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COMMENTARY

Cowden Syndrome: A Critical Review of the Clinical Literature

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Abstract Cowden syndrome (CS) is a multi-system disease involving hamartomatous overgrowth of tissues of all three embryonic origins and increased risks for thyroid, breast and possibly other cancers. Benign breast, thyroid, uterine and skin lesions are also common. Approximately 80% of patients with CS have an identifiable germline mutation in the *PTEN* gene. The majority of the existing data on the frequencies of component clinical features have been obtained from compilations of case reports in the literature, many of which predate the establishment in 1996 of consensus diagnostic criteria. Many of these reports also suffer from ascertainment bias which emphasized the dermatologic features of the disease. This paper presents an overview of Cowden syndrome focusing on a critical evaluation of the major literature on the component cancers, benign features, and molecular findings in CS, noting the limitations of the published data.

Keywords Cowden syndrome · *PTEN* · *PTEN* hamartoma tumor syndrome · PHTS

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Introduction

Cowden syndrome, an autosomal dominant disorder, is one of a spectrum of clinical disorders that have been linked to germline mutations in the *PTEN* gene. The *PTEN* (*p*hosphatase and *ten*sin homolog on chromosome 10) tumor suppressor gene is a dual specificity phosphatase with multiple and as yet incompletely understood roles in cellular regulation. As a lipid phosphatase it is known to signal down the PI3K/Akt pathway to cause G1 cell cycle arrest and apoptosis. Its protein phosphatase activity has also been shown to regulate cell-survival pathways, such as the mitogen-activated kinase (MAPK) pathway. Its homology to the focal adhesion molecules tensin and auxilin suggests that it may play a role in cellular migration and focal adhesion. Thus *PTEN* could potentially play significant roles in a number of molecular pathways regulating cellular proliferation, migration and apoptosis, all processes that are important in the regulation of normal cellular growth (Tamguney and Stokoe 2007). Clinically, germline mutations in *PTEN* have been associated with a broadening spectrum of disorders, including Cowden syndrome, Bannayan-Riley-Ruvalcaba syndrome, Proteus or Proteus-like syndrome, adult Lhermitte–Duclos disease, and autism-like disorders associated with macrocephaly.

Bannayan–Riley–Ruvalcaba syndrome (BRRS) is a congenital disorder whose cardinal features include macrocephaly, hamartomatous intestinal polyps, lipomas and pigmented penile macules. Additional features include developmental delay, large birth weight, joint hyperextensibility, and a myopathic process in proximal muscles (Gorlin et al. 1992). Consensus diagnostic criteria have not been established but diagnoses are usually based on the presence of the cardinal features. Initially thought to be a

separate disease, BRRS was subsequently shown to be allelic to CS, with approximately 60% of patients with BRRS having detectable coding sequence mutations in *PTEN* (Marsh et al. 1999).

Proteus syndrome is a complex and highly variable disorder involving hamartomatous tissue overgrowth, congenital malformations, hyperostosis, and epidermal and connective tissue nevi which occur in a mosaic pattern (Biesecker et al. 1999). While germline *PTEN* mutations have been identified in a subset of patients with features of Proteus syndrome (Zhou et al. 2000, 2001a), there is some debate over whether *PTEN* mutations have been identified in patients actually meeting the diagnostic criteria for Proteus syndrome (Cohen et al. 2003).

Lhermitte–Duclos disease (LDD) is a dysplastic gangliocytoma of the cerebellum. As reviewed below, it appears that the majority, if not all, adult onset LDD occurs in patients with germline mutations in the *PTEN* gene, sometimes in absence of other clinical signs of CS/BRRS (Zhou et al. 2003a). Germline *PTEN* mutations are less common in patients with childhood onset LDD, however.

Germline mutations in *PTEN* also cause a subset of cases of combined autism spectrum disorders and macrocephaly, with or without other personal or family history consistent with CS/BRRS (Butler et al. 2005; Herman et al. 2007). It appears that the degree of macrocephaly may indicate the likelihood of finding a mutation. In one report *PTEN* mutations were found in 3 of 18 (17%) patients with ASD and head circumferences 2.5 standard deviations (SD) or more above the mean (with the three positive patients having head circumferences of 4, 7 and 8 SD above the mean), while in another cohort of 88 patients with ASD and head circumferences only 2 SD or greater, only one mutation was found, in a boy with a head circumference 9.6 SD above the mean (Butler et al. 2005; Buxbaum et al. 2007).

Juvenile polyposis syndrome (JPS) presents with hamartomatous polyps in the stomach, small intestine, colon, and rectum and increased risks for a number of malignancies. Mutations in the *MADH4* and *BMPR1A* genes are found in approximately 50% of patients (Howe et al. 1998, 2001). While some reports have sugested that germline *PTEN* mutations can occur in JPS (S. C. Huang et al. 2000; Lynch et al. 1997; Olschwang et al. 1998), others have suggested that these individuals actually have CS (Kurose et al. 1999). In another case a germline *BMPR1A* mutation was identified in a patient with only colonic polyposis but a family history suggestive of Cowden syndrome (Zhou et al. 2001b). The authors felt that on the basis of the mutation status this patient should be classified as having JPS rather than CS.

The focus of the present review is on Cowden syndrome exclusively, with an emphasis on reviewing the reported frequencies of the component features of the syndrome, and the data supporting those findings.

Molecular Genetics

CS was mapped to the 10q22–23 locus in 1996 (Nelen et al. 1996), and *PTEN* mutations were first reported in individuals with CS in 1997 (Nelen et al. 1997; Liaw et al. 1997). Germline coding sequence mutations in *PTEN* are generally reported to be found in 80% of patients with CS. However mutation detection rates using DNA sequencing in patients meeting CS diagnostic criteria have ranged from 4 of 5 (80%) patients (Liaw et al. 1997), 9 of 19 (47%) patients (Nelen et al. 1997), 30 of 37 (81%) patients (Marsh et al. 1998b), and 8 of 13 (61%) patients (Nelen et al. 1999). Tsou et al., also using DNA sequencing, found mutations in only 3 of 27 (11%) families with individuals meeting Consortium diagnostic criteria for CS (Tsou et al. 1997). In addition, in 2 of 4 families with multiple affected relatives but no detectable mutation they were able to exclude linkage to *PTEN*, supporting locus heterogeneity. In contrast, the original report on linkage to the 10q22–23 locus found no evidence for genetic heterogeneity among 12 CS families originating from 4 different countries (Nelen et al. 1996). In a recent report germline genetic variants were found in the *SDHB* and *SDHD* genes in a cohort of patients with CS or a CS-like phenotype (Ni et al. 2008). None of the patients with genetic variants met current NCCN diagnostic criteria for Cowden syndrome, however.

