Updated December 2019 (NCCN v1.2020)

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.[1-3] 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

***PTEN* Mutation Carrier Cancer Risks[2,4-8]**	**General Population Lifetime Cancer Risks**	**Surveillance/Management Recommendations[9]**

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%	4.2%	*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.[6,8] 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[5]
  - Mucocutaneous lesions, including facial trichilemmomas, mucosal papillomatous papules, and acral and plantar keratosis.[1,2] Other benign cutaneous lesions including lipomas and macular pigmentation of the glans penis[5]
  - Benign thyroid disease including multinodular goiter, adenomatous nodules, follicular adenomas and Hashimoto's thyroiditis[4,5,11-13]
  - Macrocephaly and dolichocephaly[5]
  - Developmental delay, intellectual disability, and autism spectrum disorder[5,14,15]
  - Vascular anomalies (including multiple intracranial developmental venous anomalies)[4,8,16]
  - Fibrocystic breast disease, uterine fibroids, and ovarian cysts have been described;[4,8,13,17,18] 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[12]
- Additional Management Recommendations[9]
  - 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)[19]
- 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

1. Eng C. PTEN Hamartoma Tumor Syndrome. In: Adam MP, Ardinger HH, Pagon RA, et al., eds. *GeneReviews.* Seattle (WA): University of Washington, Seattle; 1993.
2. Leslie NR, Longy M. Inherited PTEN mutations and the prediction of phenotype. *Seminars in cell & developmental biology.* 2016;52:30-38.
3. Eng C. PTEN: one gene, many syndromes. *Human mutation.* 2003;22(3):183-198.
4. Mester J, Eng C. Cowden syndrome: recognizing and managing a not-so-rare hereditary cancer syndrome. *Journal of surgical oncology.* 2015;111(1):125-130.
5. Mester J, Charis E. PTEN hamartoma tumor syndrome. *Handbook of clinical neurology.* 2015;132:129-137.
6. Tan MH, Mester JL, Ngeow J, Rybicki LA, Orloff MS, Eng C. Lifetime cancer risks in individuals with germline PTEN mutations. *Clinical cancer research : an official journal of the American Association for Cancer Research.* 2012;18(2):400-407.
7. Riegert-Johnson DL, Gleeson FC, Roberts M, et al. Cancer and Lhermitte-Duclos disease are common in Cowden syndrome patients. *Hereditary cancer in clinical practice.* 2010;8(1):6.
8. Bubien V, Bonnet F, Brouste V, et al. High cumulative risks of cancer in patients with PTEN hamartoma tumour syndrome. *Journal of medical genetics.* 2013;50(4):255-263.
9. NCCN Clinical Practice Guidelines in Oncology®: Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic. Version 1.2020. 2019.
10. Ngeow J, Stanuch K, Mester JL, Barnholtz-Sloan JS, Eng C. Second malignant neoplasms in patients with Cowden syndrome with underlying germline PTEN mutations. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2014;32(17):1818-1824.
11. Nieuwenhuis MH, Kets CM, Murphy-Ryan M, et al. Cancer risk and genotype-phenotype correlations in PTEN hamartoma tumor syndrome. *Familial cancer.* 2014;13(1):57-63.
12. Pilarski R, Stephens JA, Noss R, Fisher JL, Prior TW. Predicting PTEN mutations: an evaluation of Cowden syndrome and Bannayan-Riley-Ruvalcaba syndrome clinical features. *Journal of medical genetics.* 2011;48(8):505-512.
13. Salem OS, Steck WD. Cowden's disease (multiple hamartoma and neoplasia syndrome). A case report and review of the English literature. *Journal of the American Academy of Dermatology.* 1983;8(5):686-696.
14. Varga EA, Pastore M, Prior T, Herman GE, McBride KL. The prevalence of PTEN mutations in a clinical pediatric cohort with autism spectrum disorders, developmental delay, and macrocephaly. *Genetics in medicine : official journal of the American College of Medical Genetics.* 2009;11(2):111-117.
15. Frazier TW, Embacher R, Tilot AK, Koenig K, Mester J, Eng C. Molecular and phenotypic abnormalities in individuals with germline heterozygous PTEN mutations and autism. *Molecular psychiatry.* 2015;20(9):1132-1138.
16. Tan WH, Baris HN, Burrows PE, et al. The spectrum of vascular anomalies in patients with PTEN mutations: implications for diagnosis and management. *Journal of medical genetics.* 2007;44(9):594-602.
17. Schrager CA, Schneider D, Gruener AC, Tsou HC, Peacocke M. Clinical and pathological features of breast disease in Cowden's syndrome: an underrecognized syndrome with an increased risk of breast cancer. *Human pathology.* 1998;29(1):47-53.
18. Starink TM, van der Veen JP, Arwert F, et al. The Cowden syndrome: a clinical and genetic study in 21 patients. *Clinical genetics.* 1986;29(3):222-233.
19. Mester J, Eng C. Estimate of de novo mutation frequency in probands with PTEN hamartoma tumor syndrome. *Genetics in medicine : official journal of the American College of Medical Genetics.* 2012;14(9):819-822.