

## NCCN

# Genetic/Familial High-Risk Assessment: Breast and Ovarian, Version 1.2014

## Clinical Practice Guidelines in Oncology

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### Overview

All cancers develop as a result of mutations in certain genes, such as those involved in the regulation of cell growth and/or DNA repair,<sup>1,2</sup> although not all of these mutations are inherited from a parent. For example, sporadic mutations can occur in somatic/tumor cells only, and de novo mutations can occur

### Abstract

During the past few years, several genetic aberrations that may contribute to increased risks for development of breast and/or ovarian cancers have been identified. The NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast and Ovarian focus specifically on the assessment of genetic mutations in *BRCA1/BRCA2*, *TP53*, and *PTEN*, and recommend approaches to genetic testing/counseling and management strategies in individuals with these mutations. This portion of the NCCN Guidelines includes recommendations regarding diagnostic criteria and management of patients with Cowden Syndrome/*PTEN* hamartoma tumor syndrome. (*J Natl Compr Canc Netw* 2014;12:1326–1338)

### NCCN Categories of Evidence and Consensus

**Category 1:** Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

**Category 2A:** Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

**Category 2B:** Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.

**Category 3:** Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise noted.

Clinical trials: NCCN believes that the best management for any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

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### Disclosures for the NCCN Genetic/Familial High-Risk Assessment: Breast and Ovarian Panel

At the beginning of each NCCN Guidelines panel meeting, panel members review all potential conflicts of interest. NCCN, in keeping with its commitment to public transparency, publishes these disclosures for panel members, staff, and NCCN itself.

Individual disclosures for the NCCN Genetic/Familial High-Risk Assessment: Breast and Ovarian Panel members can be found on page 1338. (The most recent version of these guidelines and accompanying disclosures are available on the NCCN Web site at [NCCN.org](http://NCCN.org).)

These guidelines are also available on the Internet. For the latest update, visit [NCCN.org](http://NCCN.org).

## Journal of the National Comprehensive Cancer Network

for the first time in a germ cell (ie, egg or sperm) or in the fertilized egg itself during early embryogenesis. However, family studies have long documented an increased risk of several forms of cancer among first-degree relatives (ie, parents, siblings, and children) and second-degree relatives (ie, grandparents, aunts or uncles, grandchildren, and nieces or nephews) of affected individuals. These individuals may have an increased susceptibility to cancer as the result of one or more gene mutations present in parental germline cells; cancers developing in these individuals may be classified as hereditary or familial cancers.

Hereditary cancers are often characterized by mutations associated with a high probability of cancer development (ie, a high-penetrance genotype), vertical transmission through either mother or fa-

ther, and an association with other types of tumors.<sup>3,4</sup> Hereditary cancers often have an early age of onset and exhibit an autosomal dominant inheritance pattern (ie, a mutation in only one copy of a gene). Familial cancers share some but not all features of hereditary cancers. For example, although familial breast cancers occur in a given family more frequently than in the general population, they generally do not exhibit the inheritance patterns or onset age consistent with hereditary cancers. Familial cancers may be associated with chance clustering of sporadic cancer cases within families, genetic variation in lower-penetrance genes, a shared environment, or combinations of these factors.<sup>5-8</sup>

Assessment of an individual's risk for familial or hereditary cancer is based on a thorough evaluation

Text cont. on page 1332.

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## Genetic/Familial High-Risk Assessment: Breast and Ovarian, Version 1.2014

## Cowden Syndrome/PHTS

COWDEN SYNDROME/PTEN HAMARTOMA TUMOR SYNDROME TESTING CRITERIA<sup>a,b</sup>

FOLLOW-UP

- Individual from a family with a known *PTEN* mutation
- Individual meeting clinical diagnostic criteria<sup>c</sup> for CS/PHTS
- Individual with a personal history of:
  - ▶ Bannayan-Riley-Ruvalcaba syndrome (BRRS) or
  - ▶ Adult Lhermitte-Duclos disease (cerebellar tumors) or
  - ▶ Autism spectrum disorder and macrocephaly or
  - ▶ Two or more biopsy-proven trichilemmomas or
  - ▶ Two or more major criteria (one must be macrocephaly) or
  - ▶ Three major criteria, without macrocephaly or
  - ▶ One major and ≥3 minor criteria<sup>d</sup> or
  - ▶ ≥4 minor criteria

- At-risk individual<sup>e</sup> with a relative with a clinical diagnosis of CS/PHTS or BRRS for whom testing has not been performed
  - ▶ The at-risk individual must have the following:
    - ◊ Any one major criterion or
    - ◊ Two minor criteria

CS/PHTS  
testing criteria  
met<sup>f</sup>CS/PHTS  
testing criteria  
not metIndividualized  
recommendations  
according to  
personal and  
family historyMajor criteria:

- Breast cancer
- Endometrial cancer
- Follicular thyroid cancer
- Multiple GI hamartomas or ganglioneuromas
- Macrocephaly (megaloccephaly) (ie, ≥97%, 58 cm in adult women, 60 cm in adult men)<sup>g</sup>
- Macular pigmentation of glans penis
- Mucocutaneous lesions<sup>h</sup>
  - ▶ One biopsy proven trichilemmoma
  - ▶ Multiple palmoplantar keratoses
  - ▶ Multifocal or extensive oral mucosal papillomatosis
  - ▶ Multiple cutaneous facial papules (often verrucous)

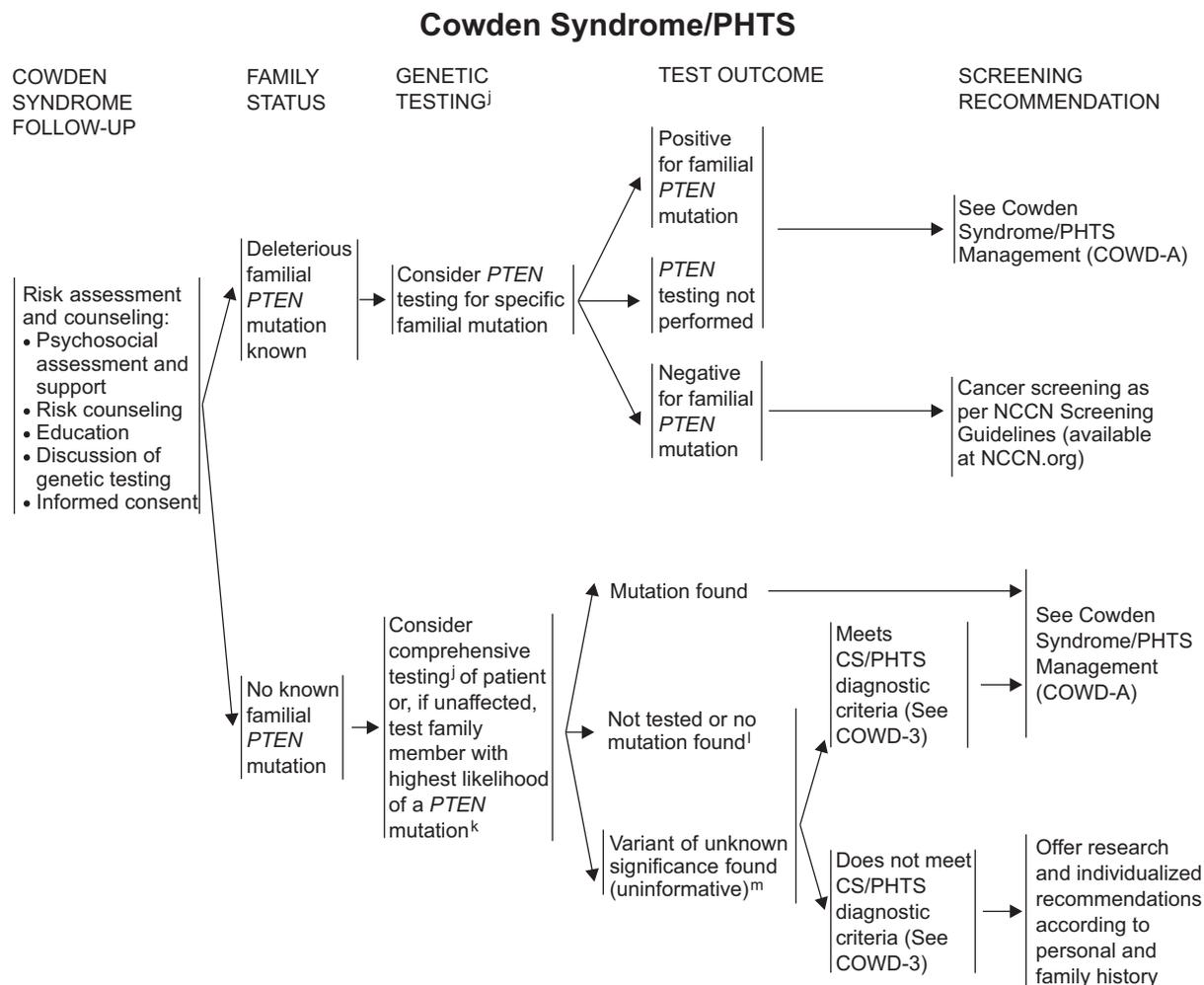
Minor criteria:<sup>i</sup>

- Autism spectrum disorder
- Colon cancer
- ≥3 esophageal glycogenic acanthoses
- Lipomas
- Mental retardation (ie, IQ ≤75)
- Papillary or follicular variant of papillary thyroid cancer
- Thyroid structural lesions (eg, adenoma, nodules, goiter)
- Renal cell carcinoma
- Single GI hamartoma or ganglioneuroma
- Testicular lipomatosis
- Vascular anomalies (including multiple intracranial developmental venous anomalies)

