



## Cowden Syndrome: What Oncology Nurses Need to Know About Increased Risk of Developing Certain Cancers

Laura Curr Beamer, DNP, AOCNP®, AOCNS®, APNG

Cowden syndrome (CS) is a genetic disorder characterized by multiple benign tissue growths (i.e., hamartomas) and an increased risk of developing specific cancers, such as breast, thyroid, kidney, endometrial, or colorectal cancer (Genetics Home Reference, 2012). This genetic syndrome was named after a person diagnosed with the disorder (Lloyd & Dennis, 1963). CS is part of a larger syndrome called *PTEN* hamartomatous syndrome, which also includes Bannayan-Riley-Ruvalcaba syndrome, *PTEN*-related Proteus syndrome, and Proteus-like syndrome (Eng, 2014).

### Basic Genetics

Cowden syndrome is transmitted from parent to child through an autosomal dominant pattern of inheritance. An autosome is a chromosome that does not convey gender, therefore an autosome is any chromosome other than the sex chromosomes X and Y. Genetic disorders that are transmitted on autosomal chromosomes occur in males and females. Dominant means the genetic condition may occur (i.e., be expressed) when only one copy of the genetic mutation is present. CS is most frequently caused by a mutation in the *PTEN* gene (Genetics Home Reference, 2012). A healthy *PTEN* gene suppresses tumors from forming. A mutation in the *PTEN* gene leads to uncontrolled cell growth, formation of hamartomas, and can potentially lead to the development of certain cancers. Hamartomas are an overgrowth of normal appearing and functioning mature cells that resemble, but are not, true tumors (MedlinePlus, 2014). CS is also caused by mutations in the *KLLN*, *SDHB*, or *SDHD* gene, but

they are less common than *PTEN* (Genetics Home Reference, 2012).

### Diagnosis

Penetrance refers to the proportion of individuals with a genetic mutation that actually develop the clinical manifestations of the genetic disorder in the presence of a genetic mutation (Genetics Home Reference, 2014). The expected penetrance of the *PTEN* gene is 90% by late in the second decade of life and 99% in the third decade of life with skin manifestations as the most common finding (Eng, 2014).

The diagnosis of CS can be made via genetic testing or by assessment of clinical findings. Genetic testing may include full sequencing or multiplex ligation-dependent probe amplification of a single gene or a panel of genes. Full sequencing of a gene involves examining one base pair at a time, much like the spell-checking function on a word-processing computer program. Multiplex ligation-dependent probe amplification helps to identify deletions and duplications of genetic information that full sequencing cannot recognize (Stuppia, Antonucci, Palka, & Gatta, 2012). Panels of genetic tests allow for the full sequencing and multiplex ligation-dependent probe amplification of multiple genes related to a more global genetic problem such as a family history of breast, thyroid, kidney, endometrial, or colorectal cancer. To confirm the clinical diagnosis of CS, a panel test that includes the *PTEN* gene and closely matches the cancers seen in a family would be ordered.

Cowden syndrome is associated with numerous clinical findings that can be isolated findings. However, many of these findings can also be associated

with other syndromes. Some clinical findings were previously felt to be pathognomonic (i.e., distinctively characteristic) for CS, but a systematic analysis of diagnostic criteria by Pilarski et al. (2013) did not provide evidence for any pathognomonic clinical features of CS. Major and minor diagnostic criteria have been established to help the healthcare provider sort through physical findings and make a clinical diagnosis of CS. See Figure 1 for a listing of these criteria. The major and minor criteria from Figure 1 are used, as described in Figure 2, to make a clinical diagnosis.

Physical assessment is a quick, easy, noninvasive, and inexpensive method to screen for CS. Macrocephaly is one of the major criteria of CS (Mester, Tilot, Rybicki, Frazier, & Eng, 2011). The occipital-frontal circumference, or head circumference, is measured in centimeters just above the ears and around the largest portion of the head. Macrocephaly is identified when the head circumference is at or above the 97th percentile for the gender and height of an adult (Bushby, Cole, Matthew, & Goodship, 1992). Common skin findings in CS include trichilemmomas (i.e., small, skin-colored papules on the face, ears, and neck) (DermNet NZ, 2013), plantopalmar keratotic pits (i.e., indentations that are best seen after soaking the hands and feet in warm water), and acral hyperkeratotic papules (i.e., thickened, callous-like tissue). Oral findings often include papillomas (i.e., hamartomas) of the gingiva and the buccal mucosa, giving it a cobblestone appearance.

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Lhermitte-Duclos disease is another clinical finding that may be found in CS. Lhermitte-Duclos disease is caused by a dysplastic gangliocytoma of the cerebellum (i.e., benign brain tumor) and tends to cause symptoms seen in

the third or fourth decade of life (Office of Rare Diseases Research, 2011). These symptoms include headache, nausea, visual disturbances, ataxia, and other signs of cerebellar dysfunction (Office of Rare Diseases Research, 2011).

