Title: Cancer and Overgrowth Manifestations of *PTEN* Hamartoma Tumour Syndrome: Management Recommendations from the International *PTEN* Hamartoma Tumour Syndrome Consensus Guidelines Working Group

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Abstract

Purpose: *PTEN* hamartoma tumour syndrome (PHTS) is an autosomal dominant cancer-predisposition and overgrowth syndrome occurring due to pathogenic germline variants in the *PTEN* gene, with an increased risk of both benign and malignant tumours involving the breast, colon, endometrium, thyroid, skin, and kidney. The objective of these clinical guidelines was to use the latest knowledge to generate an international consensus resource for providers, researchers, and individuals with PHTS on the best practices in the surveillance and management of cancer and overgrowth in PHTS.

Experimental Design: The International PHTS Cancer and Overgrowth Guidelines Working Group was established, comprising a core group of six international experts in the diagnosis and management of PHTS. The Working Group held joint meetings with PHTS individuals and their advocates. Informed by the literature, the Working Group met regularly between 2022 and 2024 to produce guideline statements, refined through iterative feedback. A modified Delphi approach was used with an independent external panel of PHTS, genetics and cancer experts to establish final consensus guidelines.

Results: Clinical consensus recommendations for the surveillance and management of cancer and overgrowth in individuals with PHTS were formed. Guidelines encompass the recommended practices in cases of breast, colon, endometrial, thyroid, and kidney cancers, as well as overgrowths.

Conclusions: The clinical management of individuals with PHTS is complex and necessitates a multidisciplinary approach. We generated international consensus guidelines for the surveillance

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and management of cancer and overgrowth in PHTS aiming at improving care for affected individuals and families.

Funding: *PTEN* Research Foundation

Keywords: *PTEN*; PHTS; PTEN hamartoma tumour syndrome; cancer; overgrowth

Statement of Translational Relevance:

These clinical guidelines for PTEN hamartoma tumour syndrome (PHTS) surveillance and management have direct implications for improving patient care and outcomes. By providing standardized, evidence-based recommendations for cancer screening and overgrowth management across multiple affected organ systems, healthcare providers can deliver more consistent and comprehensive care to PHTS patients. The international consensus approach, incorporating input from both medical experts and patient advocates, ensures the guidelines are both clinically robust and practical for implementation. These recommendations will particularly benefit genetic counselors, oncologists, and primary care physicians in making informed decisions about individualized surveillance programs, potentially enabling earlier cancer detection and more effective intervention strategies for PHTS patients worldwide.

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Introduction

PTEN hamartoma tumour syndrome (PHTS) is an autosomal dominant cancer-predisposition and overgrowth disorder caused by pathogenic germline variants in the phosphatase and tensin homolog (*PTEN*) gene located on chromosome 10q23 (1,2). PHTS is a molecular diagnosis that encompasses various clinically heterogenous syndromes including Cowden Syndrome (CS), Bannayan-Riley-Ruvalcaba Syndrome (BRRS), Proteus syndrome, (PS) and Proteus-like syndrome, irrespective of clinical presentation (3). *PTEN* is a tumour suppressor gene that canonically functions within the cytoplasm to antagonize the PI3K/AKT/mTOR signalling pathway, which promotes cell growth, survival, and proliferation (4). *PTEN* also localizes to the nucleus where it plays an essential role in maintaining genomic integrity through physical interaction with centromeres and in controlling DNA repair (5). Individuals with PHTS may experience a variety of signs and symptoms including macrocephaly, abnormal skin growths, vascular manifestations, autism spectrum disorder, and learning and developmental delays (6–9). Notably, individuals with PHTS have significantly elevated lifetime risks of both benign and malignant tumours involving various organs such as the breasts, colon, endometrium, thyroid, skin, and kidney (6–12).

Guidelines on the clinical management of PHTS—primarily focusing on cancer surveillance—have been published by Schultz and colleagues (paediatric guidelines), the National Comprehensive Cancer Network (NCCN) in the United States and by the European Reference Network (ERN) for Genetic Tumour Risk Syndromes (GENTURIS) in Europe (13–16).

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To provide the best practices based on latest knowledge and literature in the surveillance and management of cancer and overgrowth in PHTS individuals, the International PHTS Cancer and Overgrowth Guidelines Working Group was established. Overgrowth in the context of this working group and these guidelines refers generally to benign tumours occurring in individuals with PHTS. The Working Group comprised a set of six international experts (the core group) in the diagnosis and management of PHTS, including cancer genetics and genomics, medical oncology, and various cancer specialists and experts. The core group had joint meetings with individuals with PHTS and advocates representing the PTEN Foundation, a non-profit patient-led community for PHTS. The core group utilized a modified Delphi approach to achieve further consensus among a wider international panel of experts in cancer and overgrowth (the external panel). Our primary aim was to generate an evidence-based PHTS individual- and provider-centred resource highlighting international consensus for the practical management of cancer and overgrowth in individuals with PHTS. Of note, because the care of individuals with PTHS is highly multidisciplinary, additional guidelines for neurologic care, dermatologic care, and vascular malformations in PHTS are in various stages of preparation by additional expert groups.

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Methods

Search strategy and article selection criteria

A comprehensive literature search was performed initially on September 19, 2022. An updated literature search was performed on January 4, 2023 to include articles published after the original search to capture studies not included in the initial search. We used OVID MEDLINE and EMBASE databases of all articles published between 2002 and 2023. Search terms for OVID MEDLINE and EMBASE utilized the following terms (alone or in combination with): "*PTEN* Hamartoma Tumour Syndrome", "Cowden Syndrome", "Bannayan-Riley-Ruvalcaba Syndrome", "Proteus syndrome", "Proteus-like syndrome", "Lhermitte Duclos", "PHTS", "*PTEN* or *PTEN* Phosphohydrolase".

