ERN GENTURIS CANCER SURVEILLANCE GUIDELINE FOR INDIVIDUALS WITH *PTEN* HAMARTOMA TUMOUR SYNDROME (PHTS)

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Authors: Nicoline Hoogerbrugge, Ana Blatnik, Charlotte Kvist Lautrup, Robert Hüneburg, Daniela Turchetti, Guideline Group*, Emma Tham, Sjaak Pouwels, Marc Tischkowitz.

*** Author names and affiliations are presented on the following pages**

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Document main authors, Core Working Group of the guideline group in alphabetical order:

Author	Speciality/Role	Affiliation
Ana Blatnik, MD, PhD	clinical geneticist	Institute of Oncology Ljubljana, Ljubljana, Slovenia Member of ERN GENTURIS
Charlotte Kvist Lautrup, MD, PhD	clinical geneticist	Aarhus University Hospital, Aarhus, Denmark Member of ERN GENTURIS
Nicoline Hoogerbrugge, MD, PhD	internal medicine - oncogeneticist (cochair)	Radboud university medical center, Nijmegen, the Netherlands Member of ERN GENTURIS
Robert Hüneburg, MD	gastroenterologist	National Center for Hereditary Tumor Syndromes, University Hospital Bonn, Bonn, Germany Member of ERN GENTURIS
Sjaak Pouwels, MD, PhD (mult)	surgical resident and community representative	Bielefeld University Medical School and University Hospital OWL – Campus Klinikum Lippe, Detmold, NRW, Germany Medical University of Gdansk, Gdansk, Poland
Emma Tham, MD, PhD	clinical geneticist	Karolinska University Hospital, Karolinska Institutet, Stockholm, Sweden Member of ERN GENTURIS
Marc Tischkowitz, MD, PhD	medical geneticist (cochair)	National Institute for Health Research Cambridge Biomedical Research Centre, University of Cambridge, Cambridge, UK Supporting partner of ERN GENTURIS
Daniela Turchetti, MD	clinical geneticist	IRCCS Azienda Ospedaliera Di Bologna, University of Bologna, Bologna, Italy Member of ERN GENTURIS

Document main authors, other members of the guideline group in alphabetical order:

Author	Speciality/Role	Affiliation
Anne van Altena, MD, PhD	gynaecologist	Radboud university medical center, Nijmegen, the Netherlands Member of ERN GENTURIS

Frédéric Caux, MD, PhD	dermatologist	Avicenne Hospital, Assistance Publique-Hôpitaux de Paris, Sorbonne Paris Nord University, Bobigny, France
Sophie Da Mota Gomes	community representative	PTEN Official France, Chauvry, France
Kelly Kearley	community representative	PTEN UK and Ireland, Hartley Wintney, United Kingdom
Thera Links, MD, PhD	internist endocrinologist	University of Groningen, University Medical Center Groningen, Groningen, the Netherlands Member of ERN GENTURIS
Per-Olof Lundgren, MD, PhD	urologist	Karolinska University Hospital and Karolinska Institutet, Stockholm, Sweden Member of ERN GENTURIS
Ritse Mann, MD, PhD	radiologist	Radboud university medical center, Nijmegen, the Netherlands Netherlands Cancer Institute, Amsterdam, the Netherlands members of ERN GENTURIS
Inga-Lena Nilsson, MD, PhD	endocrine surgeon	Karolinska University Hospital and Karolinska Institutet, Stockholm, Sweden Member of ERN GENTURIS
Chella (RS) van der Post, MD, PhD	pathologist	Radboud university medical center, Nijmegen, the Netherlands Member of ERN GENTURIS
Jolanda H. Schieving, MD, PhD	paediatric neurologist	Amalia Children's Hospital, Radboud university medical center, Nijmegen, the Netherlands Member of ERN GENTURIS
Alex Teulé, MD	medical oncologist	Hospital Germans Trias I Pujol - Institut Catala d'Oncologia, Barcelona, Spain Member of ERN GENTURIS

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(HUS Helsinki University Hospital and OYS Oulu University Hospital), Helsinki, Finland*; The Hospital District of Southwest Finland, Turku University Hospital, Turku, Finland*; Institut Curie, Paris, France*; Rouen University Hospital, Rouen, France*; Center for Hereditary Tumor Syndromes (CHT), University Hospital Bonn, Bonn, Germany*; Hereditary Cancer Syndrome Center Dresden, Dresden, Germany*; Universitätsklinikum Erlangen, Erlangen, Germany*; Universitätsklinikum Hamburg-Eppendorf, Hamburg, Germany*; Medizinische Hochschule Hannover, Hannover, Germany*; Medizinisch Genetisches Zentrum, Munich, Germany*; Aghia Sophia Children's Hospital, Athens, Greece*; University of Pécs, Pécs, Hungary*; Azienda Ospedaliero-Universitaria di Bologna, Bologna, Italy*; Fondazione IRCCS CA'Granda Ospedale Maggiore Policlinico, Milano, Italy*; Fondazione IRCCS Istituto Nazionale dei Tumori, Milano, Italy*; Fondazione IRCCS Istituto Neurologico Carlo Besta, Milano, Italy*; Azienda Ospedaliera di Padova, Padua, Italy*; Azienda Ospedaliero-Universitaria di Parma, Parma, Italy*; Fondazione Policlinico Universitario A. Gemelli, Rome, Italy*; IRCCS Ospedale Pediatrico Bambino Gesù, Rome, Italy*; Azienda Ospedaliero-Universitaria Senese, Siena, Italy*; Pauls Stradins Clinical University Hospital, Riga, Latvia*; Centre Hospitalier du Luxembourg, Luxembourg, Luxembourg; Mater Dei Hospital, Msida, Malta; Netherlands Cancer Institute - Antoni van Leeuwenhoek, Amsterdam, the Netherlands*; University Medical Center Groningen, Groningen, the Netherlands*; Leiden University Medical Center, Leiden, the Netherlands*; Radboud university medical center, Nijmegen, the Netherlands*; Erasmus Medical Center, Rotterdam, the Netherlands*; Haukeland University Hospital, Bergen, Norway; Pomeranian Medical University - University Clinical Hospital no 1, Szczecin, Poland*; Instituto Português de Oncologia de Lisboa Francisco Gentil, EPE, Lisbon, Portugal*; Unidade Local de Saúde (ULS) São João, Porto, Portugal*; Porto Comprehensive Cancer Center, Porto, Portugal*; Institute of Oncology Ljubljana, Ljubljana, Slovenia*; Hospital Germans Trias I Pujol - Institut Catala d'Oncologia, Barcelona, Spain*; Hospital Sant Joan de Déu, Barcelona, Spain*; Karolinska University Hospital, Stockholm, Sweden*.

* ERN GENTURIS Full Members

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1. ABSTRACT

Background: *PTEN* hamartoma tumour syndrome (PHTS) is a diverse multi-system disorder predisposing to a high hereditary risk of breast, thyroid, endometrial and a moderate risk of renal, and colorectal cancer and skin melanoma. Besides the risk of cancer, PHTS is also associated with benign tumours such as skin and connective tissue tumours, vascular malformations, and neurodevelopmental disorders, including autism spectrum disorders.

New evidence on cancer risks and the effectiveness of surveillance has been published since the last iteration of the European Reference Network on Genetic Tumour Risk Syndromes (ERN GENTURIS) guidelines from 2020, necessitating the update presented here.

Methods: A comprehensive literature review was undertaken, and guidelines were revised by clinicians with PHTS expertise from relevant medical disciplines, together with PHTS patients and their representatives.

Results: Revised recommendations were put forward for surveillance for breast, thyroid, endometrial, renal, and colorectal cancer and skin melanoma.

Conclusion: The proposed cancer surveillance recommendations for PHTS require significant patient commitments as well as a coordinated multidisciplinary medical approach. There is a need for prospective evaluation of the effectiveness of these recommendations in the PHTS population.

2. GUIDELINE SUMMARY

This guideline has been drawn from the best available evidence and the consensus of experts in this area, and it is regularly updated to reflect changes in evidence. Clinicians are encouraged to follow these recommendations, facilitating evidence-based follow-up for individuals with PHTS.