<sup>a</sup>These are testing criteria; clinical diagnostic criteria appear on COWD-3.<sup>b</sup>If 2 criteria involve the same structure/organ/tissue, both may be included as criteria.<sup>c</sup>Pilarski R, Burt R, Kohlmann W, et al. Cowden syndrome and the PTEN hamartoma tumor syndrome: systematic review and revised diagnostic criteria. *J Natl Cancer Inst* 2013;105:1607-1616.<sup>d</sup>If an individual has two or more major criteria, such as breast cancer and non-medullary thyroid cancer, but does not have macrocephaly, one of the major criteria may be included as one of the three minor criteria to meet testing criteria.<sup>e</sup>An at-risk individual can be defined as a first-degree relative of an affected individual and/or proband. If a first-degree relative is unavailable or unwilling to be tested, more distant relatives should be offered testing.<sup>f</sup>Patients who have received an allogeneic bone marrow transplant should not have molecular genetic testing via blood or buccal samples because of unreliable test results from contamination by donor DNA. If available, DNA should be extracted from a fibroblast culture. If this source of DNA is not possible, buccal samples can be considered, subject to the risk of donor DNA contamination.<sup>g</sup>Roche AF, Mukherjee D, Guo SM, Moore WM. Head circumference reference data: birth to 18 years. *Pediatrics* 1987;79:706-712.<sup>h</sup>The literature available on mucocutaneous lesions is not adequate to accurately specify the number or extent of mucocutaneous lesions required to be a major criterion for CS/PHTS. Clinical judgement should be used.<sup>i</sup>Insufficient evidence exists in the literature to include fibrocystic disease of the breast, fibromas, and uterine fibroids as diagnostic criteria.

COWD-1

## Genetic/Familial High-Risk Assessment: Breast and Ovarian, Version 1.2014



<sup>j</sup>Comprehensive genetic testing should include full sequence analysis, deletion/duplication analyses, and promoter analysis.

<sup>k</sup>Testing of unaffected family members when no affected member is available may be considered. Significant limitations of interpreting test results should be discussed.

<sup>l</sup>If no mutation is found, consider other hereditary breast cancer syndromes, such as HBOC (HBOC-1\*) and/or Li-Fraumeni syndrome (LIFR-1\*). For additional information on other genetic mutations associated with breast/ovarian cancer risk for which genetic testing is clinically available, see GENE-1\*.

<sup>m</sup>Testing family members for a variant of unknown significance should not be used for clinical purposes. Consider referral to research studies that aim to define functional impact of variant.

\*Available online, in these guidelines, at NCCN.org.

COWD-2

## Cowden Syndrome/PHTS

### REVISED PTEN HAMARTOMA TUMOR SYNDROME CLINICAL DIAGNOSTIC CRITERIA<sup>n</sup>

#### MAJOR CRITERIA:

- Breast cancer
- Endometrial cancer (epithelial)
- Thyroid cancer (follicular)
- Gastrointestinal hamartomas (including ganglioneuromas, but excluding hyperplastic polyps;  $\geq 3$ )
- Lhermitte-Duclos disease (adult)
- Macrocephaly ( $\geq 97$  percentile: 58 cm for females, 60 cm for males)
- Macular pigmentation of the glans penis
- Multiple mucocutaneous lesions (any of the following):
  - Multiple trichilemmomas ( $\geq 3$ , at least one biopsy proven)
  - Acral keratoses ( $\geq 3$  palmoplantar keratotic pits and/or acral hyperkeratotic papules)
  - Mucocutaneous neuromas ( $\geq 3$ )
  - Oral papillomas (particularly on tongue and gingiva), multiple ( $\geq 3$ ) OR biopsy-proven OR dermatologist-diagnosed

#### MINOR CRITERIA:

- Autism spectrum disorder
- Colon cancer
- Esophageal glycogenic acanthoses ( $\geq 3$ )
- Lipomas ( $\geq 3$ )
- Mental retardation (ie, IQ  $\leq 75$ )
- 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 2 major criteria with or without minor criteria; or
2. One major and 2 minor criteria; or
3. Three minor criteria.

<sup>n</sup>Pilarski R, Burt R, Kohlman W, et al. Cowden syndrome and the PTEN hamartoma tumor syndrome: systematic review and revised diagnostic criteria. J Natl Cancer Inst 2013;105:1607-1616.

