However, thyroid neoplasms are very common in the general population, where the prevalence of thyroid nodules ranges from 2% to 6% (based on physical exam) to 19% to 35% (based on ultrasound) to 65% (based on autopsy) (109). Multinodular goiter (MNG), defined as an enlarged thyroid with multiple nodules, is present in approximately 4% of the population (110). Hashimoto's thyroiditis (ie, chronic lymphocytic thyroiditis or chronic autoimmune thyroiditis) occurs in 2% of the population (111). Thyroid nodules, adenoma, or goiter have been reported in 30% to 68% of adults and 2% to 14% of children with *PTEN* mutations (7,17). The data have generally been aggregated, which prevents distinguishing the proportion of cases presenting with MNG vs solitary nodules. Tan et al. did look separately at Hashimoto's thyroiditis, and they reported a prevalence of 3% to 21% in individuals with *PTEN* mutations (17).

Few studies have provided detailed descriptions of the clinical features and pathology of thyroid nodules in *PTEN* mutation carriers. A pathologic review of 20 individuals who underwent total or partial thyroidectomy revealed that all glands had multiple findings, with the most common being MNG (75%), frequently occurring in a background of thyroiditis (55%) (112). Another study that reviewed the thyroid pathology of 25 individuals with *PTEN* mutations found MNG in 78%, frequently occurring with thyroiditis (50%) (113). A final study examined the thyroid pathology of seven children with *PTEN* mutations. The age of diagnosis of thyroid nodules ranged from 6 to 12 years, and thyroid nodules were one of the presenting features in four of the seven children (114). However, all these studies have only evaluated individuals who presented with thyroid disease, and the frequency and clinical presentation in unselected mutation carriers is unknown. No studies that look at the likelihood of detecting a *PTEN* mutation in individuals presenting only with benign thyroid disease have yet been done.

The majority of thyroid cancers in the general population are classified as differentiated, with papillary thyroid cancer accounting for approximately 80% to 85% and follicular thyroid cancer accounting for only about 15%. The general population lifetime risk for a clinical diagnosis of differentiated thyroid cancer is approximately 1% (115). In comparison, the lifetime risk of thyroid cancer in *PTEN* mutation carriers has generally been reported to be 3% to 10% (42). Recent analyses of two cohorts of *PTEN* mutation carriers have projected that the risk may be as high as 35% to 38%; however, as history of thyroid cancer was one of the possible eligibility criteria for testing, this ascertainment bias may have resulted in these substantially higher estimates (36,58). Among confirmed mutation carriers who develop thyroid cancer, both papillary (including follicular variant) (56%–60%) and follicular (25%–45%) cancer have been reported (112,116). Although papillary thyroid cancer is frequently identified in the thyroid pathology of *PTEN* mutation carriers, some of these diagnoses may be incidental. Laury et al. (112) reported that six of 12 cases of papillary thyroid cancer in *PTEN* mutation carriers were microcarcinomas. Autopsy studies have indicated that the general population rate of thyroid microcarcinomas is between 36% and 50% (117,118). Follicular thyroid cancer, on the other hand, appears to be over-represented in mutation carriers compared with the general population and thus may have greater value in predicting *PTEN* mutation status. A study comparing individuals with thyroid cancer who had a confirmed *PTEN* mutation vs those who had some features of CS but no identified mutation found that the proportion of papillary thyroid and follicular thyroid cancer in the mutation carriers was 56% and 25%, indicating an over-representation of follicular thyroid cancer, whereas those without mutations had a cancer distribution similar to the general population (76% papillary, 8% follicular) (116).

To date, only one study has looked at the prevalence of *PTEN* mutations in unselected individuals presenting with differentiated thyroid cancer. Analysis of 259 individuals identified two with germline *PTEN* mutations. Both had follicular thyroid cancer and other features of *PTEN* hamartoma tumor syndrome such as macrocephaly. Subset analysis of the data indicated that two of 42 follicular thyroid cancer cases harbored *PTEN* mutations (119). Another study looked at the prevalence of *PTEN* mutations in women presenting with both primary breast and thyroid cancer. No mutations were identified among these cases presenting with this phenotype (120).

The current data support the hypothesis that both benign thyroid disease and thyroid cancer are part of the PHTS. However, the high frequency of thyroid disease in the general population means that when taken on their own, thyroid neoplasms have a low predictive value for identifying mutations carriers. Based on the data available, we recommend specifying only follicular thyroid cancer as a major criterion and including papillary thyroid cancer, benign thyroid nodules, and MNG as minor diagnostic criteria.

Assessment of Revised Criteria

Of 48 patients with *PTEN* mutations who were seen at our institutions and who had full clinical evaluations, 44 met our revised diagnostic criteria. The four that did not included two children (aged 5 and 6 years) and two adults (ages 33 and 35 years) who had not had colonoscopies, suggesting that the features necessary to meet diagnostic criteria may not all be present or apparent in earlier life. Thus additional clinical judgment may be necessary when applying these criteria to pediatric and early adult patients. Although this is a limited cohort, it provides evidence of the improvement in sensitivity that these revised criteria provide over the current consortium criteria.