Families with a member with Bannayan–Riley–Ruvalcaba syndrome and also other relatives with features of CS (so called overlap families) are said to have the highest mutation rates (Eng 1997). Ten of 11 (91%) such overlap families were found to have *PTEN* mutations, where "overlap" was loosely defined as one family member meeting BRRS diagnostic criteria and at least one other family member having either uterine cancer, breast cancer, a breast fibroadenoma, trichilemmomas, or papillomatous papules of the skin (Marsh et al. 1999).

Additional molecular studies have been done in CS. The use of a whole gene cDNA probe in four of the five mutation-negative patients in one early cohort failed to detect a gene deletion (Nelen et al. 1999). More recently, using real time and multiplex PCR, Zhou et al. found no evidence of large *PTEN* gene deletions or rearrangments among the 95 CS patients for whom no coding sequence mutation had been identified using denaturing gel gradient electrophoresis (Zhou et al. 2003b). In another recent report, 80 unrelated patients with clinically diagnosed CS (15 cases), or a CS-like phenotype (primarily macrocephaly and lipomas; 65 cases), who were negative for *PTEN* mutations using denaturing gel gradient electrophoresis, were screened for large rearrangements using multiplex amplifiable probe hybridization (MAPH; Chibon et al. 2008). Deletions were found in four patients—two restricted to the *PTEN* gene and two involving at least two

adjacent genes. Three of the 15 patients with clinically-diagnosed CS had deletions, while the one patient classified among the 65 CS-like patients who was found to have a deletion actually had a CS/BRRS-like phenotype (cerebellar hamartoma, lipomas and speckled penis). And finally, it has been shown using DNA sequencing that approximately 10% (9 of 95) of mutation-negative CS patients (i.e., about 2% of all CS patients) have a variant in the *PTEN* promoter (Zhou et al. 2003b). Protein expression studies suggested that these variants could be deleterious.

The new mutation rate for *PTEN* is unknown. While some have projected a low mutation frequency (Nelen et al. 1999), a number of cases of apparently spontaneous mutations have been identified in cases in which both parents have tested negative for a mutation found in their child (R. Pilarski, unpublished data). At least one case of apparent germline mosaicism has also been identified (R. Pilarski, A. Gammon, T. Prior, unpublished data).

Clinical Overview

Cowden syndrome is a multi-system disorder involving increased risks for a number of malignancies as well as benign hamartomatous overgrowth of various tissues. CS was first described in 1963 (Lloyd and Denis 1963), and was named after the family in which it was reported. Little more appeared in the literature until 1972 when Weary et al. described an additional set of five patients, expanding the spectrum of component features and suggesting that the syndrome be renamed the "multiple hamartoma syndrome" (Weary et al. 1972). The prevalence of CS has been estimated to be between 1/200,000 and 1/250,000, based on projections from a study of the Dutch national registry in which 45 patients were clinically identified among 4.5 million individuals age 25 years old and older (Nelen et al. 1999). Diagnostic criteria for CS were initially proposed in 1983 (Salem and Steck 1983), and later revised by consensus of an international consortium of researchers who mapped the disease to the 10q22–23 locus (Nelen et al. 1996). Clinical diagnoses since that time have been based on these "Consortium criteria", which require the patient to have a requisite number of diagnostic criteria, which are divided into groups of "pathognomonic", "major" and "minor" criteria based on their significance (Table 1).

Modifications to the original Consortium diagnostic criteria have been proposed, including the addition of endometrial cancer as a major criterion (Eng 2000), and renal cell carcinoma as a minor criterion (Pilarski and Eng 2004). More recently it was proposed that adult Lhermitte-Duclos disease (LDD) be moved into the pathognomonic category (Zbuk et al. 2006) based on evidence reviewed below. In the process, however, the requirement that LDD *or* macrocephaly must be one of the two major criteria needed to meet category 2 of the operational diagnostic criteria was dropped. This led to a situation in which a single individual with both breast and thyroid cancers or breast and endometrial cancers would meet CS diagnostic criteria. The available data suggest that the likelihood that such a person has a *PTEN* mutation is quite low, however (see below), and the National Comprehensive Cancer Network has corrected this oversight in its most recent

Table 1 Cowden Syndrome Diagnostic Criteria

Criteria	
Pathognomonic criteria	•Lhermitte-Duclos disease (LDD) – adult •Mucocutanous lesions: Trichilemmomas, facial Acral keratoses Papillomatous lesions
Major criteria	•Breast Cancer •Thyroid Cancer (papillary or follicular) •Macrocephaly (≥97%ile) •Endometrial cancer
Minor criteria	•Other structural thyroid lesions (e.g., adenoma, multinodular goiter) •Mental retardation (i.e., IQ ≤ 75) •Gastrointestinal hamartomas •Fibrocystic disease of the breast •Lipomas •Fibromas •Genitourinary tumours (e.g., uterine fibroids, renal cell carcinoma) or •Genitourinary structural malformations •Uterine fibroids
Operational diagnosis in an Individual	Any of the following: 1. Mucocutanous lesions alone if: (a) There are six or more facial papules, of which three or more must be trichilemmoma, or (b) Cutaneous facial papules and oral mucosal papillomatosis, or (c) Oral mucosal papillomatosis and acral keratoses, or (d) Palmoplantar keratoses, six or more 2. Two or more major criteria, but one must include macrocephaly or LDD; or 3. One Major and three minor criteria; or 4. Four minor criteria.
Operational diagnosis in a family where one individual is diagnostic for Cowden	1. One pathognomonic criterion; or 2. Any one major criterion with or without minor criteria; or 3. Two minor criteria; or 4. History of Bannayan–Riley–Ruvalcaba syndrome

(National Comprehensive Cancer Network 2008)

practice guidelines (National Comprehensive Cancer Network 2008). Currently, a single individual meets clinical diagnostic criteria if they have either (1) adult Lhermitte–Duclos disease or a requisite number of mucocutaneous features; (2) macrocephaly plus one other major criterion; (3) one major and three minor criteria; or (4) four minor criteria. The diagnostic criteria are less stringent if another family member has already been diagnosed with CS.