COWD-3

## Genetic/Familial High-Risk Assessment: Breast and Ovarian, Version 1.2014

**Cowden Syndrome/PHTS**

## COWDEN SYNDROME/PHTS MANAGEMENT

WOMEN

- Breast awareness<sup>1</sup> starting at age 18 y
- Clinical breast examination, every 6-12 mo, starting at age 25 y or 5-10 y before the earliest known breast cancer in the family
- Annual mammography and breast MRI screening starting at age 30-35 y or individualized based on earliest age of onset in family<sup>2,3</sup>
- For endometrial cancer screening,<sup>4</sup> encourage patient education and prompt response to symptoms. Consider annual random endometrial biopsies and/or ultrasound beginning at age 30-35 y
- Discuss risk-reducing mastectomy and hysterectomy<sup>5</sup> and counsel regarding degree of protection, extent of cancer risk, and reconstruction options
- Address psychosocial, social, and quality-of-life aspects of undergoing risk-reducing mastectomy and/or hysterectomy

MEN AND WOMEN

- Annual comprehensive physical examination starting at age 18 y, or 5 y before the youngest age of diagnosis of a component cancer in the family (whichever comes first), with particular attention to thyroid examination
- Annual thyroid ultrasound starting at age 18 y, or 5-10 y before the earliest known thyroid cancer in the family, whichever is earlier.
- Colonoscopy, starting at age 35 y, then every 5 y, or more frequently if patient is symptomatic or polyps found
- Consider renal ultrasound starting at age 40 y, then every 1-2 y
- Dermatologic management may be indicated for some patients
- Consider psychomotor assessment in children at diagnosis and brain MRI if symptoms are present
- Education regarding the signs and symptoms of cancer

RISK TO RELATIVES

- Advise about possible inherited cancer risk to relatives, options for risk assessment, and management
- Recommend genetic counseling and consideration of genetic testing for at-risk relatives

REPRODUCTIVE OPTIONS

- For women of reproductive age, advise about options for prenatal diagnosis and assisted reproduction including preimplantation genetic diagnosis. Discussion should include known risks, limitations, and benefits of these technologies. See Discussion for details.

<sup>1</sup> Women should be familiar with their breasts and promptly report changes to their health care provider. Periodic, consistent breast self-examination (BSE) may facilitate breast self awareness. Premenopausal women may find BSE most informative when performed at the end of menses.

<sup>2</sup> The appropriateness of imaging modalities and scheduling is still under study.

<sup>3</sup> High-quality breast MRI limitations include having: a need for a dedicated breast coil, the ability to perform biopsy under MRI guidance by experienced radiologists in breast MRI, and regional availability. Breast MRI is preferably performed on days 7-15 of a menstrual cycle for premenopausal women.

<sup>4</sup> Data are limited regarding the lifetime risk of endometrial cancer in CS/PHTS. Surveillance screening and surgical intervention should be on an individual basis.

<sup>5</sup> Oophorectomy is not indicated for CS/PHTS alone but may be indicated for other reasons.

COWD-A

Text cont. from page 1327.

of the family history. With respect to hereditary cancers, advances in molecular genetics have identified several genes associated with inherited susceptibility to breast and/or ovarian cancers (eg, *BRCA1*, *BRCA2*, *PTEN* [phosphatase and tensin homolog], *TP53*, *CDH1*) and provided a means of characterizing the specific gene mutation or mutations present in certain individuals and families exhibiting an increased risk of cancer. The field of cancer genetics has implications for all aspects of cancer management in individuals with hereditary or familial cancers, including prevention, screening, and treatment.

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Genetic/Familial High-Risk Assessment: Breast and Ovarian (to view the complete guidelines, visit [NCCN.org](http://NCCN.org)) were developed with an acute awareness of the preliminary nature of much of the existing knowledge regarding the clinical application of the rapidly emerging field of molecular genetics, and with an appreciation for the need for flexibility when applying these guidelines to individual families. Furthermore, it should be emphasized that these guidelines were not developed as a substitute for professional genetic counseling. Rather, they are intended to serve as a resource for health care providers to identify individuals who may benefit from cancer risk assessment and genetic counseling, to provide genetic counselors with an updated tool to help assess individual breast and ovarian cancer risk and guide decisions related to genetic testing, and to facilitate a multidisciplinary approach in the management of individuals at increased risk for hereditary breast and/or ovarian cancers.

Although several cancers are associated with hereditary familial cancer syndromes, the main focus of these NCCN Guidelines is the management of breast and ovarian cancer risk. During the past few years, several genetic aberrations that may contribute to increased risks for development of breast and/or ovarian cancers have been identified; these guidelines focus specifically on the assessment of genetic mutations in *BRCA1/BRCA2*, *TP53*, and *PTEN*, and recommend approaches to genetic testing/counseling and management strategies in individuals with these mutations.

This portion of the NCCN Guidelines includes recommendations regarding diagnostic criteria and management of patients with Cowden syndrome/*PTEN* hamartoma tumor syndrome (PHTS). To

view the full and most recent version of these guidelines, visit [NCCN.org](http://NCCN.org).