## Implications for Oncology Nurses

Tan et al. (2012) found approximate lifetime risks of 85% for breast cancer, 35% for thyroid cancer, 34% for kidney cancer, 28% for endometrial cancer, 9% for colorectal cancer, and 6% for melanoma. Except for the inclusion of melanoma, these findings are congruent with the National Comprehensive Cancer Network (2014) Clinical Practice Guidelines for Genetic/Familial High-Risk Assessment: Breast and Ovarian.

Screening and prevention are important considerations for patients with CS. Experts from within the National Comprehensive Cancer Network (2014)–member institutions have developed a guideline on enhanced screening and management for individuals with CS. Guidelines for women include breast awareness starting at age 18 years, clinical breast examinations, annual screening mammography and breast magnetic resonance imaging (MRI), education to report signs and symptoms of endometrial cancer, discussion and counsel about risk-reduction methods, cancer risk, and reconstruction options, as well as psychosocial, social, and quality-of-life aspects of risk-reduction surgery (National Comprehensive Cancer Network, 2014). Guidelines for men and women include annual comprehensive examinations starting at age 18 years or five years before the age of the earliest CS-related cancer diagnosis in the family with special attention to thyroid examinations, annual thyroid ultrasound, colonoscopy starting at age 35 years, dermatologic management, renal ultrasound starting at age 40 years, and education about the signs and symptoms of cancer (National Comprehensive Cancer Network, 2014). Guidelines for children include psychomotor assessment at diagnosis of CS and a brain MRI if symptoms exist (National Comprehensive Cancer Network, 2014). Individuals with CS are at increased risk for first and second primary malignancies making enhanced surveillance paramount for their care (Ngeow, Stanuch, Mester, Barnholtz-Sloan, & Eng, 2014).

### Major Criteria

#### Cancer

- Breast
- Endometrial (epithelial)
- Thyroid (follicular)

#### Benign lesions

- Mucocutaneous lesions (any of the following):
  - Trichilemmoma (3 or more, 1 biopsy proven)
  - Acral keratosis (3 or more plantopalmar keratotic pits and/or acral hyperkeratotic papules)
  - Neuromas
  - Oral papillomas (tongue and gingiva, 3 or greater) or biopsy proven or diagnosed by a dermatologist
  - Gastrointestinal hamartomas (including ganglioneuromas, but excluding hyperplastic polyps)

#### Other findings

- Macrocephaly (97th percentile or greater)
- Lhermitte-Duclos disease (adults)
- Macular pigmentation of the glans penis

### Minor Criteria

#### Cancer

- Colon
- Kidney (renal cell)
- Thyroid (papillary or “follicular variant of papillary”)

#### Other findings

- Thyroid structural lesions (e.g., adenoma, multinodular goiter)
- Autism spectrum disorder
- Esophageal glycogenic acanthoses (3 or greater)
- Lipomas (3 or greater)
- Intellectual disability (IQ of 75 or less)
- Testicular lipomatosis
- Vascular anomalies (including multiple intracranial developmental venous anomalies)

### Figure 1. Major and Minor Revised Criteria Used in the Clinical Diagnosis of Cowden Syndrome and PTEN Hamartoma Tumor Syndrome

Note. From “Cowden Syndrome and the PTEN Hamartoma Tumor Syndrome: Systematic Review and Revised Diagnostic Criteria,” by R. Pilarski, R. Burt, W. Kohlman, L. Pho, K.M. Shannon, and E. Swisher, 2013, *Journal of the National Cancer Institute*, 105, p. 1613. Copyright 2013 by Oxford University Press. Adapted with permission.

### Operational (clinical) diagnosis in an individual

- Three or more major criteria, but one must include macrocephaly, Lhermitte-Duclos disease, or gastrointestinal hamartomas
- Two or three minor criteria

### Operational (clinical) diagnosis in a family where one individual meets Cowden syndrome criteria or has a PTEN mutation

- Any two major criteria with or without minor criteria
- One major and two minor criteria
- Three minor criteria

### Figure 2. Guidelines for Making an Operational (Clinical) Diagnosis of Cowden Syndrome and PTEN Hamartoma Tumor Syndrome

Note. From “Cowden Syndrome and the PTEN Hamartoma Tumor Syndrome: Systematic Review and Revised Diagnostic Criteria,” by R. Pilarski, R. Burt, W. Kohlman, L. Pho, K.M. Shannon, and E. Swisher, 2013, *Journal of the National Cancer Institute*, 105, p. 1613. Copyright 2013 by Oxford University Press. Adapted with permission.

Laura Curr Beamer, DNP, AOCNP®, AOCNS®, APNG, is an assistant professor in the School of Nursing and Health Studies in the College of Health and Human Sciences at Northern Illinois University in DeKalb and a doctoral candidate at the University of Utah in Salt Lake City. No financial relationships to disclose. Beamer can be reached at lbeamer@niu.edu, with copy to editor at ONFEditor@ons.org.

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## Genetics & Genomics

This feature aims to educate oncology nurses about the emerging role of genetics and genomics in cancer care. Possible submissions include, but are not limited to, application of genetics and genomics in clinical practice, screening and surveillance, case studies to present new ideas or challenge current notions, and ethical issues. Manuscripts should

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