The penetrance of CS is said to be nearly complete, and it approaches 90% by age 20 (Eng 1997). The evidence for this figure comes from older reviews of published cases (Starink et al. 1986). However these cases predated the development of the Consortium diagnostic criteria, and the diagnoses in most cases were based primarily on the presence of mucocutaneous features. Not coincidentally, the high penetrance rates were influenced heavily by the presence of these mucocutaneous features. Accurate penetrance estimates for patients diagnosed using the Consortium diagnostic criteria are not available.

Component Cancers

The commonly reported rates of cancers in patients with CS are 25–50% for breast cancer and 3–10% for non-medullary thyroid cancer (Table 2). These figures are frequency counts taken from compilations of cases published in the literature, rather than lifetime risks projected from unselected patient cohorts. The single largest patient series in any of these reports was 21 patients (Starink et al. 1986). As mentioned above, the bulk of the available data comes from papers published prior to establishment of the Consortium diagnostic criteria, and diagnoses were usually based primarily on the presence of the mucocutaneous features of CS (Salem and Steck 1983; Starink 1984; Starink et al. 1986). Since these papers were primarily reviewing cases published in the literature, many of the same cases overlap between the various reports. In addition, since the cases in the literature tended to be diagnosed with CS at relatively young ages (often in their thirties and forties), it is possible that the patients reported as unaffected in these series may have later developed cancer, which would make the following figures underestimates. Nonetheless, these represent the best data available.

Table 2 Commonly Reported Manifestations of Cowden Syndrome

Manifestations	Prevalence
Mucocutaneous lesions	90–100%
Trichilemmomas	
Acral keratoses	
Verucoid or papillomatous papules	
Thyroid abnormalities	50–67%
Goiter	
Adenoma	
Cancer	3–10%
Breast lesions	
Fibroadenomas/fibrocystic disease	76% of affected females
Adenocarcinoma	25–50% of affected females
Gastrointestinal lesions	40%
Hamartomatous polyps	
Macrocephaly	
Genitourinary abnormalities	44% of females
Uterine leiomyoma	Multiple, early onset

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Breast Cancer

The risk of developing breast cancer in CS is generally reported to be 25–50%, compared to 12% for women in the general population (Ries et al. 2008). The average age of diagnosis is said to be between 38 and 46 years of age. While breast cancer is undoubtedly the most common component cancer of CS, the true lifetime risk and mean age of diagnosis cannot be accurately determined from the existing data. Only two cases of CS males with breast cancer have been reported.

Breast cancer was first clearly recognized to be a component feature of CS in 1978 (Brownstein et al. 1978), and is now felt to be the most common CS malignancy, with an estimated 25–50% of female patients affected. Brownstein, Wolf and Bikowski reported that 10 of 21 (~50%) female CS patients that they were aware of (from the literature and their own experience) had been diagnosed with breast cancer (Brownstein et al. 1978). The eleven unaffected cases ranged in age from 20 to 45 years old (median age 36); three of these women had mothers with breast cancer. One of the mothers was noted to have CS, but no comment is made regarding the other two.

Starink et al., reporting on the largest series of cases published to that date, found breast cancer in 22% (4/18) of their female CS patients (Starink et al. 1986). The mean age of all the female patients (affected and unaffected with breast cancer) was 42 years old. The diagnosis of CS for these patients was based entirely on dermatologic features. In combining their 18 cases with 45 others reported in the literature they found an overall 28% (18/63) rate of ductal adenocarcinoma in female CS patients. However 44% (7/16) of the female CS patients over age 50 had breast cancer. The average age of the patients without breast cancer was only 36 years old, again suggesting that these figures may well underestimate the lifetime breast cancer risk. Another report, again reviewing cases collected from the literature, found breast cancer diagnosed in only 18% (12/65) of female patients (Hanssen and Fryns 1995).

Bilateral breast cancer was found in four of the ten breast cancer cases reported by Brownstein et al. (1978) and 6 of the 18 cases reported by Starink et al. (1986). The risk for a second primary breast cancer in CS is not known, however. While two cases of males with deleterious *PTEN* mutations and early onset breast cancer (41 and 43 years old) have been reported (Fackenthal et al. 2001; Marsh et al. 1998b), it is not yet known whether male breast cancer is truly a component of CS, and if so at what frequency. Starink et al. (1986) noted that they did not include a poorly documented possible case of male breast cancer in their report.

The "average" age of breast cancer diagnosis in CS patients is usually said to be between 38 and 46 years of age. This is extrapolated from the case cohorts reviewed above in which Brownstein et al. (1978) found a median age of diagnosis of 46 years among 10 patients, Starink (1984) found a median age of 41 years (range 20–62) among 15 cases, and Starink et al. (1986) found an average age of 38 years (range 14–66) among 18 cases. Schrager et al. (1997), reporting on the breast pathology in 19 women with CS, noted breast cancer onset ranging from 33 to 74 years of age, with a mean of 46 years. They noted no distinguishing differences in cancer histopathology compared to the general population.

Thyroid Cancer

Thyroid cancer is reported to be the second most common cancer in patients with CS. The chance of developing thyroid cancer in CS is generally reported to be approximately 3–10%, (Eng 1997), compared to a lifetime risk of less than 1% in the general population (Ries LAG 2008). The thyroid cancer in CS is exclusively of follicular or papillary histology; medullary thyroid cancer is not felt to be part of the syndrome. As with breast cancer, however, the true lifetime risk of thyroid cancer cannot be determined from the existing data. While follicular thyroid cancer is said to be more common than papillary, there is limited data to support this and some evidence to contradict it. The average age of diagnosis is unknown, but childhood onset has been reported.

The risks quoted for thyroid cancer in CS are based on reports among the same case cohorts that were cited above for breast cancer frequencies: Salem and Steck (1983) found thyroid cancer reported in 3/46 cases (6.5% overall; but 3/25 or 12% of female patients and 0/21 male patients were affected), Starink et al. (1986) found thyroid cancer reported in 3/100 cases (3% overall; but 3/63 or 5% of female patients and 0/37 male patients) and Hanssen and Fryns (1995) in 7/98 (7% overall). Again it should be noted that overlap of cases exists among these reports.

Limited data from the existing literature suggest that the majority of thyroid cancers in CS are of follicular histology. The three cases of thyroid cancer reported by Starink et al. (1986) were follicular adenocarcinomas, although one showed papillary features. Longy and Lacombe (1996), citing reports of follicular carcinomas in 10 and 13 year-old children and a papillary carcinoma in a 17-year-old male, state that there "appears to be clear predominance of follicular types of carcinoma", without further referencing the statement. A 1999 report on the pathological findings in thyroid specimens from 11 patients (from six families) meeting Consortium diagnostic criteria found that nine showed follicular adenomas and two of those also had follicular carcinomas. These reports are in contrast to our own data in which the majority of documented thyroid cancers in 206 patients with *PTEN* mutations were of papillary histology (5/15) or follicular variant of papillary histology (5/15) (R. Pilarski, C. Eng, unpublished data).

