Cowden Syndrome/PTEN Hamartoma Tumor Syndrome: PTEN Mutations

The PTEN Hamartoma Tumor Syndrome (PHTS) is a spectrum of highly variable conditions with overlapping features. This spectrum includes Cowden syndrome (CS), Bannayan-Riley-Ruvalcaba syndrome (BRRS), and PTEN-related autism spectrum disorder.\(^1\) The term PHTS describes any individual with a germline pathogenic PTEN mutation, regardless of their clinical presentation.\(^4\)

PHTS is a multisystem syndrome primarily characterized by noncancerous (benign), tumor-like growths called hamartomas that can develop throughout the body. There is also an increased risk of adult-onset cancers.\(^5\)

Cancer Risks and General Management Recommendations

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<th>PTEN Mutation Carrier Cancer Risks(^2,4,8)</th>
<th>General Population Lifetime Cancer Risks</th>
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| Female Breast: Primary: 33-60% Second Primary: 29% within 10 years\(^10\) | 12.4% | **Surveillance**  
  - Breast awareness, including periodic, consistent breast self exams, starting at age 18 years  
  - Clinical breast exam every 6-12 months starting at age 25 years, or 5-10 years before the earliest breast cancer diagnosis in the family (whichever comes first)  
  - Annual mammogram with consideration of tomosynthesis and breast MRI with contrast at age 30-35 years, or 5-10 years before the earliest breast cancer diagnosis in the family (whichever comes first)  
  - Age >75 years: Management should be considered on an individual basis  
  **Surgery**  
  - Discuss option of risk-reducing mastectomy, including degree of protection, reconstruction options, and risks  
    - Family history and residual breast cancer risk with age and life expectancy should be considered  
    - For those with a clinical diagnosis of Cowden syndrome, consideration of risk-reducing surgery should be based on family history |
| Thyroid (typically follicular): 34-38% | 1.2% | **Surveillance**  
  - Annual thyroid ultrasound starting at age 7 years |
| Kidney (typically papillary renal cell or chromophobe): 34-35% | 1.7% | **Surveillance**  
  - Consider renal ultrasound at age 40, then every 1-2 years |
| Endometrial: 28% | 2.9% | **Surveillance**  
  - Patient education and prompt medical attention to symptoms (e.g., abnormal or postmenopausal uterine bleeding)  
  - Consider starting endometrial cancer screening by age 35 years  
  - Endometrial biopsy every 1-2 years can be considered  
  - Transvaginal ultrasound for postmenopausal women may be considered at the clinician’s discretion (not recommended for premenopausal women) |
Surgery
- Discuss option of hysterectomy upon completion of childbearing, including degree of protection, extent of cancer risk, and reproductive desires

Colon Cancer: 9%

Surveillance
- Colonoscopy starting at age 35 y, or 5-10 years before the earliest known colon cancer in the family (whichever comes first), then every 5 years or more frequently if patient is symptomatic or polyps are found

Other Cancer Risks: Increased risks for melanoma, central nervous system cancers and male breast cancer have also been reported. Currently, there are no consensus management guidelines for these other cancers. Individuals with a PTEN mutation are encouraged to discuss these cancer risks, along with family history and personal risk factors, with their healthcare providers to establish an appropriate surveillance regimen.

Other Clinical Features and Additional Management Recommendations

- Other Clinical Features
  - Lhermitte-Duclos disease, a rare benign brain tumor defined as a cerebellar dysplastic gangliocytoma
  - Mucocutaneous lesions, including facial trichilemmomas, mucosal papillomatous papules, and acral and plantar keratosis. Other benign cutaneous lesions including lipomas and macular pigmentation of the glans penis
  - Benign thyroid disease including multinodular goiter, adenomatous nodules, follicular adenomas and Hashimoto's thyroiditis
  - Macrocephaly and dolichocephaly
  - Developmental delay, intellectual disability, and autism spectrum disorder
  - Vascular anomalies (including multiple intracranial developmental venous anomalies)
  - Fibrocystic breast disease, uterine fibroids, and ovarian cysts have been described; however, because fibrocystic breasts and uterine fibroids are common in the general population, it is uncertain if these are significant in their association with PHTS

- Additional Management Recommendations
  - Annual comprehensive physical exam starting at age 18 years, or 5 years before the youngest age of diagnosis of a PHTS-related cancer in the family (whichever comes first), with particular attention to thyroid exam
  - Annual dermatology examinations are recommended due to the possible increased risk of melanoma and the prevalence of other skin characteristics with Cowden syndrome
  - Consider psychomotor assessment in children at diagnosis, and brain MRI if there are symptoms

Implications for Family Members/Reproductive Considerations

- First-degree relatives (i.e., parents, siblings, and children) have a 50% chance to have the familial PTEN mutation. Second-degree relatives (i.e., nieces/nephews, aunts/uncles, and grandparents) have a 25% chance to have the familial mutation.
- An estimated 10-48% of PTEN mutations occur de novo (i.e., a spontaneous mutation not inherited from either parent)
- For carriers of a known mutation, assisted reproduction (with or without egg or sperm donation), pre-implantation genetic testing, and prenatal diagnosis options exist.
- All family members are encouraged to pursue genetic counseling to clarify their risks. Family members can visit www.FindAGeneticCounselor.com to find genetic services near them.
References