Discussion

The International Cowden Consortium diagnostic criteria were drafted in 1996 based on expert opinion and published cases. Because standard diagnostic criteria did not exist for many years after the initial report of the syndrome, diagnoses were inconsistently made and initially relied heavily on the dermatological

features of the disease. The adoption of consensus diagnostic criteria was a major step forward, but they were not based on a systematic ascertainment of the clinical features of the disease. Although the identification of the *PTEN* gene in 1997 led to the ability to molecularly define the syndrome, it has not led to a rigorous reassessment of the diagnostic criteria. Furthermore, it has now been shown that mutations in the same gene are associated with other diseases (BRRS) and additional clinical features not included in the consortium criteria. Other data have shown that the reported proportion of patients meeting consortium criteria who have detectable *PTEN* mutations (80%) was inaccurate, and the true figure may be closer to about 30% to 35% (7,17). In addition, many of the combinations of clinical features that meet consortium diagnostic criteria, such as the parings of macrocephaly and breast, thyroid, or endometrial cancer, have limited value in predicting *PTEN* mutations (7). We thus sought to review the existing literature for evidence-based guidance to revise and expand the CS diagnostic criteria, both to include the broader spectrum of *PTEN*-associated clinical features that are part of PHTS and to increase the positive predictive value of the criteria.

Any assessment of this type faces substantial limitations based on the quality of the data in the literature. For this study, much of the literature on PHTS-related conditions and patients with *PTEN* mutations is anecdotal, is based on small numbers of patients, or was published before the adoption of consensus diagnostic criteria. More recent studies that were done on much larger patient cohorts face notable ascertainment biases in that patients were selected for testing based on the number and extent of the clinical features they demonstrated, which would lead to overestimates for many of the cardinal features of the disease. The impact of this is most clear in the recent projections by several groups of lifetime cancer risks that seem out of proportion with those seen in real-life clinical practice (36,58) and that have been questioned by some (121). Unfortunately there are no studies of *PTEN* testing on substantial numbers of unselected patients nor are there likely to be given the rarity of these mutations. Thus, despite its flaws, an assessment such as this one provides the best available means of developing diagnostic criteria.

Another inherent limitation is the circularity of defining CS or any of the PHTS conditions. If these are clinically defined conditions, do those cases meeting clinical diagnostic criteria but not demonstrating a mutation represent either missed *PTEN* mutations, genetic heterogeneity, or phenocopies? Or should they be defined by presence of a *PTEN* mutation, in which case absence of a mutation indicates that the patient does not have a diagnosis (or more rarely may have a missed mutation)? The individual clinical features seen in PHTS patients are often common in the general population, and many individuals or families will by chance have coincidental occurrences of multiple features. Because there is no other objective measurement by which to define clinical criteria, we felt the most appropriate approach was to assess the features shown to be associated with *PTEN* mutations and build the clinical diagnostic criteria around those.

We felt that despite the limitations of the available data, it is important to produce a more evidence-based revision and expansion of the diagnostic criteria for use in clinical practice. Our review of the literature has led to a number of important conclusions. We felt there was insufficient evidence to classify any of the clinical features as pathognomonic. We felt there was no sufficient evidence to support the inclusion of benign breast disease, uterine fibroids, genitourinary malformations, or brain tumors other than LDD. We felt there was evidence to include a number of additional features, including autism spectrum disorders, colon cancer, esophageal glycogenic acanthosis, penile macules, renal cell carcinoma, testicular lipomatosis, and vascular anomalies. We also felt that recent literature demonstrated that the consortium criteria were too lax, and we thus have made the revised criteria more stringent by requiring the presence of more clinical features in order to make a diagnosis.

Our revised criteria are presented in Table 1. As noted above, the majority (n = 44 of 48) of patients in our institutions who had full clinical evaluations met these revised criteria, with only two children and two adults who had not had colonoscopies not meeting them. Although these are limited data and more studies are needed, they suggest a substantial improvement in the specificity of these criteria. Thus we propose that this new set of PHTS diagnostic criteria be used from this point forward in making clinical

Table 1. Revised *PTEN* hamartoma tumor syndrome clinical diagnostic 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 (≥97 percentile: 58 cm for females, 60 cm for males)
Macular pigmentation of the glans penis
Multiple mucocutaneous lesions (any of the following):
Multiple trichilemmomas (≥3, at least one biopsy proven)
Acral keratoses (≥3 palmoplantar keratotic pits and/or acral hyperkeratotic papules)
Mucocutaneous neuromas (≥3)
Oral papillomas (particularly on tongue and gingiva), multiple (≥3)
OR biopsy proven OR dermatologist diagnosed
Minor criteria
Autism spectrum disorder
Colon cancer
Esophageal glycogenic acanthosis (≥3)
Lipomas (≥ 3)
Mental retardation (ie, IQ ≤ 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)
Operational diagnosis in an individual (either of the following)
1. Three or more major criteria, but one must include macrocephaly, Lhermitte-Duclos disease, or gastrointestinal hamartomas; or
2. Two major and three minor criteria.
Operational diagnosis in a family where one individual meets revised *PTEN* hamartoma tumor syndrome clinical diagnostic criteria or has a *PTEN* mutation:
1. Any two major criteria with or without minor criteria; or
2. One major and two minor criteria; or
3. Three minor criteria.

diagnoses of these *PTEN*-related diseases. As always, molecular testing is recommended whenever possible, both to confirm a clinical diagnosis and to facilitate testing of at-risk relatives.

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