While the average age of diagnosis of thyroid cancer in CS in not known, it should be noted that, in addition to the cases mentioned above, childhood onset has been reported in at least three other children as young as 11 and 13 years of age (Tan et al. 2007).

Breast and Thyroid Double Primary Cancer Patients

As noted above, removal of macrocephaly and Lhermitte-Duclos disease as a required major criterion for category 2 of the CS diagnostic criteria led to a situation in which a woman with breast and thyroid double primary cancers would meet CS diagnostic criteria. However Marsh et al. (1998a) published a report on PTEN mutation analysis in 64 CS-like families (i.e., families not meeting CS diagnostic criteria). Among these were 22 families with breast and thyroid cancer together in at least one person and 32 families with breast and thyroid cancers in different persons. No mutations were found in any of the families with a member with breast/thyroid double primary cancers. Only one *PTEN* gene alteration was identified among the 64 families—an L70P missense variant in the last nucleotide of exon 3 which was predicted to affect splicing (no data provided) and was not seen in 100 normal alleles studied. This variant was found in a male with follicular thyroid carcinoma diagnosed at age 31 who had a mother with bilateral breast cancer at ages 49 and 53 and endometrial cancer at age 63. His mother was not tested for the variant. Macrocephaly, skin lesions and other signs of CS were absent in this family, and the patient did not meet Consortium diagnostic criteria. As noted above, the NCCN has recently revised its diagnostic criteria to again require that macrocephaly be one of the two major criteria for CS diagnostic category 2 (National Comprehensive Cancer Network 2008).

Endometrial Cancer

The risk for endometrial adenocarcinoma in Cowden syndrome has been estimated to be approximately 5–10% (Eng 2000), compared to the 2.5% lifetime risk for women in the general population (Ries et al. 2008). As with the other component cancers of CS, the lifetime risk cannot be determined from the available data.

Although the evidence is clear that somatic *PTEN* mutations play an important role in the process of endometrial carcinogenesis, the evidence that germline mutations increase the risk for endometrial cancer is limited. *PTEN* is known to be frequently somatically mutated in endometrioid endometrial cancer and in precancerous endometrial tissues (Mutter et al. 2000). A mouse model carrying a heterozygous *PTEN* mutation was also shown to have high rates of breast and endometrial cancers (Stambolic et al. 2000). Salem and Steck (1983) reported endometrial cancer in 1/25 (4%) of their female CS patients. Starink et al. (1986) reported four known cases among 63 females (6.3%) with CS; the ages of diagnosis were 39, 58, and 59 years old, and unknown in one case. The study by Marsh et al. (1998a) noted previously of 64 CS-like families found one *PTEN* variant in a male thyroid cancer patient whose mother had bilateral breast cancer and endometrial cancer (Marsh et al. 1998a). As noted, however, the mother was not tested for the missense variant. DeVivo et al. (2000) used single stranded conformation polymorphism (SSCP) analysis to test for *PTEN* mutations among 103 women from the Nurses' Health Study who had been diagnosed with two or more primary cancers. Two different missense variants were found: two patients had V158L and three patients had V119L. One of the women with the V119L variant had been diagnosed with both endometrial and breast cancers, while a second patient with V119L was diagnosed with endometrial and ovarian cancers. These variants occurred in evolutionarily conserved positions, and showed impaired tumor suppressor activity on a colony suppression assay, but their frequency was not assessed in a control population and they have not been reported in patients with Cowden syndrome. Of the 17 patients with both breast and endometrial primary cancers in this cohort, only the one (6%) was found to have any alteration in *PTEN*. As noted above, the NCCN has recently revised its CS criteria so that women with breast and endometrial double primary cancers do not meet diagnostic criteria (National Comprehensive Cancer Network 2008). In another report, SSCP analysis was used to screen for *PTEN* mutations in a retrospective cohort of 240 consecutive endometrial cancer patients (Black et al. 2005). No mutations were identified in any of the patients. Thus it appears that *PTEN* mutations are an unlikely cause of endometrial cancer outside of a personal history suggestive of CS.

Other Cancers

The risks for a range of other cancers, such as renal cell carcinoma, cutaneous melanoma, and colon cancer have also been suggested to be increased in CS. There is insufficient data to support these associations, however.

The risks for renal cell carcinoma and cutaneous melanoma have been suggested to be increased based on case reports. A few case reports of renal cell carcinoma in CS patients exist, as well as a report of a CS patient with both renal cell carcinoma and a Merkel cell cancer of skin (Haibach et al. 1992). In one patient with a deleterious *PTEN* mutation and multiple cancers, loss of the normal *PTEN* allele was demonstrated in specimens from her renal cell carcinoma, uterine carcinoma, breast ductal carcinoma *in situ* and thyroid adenoma, supporting the role of *PTEN* in the development of these neoplasms (Lynch et al. 1997).

While somatic PTEN mutations are common in cutaneous malignant melanoma (Guldberg et al. 1997), there are only individual cases reported in the literature of melanoma in patients with Cowden syndrome (Greene et al. 1984; Longy and Lacombe 1996; Reifenberger et al. 2003; Salem and Steck 1983). No *PTEN* mutations were found among nine women with breast and melanoma double primary cancers from the Nurses' Health Study discussed above (De Vivo et al. 2000). Thus there are no published data to clearly establish the risk for melanoma in patients with CS.

While colon cancer has been said to be increased in patients with CS in some reports, this again is based on a small number of case reports (Hover et al. 1986; Salem and Steck 1983; Taylor et al. 1989). Starink et al. (1986) identified one case of colon cancer in a patient with multiple polyps and two cases of cecal cancer in patients without polyps reported. Marra et al. (1994), in reviewing the gastrointestinal findings in 126 CS cases reported in the literature, identified colon cancer in four patients, with a mean age of diagnosis of 48.7 years (Marra et al. 1994). More recently a patient with a germline PTEN missense mutation was reported who had two separate colon adenocarcinomas arising within hamartomatous polyps (Bosserhoff et al. 2006).

A number of other cancers have been reported in patients with CS. In their review of 100 cases reported in the literature Starink et al. (1986) noted 1 case each of transitional cell carcinoma of bladder and renal pelvis; one case of ovarian cancer, and two cases cervical cancer. Miscellaneous case reports have noted other cancers as well. There is currently insufficient data to determine whether any of these malignancies are seen at increased rates in patients with CS, however.