Table 1. Summary of the surveillance protocol

	Surveillance	*Interval*	*From age*	*Strength**
Breast cancer	MRI	as for *BRCA1***	25	Strong
	Mammography	as for *BRCA1***	40 **	Strong
	Risk reducing surgery offered	Yes	25	Strong
Thyroid cancer	Ultrasound (US)	Yearly, frequency decreases to every 2-3 years after 2 USs with no suspicious findings	10-18	Surveillance: strong, Age: weak, Interval: moderate
Endometrial cancer	Ultrasound (endometrial biopsy can be considered)	Yearly	35-40	Moderate
Renal cancer	Baseline imaging	No further surveillance unless required by baseline outcome	35-40	Moderate
Colorectal cancer (CRC)	Baseline colonoscopy preferably in expert centre	No further surveillance unless required by baseline outcome or CRC family history	35-40	Strong
Skin melanoma	Baseline skin examination by dermatologist or expert	No further surveillance unless required by baseline outcome	30	Moderate

* This grading is based on published articles and expert consensus, see chapter 8.1: strong – expert consensus AND consistent evidence, moderate – expert consensus WITH inconsistent evidence AND/OR new evidence likely to support the recommendation, weak – expert majority decision WITHOUT consistent evidence.

** Most national guidelines for *BRCA1* surveillance recommend yearly surveillance with MRI and mammography every 1-2 years.

3. INTRODUCTION

PTEN hamartoma tumour syndrome (PHTS), OMIM:158350, ORPHA:306498, is caused by germline pathogenic variants in the *PTEN* (phosphatase and tensin homolog) gene. Older terms for PHTS, such as Cowden syndrome (CS), Bannayan-Riley-Ruvalcaba syndrome (BRRS), Lhermitte-Duclos disease, Segmental outgrowth-lipomatosis-arteriovenous malformation-epidermal nevus syndrome (SOLAMEN) and Proteus-like syndrome can be confusing and should no longer be used. PHTS is a diverse multi-system disorder. Individuals with PHTS have an increased risk of breast, thyroid, endometrial, and possibly of colorectal, and renal cancer, and skin melanoma (Pilarski 2019). PHTS also predisposes to the development of multiple hamartomatous growths including benign polyps in the gastrointestinal tract and skin lesions, and for neurodevelopmental disorders, including autism spectrum disorders (Dhawan et al. 2024).

Earlier studies reported average lifetime risks of cancer in individuals with PHTS range from 85-89% for any cancer, 67-85% for female breast cancer, 6-38% for thyroid cancer, 19-28% for endometrial cancer, 2-34% for renal cancer, 9-20% for colorectal cancer and 0-6% for melanoma (Starink et al. 1986, Riegert-Johnson et al. 2010, Tan et al. 2012, Bubien et al. 2013, Nieuwenhuis et al. 2014). These estimates are likely to be at the upper end of the true range because of ascertainment bias in published studies. The latest study (Hendricks et al. 2023) has excluded index cases when calculating cumulative risk, which reduces ascertainment bias and likely provides more accurate risk estimates, which are lower than were previously published (Table 1). Ultimately, larger prospective studies, including those individuals diagnosed in childhood because of developmental problems, and asymptomatic relatives with *PTEN* germline pathogenic variant, will be needed to further refine the risks.

Table 1: Cumulative risks of tumours in individuals with PHTS

Cancer	**Cumulative risk estimates according to Hendricks et al. 2023** (Hendricks et al. 2023) Cumulative cancer risks at age 70 are depicted with 95% confidence intervals (95% CI) as ranged from "the analysis excluding cancer- patients" to "the analysis including cancer-index patients". Please note that although we provide the cumulative cancer risks up to age 70 years, there are very few data on PHTS individuals over 60-70 years leading to wider confidence intervals of risk estimates in this age range.
Breast	Female breast cancer risk ranged from 60% (95% CI, 47-72%) to 80% (95% CI, 65-92%). Median age 42 years (IQR 37-48). Breast cancer risk is strongly increased compared to the general population.
Thyroid	Thyroid cancer is usually follicular, rarely papillary, hardly ever medullary. Thyroid cancer risk ranged from 17% (95% CI, 8-32%) to 29% (95% CI, 15-53%). Median age 42 years (IQR = 30-48). Thyroid cancer risk is strongly increased compared to the general population.
Endometrial	Endometrial cancer risk ranged from 33% (95% CI, 16-62%) to 6% (95% CI, 2-19%). Median age 49 years (IQR = 47-60). Endometrial cancer risk is strongly increased compared to the general population.
Renal	Renal cancer risk ranged from 3% (95% CI, 1-11%) to 9% (95% CI, 3-22%). Median age 51 years. Renal cancer risk is increased compared to the general population.
Colorectal	Colorectal cancer risk ranged from 5% (95% CI, 1-15%) to 15% (95% CI, 5-39%). Median age 59 years (IQR = 53-64). Colorectal cancer risk is slightly increased compared to the general population.
Melanoma	Melanoma risk ranged from 6% (95% CI, 2-12%) to 12% (95% CI, 4-30%). Median age 30 years (IQR = 27-39). Melanoma risk is increased compared to the general population.

PHTS is rare and its diagnosis relies on the identification of a germline pathogenic variant in *PTEN*. Early identification of individuals and appropriate surveillance are key to the timely detection of premalignant or early cancer lesions and can precede the development of advanced cancer by several years (Molvi et al. 2015). Individuals with PHTS have an increased risk of various cancer which are amenable to early detection.

4. COMPOSITION OF THE GUIDELINE GROUP

The ERN GENTURIS guideline group for cancer surveillance for individuals with PHTS (ERN GENTURIS PHTS guideline group) was established by 17 experts from nine countries and three patient representatives acting as community representatives, one of whom is also a medical expert in PHTS. The ERN GENTURIS PHTS guideline group was supported by a core working group (n=8) which comprised ERN GENTURIS healthcare provider members from different Member States and other experts who are recognised European experts in the PHTS and/or have clinical practice experience and/or specialise in the diagnosis and management of individuals with PHTS.

In order to recruit members for the ERN GENTURIS PHTS guideline group, including its core working group, a request for willing participants was made within ERN GENTURIS. ERN GENTURIS members with expertise in PHTS and additional non-ERN GENTURIS European experts were selected for the core working group (the requirement to have at least 2 ERN GENTURIS health care providers from at least 2 Member States was met). Afterwards, the core working group suggested European experts in the field (colleagues) for the ERN GENTURIS PHTS guideline group.

The core working group met online monthly and drafted the guideline scope, clinical questions, recommendations, and guideline document and obtained feedback from the ERN GENTURIS PHTS guideline group. The recommendations were finalised in a modified Delphi approach in which the core working group, guideline group (including patient representatives) and additional experts participated (see chapter 8).

Additional experts to participate in the modified Delphi approach were either suggested by the ERN GENTURIS PHTS Guideline Group or responded to the request to participate in the Delphi survey circulated within the ERN GENTURIS network. When representation from specific European countries was low, ERN GENTURIS national coordinators of the respective country were contacted and encouraged to suggest local experts. During the selection of the final group of experts we took into account the coverage of all specialists and all European countries. However, multidisciplinary coverage was the priority selection criterion.

Approach to secure views and preference of target population

The ERN GENTURIS PHTS guideline group was supported by three patient representatives from a patient advocacy group. One patient representative, who is also a medical doctor with PHTS expertise, was part of the core working group and present during these meetings. Patient representatives were recruited within ERN GENTURIS and with help of their experts.

Involving patient and parent representatives in the development of these guidelines and within the ERN GENTURIS PHTS guideline group helped ensure that:

- the questions addressed are relevant to individuals with a genetic tumour risk syndrome (genturis) and will make a positive impact on patient care.
- important aspects of the experience of conditions are considered.
- critical clinical and patient focused outcomes are identified and prioritised.
- the balance of the benefits and harms related to the intervention is appropriately considered when recommendations are formulated in conjunction with patient values and preferences.