### ***PTEN* Hamartoma Tumor Syndrome**

The spectrum of disorders resulting from germline mutations in *PTEN*<sup>9</sup> are referred to as PHTS. The spectrum of PHTS includes Cowden syndrome, Bannayan-Riley-Ruvalcaba syndrome, Adult Lhermitte-Duclos disease, Proteus-like syndrome,<sup>10-12</sup> and autism spectrum disorders with macrocephaly.<sup>11-13</sup> The estimated penetrance of *PTEN* mutation is high ( $\approx 80\%$ ).<sup>14</sup>

Cowden syndrome, a rare hereditary cancer syndrome, was first described in 1963 and named after the Cowden family, the first family documented with signs of the disease.<sup>15</sup> The incidence of Cowden syndrome has been reported to be 1 in 200,000, although it is likely to be underestimated because of difficulties associated with making a clinical diagnosis of the disease.<sup>16,17</sup> Cowden syndrome is an autosomal dominant disorder, and most cases are associated with germline mutations in the *PTEN* gene.

Cowden syndrome is the most well-studied PHTS disorder associated with a documented predisposition to malignancies. Hence, the NCCN Genetic/Familial High-Risk Assessment: Breast and Ovarian Panel developed evidence-based guidelines listing the diagnostic criteria, risk assessment, counseling, and management of patients with Cowden syndrome/PHTS.

Hamartomas (benign tumors resulting from an overgrowth of normal tissue) is a common manifestation of the PHTS syndromes. Cowden syndrome is associated with multiple hamartomatous and/or cancerous lesions in various organs and tissues, including the skin, mucous membranes, breast, thyroid, endometrium, and brain.<sup>11,18</sup> However, it has been suggested that patients with other PHTS diagnoses associated with *PTEN* mutations should be assumed to have Cowden-associated cancer risks. In a study of patients meeting diagnostic criteria for Cowden syndrome (N=211; identified from published literature and records from a single institution), the cumulative lifetime risk of any cancer was 89%.<sup>19</sup> *PTEN* mutations had been identified in 97 of 105 patients (92%) who underwent testing. The cumulative lifetime cancer risks for all evaluable patients (n=210) were 81% for female breast cancer, 21% for thyroid cancer, 19% for endometrial cancer, 15% for renal

cancer, and 16% for colorectal cancer.<sup>19</sup> In a prospective study that evaluated genotype-phenotype associations between *PTEN* mutations and cancer risks,<sup>20</sup> deleterious germline mutations in *PTEN* were identified in 368 patients.

Calculation of age-adjusted standardized incidence ratios (SIRs) using cancer incidence data from the SEER database showed elevated SIRs among individuals with *PTEN* mutations for breast cancer (25.4), thyroid cancer (51.1), endometrial cancer (42.9), colorectal cancer (10.3), renal cancer (30.6), and melanoma (8.5). The estimated cumulative lifetime cancer risks were 85% for breast, 35% for thyroid, 28% for endometrial, 9% for colorectal, 34% for renal, and 6% for melanoma.<sup>20</sup> In another study in individuals with PHTS found to have deleterious germline *PTEN* mutations (N=154; detailed information available in n=146), age- and gender-adjusted SIRs were elevated for female breast cancer (39.1), endometrial cancer (48.7), female thyroid cancer (43.2), male thyroid cancer (199.5), female melanoma (28.3), and male melanoma (39.4).<sup>21</sup> The cumulative lifetime cancer risks in these individuals were 77% for female breast cancer and 38% for thyroid cancer. The cumulative lifetime risk for any cancer was 85% overall, and women with PHTS were found to have a 2-fold greater cancer risk compared with men with PHTS. However, all 3 of these studies have significant ascertainment biases, in that patients were usually selected for *PTEN* testing based on the presence of these malignancies, which would inflate the projected lifetime cancer estimates.

### Cowden Syndrome

Women diagnosed with Cowden syndrome have a lifetime risk for breast cancer traditionally estimated at 25% to 50%, with an average age at diagnosis of 38 to 46 years.<sup>11,18,22</sup> As discussed previously, studies have reported a higher cumulative lifetime risk of breast cancer (77%–85%) in individuals with Cowden syndrome or *PTEN* mutations.<sup>19–21</sup> Only 2 cases of breast cancer have been reported in men with Cowden syndrome.<sup>11</sup> Thyroid disease, including benign multinodular goiter, adenomatous nodules, and follicular adenomas, has been reported to occur in up to approximately 70% of individuals with Cowden syndrome,<sup>23</sup> and the lifetime risk of thyroid cancer (follicular or papillary) has been estimated at 3% to 10%.<sup>11,24</sup> A higher cumulative lifetime risk of thyroid cancer (21%–38%) was reported in several

recent studies in individuals with Cowden syndrome or *PTEN* mutations (discussed previously).<sup>19–21</sup>

