



Oncogenetic testing and follow-up for Cowden syndrome (or PTEN hamartoma tumour syndrome - PHTS)

Cowden syndrome is a rare, multisystem disease that causes increased risks for malignancies (breast, thyroid, and endometrial) as well as benign hamartomatous overgrowth of tissues (skin, colon, thyroid, etc).

The term PTEN hamartoma^a tumour syndrome (PHTS) has been used to refer to a spectrum of disorders that have been linked to germline mutations in the phosphatase and tensin homolog (PTEN) gene, including Cowden syndrome (CS), Bannayan-Riley-Ruvalcaba syndrome (BRRS), adult Lhermitte-Duclos disease (LDD), and autism spectrum disorders associated with macrocephaly.¹

Cowden syndrome has a prevalence of about 1 in 250 000 in the Dutch population with a low mutation frequency.²

^a Hamartoma is a benign tumor-like nodule composed of an overgrowth of mature cells and tissues normally present in the affected part, but with disorganization and often with one element predominating



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1. Diagnostic testing criteria (NCCN Testing Criteria)

The following testing criteria should be considered when deciding for counselling, genetic testing and follow-up:

Cowden Syndrome PTEN Gene Testing Criteria

- Individual from a family with a known PTEN gene mutation;
- Individual meeting clinical diagnostic criteria for Cowden Syndrome;
- Individual with a personal history of:
 - Bannayan-Riley-Ruvalcaba syndrome (BRRS) OR
 - Adult Lhermitte-Duclos disease (cerebellar tumours) 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 \geq three minor criteria** OR
 - \geq Four minor criteria**
- Individual with a relative with a clinical diagnosis of Cowden syndrome or BRRS for whom testing has not been performed
 - The at-risk individual must have the following:
 - o Any one major criterion* OR
 - o Two minor criteria**



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* Major criteria:

- Breast cancer
- Endometrial cancer
- Follicular thyroid cancer
- Multiple gastrointestinal hamartomas or ganglioneuromas
- Macrocephaly
- Macular pigmentation of glans penis (a discolored area on the skin)
- Mucocutaneous lesions
 - One biopsy proven trichilemmoma
 - Multiple palmoplantar keratoses (abnormal thickening of the hands and feet)
 - Multifocal or extensive oral mucosal papillomatosis
 - Multiple cutaneous facial papules (often verrucous)

** Minor Criteria:

- Autism spectrum disorder
- Colon cancer
- Esophageal glycogenic acanthosis (≥ 3)
- Mental retardation (i.e. IQ <75)
- Papillary or follicular variant of papillary thyroid cancer
- Thyroid structural lesions (such as adenoma, nodule(s), goiter)
- Renal cell carcinoma



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- Vascular anomalies (including multiple intracranial developmental venous anomalies)
- Lipomas (benign soft tissue tumour)
- Single gastrointestinal hamartoma or ganglioneuroma
- Testicular lipomatosis

2. Follow-up of women at high risk

The efficacy, risk, and benefits of cancer screening in Cowden syndrome are unknown.⁴ Recommendations listed below are suggested in the scientific literature and are based on expert opinions.

- For women with a proven PTEN mutation who opt for screening rather than for prophylactic bilateral mastectomy, yearly MRI is recommended from the age of 25 years onwards. From the age of 40 years onwards, yearly MRI and yearly mammography with an interval of six months between both examinations can be used.
- Mammography should be used with prudence between 30 and 40 years but should not be used before age 30.
- Ultrasound is useful to reduce the number of false positives when MRI is difficult to interpret.
- No studies have assessed efficacy of prophylactic mastectomy in Cowden Syndrome. Without recommending such intervention, healthcare professionals can discuss with each patient the balance benefits/harms of preventive surgery (risk-reducing mastectomy) and counsel regarding degree of protection, extent of cancer risk and reconstruction options.³
- Annual screening with ultrasound of the thyroid gland could be considered, starting at age 18 y.⁴
- Because data regarding lifetime risk of endometrial cancer are limited, surveillance screening (ultrasound and/or endometrial biopsy has been suggested to begin at age 35–40 or 5 years before the earliest endometrial cancer in the family)⁴ and surgical intervention (hysterectomy) should be on an individual basis.
- Colonoscopy can be considered, starting at age 35 y, then every 5-10 y or more frequently if patient is symptomatic or polyps were found.³
- If there is a family history of renal cell cancer, an annual urinalysis has been suggested, supplemented by cytology and renal ultrasound.⁴



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References

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