The representatives from the patient advocacy group advised on the scope, target population, and clinical questions the guideline aimed to address and gave a patient perspective on the findings of the literature review and the consensus recommendations and provided feedback on the plain language summary.

Additional input from two patient representatives was obtained in the modified Delphi approach (see chapter 8).

5. CONFLICT OF INTERESTS

All members of the ERN GENTURIS PHTS guideline group, including the core working group, have provided disclosure statements on all relationships that they have that might be perceived to be a potential source of a conflict of interest.

Robert Hüneburg reported receipt of grants/research supports from German Cancer Aid, Wilhelm Sander-Stiftung and receipt of honoraria or consultation fees from Bristol Myers Squibb, Janssen Pharmaceuticals, and Fujifilm Europe. Daniela Turchetti reported receipt of honoraria or consultation fees from Astra Zeneca. Emma Tham reported receipt of grants/research supports from local authorities (Region Stockholm) and private foundations such as the Cancer Foundation, the Childhood Cancer Foundation, the JapSwe Foundation and Fight Kids Cancer (as part of a European collaboration). Per-Olof Lundgren reported receipt of honoraria or consultation fees from MSD for lecture fees. Ritse Mann reported receipt of grants/research supports from Bayer Healthcare, Siemens Healthineers, Beckton Dickinson, ScreenPoint Medical, Lunit, Koning, and PA Imaging. Alex Teule reported receipt of grants/research supports from Thermo Fisher Scientific and receipt of honoraria or consultation fees from Novartis, Esteve, and Advanz Pharma.

All participants of the ERN GENTURIS PHTS Delphi survey gave provided disclosure statements on all relationships that they have that might be perceived to be a potential source of competing interests. Nathalie Chabbert-Buffet reported receipt of grants/research supports and receipt of honoraria or consultation fees from Gedeon Richter, Exeltis, Theramex, and Besins Healthcare. Segolène Hescot and Barbara Jarząb reported receipt of honoraria or consultation fees from Ipsen and Eisai. Barbara Jarząb also reported receipt of honoraria or consultation fees from Novartis, Amgen, Astra Zeneca, Bayer, Exelixis, Oxygene, Lilly, Pfizer, Sanofi, Sobi, and Ewopharma. Arvids Irmejs reported receipt of grants/research supports from Lindex and receipt of honoraria or consultation fees from Astra Zeneca, Novartis, and GSK. Svetlana Lagercrantz reported receipt of honoraria or consultation fees from Arkus AI. Angela Mastronuzzi reported receipt of honoraria or consultation fees from Opocrin SpA. Iria Neri reported receipt of honoraria or consultation fees from Sanofi and La Roche Posay, as well as participation in a company sponsored speaker's bureau: Sanofi and AbbVie. Isadora Rosa reported participation in a company sponsored speaker's bureaus: Janssen, AbbVie, Faes Farma, and Ferring. Hector Salvador reported receipt of honoraria or consultation fees as well as participation in a company sponsored speaker’s bureau from Alexion. Karin Wadt reported receipt of honoraria or consultation fees from Seagen Denmark ApS. Emma Woodward reported receipt of grants/research supports as well as honorarium from Cancer Research UK.

6. PURPOSE AND SCOPE OF THIS GUIDELINE

6.1. WHY WAS THIS GUIDELINE PRODUCED?

Since the publication of the ERN GENTURIS guideline in 2020 (Tischkowitz et al. 2020) there has been considerable new evidence published. This guideline addresses surveillance for increased risk of cancer by tumour site, what modality should be used for surveillance, at what age to start surveillance for each cancer and how often to repeat surveillance investigations.

6.2. WHO IS THE GUIDELINE FOR?

The ERN GENTURIS *PTEN* hamartoma tumour syndrome (PHTS) guideline group have prepared this guideline document to assist healthcare professionals that are part of the multidisciplinary team discussing the surveillance of individuals with a confirmed germline pathogenic variant in *PTEN*.

Clinical guidelines are statements to support decision making, based on systematically evaluated evidence, for a specified clinical circumstance. Whilst clinical guidelines are based on the latest published evidence, care and treatment of each affected individual remains primarily the responsibility of their medical professionals. Decisions for care should always be based on the individual needs, personal preferences and individual circumstances of each patient. Clinical guidelines should support clinical decision making but never replace clinical professional assessment and shared decision making (patient and multidisciplinary team). Guidelines present recommendations based on expert opinion and published evidence and are not mandates. They do not signify nor intend to be a legal standard of care.

6.3. WHAT IS THE GUIDELINE ABOUT?

6.3.1 SCOPE

The scope of this guideline was set to define and agree on what is currently know about the efficacy, frequency and potential methods for surveillance, for breast, thyroid, endometrial, renal, or colorectal cancers or skin melanoma in PHTS. For ovarian cancer, the risk (if any) is not sufficiently established to consider surveillance at present. This guideline seeks to balance the risk of harm from the over-diagnosis of cancer with the potential benefits of early identification of cancers.

6.3.2 HEALTH QUESTIONS

Key clinical questions include, but are not restricted, to:

• What is currently known about the efficacy, frequency and potential surveillance methods for breast, thyroid, endometrial, renal, or colorectal cancers, or skin melanoma in PHTS?

For the different tumour types (breast, thyroid, endometrial, renal, colorectal, skin):

o What methods (image modality) should be used in surveillance of [tumour type]?

o At what age should surveillance of [tumour type] start?

o What is the frequency for surveillance of [tumour type]?

6.3.3 POPULATION

The target population for this guideline is all individuals with PHTS.

6.3.4 CARE SETTING AND IMPLEMENTATION OF THE GUIDELINE

This guideline has been prepared to support the decision making of health professionals that are part of the multidisciplinary team discussing surveillance of individuals who have a diagnosis of PHTS. Individuals with PHTS and other interested parties can also use the guideline.

Implementation of this guideline will require dissemination to the different stakeholders. Preferably, this European guideline should be adopted and diffused by the national Direction of Health of each European country, but the guideline could also be disseminated through relevant medical societies including clinical genetics, dermatology, endocrinology, radiology, gastroenterology, neurology, urology, surgery, pathology, gynaecology and oncology. Given the rarity of the condition, the implementation of the guidelines is not expected to involve significant costs, especially when balanced with the benefits associated with prevention/early detection. However, implementation will require the presence of expert centres of staff with expertise in PHTS to be able to organise and manage surveillance and to register the patient outcomes.

The main barrier of providing the right care to individuals with PHTS is the lack of awareness for these rare genetic tumour risk syndromes. As a consequence, small countries might not have the needed expertise (expert centres or clinicians specialised in the syndrome) or the needed equipment available in their centre (such as availability of MRI). This is one of the reasons why the European Reference Networks were launched in 2017. ERN GENTURIS raises awareness for all genetic tumour risk syndromes. ERN GENTURIS connects more than 50 European expert centres and improves access to diagnosis, treatment and the provision of high-quality healthcare for patients with a rare and/or complex genetic tumour risk syndrome, no matter where they live in Europe (Engels et al. 2025). With this guideline we provide recommendations for cancer surveillance in individuals with PHTS. Other

tools to facilitate the implementation of this guideline and also developed by the ERN GENTURIS PHTS guideline group are: a pocket guide (a guideline summary presented on a pocket card), a journal publication (a concise version of the full guideline document, published in a peer-reviewed journal), a plain language summary (to provide a clear summary of the guideline using non-technical language, making it accessible to a wider network or readers, including patients), a care pathway including a review checklist and a patient journey (which provides the patient with a first impression of what to expect). ERN GENTURIS also uses the Clinical Patient Management System, a dedicated IT platform through which ERN GENTURIS can convene virtual' advisory boards of medical specialists to discuss complex patient cases with other ERN members.

6.3.5 EPIDEMIOLOGY & AETIOLOGY

Epidemiology: The prevalence of PHTS was previously estimated to be 1 in 200,000-250,000 (Eng 2000, Gammon et al. 2016) but is now thought to be higher at around 1 in 9,000 to 1 in 15,000 (Rowlands et al. 2024, White et al. 2025).