Non-malignant Component Features

In addition to the malignancies discussed above, individuals with CS are felt to be at increased risk for benign hamartomatous overgrowth of a number of tissues. Table 2 lists the generally estimated risks for benign features in CS. The data supporting these are discussed below.

Arteriovenous Malformations and Hemangiomas

Hemangiomas, which are found in 5–10% of children in the general population (Drolet et al. 1999), have been seen at increased rates in CS, with frequencies of 22% of 46 cases (Salem and Steck 1983), 35% of 87 cases (Hanssen et al. 1993) and 34% of 98 cases (Hanssen and Fryns 1995) reported. Non-specified vascular malformations were seen in 18% of the 100 cases reviewed by Starink et al. (1986). Arteriovenous malformations (AVMs) are less frequently reported but have been noted in multiple case reports (Turnbull et al. 2005). Hemangiomas and AVMs are both component features of Bannayan–Riley–Ruvalcaba syndrome (BRRS), which is known to be allelic to CS. These findings are consistent with research showing that PTEN plays a role in regulating VEGF-regulated angiogenesis (Huang and Kontos 2002; Koul et al. 2002). More recently the vascular anomalies of 26 mutation-positive CS or BRRS patients presenting at one center were reviewed (Tan et al. 2007). The authors found that the anomalies were typically multifocal fast-flow intramuscular lesions and/or intracranial developmental anomalies (the latter seen in eight of nine CS patients who underwent brain MRI with contrast in their study, but in only 2% of the general population). None of the 26 patients in this study had hemangiomas or other endothelial tumors.

Brain Lesions

While a broad range of brain lesions and malignancies have been reported in patients with CS, there is data to substantiate an increased risk only for Lhermitte–Duclos disease.

Since brain imaging is rarely done on asymptomatic individuals, a precise estimate of the frequency of brain lesions in CS patients (both symptomatic and asymptomatic) is not available. However one report exists of brain MRIs done on 20 asymptomatic CS patients ascertained through dermatology clinics in France (Lok et al. 2005). The mean age of the patients was 42 years (range 9 to 72 years). Seven of the 20 patients had specific brain abnormalities identified, including three patients with Lhermitte-Duclos disease(LDD), six patients with vascular malformations (venous and cavernous angiomas, three of whom also had LDD), and one patient with a meningioma.

Lhermitte-Duclos disease (dysplastic gangliocytoma of the cerebellum) is a rare, slow growing, non-malignant hamartomatous brain lesion. It is usually diagnosed in the twenties or thirties, although it ranges from infancy to the seventies. Symptoms initially include headaches, cerebellar ataxia, and visual problems, while advancing disease leads to increased intracranial pressure (Lok et al. 2005). MRI is the preferred diagnostic imaging modality, and treatment is through surgical excision. It was first recognized to be associated with CS in 1991 (Padberg et al. 1991), but numerous cases have now been identified. Tan and Ho recently reviewed the literature and identified 54 cases of LDD associated with CS. Nonetheless the frequency of LDD in patients with CS is unknown (Tan et al. 2007). Zhou et al. (2003a, b) performed *PTEN* analysis on DNA extracted from paraffin-embedded LDD tumor samples from 18 patients. Mutations were identified in all 15 adult patients but in none of the three children. Germline DNA samples were available from six of the adult cases, and genetic analysis confirmed that the mutations were of germline origin in all six. This led the authors to conclude that while LDD can be seen in children with CS, adult LDD is nearly pathognomic for CS. Clinical information was only available on three of the six patients with confirmed germline mutations, however; two had features of CS while one did not. A review on 14 patients in the literature with LDD diagnosed under age 18 found that three had diagnoses of CS, eight had no signs of the disease, and three had insufficient information provided by which to make or rule out a diagnosis (Robinson and Cohen 2006). The authors also noted, however, that many of the symptoms of CS do not present in childhood. While usually only a single family member is affected, a mother and son with LDD and a father and son with both CS and LDD have been reported (Ambler et al. 1969; Lachlan et al. 2007).

Meningiomas were first noted in CS by Starink et al. (1986). At least seven cases have now been reported, two in patients who also had LDD (reviewed in Lok et al. 2005). The frequency of these lesions in CS has not been determined, however. The high frequency (30%) of hamartomatous vascular malformations seen by Lok et al. (2005) in asymptomatic CS patients has not been previously noted. The venous angiomas they identified are rarely associated with clinical symptoms, however, while the cavernous angiomas can be associated with refractory seizures.

Breast Disease

Benign breast disease is common in CS, and presents with varying and often complex histologies. However, given that

up to 60% of premenopausal women in the general population may develop fibrocystic breast disease (Love et al. 1982), and 2–23% of young women have breast fibroadenomas (Santen and Mansel 2005), the magnitude of the risk increase in benign breast disease reportedly seen in CS is not clear.

Brownstein et al. (1978), in first noting the increased risk for breast cancer in women with CS, also noted the presence of benign breast diseases such as fibrocystic disease, intraductal papillomatosis and fibroadenomas. Benign breast disease is now felt to affect about 75% of women with CS. In Salem and Steck's (1983) review of CS cases, diagnosed primarily on skin findings, 16/25 women (64%) were reported to have fibrocystic breast disease, although it is not clear whether the cases were clinically or pathologically diagnosed. Starink (1984) reviewed 51 cases of women with CS (median age 39 years old) and found fibrocystic disease or fibroadenomas in 59% and ductal papillomas in 14%; 76% of females had some breast lesion, either benign or malignant. In a later review of 63 female cases, 52% were reported to have fibrocystic disease and 70% had some breast abnormality, including cancer (Starink et al. 1986). Hanssen and Fryns (1995) found benign breast disease reported in 35 of 65 (54%) female CS cases they found in the literature.

Schrager et al. (1997) reported on the histopathologic findings in 59 breast cancer specimens from 19 women with CS and breast disease. However, the CS diagnoses were made using the pre-Consortium diagnostic criteria proposed by Salem and Steck (1983), and it is not possible from the information provided to determine how many also meet current Consortium diagnostic criteria. The authors found widespread and complex pathology, including ductal hyperplasia, intraductal papillomatosis, apocrine metaplasia, adenosis, lobular atrophy, fibroadenomas and fibrocystic changes, ductal carcinoma in situ and infiltrating ductal carcinoma. Lobules were often replaced with densely fibrotic hyalinized nodules which gave the appearance of breast hamartomas. The hamartomatous lesions in these patients, however, were more diffuse and more often multifocal and bilateral than in patients without CS. While this was a selected series of biopsied patients and the frequencies of the various tissue abnormalities cannot be projected to CS patients in general, it was particularly striking that most patients had "exuberant", highly complex and frequently bilateral breast disease featuring multiple histopathologic abnormalities.