As in many other hereditary cancer syndromes, affected individuals are more likely to develop bilateral and multifocal cancer in paired organs.<sup>14</sup> Although not well defined, women with Cowden syndrome may have a 5% to 10% risk of endometrial cancer.<sup>11,25</sup> A higher lifetime risk of endometrial cancer (19%–28%) in women with Cowden syndrome or *PTEN* mutations has been reported.<sup>19,20</sup> As discussed earlier, increased lifetime risks for colorectal cancer (9%–16%), renal cancer (15%–34%), and melanoma (6%) have also been reported in individuals with Cowden syndrome or *PTEN* mutations.<sup>19,20</sup> In addition, brain tumors and vascular malformations affecting any organ are occasionally seen in individuals with Cowden syndrome, although the risks for developing these conditions are not well defined.<sup>11</sup> However, most of the data on the frequencies of the clinical features of Cowden syndrome are from compilations of case reports of relatively young individuals who may have subsequently developed additional signs of the disease (ie, new cancerous lesions), and these data are also likely to be confounded by selection bias.<sup>11</sup> Furthermore, a considerable number of these studies were published before the establishment in 1996 of the International Cowden Consortium operational diagnostic criteria for the syndrome, which were based on published data and the expert opinion of individuals representing a group of centers mainly in North America and Europe.<sup>11,26</sup>

Classic clinical features of Cowden syndrome include mucocutaneous papillomatous papules, palmo-plantar keratoses, and trichilemmomas (ie, benign tumors derived from the outer root sheath epithelium of a hair follicle).<sup>11,27</sup> Most individuals with Cowden syndrome exhibit characteristic mucocutaneous lesions by their 20s, and these lesions have been reported to occur in 99% of individuals with Cowden syndrome, showing nearly complete penetrance.<sup>10,28</sup> The presence of 2 or more trichilemmomas has been reported to be pathognomonic for Cowden syndrome.<sup>29,30</sup> However, because most of this evidence is from older literature, the association between these 2 entities may be somewhat overestimated.<sup>11</sup> Individuals with a solitary trichilemmoma who do not have Cowden syndrome have been reported.<sup>29,30</sup> Nevertheless, because of the strong association between these lesions and Cowden syndrome, and

the difficulty in clinically distinguishing between a trichilemmoma and another mucocutaneous lesion, a diagnosis of trichilemmoma must be histologically confirmed.

It has historically been reported that approximately 40% of individuals with Cowden syndrome have gastrointestinal polyps (often colonic), although newer data suggest that this risk may be 80% or higher. An analysis of *PTEN* mutation carriers reported gastrointestinal polyps in 93% of patients.<sup>31</sup> The polyps are often hamartomatous, although ganglioneuromas (ie, rare, benign peripheral nervous system tumors) and many other histologies have also been reported to frequently occur.<sup>11,32</sup> Importantly, early-onset (age <50 years) colorectal cancer has been reported in 13% of patients with *PTEN* mutation–associated Cowden syndrome, suggesting that routine colonoscopy may be warranted in this population.<sup>31</sup>

#### Adult Lhermitte-Duclos Disease

Adult Lhermitte-Duclos disease (LDD) and autism spectrum disorder characterized by macrocephaly are strongly associated with Cowden syndrome.<sup>10,14,19,33</sup> LDD is a dysplastic gangliocytoma of the cerebellum, a rare, slow growing, benign hamartomatous lesion of the brain.<sup>11,19</sup> In a study of individuals meeting the diagnostic criteria for Cowden syndrome, the cumulative lifetime risk of LDD was reported to be 32%.<sup>19</sup> The preponderance of evidence supports a strong association between adult-onset LDD and the presence of a *PTEN* gene mutation,<sup>14</sup> although exceptions have been reported.<sup>34</sup> In addition, a large body of evidence supports that 10% to 20% of individuals with autism spectrum disorder and macrocephaly carry germline *PTEN* mutations.<sup>13,35–38</sup> Macrocephaly (defined as head circumference >97th percentile)<sup>39</sup> is a common finding in patients with Cowden syndrome. Approximately 80% of individuals with this syndrome are estimated to exhibit this clinical finding.<sup>11</sup>

#### Bannayan-Riley-Ruvalcaba Syndrome

The Bannayan-Riley-Ruvalcaba syndrome (BRRS) variant of PHTS has been characterized by the presence of multiple lipomas, gastrointestinal hamartomatous polyps, macrocephaly, hemangiomas, developmental delay, and, in men, pigmented macules on the glans penis,<sup>40</sup> although formal diagnostic criteria have not been established for this syndrome. *PTEN* gene mutations have been reported in approximately 60% of

individuals characterized with BRRS.<sup>41</sup> Furthermore, in another study, 10% of patients with BRRS for whom a *PTEN* gene mutation test was negative were shown to be carriers of large *PTEN* gene deletions.<sup>33</sup>