Aetiology: In 1997, pathogenic variants in the *PTEN* gene, located on 10q23.3, were first confirmed to be the cause of PHTS, an autosomal dominant condition (Nelen et al. 1997). *PTEN* (phosphatase and tensin homolog) is a tumour suppressor gene, the loss of which results in increased cell proliferation and survival leading to tumorigenesis (Eng 2000, Bubien et al. 2013, Gammon et al. 2016, Hansen-Kiss et al. 2017). In approximately 80% of the PHTS cases, germline predicted pathogenic variants in the *PTEN* are detected with almost 45% arising *de novo* (Mester et al. 2012, Gammon et al. 2013).

7. RECOMMENDATIONS

7.1. GENERAL CONSIDERATIONS

Individuals with *PTEN* hamartoma tumour syndrome (PHTS) have a high hereditary risk of cancer, especially breast, endometrial, and thyroid cancer. The prognosis of these PHTS-related cancers is comparable to the general population (Hendricks et al. 2025). However, because of a higher cancer incidence, overall mortality is higher in females with PHTS than in the general population (Hendricks et al. 2025). These findings, and the high survival observed in early-stage cancer, emphasise the importance of recognising PHTS early to facilitate prevention and early detection of cancer by surveillance and risk reducing surgery.

Surveillance of individuals with PHTS should preferably be performed and interpretated by PHTS-medical experts, with at least 10 adults with PHTS per year under surveillance. In individuals with PHTS, most often the number of benign lesions (for instance in breasts, thyroid or colon) outnumber the malignant lesions. This may very much hinder interpretation of results by non-experts causing avoidable morbidity. Additionally, autism spectrum disorders, which often occur in individuals with PHTS, need medical expertise for proper management and to prevent avoidable distress.

We recommend that all individuals with PHTS receive instructions on healthy lifestyle in general as well as guidance on cancer awareness to facilitate prompt attention by a health care professional.

Recommendations in this guideline are divided into six sections: breast cancer, thyroid cancer, endometrial cancer, renal cancer, colorectal cancer, and skin melanoma.

7.2. BREAST CANCER RECOMMENDATIONS

Recommendations		Strength
Rec. 1	Women should be offered surveillance for breast cancer.	Strong
Rec. 2	Surveillance for breast cancer in PHTS should include MRI. *	Strong
Rec. 3	Surveillance for breast cancer with MRI should probably start at age 25. In post-menopausal women, an individual assessment of the need for continued MRI surveillance is recommended.	Strong
Rec. 4	Surveillance for breast cancer should be performed as for *BRCA1* and *BRCA2**.	Strong
Rec. 5	Risk reduction surgery should be offered as an alternative to intensive surveillance in an individual risk management discussion.	Strong

* Most national guidelines for *BRCA1* surveillance recommend yearly surveillance with MRI and mammography every 1-2 years.

7.3. THYROID CANCER RECOMMENDATIONS

Recommendations		Strength
Rec. 1	Individuals should be offered surveillance for thyroid cancer.	Strong
Rec. 2	Surveillance for thyroid cancer in PHTS should be by ultrasound.	Strong
Rec. 3	Surveillance for thyroid cancer should probably start between 10 and 18 years of age.	Weak
Rec. 4	Individuals should be offered surveillance for thyroid cancer annually initially. Individuals with two ultrasound examinations with no suspicious findings should probably be re-scanned at an increased interval of two to three years as clinically indicated.	Moderate

7.4. ENDOMETRIAL CANCER RECOMMENDATIONS

Recommendations		Strength
Rec. 1	Women should probably have surveillance for endometrial cancer.	Moderate
Rec. 2	If surveillance for endometrial cancer is offered, it should probably start at 35-40 years.	Moderate
Rec. 3	If surveillance for endometrial cancer is offered, it should probably be via transvaginal ultrasonography done at least annually. Endometrial biopsy can be considered.	Moderate
Rec. 4	There is no clear clinical indication for endometrial cancer risk reducing surgery (hysterectomy). It can be considered in an individual risk management discussion.	Moderate

7.5. RENAL CANCER RECOMMENDATION

Recommendations		Strength
Rec. 1	Individuals should be offered a baseline imaging exam at age 35 - 40 years for renal cell carcinoma (RCC). ##	Moderate

Where renal baseline imaging is normal, further regular surveillance is not recommended, just follow-up based on signs and symptoms.

7.6. COLORECTAL CANCER RECOMMENDATIONS

Recommendations		Strength
Rec. 1	Baseline colonoscopy should be undertaken at 35-40 years to assess polyp load, preferably in an expert centre. Interval of monitoring is guided by the number, size and pathology of resected polyps. In individuals with a family history of early-onset colorectal cancer, earlier colonoscopy may be warranted.	Strong
Rec. 2	In individuals with only hamartomas or no polyps at baseline colonoscopy, colorectal cancer surveillance may follow general population guidelines. However, a repeat colonoscopy after 5 to 10 years can be considered.	Strong

7.7. SKIN MELANOMA RECOMMENDATION

Recommendation		Strength
Rec. 1	Individuals probably should have a baseline skin examination performed by a doctor with expertise in this condition at age 30, further surveillance as required###.	Moderate

In case of a normal dermatological baseline examination, further regular surveillance is not recommended, just follow-up based on signs and symptoms.

8. METHODS FOR GUIDELINE DEVELOPMENT

8.1. FORMULATING AND GRADING STATEMENTS AND CONSENSUS BUILDING

Guideline development process

The process for developing this guideline is based on the principles of Grading of Recommendations Assessment, Development and Evaluation (GRADE) to ensure the quality of the guidelines, but it tailored for rare disease guidelines, using an "enhanced GRADE' approach to mitigate the challenges associated with rare disease research (Bolz-Johnson et al. 2025). This approach includes a comprehensive literature search with expert opinion (from clinicians with [disease name] expertise as well as [disease name] patients) to ensure that guidelines are both evidence-based and clinically relevant to the complex needs of rare disease populations.

Literature search

The guidelines were formulated on the basis of 106 published articles extracted from Pubmed and additional hand searching, and expert recommendations. The following search terms were used:

Search: (screening[title/abstract] OR surveillance[title/abstract]) AND (PTEN[title] OR Cowden[Title]) AND "humans" OR "humans"[MeSH Terms] Filters: from 2019 - 2024

(("screening"[Title/Abstract] OR "surveillance"[Title/Abstract]) AND ("PTEN"[Title] OR "Cowden"[Title]) AND "humans" OR "humans"[MeSH Terms]) AND (2019:2024[pdat])

Search: (screening[title/abstract] OR surveillance[title/abstract]) AND (PHTS[title]) AND "humans" OR "humans"[MeSH Terms]

Date of searches: 16th Sept 2024.

Of these 106 articles screened, 30 were selected for full paper review as they could potentially answer the health questions (see 6.3.2) addressed in this guideline. In the end, 16 papers (see appendix 2) contained evidence directly related to the previous recommendations and were included in this guideline.

Method for formulating recommendations

Literature was reviewed along with expert opinion to draft recommendations based on literature and experts' experiences and knowledge.

Recommendations were mainly written in one of four stylistic formats: Should, Should Probably, Should Probably Not, Should Not

- Should & Should Not, were taken to mean most well-informed people (those who have considered the evidence) would take this action.
- Should Probably & Should Probably Not, were taken to mean: the majority of informed people would take this action, but a substantial minority would not.

In day-to-day practice, clinicians will not have the time to explore the evidence as thoroughly as a guideline group, nor devote as much thought to the trade-offs, or the possible underlying values and preferences in the population. To ensure clinicians have a complete overview, the core working group has made recommendations even when confidence in effect estimate is low and/or when desirable and undesirable consequences are closely balanced.

Grading of the recommendations

The quantification of strength for a recommendation involves careful consideration of harms and benefits. As a general note for these recommendations, the harms that a recommendation seeks to address are often clear, however, the magnitude of the benefit of a specific recommendation may not be as clear.

As the volume of peer-reviewed evidence for rare diseases is typically limited due to the small population sizes, and it is unlikely that the evidence will ever reach a fraction of that for more common diseases, it creates a difficulty when considering the grading of the strength of evidence using Grading of Recommendations Assessment, Development and Evaluation (GRADE).