Identified articles were imported into the Covidence systematic review software, where studies were deduplicated and screened. Studies reporting on incidence, prevalence, morbidity, or mortality of cancer and overgrowth as it related to PHTS were included. Publications without English translation were excluded. Review articles, editorials, opinion pieces, and meeting abstracts/posters were also excluded. Cumulatively, 5,222 studies were identified between both database searchers with 1,445 duplicates that were subsequently removed. Following screening, 3,400 studies were excluded for failing inclusion criteria, and 377 published articles were included for data extraction. Studies were categorized by study type (e.g., case report, case series, therapeutic trials, etc.). Elements extracted from each study included: study population, study design, intervention, outcomes measured, and result summary. Core members of the International

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PHTS Consensus Guidelines Working Group convened regularly between 2022 and 2024 and developed guidelines based on the extracted articles.

Evidence Grading Criteria

Like many rare diseases, the number of peer-reviewed articles with high-level evidence available to inform these guidelines was limited. We used an evidence grading scale to balance the weight of both published evidence and expert experience and knowledge as implemented by Tischkowitz et al. (2020) (15). The scale is as follows: (i) strong evidence: consistent evidence with new evidence unlikely to change recommendation and expert consensus; (ii) moderate evidence: inconsistent evidence or significant new evidence expected and expert consensus and (iii) weak evidence: inconsistent evidence and expert consensus. Statements with limited/no evidence and limited expert agreement were classified in separate sections as expert opinion statements.

Modified Delphi Approach

As part of a comprehensive effort to develop international consensus surveillance and management guidelines for cancer and overgrowth in PHTS, the International PHTS Consensus Guidelines Working Group undertook a two-stage modified Delphi approach to achieve consensus on guideline recommendations among the core group members. There were parallel Working Groups focused on neurodevelopmental and neurological features of PHTS, vascular anomalies, dermatological features, and genetics. The core group members (n=6) for the Cancer and Overgrowth Working Group and the Patient Advisory Group convened regularly from 2022

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to 2024 to discuss and develop guideline statements informed by the literature (literature search strategy listed in the Methods section) and graded as strong, moderate, or weak evidence, or expert opinion statements with limited evidence and limited expert agreement. The first stage involved meetings of core group members until consensus was reached—defined as 100% agreement amongst the core group. The second stage of our modified Delphi approach consisted of an independent external panel of experts (listed in the Acknowledgements) providing feedback on draft guideline statements. This panel, selected for their clinical expertise in PHTS, participated in two rounds of standardized Delphi surveys until consensus was reached—defined as 80% agreement amongst the external panel of experts. For each recommendation, the external panel of experts voted whether to keep, remove, or modify the recommendation. Experts were also given the option to provide a free-text response to support their decision or to suggest changes. Responses were anonymized and reviewed after each round of the Delphi process. The core group members and patient advocates held a joint meeting after every round to discuss and amend statements based on anonymized feedback until 100% agreement was reached amongst the core group. The patient advocates were present at the meetings and often provided input on the psychosocial aspects as well as practical aspects of undergoing cancer surveillance and treatment as part of PHTS. The advocates were also present at the discussions following the feedback from the modified Delphi rounds.

Data Availability

The data generated in this study are available within the article and its supplementary data files. Any additional requests or questions may be directed to the corresponding author.

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Results

The presented guideline statements apply to individuals with a germline pathogenic variant in the *PTEN* gene unless otherwise stated. Clinical consensus recommendations for breast, thyroid, colon, endometrial, and renal cancers in individuals with PHTS are summarized in **Tables 1-7**. Agreements for modified Delphi rounds 1 and 2 are presented in **Supplementary Tables 1 and 2**, respectively.

General management, risk-reduction, and surveillance recommendations for cancer and overgrowth in PHTS (applies to all organ systems discussed in the results section)

Individuals with pathogenic germline variants in *PTEN* have a predisposition to developing different cancers such as breast cancer, colon cancer, endometrial cancer, thyroid cancer, and renal cancer (6–12). In females with germline pathogenic *PTEN* variants, the lifetime risk for breast and endometrial cancers is reported as 67-91% and 19-48%, respectively. Similarly, there are elevated lifetime risks for colorectal (9-20%), renal (10-30%), and thyroid cancers (17-38%) (2,7–12,17–19). The cumulative cancer risks as reported by various studies are potentially overestimated due to ascertainment bias and small cohorts with limited follow-up time, yet cancer risks are likely underestimated in older individuals (10). Owing to the high lifetime risk of malignancy, at the time of PHTS diagnosis, consultation with a multidisciplinary team (including medical genetics, gastroenterology, endocrinology, gynaecology, urology, medical oncology, surgery, and radiation oncology, as needed) at an experienced medical centre is recommended. Further, a self-reported survey of lifestyle factors in individuals with PHTS encompassing

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alcohol use, smoking, body mass index, and physical activity, did not find statistically significant differences between those with and without breast cancer. Although limited by sample size, the observed effect sizes for lifestyle factors impacting cancer risk were similar to that of the general population, underscoring that there are no indications to deviate from lifestyle recommendations for general population in PHTS (20).

The treatment for most cases of malignant disease involves chemotherapy and/or radiotherapy. There were only a limited number of case reports where authors speculated or suggested that individuals with PHTS developed chemotherapy- or radiotherapy-induced secondary malignancies at a rate greater than the unaffected population (18,21–26). Indeed, the rates of chemotherapy- or radiotherapy-induced secondary malignancies have not been shown to be increased in individuals with PHTS in any large-scale prospective trial, and generally it is felt that standard treatments should not be withheld from individuals with PHTS when accounting for the balance of potential risks and benefits.

Affected individuals may also require psychosocial care. While there is strong evidence for psychosocial care and support in the cancer population, there are no specific studies addressing this in the PHTS population (27). Psychosocial supports may include psychiatry, clinical psychology, and counselling/therapy resources. Given that nearly 25% of individuals with PHTS meet diagnostic criteria for autism spectrum disorder, and there are heterogeneous neuropsychological profiles among individuals with PHTS, psychosocial care should be tailored to meet individual needs (27). Allied health is also recommended for all individuals as needed, and includes physical, occupational, speech therapy, social work, and child life services.