Gastrointestinal Disease

Because asymptomatic individuals often do not undergo endoscopic surveillance, the generally reported frequency of gastrointestinal disease in CS (40%) may be an underestimate. Several studies suggest that 70–80% of CS patients who undergo a full GI workup will demonstrate polyps.

Polyps of the gastrointestinal tract have generally been said to affect about 40% of CS patients. These are primarily in the colon but can be found throughout the GI tract. Salem and Steck (1983) found gastrointestinal hamartomas in 16/46 (35%) patients reported in the literature, including colon and rectum (14 cases), stomach (eight cases), small bowel (duodenum, jejunum, ileum, six cases), and esophagus (four cases). Likewise Starink et al. (1986) and Hanssen and Fryns (1995) found GI lesions noted in 35% and 42%, respectively, of cases reported in the literature. These frequencies are likely underestimates, however, as screening of asymptomatic patients is rarely attempted, and polyp frequencies may be significantly higher when prospective screening is done (Merg and Howe 2004). Indeed, one review found digestive tract lesions in 71% of 45 CS patients who had been examined (Chen et al. 1987). Another group reviewed 126 CS cases reported in the literature, and found that of 42 patients who had had a complete GI work-up, 36 (85%) had some GI involvement (Marra et al. 1994). These were primarily polyps, which were reported throughout the GI tract. Of particular interest, 11 patients were found to have adenomatous polyps, which accounted for approximately 25% of the polyps which were histologically characterized. Thirteen patients had polyps of more than one histopathologic type. Carlson et al. found colonic lesions reported in 13 of 17 (76%) patients who had undergone lower GI examinations (Carlson et al. 1984). They also identified nine patients in the literature reported to have upper GI tract polyps, either alone (three patients) or along with lower GI polyps (six patients). A caveat, again, is that the reports of most of these patients predate the development of the Consortium diagnostic criteria.

While the polyps in CS are primarily hamartomatous, accurate histologies for the GI lesions found in CS patients are often absent from the cases reported in the literature. Other histopathologies that have been reported included hyperplastic, inflammatory, juvenile, leiomyomatous, lipomatous, lymphoid and neuromatous (Carlson et al. 1984; Marra et al. 1994; Merg and Howe 2004). Given the inconsistency of histopathologic diagnosis of GI polyps in general, this is perhaps not completely unexpected (Sweet et al. 2005). It is currently felt that the GI adenomas reported in patients with CS are coincidental, rather than related to the disease.

Diffuse glycogenic acanthosis of the esophagus may also be relatively common in CS, although the incidence is unknown (Kay et al. 1997; McGarrity et al. 2003). One author has suggested, however, that the co-occurrence of glycogenic acanthosis and colonic polyposis is rare outside

of CS and should be considered pathognomonic for this disease (Kay et al. 1997). Colonic ganglioneuromas are classified as hamartomas (Chan and Haghighi 2006); while considered to be a component tumor of CS, the incidence of this lesion in CS is also not known (Lashner et al. 1986).

Genitourinary Problems

Genitourinary problems, primarily uterine fibroids but also malformations, reportedly affect over 40% of women with CS. The existing data do not indicate a rate of uterine fibroids greater than that seen in the general population, while no assessment can be made about a possible association between CS and genitourinary malformations.

A range of female genitourinary problems have been noted in a few reports on CS patients. Salem and Steck (1983) found ovarian cysts in 24% of female CS patients in the literature. Among 63 female cases reviewed by Starink et al. (1986), menstrual irregularities were reported in 33%, ovarian abnormalities (primarily cysts) in 19%, vaginal and vulvar cysts in 6% and uterine fibroids in only 5–7%. There is surprisingly little data on the incidence of uterine fibroids in the general U.S. population for comparison, but the primary paper reporting US data estimated that 70% of Caucasian women and 80% African American women have uterine fibroids by age 50 (Day Baird et al. 2003). Uterine fibroids cause symptoms in about 20% of reproductive age women (Boyle and Torrealday 2008). It is difficult to determine the rate of ovarian cysts in the general population since ultrasound cannot distinguish between them and normal or leuteized follicles. In one report in which transvaginal ultrasounds were done on a random sample of reproductive aged women, a ovarian cyst prevalence of 6.6% was reported (Borgfeldt and Andolf 1999). Thus it is not clear whether uterine fibroids or ovarian cysts are seen at increased frequency in CS. And while genitourinary malformations and tumors are one of the minor diagnostic criteria for CS, there is no data supporting an increased frequency of non-fibroid genitourinary anomalies in the disease.

Macrocephaly

Macrocephaly (defined as a head circumference greater than the 97th percentile) has been said to affect approximately 40% of CS patients (Eng 1997), but the reported frequencies vary widely in the literature. More recent evidence suggests that 80% or more of patients with CS have macrocephaly.

Starink et al. (1986) found macrocephaly reported in 21% of 100 cases in the literature (although they saw it in 70% of their own 21 cases). Hanssen and Fryns (1995) found macrocephaly reported in 38/98 (39%) cases from the literature. Head circumference was said to be normal at birth but became enlarged within the first year of life. It is likely that head circumferences was not measured in at least some early case reports, when the diagnosis was based primarily on dermatologic findings. Nelen et al. (1999) reported macrocephaly in 24/25 (96%) patients from five families; interestingly, 5/12 family members without CS also had macrocephaly, suggesting cosegregation of a gene for isolated macrocephaly. Lok et al. (2005) found macrocephaly in 13/20 (65%) patients presenting to dermatology clinics. Tan et al. (2007) found macrocephaly in all 23 PTEN mutation-positive patients who had had their head circumferences measured in their study. Similarly, in a recent report on 42 patients from 25 families with PTEN mutations and either CS or BRRS, 100% had macrocephaly (Lachlan et al. 2007). Given that head circumference was not uniformly reported in the earlier reported cases, it is possible that the true frequency of macrocephaly in mutation-positive CS patients may be closer to the 80% range or higher. In our own cohort of 206 patients with PTEN mutations, 80% of those meeting CS diagnostic criteria had macrocephaly (R. Pilarski, unpublished data).