As is typical for many rare diseases, the volume of peer-reviewed evidence available for consideration for these guidelines was small and articles were typically based on small samples or series. If the evidence was categorised and graded using standard approaches designed to differentiate evidence when there are larger cohorts and several publications to evaluate, then all knowledge of PHTS would be assessed as low-grade evidence. This is not an accurate reflection of the combination of experts' experience and clinical consensus with the available evidence. This is further compounded as there is a low likelihood of additional volumes of evidence that could change the recommendations.

For this reason, and to balance the weight of both published evidence and quantify the wealth of expert experience and knowledge, ERN GENTURIS uses the following scale to grade the recommendations:

Strength	Grading of Recommendation
Strong	Expert consensus AND consistent evidence
Moderate	Expert consensus WITH inconsistent evidence AND/OR new evidence likely to support the recommendation
Weak	Expert majority decision WITHOUT consistent evidence

Expert consensus (an opinion or position reached by a group as whole) or expert majority decision (an opinion or position reached by the majority of the group) is established after reviewing the results of the modified Delphi approach (step 9) within the Core Working Group.

To summarise, for our grading of the recommendations, we assess all available evidence. Evidence is not only the published observational studies, but also the real-world evidence based on clinical and patient expertise. The guideline group assesses all these sources of evidence and quantifies if the evidence points in the same direction (consistent) or not (inconsistent). The guideline group then decides to issue strong or conditional draft recommendations. These draft recommendations are then graded in a modified Delphi survey to reach structured expert consensus, including active engagement of affected individuals and patient representatives, specifically balancing the desirable and undesirable consequences of surveillance and alternative care strategies, quality of evidence, and values and preferences held by the patient representatives.

Consensus building using a modified Delphi approach

After drafting recommendations amongst the core working group, these were subjected to a modified Delphi assessment to overcome the issue of variability in recommendations for specific (national) health care setting and to account for the recommendations based on indirect (scarce) evidence. Delphi is a structured communication technique or method in which opinions of a large number of experts are asked on a topic in which there is no consensus, and this was used as a consensus building exercise. The goal is to reach consensus after several rounds of questionnaires.

Experts included in this exercise were the members of the ERN GENTURIS PHTS guideline group (including the core working group and 3 patient representatives), as well as other (external) experts

identified by the ERN GENTURIS PHTS guideline group or respondents to the request to participate in the Delphi survey circulated within the ERN GENTURIS network.

The survey consisted of two rounds, in which the threshold for consensus was defined by a simple majority of the survey participants agree with the recommendation (>60% rated "agree" or "totally agree"), in accordance to the threshold of consensus used in other ERN GENTURIS guidelines (Evans et al. 2022, Carton et al. 2023, Colas et al. 2024, Geilswijk et al. 2024, Farschtschi et al. 2026). Recommendations were graded using a 4-point Likert scale (totally disagree, disagree, agree, totally agree), and a justification for each rating was optional in a free text format. Even if consensus was met, recommendations were still modified if a higher consensus was though achievable from written responses.

The Delphi participants were asked to indicate their expertise per tumour type and grade the recommendations in which they had expertise. The modified Delphi survey also included an option to indicate that you do not have tumour-specific expertise and would like to grade the recommendations from a general perspective. Agreement percentages were calculated for all respondents as well as specified for the tumour-specific expertise group and those who answered from a general perspective. All recommendations (n=17) based on the original guideline and adapted by the core working group were selected to proceed in the Delphi procedure. The facilitator of the Delphi survey provided anonymised summaries of the experts' decisions after each round as well as the reasons they provided for their judgements. All recommendations passed the threshold for consensus in the first round. The core working group discussed the anonymised summary of comments given to all recommendations in the first round and decided to adjust 10 recommendations for the second round. These were subjected to the expert's opinion in the second round of the survey. For each recommendation, the original recommendation with the overall rating from the first round was presented, as well as the new recommendation, where changes to the original were indicated. All recommendations passed the threshold for consensus and reached similar or higher percentage of agreement. As a result of the modified Delphi, 17 recommendations (agreement between 72 - 98%) are included in this manuscript.

We would like to thank the experts who were specifically participated in the Delphi survey (in alphabetical order):

Name	Speciality / Role	Healthcare provider
Claudio Ales	Community representative	PTEN Italia Association, Palermo, Italy
Aude Beyens, MD, PhD	Dermatology / Clinical genetics	Ghent University Hospital, Ghent, Belgium Member of ERN GENTURIS
Tanya M. Bisseling, MD, PhD	Gastroenterology	Radboud university medical center, Nijmegen, the Netherlands Member of ERN GENTURIS
Ignacio Blanco, MD, PhD	Clinical genetics	Hospital Germans Trias I Pujol, Barcelona, Spain Member of ERN GENTURIS
Helen Bolton, MD, PhD	Gynaecological Oncology	Cambridge University Hospitals NHS Trust, Cambridge, UK
D.G.M. Bosch, MD, PhD	Clinical genetics	ErasmusMC, Rotterdam, the Netherlands Member of ERN GENTURIS
Bruno Buecher, MD, PhD	Gastroenterology	Institut Curie, Paris, France Member of ERN GENTURIS
Henriett Butz, MD, PhD	Clinical genetics	National Institute of Oncology, Budapest, Hungary
Nathalie Chabbert-Buffet, MD, PhD	Gynaecology & Endocrinology	Tenon Hospital APHP Sorbonne University, Paris, France
Chrystelle Colas, MD, PhD	Clinical genetics	Institut Curie, Paris, France Member of ERN GENTURIS
Remco van Doorn, MD, PhD	Dermatology	Leiden University Medical Center, Leiden, the Netherlands; Antoni van Leeuwenhoek Netherlands Cancer Institute - Antoni van Leeuwenhoek hospital, Amsterdam, the Netherlands Members of ERN GENTURIS
Maria Elmberg	Gastroenterology	Hereditary Cancer Unit, Cancer Division, Karolinska University Hospital, Sweden Member of ERN GENTURIS
Marica Eoli, MD	Neurology	Fondazione IRCCS Istituto Neurologico C. Besta, Milan, Italy Member of ERN GENTURIS
Carla Ferrándiz-Pulido MD, PhD	Dermatology	Hospital Universitari Vall d'Heborn, Barcelona, Spain Member of ERN GENTURIS
Lenka Foretova	Clinical genetics	Masaryk Memorial Cancer Institute, Brno, Czech Republic Member of ERN GENTURIS

Sophie Frank, MD	Gynaecology	Institut Curie, Paris, France Member of ERN GENTURIS
Maurizio Genuardi, MD	Clinical genetics	Catholic University of the Sacred Heart, Rome, Italy Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy Member of ERN GENTURIS
Cristina Alessandra Grugnetti, PhD	Endocrinology and Gynaecology	Bellinzona – Svizzera, Switzerland
Frederik J. Hes, MD, PhD	Clinical genetics	Vrije Universiteit Brussel (VUB), Universitair Ziekenhuis Brussel (UZ Brussel), Brussels, Belgium Member of ERN GENTURIS
Segolène Hescot, MD, PhD	Endocrinology	Institut Curie, Paris, France Member of ERN GENTURIS
Arvids Irmejs, MD, PhD	Surgery	Pauls Stradins Clinical University Hospital; Institute of Oncology and Molecular Genetics, Riga Stradins University, Riga, Latvia Member of ERN GENTURIS
Barbara Jarząb, MD	Endocrinology	MSC National Research Institute of Oncology Gliwice Branch, Gliwice, Poland
C. Christofer Juhlin, MD, PhD	Pathology	Karolinska Institutet, Stockholm, Sweden Karolinska University Hospital, Stockholm, Sweden Member of ERN GENTURIS
Katherine Lachlan, MD	Clinical genetics	Southampton University, Southampton, UK Wessex Clinical Genetics Service, University Hospital Southampton NHS Trust.
Svetlana Lagercrantz, MD, PhD	Oncology	Karolinska Comprehensive Cancer Center, Hereditary Cancer Unit, Karolinska University Hospital, Stockholm, Sweden. Member of ERN GENTURIS
Verena Steinke- Lange, MD	Clinical genetics	MGZ – Medical Genetics Center, Munich, Germany Member of ERN GENTURIS
Pedro Louro, MD	Clinical genetics	ULS São João, Porto, Portugal Member of ERN GENTURIS