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Recommendations:

Management

1. **We recommend that individuals with PHTS undergo standard of care treatment for specific malignancies, as determined by the most current local guidelines (e.g., National Comprehensive Cancer Network). (100% Extended Panel Delphi Agreement; Strong Evidence)**

Expert Opinion Statements:

Management

2. **There is no direct evidence to suggest that individuals with PHTS are at increased risk of developing secondary malignancies due to the effects of chemotherapy and/or radiotherapy. These concerns should not preclude individuals from receiving the standard of care for organ-specific cancer treatments. (100% Extended Panel Delphi Agreement; Limited/Weak Evidence)**
3. **Physicians should be aware of psychosocial needs and offer support as well as adjunctive allied health, when indicated, to individuals with PHTS. (100% Extended Panel Delphi Agreement; Limited/Weak Evidence)**

Risk-reduction

4. **All PHTS individuals and caregivers, irrespective of age, should be counselled on minimizing or avoiding domestic and occupational exposure to known carcinogens, given the increased lifetime malignancy risk in this condition (e.g., smoking, obesity, and alcohol). (100% Extended Panel Delphi Agreement; Limited/Weak Evidence)**

Surveillance

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5. **All individuals at the time of PHTS diagnosis, should undergo a comprehensive physical exam, which can be done by a primary care provider. Clinicians should provide individuals with education regarding the signs and symptoms of organ-specific cancers and discuss relevant surveillance recommendations for malignancy. (100% Extended Panel Delphi Agreement; Limited/Weak Evidence)**

Breast Cancer

Breast cancer is the most common cancer in females with PHTS (7,9,12,17). Breast cancer risk in PHTS is similar to that of women with germline pathogenic variants in *BRCA1/BRCA2 (15*). The risk of breast cancer in individuals with PHTS increases between 25 – 30 years of age (9–11). The cumulative risk of developing breast cancer in females with PHTS has been reported as 67-78%, 77%, and 85-91% at 60, 70, and 80 years of age, respectively (2,7,9–12,17). Conversely, males with PHTS have not been reported to have an increased risk for breast cancer (9). Risk estimates have varied across studies. For instance, earlier studies reported a lower lifetime cancer risk between 25-50%, and the NCCN guidelines state a lifetime risk of 40-60% (28,29). However, evidence in this field is evolving as newer cohorts align between these estimates, (e.g. Hendricks and colleagues found a lifetime risk for female breast cancer at 54-78%), but this remains to be shown in confirmatory studies (10). The 10-year cumulative risk of developing second primary malignant neoplasms (SMNs) in the contralateral breast is reported as 29% (30).

At the molecular level, truncating variants in *PTEN* appear to confer a higher lifetime risk of breast cancer (9). Likewise, patients with *PTEN* promoter variants had a relatively lower lifetime

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risk of breast cancer, compared to those without variants in the *PTEN* promoter (9). Variants in the C2 domain of PTEN (amino acids 186–351) are associated with an increased risk of breast cancer in Japanese individuals (17).

Among individuals with PHTS, the sensitivity of breast MRI in detecting breast cancer has been shown to be superior to mammography (31). In a series of 39 women with PHTS undergoing a breast surveillance program with median age at first surveillance examination 38 years (range, 24–70 years), it was found that the sensitivity of MRI in detecting breast cancer was higher than that of mammography (100% vs. 50%) (31). Breast MRI is ideally performed every 12 months, during days 5-12 (follicular phase) of menses in pre-menopausal females with regular cycles, reducing background parenchymal enhancement (32). Surveillance regimens should fit within the goals of care of each individual with PHTS and should not be overly burdensome from a time or financial perspective. Per NCCN guidelines, clinicians may counsel individuals with PHTS regarding breast awareness but should note that these guidelines differ with regards to age of starting breast MRI screening (29). In PHTS, we recommend that annual breast MRI is started at age 25 years, whereas NCCN and ERN GENTURIS guidelines both recommend breast MRI to start at age 30 years (15,29). Because the youngest age of breast cancer reported in PHTS is 26 years, and the very high lifetime risk of breast cancer in PHTS, the guidelines committee agreed that beginning annual surveillance at 25 years was most appropriate (10,31).

In women with germline pathogenic variants in *BRCA1/BRCA2*, risk-reducing mastectomy (RRM) was found to be an effective risk-reducing strategy for breast cancer prevention (33–35). In a study of 639 women with germline *BRCA1/2* pathogenic variants, at a median age of 42

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years at the time of risk-reducing mastectomy, RRM reduced the risk of breast cancer by 90% at 14 years of follow up (35). A decreased risk of breast cancer has also been demonstrated following nipple-sparing mastectomy in *BRCA1* and *BRCA2* mutation carriers, leading to the consideration for individuals with *BRCA1/2* pathogenic variants to undergo risk-reducing breast surgery between 25 and 30 years of age (33). Extrapolating these data to individuals with PHTS, who have a similar lifetime risk of breast cancer, provides a rationale for the discussion of potential risk-reducing mastectomy, as outlined below.

Recommendations:

Risk-reduction

6. **Given the high lifetime risk of female breast cancer and second primary breast cancer in individuals with PHTS and pathogenic or likely pathogenic variants in *PTEN*, we recommend discussing the options of surveillance versus risk-reducing mastectomy (RRM) with an experienced high-risk breast clinic team.**

   In individuals with pathogenic or likely pathogenic variants in *PTEN*, RRM may be informed by the individual's family history of breast cancer, if known. Generally, RRM should only be considered in individuals over 25 years of age, unless otherwise clinically indicated, and counselling should include discussions relating to the degree of risk-reduction, surgical risks, and reconstructive options. The individual's life expectancy, in addition to their residual lifetime breast cancer risk should also be taken into consideration.