#### Genetic Testing Criteria for Cowden Syndrome/PHTS

The *PTEN* mutation frequency in individuals meeting International Cowden Consortium criteria for Cowden syndrome was previously estimated at approximately 80%.<sup>11,41</sup> However, evaluation of data based on samples analyzed at a single academic pathology laboratory (N=802 evaluable) reported a much lower frequency (34%) of *PTEN* mutations among individuals meeting diagnostic criteria<sup>17</sup> for Cowden syndrome.<sup>12</sup> The authors concluded that the current consortium diagnostic criteria are not as sensitive in identifying individuals with *PTEN* mutations as previously estimated. Similar results were found in a research cohort of patients with *PTEN* mutations.<sup>42</sup>

The International Cowden Consortium criteria have been updated several times since 1996<sup>10,11,17,43,44</sup> and have largely served as the basis for the list of *PTEN* mutation testing criteria included in the NCCN Guidelines. On the basis of literature reports and expert consensus, the panel revised both the list of criteria associated with this genetic syndrome and the combinations of criteria that establish which individuals are candidates for *PTEN* gene mutation testing (see COWD-A, page 1331). Similar to earlier versions, criteria are grouped into 3 general categories. Patients are considered for *PTEN* gene mutation testing based on whether they meet certain criteria or combinations of criteria from these 3 categories. The first criteria category includes individuals meeting diagnostic criteria for Cowden syndrome,<sup>43</sup> or have a personal history of BRRS, adult LDD, autism spectrum disorder with macrocephaly, or 2 or more biopsy-proven trichilemmomas. Any individual presenting with one or more of these diagnoses warrants *PTEN* testing. Some criteria from this group have occasionally been referred to as “pathognomonic,” although it is unlikely that any of these conditions can stand alone as a definitive diagnostic criterion of Cowden syndrome/PHTS. Another criterion that can be considered sufficient to warrant *PTEN* gene mutation testing is a family history that includes the presence of a known deleterious *PTEN* mutation.

The next criteria category represents major features associated with Cowden syndrome,<sup>12,17,42,43</sup> including the presence of breast cancer, macrocephaly (ie, megalcephaly),<sup>39</sup> endometrial cancer, follicular thyroid cancer, multiple gastrointestinal hamartomas or ganglioneuromas, macular pigmentation of glans penis, and certain mucocutaneous lesions that are often observed in patients with Cowden syndrome (eg, one biopsy-proven trichilemmoma, multiple palmo-plantar keratoses, multiple or extensive oral mucosal papillomatosis, multiple cutaneous facial papules). An individual meeting 2 or more major criteria, with 1 being macrocephaly, meets the testing threshold. An individual with 3 or more major criteria (without macrocephaly) are also considered to meet the threshold for testing. In addition, individuals meeting 1 major criterion and 3 or more minor criteria (discussed in the next section) also meet the testing threshold; if an individual meets 2 or more major criteria (eg, breast cancer and follicular thyroid cancer) but does not have macrocephaly, then 1 of the major criteria may be included as 1 of the 3 minor criteria to meet the testing threshold.

The final category of criteria represents features that have a minor association with Cowden syndrome,<sup>12,17,42,43</sup> including autism spectrum disorder (without macrocephaly), colon cancer, esophageal glycogenic acanthosis ( $\geq 3$ ), lipomas, mental retardation, papillary or follicular variant of papillary thyroid cancer, thyroid structural lesions (eg, adenoma, nodules, goiter), renal cell carcinoma, a single gastrointestinal hamartoma or ganglioneuroma, testicular lipomatosis, or vascular anomalies (including multiple intracranial developmental venous anomalies). The panel felt that evidence from the literature was insufficient to include fibrocystic breast disease, fibromas, or uterine fibroids as part of the testing criteria. An individual would need to exhibit 4 or more minor criteria or, as discussed earlier, 3 or more minor and 1 major criterion to meet testing criteria (see COWD-A, page 1331, and next section).

Lastly, an at-risk individual (first-degree relative of an affected individual) with at least 1 major criterion or at least 2 minor criteria, along with a relative diagnosed with Cowden syndrome or BBRS (for whom testing has not been performed), would also meet the threshold for *PTEN* testing.

Individuals not meeting testing criteria should be followed according to recommendations tailored

to their personal cancer and family history. Recently, revised and more stringent diagnostic criteria were published based on a systematic review of Cowden syndrome and PHTS<sup>45</sup> (see COWD-3, page 1330). If testing for *PTEN* mutation is not possible or no mutation was found, these revised stringent criteria could be used to diagnose PHTS. Based on the revised stringent diagnostic criteria, an operational diagnosis of PHTS in an individual should include either 3 or more major criteria, with 1 being macrocephaly, LDD, or gastrointestinal hamartomas; or 2 major and 3 minor criteria.