Marina Macchiaiolo, MD	Paediatrics, Clinical genetics	Bambino Gesù Children's Hospital, Rome, Italy Member of ERN GENTURIS
Angela Mastronuzzi, MD, PhD	Paediatric Oncology	Bambino Gesù Children's Hospital, Rome, Italy Member of ERN GENTURIS
Márta Medvecz MD, PhD	Dermatology	Semmelweis University, Budapest, Hungary
Emmanuelle Mouret-Fourme	Epidemiology and Oncogenetics	Institut Curie, Paris, France Member of ERN GENTURIS
Romana Netea-Maier, MD, PhD	Endocrinology	Radboud university medical center, Nijmegen, the Netherlands Member of ERN GENTURIS and ENDO-ERN
Iria Neri, MD	Dermatology	IRCCS Azienda Ospedaliero-Universitaria di Bologna, Bologna, Italy Member of ERN GENTURIS
Minna Pöyhönen, MD, PhD	Clinical genetics	Helsinki University and University hospital, Helsinki, Finland Member of ERN GENTURIS
Robin de Putter, MD	Clinical genetics	Ghent University Hospital, Ghent, Belgium Member of ERN GENTURIS
Alejandra Rezqallah Arón, MD	Oncology	Vall d'Hebron University Hospital and Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain. Member of ERN GENTURIS
Kerstin Rhiem, MD, PhD	Gynaecology	Center for Familial Breast and Ovarian Cancer, Center for Integrated Oncology (CIO), University Hospital Cologne, Cologne, Germany
Kleoniki Roka, MD, PhD,	Paediatric Oncology	National and Kapodistrian University of Athens, "Aghia Sophia" Children's Hospital, Athens, Greece Member of ERN GENTURIS
Isadora Rosa, MD, PhD	Gastroenterology	Instituto Português de Oncologia de Lisboa, Francisco Gentil, Lisboa, Portugal Member of ERN GENTURIS
Hector Salvador, MD	Oncology	Hospital Sant Joan de Déu Children's Hospital, Barcelona, Spain Member of ERN GENTURIS

Janneke H.M. Schuurs-Hoeijmakers, MD, PhD	Clinical genetics	Radboud university medical center, Nijmegen, the Netherlands Member of ERN GENTURIS
Ida Wiig Sørensen, MD, PhD	Clinical genetics	Haukeland University Hospital, Bergen, Norway Member of ERN GENTURIS
Irene Spinelli, MD	Gastroenterology	CEMAD, Fondazione Policlinico Universitario A. Gemelli, IRCCS, Roma Member of ERN GENTURIS
Karin A.W. Wadt, MD, PhD	Clinical genetics	University of Copenhagen, Copenhagen, Denmark Rigshospitalet, Copenhagen, Denmark Member of ERN GENTURIS
JHW de Wilt, MD, PhD	Surgery	Radboud university medical center, Nijmegen, the Netherlands Member of ERN GENTURIS
Joachim Wölfle, MD	Paediatrics Endocrinology	Friedrich-Alexander-University Erlangen-Nuremberg, Universitätsklinikum Erlangen, Erlangen, Germany Member of ERN GENTURIS
Emma R. Woodward, MD, PhD	Clinical genetics	Manchester Centre for Genomic Medicine, University of Manchester, Manchester, UK Supporting partner of ERN GENTURIS
Riina Žordania, MD, PhD	Clinical genetics	Tartu University Hospital, Tartu, Estonia Member of ERN GENTURIS

8.2. Internal and External review

ERN GENTURIS actively involved external experts from different speciality areas that are relevant to the scope of this guideline to review its findings and recommendations developed in this guideline by participation in the guideline group or as a Delphi participant. The process for developing this guideline has been based on the principles of AGREE II to ensure the quality of the guidelines. Within this process the core working group completed an internal assessment of the quality of the guideline against AGREE II criteria.

In addition, the ERN GENTURIS PHTS guideline group submitted a shortened version of the guideline to the EJHG for independent review.

ERN GENTURIS first published the guidelines for cancer surveillance in individuals with *PTEN* hamartoma tumour syndrome (PHTS) on 12 June 2020. The update of this guideline described in this document was published on 16 July 2026.

8.3. Timeline and procedure for updating the guideline

Any new evidence published will be reviewed by the ERN GENTURIS clinical leads on an annual basis to determine if the guideline should be updated. New versions will be published on the Network's website and circulated through the ERN GENTURIS Members.

8.4. Funding and Financial support

This guideline has been supported by the European Reference Network on Genetic Tumour Risk Syndromes (ERN GENTURIS), which is funded by the European Union. For more information about the ERNs and the EU health strategy, please visit http://ec.europa.eu/health/ern. Potential conflict of interest for the individual authors and Delphi participants are listed in chapter 5.

9. SUMMARY OF EVIDENCE AND GUIDELINE RECOMMENDATIONS

9.1. GENERAL CONSIDERATIONS

This chapter is identical to chapter 7.1:

Individuals with *PTEN* hamartoma tumour syndrome (PHTS) have a high hereditary risk of cancer, especially breast, endometrial, and thyroid cancer. The prognosis of these PHTS-related cancers is comparable to the general population (Hendricks et al. 2025). However, because of a higher cancer incidence, overall mortality is higher in females with PHTS than in the general population (Hendricks et al. 2025). These findings, and the high survival observed in early-stage cancer, emphasise the importance of recognising PHTS early to facilitate prevention and early detection of cancer by surveillance and risk reducing surgery.

Surveillance of individuals with PHTS should preferably be performed and interpretated by PHTS-medical experts, with at least 10 adults with PHTS per year under surveillance. In individuals with PHTS, most often the number of benign lesions (for instance in breasts, thyroid or colon) outnumber the malignant lesions. This may very much hinder interpretation of results by non-experts causing avoidable morbidity. Additionally, autism spectrum disorders, which often occur in individuals with PHTS, need medical expertise for proper management and to prevent avoidable distress.

We recommend that all individuals with PHTS receive instructions on healthy lifestyle in general as well as guidance on cancer awareness to facilitate prompt attention by a health care professional.

Recommendations in this guideline are divided into six sections: breast cancer, thyroid cancer, endometrial cancer, renal cancer, colorectal cancer, and skin melanoma.

9.2. SUMMARY OF EVIDENCE AND GUIDELINE RECOMMENDATIONS FOR BREAST CANCER

Breast cancer risk for female with germline pathogenic variants in *PTEN* is greatly increased compared to the general population. Various studies have consistently shown an increase in breast cancer risk (Tan et al. 2012, Bubien et al. 2013, Nieuwenhuis et al. 2014, Cummings et al. 2023, Hendricks et al. 2023). One recent study estimated the risk at age 70 as being 60% (95% CI, 47-72%) excluding cancer-index patients and 80% (95% CI, 65-92%) including cancer-index patients (Hendricks et al. 2023). Evidence suggests surveillance can detect breast cancer early and leads to lower tumour stage at diagnosis and improved survival in these individuals (Hoxhaj et al. 2022,

Teramae et al. 2022, Hendricks et al. 2023, Yehia et al. 2023). Breast cancers detected outside of a surveillance programme were shown to be of a higher stage (Hoxhaj et al. 2022). Females with PHTS tend to develop breast cancer early, with an age range of 16-85 years and a median age below 50 years at first diagnosis. The highest increase in breast cancer incidence was observed between the age of 30 and 40, with 15% of the individuals developing breast cancer before the age of 29 (Hoxhaj et al. 2022, Hendricks et al. 2023, Yehia et al. 2023).

Breast magnetic resonance imaging (MRI) performed annually has been shown to have the greatest sensitivity for detecting breast cancers in these individuals with mammography being of no additional benefit (Hoxhaj et al. 2022).