   In individuals for whom surveillance may be difficult to access, RRM may also be considered with the same caveats as above. The psychosocial and quality-of-life aspects

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of RRM must also be discussed with individuals with PHTS when this procedure is being considered. (95% Extended Panel Delphi Agreement; Moderate Evidence)

Surveillance

7. **Women with PHTS should undergo annual breast MRI (with contrast) from age 25 years and additional surveillance with breast mammography (with digital breast tomosynthesis), starting at age 40 years until 75-80 years of age. After 75-80 years, we recommend an individualized approach to surveillance and risk-benefit discussion with an experienced breast clinician. Following national guidelines is recommended. (95% Extended Panel Delphi Agreement; Strong Evidence)**
8. **We do not recommend that males with PHTS undergo surveillance with breast MRI, mammography, or clinical breast examinations. (100% Extended Panel Delphi Agreement; Strong Evidence)**

Expert Opinion Statements:

Medical risk reduction

9. **Depending on local practice guidelines, the following expert opinion can be considered. Though there are no specific studies examining the use of risk-reducing medication (tamoxifen, raloxifene, exemestane or anastrozole) in individuals with pathogenic or likely pathogenic variants in *PTEN*, these options may be discussed. The increased risk of endometrial cancer in individuals with an intact uterus generally precludes the risk-reducing use of the selective oestrogen receptor modulator tamoxifen (the only medication that can be used in the premenopausal setting; all four medications may be used in the postmenopausal setting). In many European countries, this is not compliant**

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with current guidelines. (92% Extended Panel Delphi Agreement; Limited/Weak Evidence)

Since there is no evidence on this topic and it is not compliant with current European guidelines, in the case of using risk-reducing medication (tamoxifen, raloxifene, exemestane or anastrozole), physicians should discuss the dearth of evidence, potential risks (e.g., possible increased endometrial cancer risk with tamoxifen use) and expected benefits of chemoprophylaxis with each individual. Local practice guidelines should be followed regarding the use of hormonal therapies.

Surveillance

10. Transgender individuals, assigned female at birth with remaining breast tissue, should undergo surveillance as above. There are no data regarding testosterone supplementation and breast cancer risk to make a recommendation. (100% Extended Panel Delphi Agreement; Limited/Weak Evidence)

Management

11. There is no contraindication to receiving gender-affirming hormone therapy (GAHT) in transgender individuals assigned male at birth. We recommend beginning breast surveillance 5 years after the start of GAHT, not before 25-30 years of age. We recommend surveillance in these individuals with breast MRI or annual mammography with consideration of tomosynthesis. (100% Extended Panel Delphi Agreement; Limited/Weak Evidence)

Thyroid Cancer

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The lifetime thyroid cancer risks in individuals with pathogenic/likely pathogenic *PTEN* variants are estimated at 17-38% at 70 and 80 years of age, respectively (7–9,11,12). Thyroid cancer risk begins to increase from around 10 years of age, with the youngest age of thyroid cancer in PHTS reported as 4 years old (8,9,36,37). While there is a potential increased risk of thyroid cancer in relatively young ages in PHTS, there is weak evidence to support surveillance of individuals throughout childhood (7,11,12,17,38,39). In a recent study, thyroid ultrasound surveillance showed differentiated thyroid carcinoma in 2 of 43 individuals before age 18 years (37). This evidence supports the recommendation of thyroid ultrasound surveillance in children from age 12 years (37,38).

Further, the clinical benefit of thyroidectomy is not clear in individuals with PHTS. The balance of the surgical risk of thyroidectomy with the potential benefit of reduced thyroid cancer risk is uncertain, particularly in the setting of straightforward biochemical surveillance for thyroid cancer.

Clinically actionable thyroid nodules are defined as nodules meeting criteria for fine-needle aspiration (FNA), according to the 2015 American Thyroid Association (ATA) criteria based on sonographic characteristics and nodule size (40). Thyroid nodules are common in PHTS during childhood or early adulthood (40). The prevalence of thyroid nodules in children with PHTS ranges from 44 – 51% (19,41,42). Individuals with PHTS and initial thyroid ultrasound without nodules are more than 90% likely to remain free of clinically actionable nodules at 3 years of follow-up and 85% at 6 years of follow-up with no individuals developing cancer over entire follow-up period (41). This supports surveillance intervals in PHTS individuals without nodules

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on ultrasound every 3-5 years and individuals with clinically nonactionable nodules every 2-3 years.

Recommendations:

Risk-reduction

12. We do not recommend routine risk-reducing thyroidectomy for individuals with PHTS. The decision to undergo thyroidectomy is individualized and should be made in conjunction with a multidisciplinary team involving thyroid surgery, endocrinology and medical genetics. (100% Extended Panel Delphi Agreement; Strong Evidence)

Surveillance

13. From age 12 years, individuals with PHTS should undergo baseline thyroid ultrasound. We recommend stratifying the surveillance interval based on ultrasound results to help minimize the burden of frequent ultrasounds, especially in young children. TSH may be checked starting at age 18 years if ultrasounds are unremarkable, or earlier if there are abnormalities on ultrasound. (95% Extended Panel Delphi Agreement; Moderate Evidence)

14. We recommend surveillance with thyroid ultrasound every 3-5 years for PHTS individuals without nodules seen on initial thyroid ultrasound, and every 2-3 years for individuals with clinically nonactionable nodules seen on initial thyroid ultrasound. Consider annual TSH surveillance in individuals over age 18 years. (100% Extended Panel Delphi Agreement; Moderate Evidence for ultrasound, Weak Evidence for TSH)

15. In individuals with PHTS and clinically actionable nodules, we recommend appropriate intervention in accordance with the American Thyroid Association (ATA) or similar

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local guidelines. In the case of benign findings on cytological examination, continued surveillance in 1-2 years is reasonable. (100% Extended Panel Delphi Agreement; Moderate Evidence)

Polyps/Colon Cancer

Gastrointestinal (GI) polyps, typically occurring as hamartomas, are common and can occur anywhere along the gastrointestinal tract of PHTS individuals (43). Upper GI and lower GI polyps with mixed histological types have shown increased risk of colorectal cancer (CRC) in PHTS individuals (43–47). The lifetime risk of colon cancer in PHTS individuals is estimated to be 9-20% (7–9,11,12,17). The age at which colon cancer risk increases in individuals with pathogenic/likely pathogenic *PTEN* variants or truncating variants begins in the early 20s, with the youngest age of CRC diagnosis being 21 years old (9). Individuals with PHTS also have an approximately 6-fold increase in developing second primary colorectal malignancies (30).