Skin Lesions

While it is reported that nearly all patients with CS have the characteristic skin lesions of the disease, the data come primarily from patients diagnosed primarily on their dermatologic findings, before adoption of the broader Consortium diagnostic criteria. It is thus possible that the data overestimate the prevalence of these lesions in patients with CS.

The majority of patients with CS (90–100%) reportedly have mucocutaneous manifestations of the disease (Starink 1984). However, as noted earlier, before the establishment of the Consortium diagnostic criteria clinical diagnoses were often based primarily or entirely on dermatologic features, thus inflating the frequency of this sign. While patients with florid mucocutaneous lesions certainly exist, other patients with CS have few and relatively insignificant skin manifestations, which could be easily overlooked on cursory exam. The hallmark feature of CS is the trichilemmoma, which is diagnosed based on histopathology. Trichilemmomas are felt to be pathognomonic for CS when multiple lesions are present. Prior to establishment of the Consortium diagnostic criteria, Brownstein et al., studying 89 biopsies from 19 patients with CS, reported that in their experience all patients with multiple trichilemmomas had CS, and all patients with CS had multiple trichilemmomas (Brownstein et al. 1979; Brownstein et al. 1977). They noted, however, that solitary trichilemmomas can be found

in individuals without CS, and that in patients with CS biopsies on multiple skin lesions may be necessary before finding several trichilemmomas. Of the 53 facial biopsies they performed on a group of CS patients, 29 were trichilemmomas. Prior to biopsy these lesions had carried clinical diagnoses such as viral warts, Darier's disease, tuberous sclerosis and neurofibromatosis. Among other biopsies they examined, 14/14 oral biopsies were fibromas and 19/22 hand/foot biopsies were keratoses. Starink and Hausman studied biopsies of 11 facial lesions from seven patients with CS, and found five of them to be trichilemmomas (Starink and Hausman 1984b). In a followup paper summarizing findings from 73 biopsies from these and other patients (21 total patients), 40/54 facial lesions were trichilemmomas (Starink et al. 1985). Again, the CS diagnoses in these cases were made prior to the adoption of the Consortium criteria.

Other dermatologic features such as papillomatous papules, acral keratoses and lipomas are commonly seen in CS. In one report of 20 biopsies of non-facial lesions from six CS patients, mixed and overlapping histopathologies were seen but it was felt that all non-palmoplantar lesions could be classified as hyperkeratotic papillomas while the two palmoplantar biopsies were hyperkeratotic acanthomas (Starink and Hausman 1984a). In their followup paper on 73 biopsies from these and other patients, dermal fibromas were found in 57% of patients while soft fibromas were found in 36% (Starink et al. 1985).

Salem and Steck (1983) reviewed 46 CS cases in the literature, again diagnosed primarily on skin findings, and reported the following:

- Cutaneous facial papules in 83%; these were flesh colored, 1–4 mm diameter lesions located anywhere on the face, ears and neck but tending to be on the central face and mouth.
- Oral mucosal papillomatosis in 83%; these were pink to slightly white, mostly smooth, 1–3 mm diameter lesions which could coalesce and cobblestone; in addition a fissured, scrotal tongue was seen in 17%.
- Acral keratoses in 64%; these were flesh-colored or slightly pigmented, flat-topped, smooth or rough 1–4 mm diameter lesions resembling flat warts; they occurred primarily on the dorsum of hands and feet, but could appear on the proximal extremities and trunk.
- Palmoplantar keratoses in 41%, these were translucent, hard papules on the palms and soles, with or without a central dell.
- Café au lait spots in 9%; these were solitary in three patients, while one patient had two lesions.

The age of onset of the mucocutaneous features was reported in 22 cases and ranged from birth to 46 years (average 22 years). Similar prevalence figures were noted by Starink et al. (1986) among 100 cases in the literature, again diagnosed primarily based on skin findings. Mucocutaneous signs were present in all patients, including multiple facial papules (85%), multiple oral papillomas (85%), acral keratoses (73%), palmoplantar keratoses (54%), dermal fibromas (24%), scrotal tongue (20%) and multiple skin tags (16%). Lesions were first noticed in the second decade, but a few fibromas or palmoplantar keratoses were occasionally present at birth. Mucocutaneous neuromas have been reported in 5–11% of CS patients, with symptoms manifesting before age 18 in over half of the cases (Salem and Steck 1983; Schaffer et al. 2006; Starink et al. 1986)

Lipomas, which are a frequent finding in patients with BRRS, are also likely more common than appreciated in CS. Salem and Steck (1983) found lipomas in 39% of 46 cases reviewed, while Starink et al. (1986) found lipomas report in 31% of 100 cases. Although the incidence and prevalence of lipomas in the general population are not known, they are felt to be quite common (Bancroft et al. 2006).

Testicular Disease

Testicular disease may be an under-recognized manifestation of CS in males, based on several publications in recent years.

Lindsay et al. first reported on a single case of a 39 year-old male with CS who presented with multiple fat-containing hamartomas of the testicles (Lindsay et al. 2003). In subsequent reports on a small series of eight males (ages 16 to 58) with documented *PTEN* mutations, testicular ultrasounds identified distinctive, multiple (>40 per patient), bilateral hyperechoic lesions in all but the youngest patient. Biopsies in four patients indicated lipomatosis, and subsequent testing indicated no apparent effect on spermatogenesis or testicular function (Woodhouse and Ferguson 2006; Woodhouse et al. 2005). The authors noted that with the exception of two case reports of solitary lipomas in otherwise normal men, fat deposits in the testicular stroma have not been previously reported in non-neoplastic testes. In addition, single cases of a testicular mixed germ cell tumor (in an adolescent) and a case of a testicular seminoma (in a 42 year-old male) have been reported in CS (Devi et al. 2007; Mazereeuw-Hautier et al. 2004). Interestingly, in one report *PTEN* knockout mice were found to develop multiple testicular teratomas (Kimura et al. 2003).

Thyroid Disease

Benign thyroid disease, including goiter and nodules, is reported to affect 50–70% of patients with CS. While goiter

is rare in the US general populations, palpable thyroid nodules occur at an estimated lifetime frequency of 5–10% (Rosen and Stone 2006). The rates in patients with CS are significantly elevated above the general population.