With evidence increasingly suggesting that breast cancer risk in PHTS is similar to that in women with germline pathogenic variants in *BRCA1/BRCA2*, many recommendations can be derived from the much larger evidence base, which exists for hereditary breast and ovarian cancer predisposition syndrome. Performing yearly breast MRI is therefore recommended from the age of 25 years. In addition, mammography every 1-2 years can be considered, preferably from the age of 40 years or in line with national guidelines for surveillance of *BRCA1* patients. Recently, Hendricks et al. reported evidence for high second primary cancer risks in individuals with PHTS, driven primarily by breast cancer diagnoses in females, with ten-year risk for second primary breast cancer after first primary breast cancer of 46% (95% CI, 33-60%) (Hendricks et al. 2025). This reinforces our recommendation to offer risk reducing surgery in individual risk management discussion.

Recommendations		Strength
Rec. 1	Women should be offered surveillance for breast cancer.	Strong
Rec. 2	Surveillance for breast cancer in PHTS should include MRI.*	Strong
Rec. 3	Surveillance for breast cancer with MRI should probably start at age 25. In post-menopausal women, an individual assessment of the need for continued MRI surveillance is recommended.	Strong
Rec. 4	Surveillance for breast cancer should be performed as for *BRCA1* and *BRCA2*.*	Strong

Rec. 5	Risk reduction surgery should be offered as an alternative to intensive surveillance in an individual risk management discussion.	Strong
References: (Riegert-Johnson et al. 2010, Tan et al. 2012, Bubien et al. 2013, Nieuwenhuis et al. 2014, Vreemann et al. 2018, Mann et al. 2019, Hoxhaj et al. 2022, Teramae et al. 2022, Hendricks et al. 2023, Yehia et al. 2023)		

* Most national guidelines for *BRCA1* surveillance recommend yearly surveillance with MRI and mammography every 1-2 years.

9.3. SUMMARY OF EVIDENCE AND GUIDELINE RECOMMENDATIONS FOR THYROID CANCER

The risk of thyroid cancer is increased in individuals with PHTS. Recent studies of two large separate PHTS cohorts have found comparable risk estimates with life time risk of 33% (95% CI, 24-40%, cumulative incidence rates by age 80 years) (Yehia et al. 2023) and 29% (95% CI, 15-53% cumulative risk at age 70 years) (Hendricks et al. 2023) , with a lower risk (17% (95% CI, 8-32%, cumulative risk at age 70 years)) in non-probands (Hendricks et al. 2023). The median age to develop thyroid cancer is 42 years (Hendricks et al. 2023).However, several recent studies have reported cases of thyroid cancer in children or adolescents with few cases diagnosed before the age of 10 years (Baran et al. 2020, Jonker et al. 2020, Smith et al. 2021, Pena-Couso et al. 2022, Teramae et al. 2022, Martinez-Rios et al. 2024, Bormans et al. 2025).

Ultrasound (US) should be used for surveillance for early detection of cancer of benign thyroid disease, which is also common in PHTS. Thyroid cancer in children with PHTS, has in general a favourable prognosis, and the evidence that early detection of thyroid cancer is associated with improved survival is weak. Furthermore, surveillance is associated with a risk of overdiagnosis of small, clinically indolent, follicular or papillary thyroid cancers (Jonker et al. 2020). Therefore, the appropriate age to initiate surveillance in children with PHTS remains uncertain. Surveillance in asymptomatic children under the age of 10 years is not recommended due to a low risk of both cancer and benign lesions in this age group (Baran et al. 2020, Jonker et al. 2020) . We therefore advise to start before the age of 18 years, but not before the age of 10 years. Two studies suggest that follow-up frequency can be reduced if there are no suspicious findings in the exams (Plitt et al. 2022, Drissen et al. 2023).

Recommendations		Strength
Rec. 1	Individuals should be offered surveillance for thyroid cancer.	Strong
Rec. 2	Surveillance for thyroid cancer in PHTS should be by ultrasound.	Strong
Rec. 3	Surveillance for thyroid cancer should probably start between 10 and 18 years of age.	Weak
Rec. 4	Individuals should be offered surveillance for thyroid cancer annually initially. Individuals with two ultrasound examinations with no suspicious findings should probably be re-scanned at an increased interval of two to three years as clinically indicated.	Moderate
References: (Riegert-Johnson et al. 2010, Smith et al. 2011, Tan et al. 2012, Bubien et al. 2013, Nieuwenhuis et al. 2014, Smpokou et al. 2015, Plamper et al. 2018, Baran et al. 2020, Jonker et al. 2020, Smith et al. 2021, Pena-Couso et al. 2022, Plitt et al. 2022, Teramae et al. 2022, Drissen et al. 2023, Hendricks et al. 2023, Yehia et al. 2023, Martinez-Rios et al. 2024, Bormans et al. 2025)		

9.4. SUMMARY OF EVIDENCE AND GUIDELINE RECOMMENDATIONS FOR ENDOMETRIAL CANCER

The risk of endometrial cancer in female carriers of germline pathogenic *PTEN* variants is increased compared to the general population. Two larger studies that include index patients have shown a cumulative risk of 28 and 48% (Tan et al. 2012, Yehia et al. 2023). The latter study had an age range of diagnosis of 21 -78 years (median 49 years) and the former showed an increase in risk from 35 years. In the one study that excluded index cases to reduce ascertainment bias, the cumulative lifetime risk of endometrial cancer by age 70 years was 33% (based on 195 non-index females). The median age of diagnosis was 49 years also in this study, with a 2% cumulative risk at 40 years and a 9% risk at 50 years (Hendricks et al., 2023). While the age-specific risk estimates remain uncertain due to small sample sizes, the increase in risk appears to start from 35 years so we suggest that surveillance starts at 35 – 40 years, which is five years later than the American (Cheng et al. 2026), international (Dhawan et al. 2025), Japanese (Takayama et al. 2023) and Danish (Smerdel et al. 2020) recommendations.

Surveillance of endometrial cancer in Lynch syndrome, a more common hereditary tumour risk syndrome where this question has been studied in more detail, has been controversial. Even without surveillance, most cases of endometrial cancer are diagnosed at an early stage due to abnormal uterine bleeding, survival is already high, and surveillance has not demonstrated a survival advantage (Ryan et al. 2021). Multiple small studies on *PTEN* and Lynch syndrome carriers have shown that endometrial surveillance with transvaginal ultrasound (TVUS) in combination with endometrial biopsy (EB) can detect hyperplasia/early cancer prior to bleeding symptoms (Gerritzen et al. 2009, Tzortzatos et al. 2015, Kwinten et al. 2023). However, EB is painful and may lead to discontinuation of surveillance. A recent retrospective study from the Netherlands with 1046 female Lynch syndrome carriers has shown that endometrial surveillance with TVUS and EB can detect more cancers, but there was no difference in stage or survival between the surveillance and non-surveillance group (Eikenboom et al. 2025). It remains unclear if a risk-reducing hysterectomy is warranted given the early detection of endometrial cancer and the excellent prognosis in most cases. Therefore, international guidelines do not recommend routine hysterectomy in PHTS (Smerdel et al. 2020, Takayama et al. 2023, Dhawan et al. 2025, Cheng et al. 2026). Thus, we recognise that hysterectomy is an option that can be discussed as part of the individualised follow-up and may be warranted in individual cases including those with multiple uterine polyps and/or notable family history of uterine cancer.

In conclusion, it is important that all women with germline pathogenic *PTEN* variants are educated on early signs of endometrial cancer. Surveillance options and the potential possibility of risk-reducing hysterectomy should be discussed on an individual basis and should be offered from 35-40 years of age. There are no studies demonstrating that routine TVUS surveillance improves outcomes, routine TVUS surveillance may be offered by some expert centres and this should ideally be done as a clinical trial.