Multiple polyps are common in individuals with PHTS with high prevalence of colonic adenomas and adenocarcinoma (48,49). Serrated polyps and adenomas were found in 38% and 36% of individuals at index colonoscopy, and 42% and 31% in individuals less than 50 years (50). Colorectal and gastric polyps were also found in 73-98% of individuals with 73% of individuals having between 1 and 50 polyps (12,17). Individuals with PHTS and colorectal cancer generally had more than 50 polyps (43,46). Case series provide low-level evidence suggesting that individuals with PHTS may be at an increased risk of gastric cancer (46,50). However, it is difficult to draw conclusions as in each series, only a single subject with gastric

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cancer was presented. One case of small bowel carcinoid tumour was reported in an individual with PHTS and CRC among a series of 156 individuals with PHTS (51). Of note, hamartomatous polyps are common in individuals with PHTS, reported in the large bowel in up to 85% of patients, with a diverse set of stromal components (lipomatous, ganglioneuromatous, and fibrous components all reported, most with at least two components) (52). Further, hamartomatous polyps in PHTS were associated with serrated polyps or conventional adenomas in nearly half of patients in one series, affirming the need for gastroenterologist-directed endoscopic surveillance in this subset of patients (52).

Pathogenic/likely pathogenic *PTEN* variants are associated with GI polyps in children; there is also now emerging evidence that upper GI polyps are more common in children with PHTS who do not have PHTS-associated autism spectrum disorder (ASD) (49,53). The most prevalent gastrointestinal features in children with PHTS are constipation and feeding issues (including dysphagia, food aversion, and aspiration) (49). Children with PHTS and GI symptoms may benefit from an evaluation for polyposis and may require colonoscopy. Adult individuals with PHTS have been reported to present with CRC prior to the diagnosis of PHTS between the ages of 41 and 71 years (38). Colonoscopy is not recommended in asymptomatic individuals younger than 35-40 years of age, as only younger PHTS individuals with symptoms should undergo evaluation.

Although mTOR inhibitors have been shown to reduce the risk of colectomy and improve protein losing enteropathy and chronic GI bleeding in juvenile polyposis of infancy (JPI) with germline *PTEN* variant without adverse effects, mTOR inhibitors are not recommended for the

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chemoprophylaxis of colon cancer or management of polyps in individuals without JPI and PHTS. PHTS individuals treated with sirolimus demonstrate regression of GI lesions (54,55). There is no strong evidence that supports the use of *COX-1/COX-2* inhibitors (e.g., ASA) in chemoprevention of polyposis and colon cancer in PHTS. Chemo-prevention trials in hereditary CRC syndromes have been conducted in familial adenomatous polyposis (FAP) individuals, but just one trial has achieved the primary outcome of reduced duodenal polyp burden (56).

Recommendations:

Risk-Reduction

16. **We do not recommend use of mTOR inhibitors for the chemoprophylaxis of colon cancer or management of polyps in individuals with PHTS. (100% Extended Panel Delphi Agreement; Moderate Evidence)**
17. **We do not recommend the use of *COX-1/COX-2* inhibitors (e.g., ASA) in chemoprevention of polyposis and colon cancer in PHTS. (100% Extended Panel Delphi Agreement; Weak Evidence)**
18. **We do not recommend risk-reducing colectomy in individuals with PHTS and polyposis. (100% Extended Panel Delphi Agreement; Weak Evidence)**

Surveillance

19. **We recommend that all individuals with PHTS undergo a baseline colonoscopy at 35-40 years. We do not recommend routine colonoscopy in individuals younger than 35-40 years old. (100% Extended Panel Delphi Agreement; Moderate Evidence)**
20. **Individuals with PHTS and a high colon polyp burden (5 or more tubular adenomas), or polyps greater than or equal to 1 cm in diameter or with high grade dysplasia, should**

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undergo colonoscopy at a 1–3-year interval, as directed by their gastroenterologist. (95% Extended Panel Delphi Agreement; Moderate Evidence)

21. **We do not recommend routine upper GI endoscopic surveillance with small bowel follow through in individuals with PHTS. (100% Extended Panel Delphi Agreement; Moderate Evidence)**

Endometrial Cancer

An increased risk of endometrial cancer is reported in individuals with PHTS, with estimates of cumulative risk of 19-33% and 48% at ages 60 and 80 years, respectively (7–9,11,17). The youngest reported age of endometrial cancer in PHTS is 14 years (57).

Endometrial cancer can be detected at an early stage and suspected in the presence of symptoms such as abnormal uterine bleeding. In a series of 25 adult individuals with PHTS in the Netherlands undergoing endometrial cancer surveillance, seven women reported abnormal uterine bleeding (58). Endometrial hyperplasia, diffuse thickening of the endometrium, is also a known premalignant sign of endometrial cancer, aiding in its early detection. Endometrial hyperplasia with or without atypia were detected in seven individuals with PHTS on endometrial biopsy and transvaginal ultrasound, of whom six individuals had asymptomatic hyperplasia and one individual had hyperplasia with atypia (58).

Transvaginal ultrasound (TVUS) surveillance for endometrial cancer in premenopausal individuals has not been shown to be sensitive or specific in PHTS, but may be considered at the

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clinician's discretion (59). TVUS alone has been shown to be less sensitive than endometrial biopsy for the diagnosis of endometrial hyperplasia in individuals with PHTS. The addition of endometrial biopsy to TVUS aids in cancer prevention by improving the detection of asymptomatic premalignancies, such as hyperplasia with and without atypia (58).