Benign structural thyroid disease (nodules, adenomas, goiter) is felt to affect 50–70% of CS patients (Harach et al. 1999). While functional thyroid disease (hypo and hyperthyroidism) are also common in CS, they are almost always accompanied by structural disease. Salem and Steck (1983) found thyroid adenomas and/or goiter (primarily nodular colloid type) in 59% of the 46 CS cases reported in the literature, making it the most frequent extra-cutaneous manifestation of the disease; thyroiditis was noted in 3/46 (6.5%), although the means of diagnosis was not specified. Starink (1984) found thyroid disease in 56/83 (67%) cases from the literature; 55/56 had palpable enlargement. Pathologic examination generally found nodular hyperplasia or follicular adenomas. A later report (Starink et al. 1986) on a total of 100 cases found goiter or adenoma in 68%. Harach et al. (1999) presented the pathologic findings from six female and five male patients, ages 9 to 43 years old (mean, 26 years), who met CS Consortium diagnostic criteria. The patients had all undergone thyroidectomies because of a goiter. The most common histopathologic features were follicular adenomas and adenomatous nodules and microadenomas. All specimens showed tumor multicentricity. Multicentric papilloid nodules occurred in four cases.

Miscellaneous Findings

A wide range of other clinical findings have been reported in patients with CS, including periodontitis and dental caries (Bagan et al. 1989; Mignogna et al. 1995; Salem and Steck 1983), skeletal abnormalities (Starink 1984), and other structural defects, including high arched palate (Salem and Steck 1983). The frequencies of these findings in CS have not been rigorously assessed, however. Developmental problems or mental retardation has been reported in 12% of cases in one report (Hanssen and Fryns 1995) and 15–20% in another (Parisi 2001). Again accurate data are not available.

PTEN Testing in Clinical Practice

CS is marked by a wide variability in the clinical presentation between patients, even within the same family. In clinical practice it can be unclear which patients are appropriate candidates for *PTEN* gene analysis. While definitive testing criteria cannot be given, patients meeting or coming close to meeting the Consortium diagnostic criteria should certainly be tested, including all patients with adult Lhermite–Duclos disease or multiple trichilemmomas. Patients with macrocephaly along with other significant CS findings are also appropriate candidates. Consideration must be given to the fact, however, that several of the minor diagnostic criteria for CS, such as fibrocystic breast disease, uterine fibroids, and benign thyroid disease are common in the general population and may run in families as isolated traits, unrelated to CS. Therefore, it is not clear how much weight these minor criteria should be given with regard to one's level of suspicion, especially in the absence of other more significant CS clinical findings in a patient. On the other hand, the dermatologic features of CS may be much less obvious than implied in the literature and absence of apparent skin lesions should not negate the value of testing in an individual having other significant signs of CS.

In contrast, the existing data do indicate that there are a number of situations where *PTEN* analysis is not indicated, in absence of other signs of the disease. These include isolated cases of early onset breast cancer (FitzGerald et al. 1998), BRCA-negative familial breast cancer (Carroll et al. 1999; Guenard et al. 2007; Haiman et al. 2006; Shugart et al. 1999; Tsou et al. 1997) and isolated cases of endometrial cancer (Black et al. 2005). In more complicated scenarios, *PTEN* testing is also not likely to be of value in families with no signs of CS other than breast and thyroid cancers in the same individual or in close relatives (Marsh et al. 1998a), breast cancer and brain cancer in the same individual or family (Lauge et al. 1999) or in women with double primary cancers in general (De Vivo et al. 2000), as reviewed above.

CS Management

Management guidelines for individuals with CS have been adopted by the NCCN (National Comprehensive Cancer Network 2008). These should be followed for all patients with germline *PTEN* mutations and all patients meeting CS diagnostic criteria. Arguably they could also be followed for specific patients with significant signs of CS but not quite meeting diagnostic criteria. The NCCN management guidelines include:

- Annual physical examinations, monthly breast self-examinations, and a baseline thyroid ultrasound (with consideration of repeating annually), starting at age 18;
- Clinical breast exams every six months, starting at age 25 (or 5–10 years before the earliest breast cancer diagnosis in the family, if younger than age 35);
- Annual mammography and breast MRI screening starting at age 30–35 (or 5–10 years before the earliest breast cancer diagnosis in the family, if younger than age 40–45);

- Consideration of prophylactic mastectomy on a case-by-case basis;
- Consideration of an annual dermatologic examination.
- Consideration of participation in clinical trials to determine the effectiveness of endometrial and renal cell cancer screening.

Summary

Cowden syndrome holds an important place in the practices of oncology and genetics as part of the differential diagnosis for hereditary breast cancer, but it also may be ascertained by dermatologists, endocrinologists, gynecologists or others who recognize the symptoms of this complex disorder. Consensus diagnostic criteria have been developed, and have been adopted by the National Comprehensive Cancer Network. Sequencing of the *PTEN* gene will detect mutations in the majority (up to 80%) of individuals who meet CS diagnostic criteria, while deletion studies and promoter sequencing appear to increase the mutation detection rate only slightly.

While much is known about the spectrum of clinical manifestations of this disease, accurate estimates of the incidences of most of the component cancers and benign features do not exist. The majority of the published data are taken from compilations of case reports and small patient series reported in the literature before the adoption of the Consortium diagnostic criteria for CS. The bulk of these cases were ascertained primarily or solely on the dermatologic features of the disease, which is in contrast to current practice where most patients are being ascertained based on personal and family histories of cancer. While the cancer rates reported in the older literature are not as likely to have been influenced by selection bias, they may well be underestimates of the lifetime risks of cancer in CS given the relatively young ages of most of the reported patients. Thus it is difficult to determine to what extent the early literature applies to currently identified patients. Nonetheless, it is the best available information for use in clinical practice and counseling.

The literature on CS clearly supports increased risks for breast cancer and non-medullary thyroid cancer, and probably for uterine cancer as well. There are insufficient data to indicate whether melanoma, renal cell carcinoma, colon cancer or other cancers are increased in patients with CS. Among the non-malignant manifestations attributed to the disease, the data support increased risks for Lhermitte–Duclos disease, gastrointestinal lesions, macrocephaly, mucocutaneous lesions, and benign thyroid disease. There is also data supporting risks for AVMs, hemangiomas and possibly testicular hamartomas in CS. Given the high frequency of benign breast disease and uterine fibroids in the general public, however, the degree of increase in risk for these disorders in CS is unclear. There are only case reports suggesting the association of genitourinary malformations, skeletal and structural defects and dental disease with CS.

Given the significant clinical manifestations of the disease, patients suspected of having CS should undergo both clinical and molecular diagnostic evaluations. A diagnosis of CS, whether made on a molecular or clinical basis, entails careful and regular screening of the patient following the guidelines set forth by the NCCN.

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