### Risk Assessment, Counseling, and Management

The assessment of individuals suspected of having Cowden syndrome/PHTS incorporates both a history of the benign and malignant conditions associated with the syndrome and a targeted physical examination, including the skin and oral mucosa, breast, and thyroid gland (see COWD-1, page 1328). The panel has included the list of diagnostic criteria associated with this genetic syndrome and the combinations of criteria that establish which individuals are candidates for *PTEN* gene mutation testing (see COWD-1 and COWD-3, pages 1328 and 1330, respectively). Following risk assessment and counseling, genetic testing should be considered in individuals for whom testing criteria are met. The NCCN Guidelines panel recommends comprehensive testing, which should include full sequencing, gene deletion/duplication analysis, and promoter analysis. Unlike the “pathognomonic” criteria, none of the individual major or minor criteria are considered by the panel to be sufficient to warrant genetic testing in the absence of other clinical evidence of Cowden syndrome/PHTS. The updated NCCN Guidelines include revised PHTS diagnostic criteria that could be used to make an operational clinical diagnosis in certain circumstances when genetic testing is not possible or the genetic test fails to detect a mutation in *PTEN* (available at NCCN.org).<sup>45</sup>

The panel recommends genetic testing in individuals who meet the criteria listed on COWD-1, page 1328. When an individual (or family member) from a family with no known familial *PTEN* mutation undergoes genetic testing and no mutation is found, testing for other hereditary breast syndromes should be considered if testing criteria are met.

Cancer is the major health risk associated with Cowden syndrome/PHTS. Therefore, the panel outlined guidelines for the prevention and early detection of cancers commonly associated with Cowden syndrome/PHTS. The panel recommends these patients undergo annual comprehensive physical examinations beginning at 18 years of age, or 5 years before the youngest age of cancer diagnosis in the family.

The recommendations for women with Cowden syndrome/PHTS focus on primary and secondary prevention options for breast cancer, because this is the most commonly associated cancer based on the available literature. The panel recommends breast awareness beginning at 18 years of age; clinical breast examination every 6 to 12 months beginning at age 25 years, or 5 to 10 years before the youngest age of breast cancer diagnosis in the family; and annual mammography and breast MRI screening beginning at age 30 to 35 years, or individualized based on the earliest age of onset in the family. Although no data are available regarding risk reduction surgery in women with Cowden syndrome/PHTS, the option of risk-reducing mastectomy should be discussed on a case-by-case basis. Oophorectomy is not indicated for Cowden syndrome/PHTS alone, but may be indicated for other reasons. Counseling for risk-reducing surgeries may include discussion of extent of cancer risk reduction/protection, risks associated with surgeries, reconstructive options, and reproductive desires. The psychosocial and quality-of-life aspects of undergoing risk-reducing surgical procedures are also important to address.

In addition, women with Cowden syndrome/PHTS are also at an elevated risk for endometrial cancers.<sup>19–21</sup> The panel recommends patient education regarding the symptoms of endometrial cancer, including the necessity of a prompt response to these symptoms. In addition, the panel recommends considering annual random endometrial biopsies and/or ultrasound beginning around 30 to 35 years of age.

Both men and women with Cowden syndrome/PHTS have approximately a 3% to 10% lifetime risk of developing thyroid cancer,<sup>11</sup> compared with approximately 1% in the general population.<sup>46</sup> The panel recommends that particular attention be given to thyroid assessment during the comprehensive physical examination. The panel also recommends annual thyroid ultrasound beginning at age 18 years or 5 to 10 years before the earliest known thyroid cancer diagnosis in the family, whichever is earlier.

Skin and mouth lesions are a common feature in individuals with Cowden syndrome/PHTS. Therefore, annual dermatologic examination should also be considered, and management of dermatologic symptoms may be indicated in some patients.

Early-onset of colorectal cancer has been reported in 13% of patients (age <50 years) with *PTEN* mutation-associated Cowden syndrome.<sup>31</sup> Therefore, the panel recommends colonoscopy starting at age 35 years, performed every 5 to 10 years, or more frequently in patients who are symptomatic or in whom polyps are found.

Individuals with Cowden syndrome/PHTS have an increased risk of renal cell carcinoma.<sup>20,21</sup> The panel recommends renal ultrasound starting at age 40 years and then every 1 to 2 years thereafter.

Mental retardation has been reported in individuals with *PTEN* mutation.<sup>12</sup> The panel recommends considering psychomotor assessment in children at diagnosis. Brain MRI is indicated only in the presence of localizing neurologic signs or symptoms.

Education regarding the signs and symptoms of cancer is important; patients should also be advised about the risk to relatives, and genetic counseling is recommended for at-risk relatives.

No published data exist on the use of prenatal diagnostics/genetic testing for *PTEN* mutations in families with Cowden syndrome/PHTS. However, for couples expressing the desire that their offspring not carry a familial *PTEN* mutation, options for prenatal diagnosis, preimplantation genetic diagnosis, and assisted reproduction can be discussed. Such counseling should include a comprehensive discussion of the potential risks, benefits, and limitations of reproductive options.

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Individual Disclosures of the NCCN Genetic/Familial High-Risk Assessment: Breast and Ovarian					
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The NCCN Guidelines Staff have no conflicts of interest to disclose.