Discussions with a multidisciplinary team about reducing endometrial cancer risk may involve consideration of hysterectomy with ovary-sparing approaches, given that current knowledge indicates that the ovarian cancer risk in PHTS is not greater than the general population. Factors such as age, desire for future fertility, and overall health status should be carefully considered.

Recommendations:

Risk-reduction

22. We do not recommend routine hysterectomy for endometrial cancer risk-reduction in PHTS individuals with a uterus. The decision to undergo hysterectomy is individualized and should be made in discussion with a multidisciplinary team involving obstetrics/gynaecology, reproductive health, and medical genetics. (100% Extended Panel Delphi Agreement; Weak Evidence)

23. For individuals with PHTS who have been diagnosed with uterine leiomyomas or endometrial hyperplasia with atypia, treatment options may include risk-reducing hysterectomy, hysteroscopy with endometrial curettage, and/or placement of a progestin-releasing intra-uterine device (IUD). Treatment decisions should be individualized and made in discussion with a multidisciplinary team involving

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obstetrics/gynaecology, reproductive health, and medical genetics. (95% Extended Panel Delphi Agreement; Weak Evidence)

Surveillance

24. **At the time of PHTS diagnosis, or at age 30-35 years, we encourage individual education and prompt response to abnormal uterine bleeding or postmenopausal bleeding. (100% Extended Panel Delphi Agreement; Weak Evidence)**
25. **In individuals over the age of 30-35 years with PHTS and unexplained or irregular vaginal bleeding, we recommend evaluation with both transvaginal ultrasound and endometrial biopsy. (100% Extended Panel Delphi Agreement; Weak Evidence)**
26. **There is limited evidence regarding routine endometrial cancer surveillance in PHTS. If the decision to offer surveillance for endometrial cancer is made, this should be part of a clinical trial. (90% Extended Panel Delphi Agreement; Weak Evidence)**

Renal Cancer

Renal cancer was found in a worldwide PHTS population with an estimated lifetime risk of 10-30% and median age of onset of 50 years (9). In a series of 455 individuals, 372 of whom had prospective follow up for a median of 6 years, the cumulative risk of renal cancer was less than 10% at 60 years (10). In a case series of 24 individuals, papillary renal cancer and chromophobe renal cell carcinoma were seen at a higher rate in individuals with PHTS compared to clear cell renal cell carcinoma, which is more common in the general population (60). There is no evidence related to the benefit of MRI over ultrasound in surveillance for renal cell carcinoma. Moreover,

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urine cytospin for red blood cells has not been validated in individuals with PHTS as a surveillance modality.

Expert Opinion Statement:

Surveillance

27. Starting at the age of 35-40 years, a surveillance ultrasound every 2 years for renal cell carcinoma may be considered in individuals with PHTS. MRI of the kidneys may also be considered. (100% Extended Panel Delphi Agreement; Limited/Weak Evidence)

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Discussion

The clinical management of individuals with pathogenic or likely pathogenic germline *PTEN* variants is complex and remains challenging due to variable expressivity, a dearth of clinical evidence, and age-related specificities. Here, we present international consensus guidelines for the surveillance and management of cancer and overgrowths associated with PHTS, excluding the management of skin cancers, aimed at standardizing and improving care for affected individuals and families. These guidelines have been developed by an internationally recognized panel of core experts and further affirmed through a modified Delphi process with an external panel of experts and patient advocates. As with all medical evidence, this is an evolving document and will be periodically reviewed and updated as new data emerge. The management of skin cancers and dermatologic findings in PHTS will be covered in a dermatology-specific guidelines statement.

Due to the rarity of PHTS, the evidence base in these guidelines is limited. The paucity of published studies constrained our ability to make recommendations on conditions that may be potentially associated with PHTS based on our clinical observations. Importantly, these guidelines have differences between published recommendations by the National Comprehensive Cancer Network (NCCN) and European Reference Network for all patients with one of the rare genetic tumour risk syndromes (ERN GENTURIS) committees (15,29). Specifically, the guidelines presented in this work do not recommend self- and clinical breast examinations, and in contrast to both the ERN and NCCN guidelines, recommend surveillance starting at age 25 years with annual breast MRI, as opposed to 30 years of age. ERN guidelines also recommend

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annual thyroid ultrasound starting at age 18 years, whereas NCCN guidelines recommend starting annual thyroid ultrasound at 7 years, and the guidelines presented in this work recommend thyroid ultrasound starting at 12 years, at a reduced frequency dictated by ultrasound findings. Of note, our recommendation for beginning thyroid surveillance at age 12 years is consistent with the recent guideline for paediatric cancer surveillance in PHTS published by Schultz and colleagues (16). Colon cancer and renal cancer surveillance guidelines are equivalent between the three guideline organizations, and none of the guidelines recommend routine surveillance for uterine cancers.

There is also a relative dearth of prospective natural history studies, constraining our understanding of the trajectory and disease progression of cancer in PHTS. Natural history and deep phenotyping studies in PHTS are underway with the hope of improving anticipatory guidance by clinicians and genetic counsellors and a better understanding of the optimal timing and specificity of interventions. Genotype-phenotype associations between *PTEN* variant and cancer risk are also limited, and at this time, it was not felt that genotype-specific recommendations could be made for individuals with PHTS, but future iterations of these guidelines may incorporate this as evidence emerges.

There are a limited number of studies in several areas of concern in PHTS individuals. Further investigations regarding increased risk of secondary malignancies due to chemotherapy/radiotherapy and the nature of metastatic disease or recurrent malignancy in individuals with and without germline *PTEN* variants are needed. This is important whilst ascertaining the risk-benefit ratio for intensive surveillance regimens. Moreover, it is not clear if

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individuals with PHTS experience increased or distinct toxicities to systemic cancer treatments. Further randomized control trials are also required to determine the efficacy of mTOR/AKT inhibitors in the treatment of PHTS-related malignancies, and we note that a phase II trial investigating AKT inhibitors treating advanced solid tumours in individuals with PHTS was terminated due to insufficient accrual (61). Two cases have been recently published of individuals with PHTS and breast cancer with durable responses to capivasertib, an inhibitor of AKT (62). A pilot study of 18 adult individuals with PHTS treated with sirolimus demonstrated regression of skin and benign gastrointestinal lesions (55). There are several case reports of individuals with germline *PTEN* variants with severe manifestations that experience partially successful and/or successful treatment of soft tissue masses/hamartomas/vascular malformations (63,64).

Several PHTS surveillance papers show conventional imaging approaches, reviewed at expert centres, were able to identify early stage PHTS disease with high level of sensitivity. For instance, annual breast cancer surveillance with MRI enables detection of early-stage breast cancers with a 100% overall sensitivity (31). Research should additionally focus on the effectiveness of other imaging modalities (e.g., whole-body magnetic resonance imaging (WBMRI), low dose fluorodeoxyglucose (FDG)-positron emission tomography (PET)) on surveillance of cancer, as well as identifying reliable predictive biomarkers for cancer risk and determining whether the lifetime cancer risks vary among individuals with PHTS of different ancestries. Of note, recent work examining the sensitivity of unbiased multi-cancer detection by identification of circulating tumour DNA has shown relatively low sensitivities for early-stage disease, with 16.8% sensitivity (95% CI 14.5-19.5%) reported for stage 1 cancers, as would be

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desirable in PHTS (65). It is also important to explore whether disparities (e.g., genetics, comorbidities, social determinants of health) exist in clinical outcomes across subgroups of individuals with PHTS. Further, the extent of financial and time toxicity that cancer treatment has on individuals with PHTS, acknowledging their increased healthcare interaction and increased risk for neurodevelopmental disabilities, remains to be studied (66,67). To this point, we note that whilst time and financial toxicity are often commented upon, there are very few follow-up studies rigorously examining their impact, and this remains a key gap for future work.

Despite the advancements in studying PHTS-related cancer and overgrowth organ systems, there are yet key details that are to be determined. For instance, the precise age for starting thyroid surveillance in PHTS individuals is not firmly delineated (68). Also, there is no sufficient evidence for volumetric follow-up in detection of growing thyroid nodules that may need workup. Further research is needed to better understand the frequency and nature of GI tract cancers, as well as the morbidity and the clinical outcomes associated with colon polyposis (subtotal/total colectomy vs. polypectomy). Lastly, further research is required to resolve the optimal surveillance frequency and modality for renal cancers in PHTS individuals, while working on determining the optimal surveillance interval for recurrence or second malignancies.

This guideline provides the most up-to-date distilled evidence for healthcare providers evaluating individuals with PHTS to perform an adequate assessment and make initial management recommendations. The development of these international consensus guidelines represents the most up-to-date standard of care for cancer and overgrowth for individuals with PHTS, irrespective of geographic location. Moving forward, it is essential to engage with the wider

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PHTS community to ensure dissemination and implementation of these recommendations. We recognize that various obstacles often exist for individuals, whether at the individual, regional, or national levels, that limit availability or access to the recommendations made here. In such circumstances, local healthcare professionals may need to adapt specific recommendations to ensure the provision of high-quality care. Concurrently, it is imperative that healthcare professionals and institutions, patient advocacy organizations, and local and national policymakers collaborate and advocate to minimize barriers to care. Such collective efforts are essential to ensure that these guidelines can be effectively put into practice, and that all individuals with PHTS receive the highest-quality care.

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Conceptualization, D.L., S.B., A.D., and C.E.; Methodology, D.L., S.B., and A.D.; Writing – Original Draft, S.B., and A.D; Data Curation, D.L., S.B., L.Y., and A.D.; Writing – Review & Editing, S.B., A.D., L.Y., K.A., A.M., M.T., S.M., J.N., N.H., C.E.; Supervision, A.D. and C.E.; Funding Acquisition, A.D and C.E.

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Tables

Table 1. Cancer surveillance recommendations for individuals with PHTS.

Cancer type	Surveillance	Gender	Interval	From age	Evidence
Breast cancer	Breast MRI	Female	Annually	25[a]	Strong
	Mammography	Female	Annually	40[a]	Strong
	Risk-reducing mastectomy (RRM)	Female	–	25	Moderate
Thyroid cancer	Thyroid Ultrasound	All	2 to 5 years[b]	12[c]	Moderate
	Biochemical Thyroid surveillance (TSH)	All	Consider Annually	18	Weak
Polyps/Colon cancer	Baseline colonoscopy	All	1-3 years[d]	35-40	Moderate
Endometrial cancer	Routine endometrial cancer surveillance[e]	All	–	–	Weak
Renal cancer	Ultrasound[f]	All	2 years	35-40	–

[a]Consider an individualized approach to surveillance and risk-benefit after age of 75-80 years

[b]Consider stratifying the surveillance interval based on ultrasound results to help minimize the burden of frequent ultrasounds, especially in young children. Surveillance with thyroid ultrasound every 3-5 years for PHTS individuals without nodules seen on initial thyroid ultrasound, every 2-3 years for individuals with clinically nonactionable nodules seen on initial thyroid ultrasound.

[c]Moderate evidence grading for age of surveillance.

[d]Consider colonoscopy at a 1–3-year interval for individuals with a high colon polyp burden (5 or more tubular adenomas), or polyps greater than or equal to 1 cm in diameter only.

[e]This should be part of a clinical trial.

[f]Expert opinion statement

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Table 2. Breast cancer recommendations for individuals with PHTS.

Recommendations	Grading
Given the high lifetime risk of female breast cancer and second primary breast cancer in individuals with PHTS and pathogenic or likely pathogenic variants in *PTEN*, we recommend discussing the options of surveillance versus risk-reducing mastectomy (RRM) with an experienced high-risk breast clinic team. In individuals with pathogenic or likely pathogenic variants in *PTEN*, RRM may be informed by the individual's family history of breast cancer, if known. Generally, RRM should only be considered in individuals over 25 years of age, unless otherwise clinically indicated, and counselling should include discussions relating to the degree of risk-reduction, surgical risks, and reconstructive options. The individual's life expectancy, in addition to their residual lifetime breast cancer risk should also be taken into consideration. In individuals for whom surveillance may be difficult to access, RRM may also be considered with the same caveats as above. The psychosocial and quality-of-life aspects of RRM must also be discussed with individuals with PHTS when this procedure is being considered.	Moderate
Women with PHTS should undergo annual breast MRI (with contrast) from age 25 years and additional surveillance with breast mammography (with digital breast tomosynthesis), starting at age 40 years until 75-80 years of age. After 75-80 years, we recommend an individualized approach to surveillance and risk-benefit discussion with an experienced breast clinician. Following national guidelines is recommended.	Strong
We do not recommend that males with PHTS undergo surveillance with breast MRI, mammography, or clinical breast examinations.	Strong

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Table 3. Breast cancer expert opinion recommendations for individuals with PHTS (Limited/Weak Evidence).

Recommendations	Grading
Depending on local practice guidelines, the following expert opinion can be considered. Though there are no specific studies examining the use of risk-reducing medication (tamoxifen, raloxifene, exemestane or anastrozole) in individuals with pathogenic or likely pathogenic variants in *PTEN*, these options may be discussed. The increased risk of endometrial cancer in individuals with an intact uterus generally precludes the risk-reducing use of the selective oestrogen receptor modulator tamoxifen (the only medication that can be used in the premenopausal setting; all four medications may be used in the postmenopausal setting). In many European countries, this is not compliant with current guidelines.	Expert Opinion
Transgender individuals, assigned female at birth with remaining breast tissue, should undergo surveillance as above. There are no data regarding testosterone supplementation and breast cancer risk to make a recommendation.	Expert Opinion
There is no contraindication to receiving gender-affirming hormone therapy (GAHT) in transgender individuals assigned male at birth. We recommend beginning breast surveillance 5 years after the start of GAHT, not before 25-30 years of age. We recommend surveillance in these individuals with breast MRI or annual mammography with consideration of tomosynthesis.	Expert Opinion

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Table 4. Thyroid cancer recommendations for individuals with PHTS.

Recommendations	Grading
We do not recommend routine risk-reducing thyroidectomy individuals with PHTS. The decision to undergo thyroidectomy is individualized and should be made in conjunction with a multidisciplinary team involving thyroid surgery, endocrinology and medical genetics.	Strong
From age 12 years, individuals with PHTS should undergo baseline thyroid ultrasound. We recommend stratifying the surveillance interval based on ultrasound results to help minimize the burden of frequent ultrasounds, especially in young children. TSH may be checked starting at age 18 years if ultrasounds are unremarkable, or earlier if there are abnormalities on ultrasound.	Moderate
We recommend surveillance with thyroid ultrasound every 3-5 years for PHTS individuals without nodules seen on initial thyroid ultrasound, and every 2-3 years for individuals with clinically nonactionable nodules seen on initial thyroid ultrasound. Consider annual TSH surveillance in individuals over age 18 years.	Moderate (Weak for TSH)
In individuals with PHTS and clinically actionable nodules, we recommend appropriate intervention in accordance with the American Thyroid Association (ATA) or similar local guidelines. In the case of benign findings on cytological examination, continued surveillance in 1-2 years is reasonable.	Moderate

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Table 5. Colon cancer recommendations for individuals with PHTS.

Recommendations	Grading
We do not recommend use of mTOR inhibitors for the chemoprophylaxis of colon cancer or management of polyps in individuals with PHTS.	Moderate
We do not recommend the use of *COX-1/COX-2* inhibitors (e.g., ASA) in chemoprevention of polyposis and colon cancer in PHTS.	Weak
We do not recommend risk-reducing colectomy in individuals with PHTS and polyposis.	Weak
We recommend that all individuals with PHTS undergo a baseline colonoscopy at 35-40 years. We do not recommend routine colonoscopy in individuals younger than 35-40 years old.	Moderate
Individuals with PHTS and a high colon polyp burden (5 or more tubular adenomas), or polyps greater than or equal to 1 cm in diameter or with high grade dysplasia, should undergo colonoscopy at a 1–3-year interval, as directed by their gastroenterologist.	Moderate
We do not recommend routine upper GI endoscopic surveillance with small bowel follow through in individuals with PHTS.	Moderate

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Table 6. Endometrial cancer recommendations for individuals with PHTS.

Recommendations	Grading
We do not recommend routine hysterectomy for endometrial cancer risk-reduction in PHTS individuals with a uterus. The decision to undergo hysterectomy is individualized and should be made in discussion with a multidisciplinary team involving obstetrics/gynaecology, reproductive health, and medical genetics.	Weak
For individuals with PHTS who have been diagnosed with uterine leiomyomas or endometrial hyperplasia with atypia, treatment options may include risk-reducing hysterectomy, hysteroscopy with endometrial curettage, and/or placement of a progestin-releasing intra-uterine device (IUD). Treatment decisions should be individualized and made in discussion with a multidisciplinary team involving obstetrics/gynaecology, reproductive health, and medical genetics.	Weak
At the time of PHTS diagnosis, or at age 30-35 years, we encourage individual education and prompt response to abnormal uterine bleeding or postmenopausal bleeding.	Weak
In individuals over the age of 30-35 years with PHTS and unexplained or irregular vaginal bleeding, we recommend evaluation with both transvaginal ultrasound and endometrial biopsy.	Weak
There is limited evidence regarding routine endometrial cancer surveillance in PHTS. If the decision to offer surveillance for endometrial cancer is made, this should be part of a clinical trial.	Weak

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Table 7. Renal cancer expert opinion recommendations for individuals with PHTS (Limited/Weak Evidence).

Recommendations	Grading
Starting at the age of 35-40 years, a surveillance ultrasound every 2 years for renal cell carcinoma may be considered in individuals with PHTS. MRI of the kidneys may also be considered.	Expert Opinion

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