Recommendations		Strength
Rec. 1	Women should probably have surveillance for endometrial cancer.	Moderate
Rec. 2	If surveillance for endometrial cancer is offered, it should probably start at 35-40 years.	Moderate

Rec. 3	If surveillance for endometrial cancer is offered, it should probably be via transvaginal ultrasonography done at least annually. Endometrial biopsy can be considered.	Moderate
Rec. 4	There is no clear clinical indication for endometrial cancer risk reducing surgery (hysterectomy). It can be considered in an individual risk management discussion.	Moderate
References: (Riegert-Johnson et al. 2010, Tan et al. 2012, Bubien et al. 2013, Nieuwenhuis et al. 2014, Moller et al. 2017, Moller et al. 2018, Teramae et al. 2022, Hendricks et al. 2023, Kwinten et al. 2023, Yehia et al. 2023)		

9.5. SUMMARY OF EVIDENCE AND GUIDELINE RECOMMENDATION FOR RENAL CANCER

Renal cancers types are varied with a preponderance of papillary subtypes (albeit based on small numbers) (Mester et al. 2012). There is a moderate increase in renal cell carcinoma (RCC) in individuals with PHTS. Based on series of 455 individuals, 372 of whom had prospective follow-up for a median of 6 years, the cumulative risk of renal cancer ranged from 3% (95% CI,1-11%) excluding cancer-index patients to 9% (95% CI, 3-22%) including cancer-index patients by 70 years (Hendricks et al. 2023). The median age to develop RCC was 51 years, while the youngest reported case in Hendricks et al. was 33 years (Hendricks et al. 2023). A second prospective longitudinal cohort study of 701 individuals estimated 18-42% risk by age 80 years (Yehia et al. 2023), however this study included individuals with variants of uncertain significance and importantly, did not correct for ascertainment which likely explains the large difference in estimates between the two studies.

In general, early identification of RCCs can lead to better outcomes (Fiori et al. 2016) and allows for less invasive therapeutic options, e.g. partial nephrectomy and ablative therapies (Wang et al. 2024). The use of MRI or ultrasound are appropriate modalities for the surveillance of RCCs (Chiarello et al. 2018, Vogel et al. 2019). This considered, there is an ongoing stage shift in renal cancer with an increasingly large proportion of patients being diagnosed with low stage disease, i.e. with small tumours, regardless of genetic predisposition. Currently, it is unknown whether early detection through surveillance offers specific benefits for renal cancer in individuals with PHTS but there is no evidence indicating that RCCs in PHTS behave differently to sporadic RCCs. Our recommendation is

(in the absence of other risk factors) to offer a baseline scan at 35-40 years rather than regular surveillance for renal cancer. We would recommend the use of MRI as modality for the baseline imaging as there is some evidence that MRI is more sensitive for papillary subtypes (Chiarello et al. 2018).

Recommendations		Strength
Rec. 1	Individuals should be offered a baseline imaging exam at age 35 - 40 years for renal cell carcinoma (RCC). ##	Moderate
References: (Choyke et al. 1990, Mihara et al. 1999, Filipas et al. 2003, Ishikawa et al. 2004, Malaeb et al. 2005, Mester et al. 2012, Smpokou et al. 2015, Fiori et al. 2016, Chiarello et al. 2018, Vogel et al. 2019, Teramae et al. 2022, Hendricks et al. 2023, Yehia et al. 2023)		

Where renal baseline imaging is normal, further regular surveillance is not recommended, just follow-up based on signs and symptoms.

9.6. SUMMARY OF EVIDENCE AND GUIDELINE RECOMMENDATIONS FOR COLORECTAL CANCER

Recent evidence confirms that individuals with PHTS have a moderately increased colorectal cancer (CRC) risk, with risk level depending on colonic polyp burden. In a large cohort study, Hendricks et al. (2023) estimated the cumulative CRC risk at 5-15% by age 70 years, while the combined risk of CRC and adenomatous polyps was about tenfold higher than in the general population (Hendricks et al. 2023). The median age to develop CRC was 59 years (Hendricks et al. 2023). Similar findings were reported by Yehia et al. in a cohort of 701 individuals, with CRC observed from age 21 years onwards (Yehia et al. 2023).

Smaller studies (e.g. (Drissen et al. 2022, Khare et al. 2022, Liu et al. 2024)) underline early and frequent polyp formation in PHTS. Data from Nieuwenhuis et al. and Bubien et al. support risk stratification based on histological and quantitative polyp characteristics (Bubien et al. 2013, Nieuwenhuis et al. 2014).

Based on this, a baseline colonoscopy between age 35 and 40 years is recommended, preferably to be performed in a centre with recognised expertise in PHTS or hereditary colorectal syndromes (e.g., healthcare providers participating in ERN GENTURIS where available). Surveillance intervals should

be risk-adapted based on polyp number, size, histology, and degree of dysplasia. Clinically relevant polyps with malignant potential include adenomas, serrated lesions, juvenile-type polyps with dysplasia, and mixed/hybrid lesions; these should be completely removed. Isolated benign hamartomatous lesions without dysplasia (e.g., few small ganglioneuromatous polyps) do not mandate intensified surveillance beyond risk-stratified intervals. Faecal immunochemical testing (FIT) is not recommended as standalone surveillance in PHTS but may complement national population screening programs in carefully selected low-risk cases (no polyps with malignant potential). In individuals with a family history of early-onset CRC, earlier initiation may be appropriate. In cases with only hamartomatous or no polyps, general population colorectal cancer surveillance intervals may be applied, with the option to repeat colonoscopy after 5-10 years.

Recommendations		Strength
Rec. 1	Baseline colonoscopy should be undertaken at 35-40 years to assess polyp load, preferably in an expert centre. Interval of monitoring is guided by the number, size and pathology of resected polyps. In individuals with a family history of early-onset colorectal cancer, earlier colonoscopy may be warranted.	Strong
Rec. 2	In individuals with only hamartomas or no polyps at baseline colonoscopy, colorectal cancer surveillance may follow general population guidelines. However, a repeat colonoscopy after 5 to 10 years can be considered.	Strong
References: (Riegert-Johnson et al. 2010, Tan et al. 2012, Bubien et al. 2013, Nieuwenhuis et al. 2014, Drissen et al. 2022, Khare et al. 2022, Teramae et al. 2022, Hendricks et al. 2023, Yehia et al. 2023, Liu et al. 2024)		

9.7. SUMMARY OF EVIDENCE AND GUIDELINE RECOMMENDATION FOR SKIN MELANOMA

Although dermatological manifestations occur in almost all individuals with PHTS, the vast majority are benign lesions (hamartomas or other types such as trichilemmomas or papillomatous lesions). There is some evidence that PHTS is also associated with an increased risk of melanoma (Tan et al.

2012, Bubien et al. 2013, Hendricks et al. 2023, Yehia et al. 2023), but risk figures are conflicting. One observational study on 546 individuals reported a risk excess, as compared with the general population (SIR), of 39 in males and 28 in females (Bubien et al. 2013), while other studies yielded lower estimates, with SIR ranging from 6.6 to 10.6 (Tan et al. 2012, Hendricks et al. 2023, Yehia et al. 2023), leading to cumulative lifetime risks ranging from 6% up to age 83 years (Tan et al. 2012) to 12% up to age 70 years (Hendricks et al. 2023). Hendricks et al. reported a median age of 30 years to develop melanoma (Hendricks et al. 2023). The level of the risk, together with the absence of evidence supporting a benefit of surveillance for every individual with PHTS, led us to recommend a baseline dermatological evaluation at the age of 30 years, with subsequent management based on individual risk assessment (including recognized factors such as phototype, presence of congenital or dysplastic naevi and/or other lesions, family history of melanoma, etc.), similar to the general population. In general, when counselling individuals (particularly those deemed to be at increased melanoma risk), awareness should be raised of the risk associated with UV exposure, referring to the WHO recommendations to avoid excessive exposure and to use sunscreen and protective clothing.

Recommendation		Strength
Rec. 1	Individuals probably should have a baseline skin examination performed by a doctor with expertise in this condition at age 30, further surveillance as required###.	Moderate
References: (Tan et al. 2012, Bubien et al. 2013, Hendricks et al. 2023, Yehia et al. 2023)		

In case of a normal dermatological baseline examination surveillance follow-up is not recommended, just follow-up based on signs and symptoms.

10. PSYCHOLOGICAL NEEDS

There are wider issues to consider beyond the technical aspects when engaging with individuals who have a genetic tumour risk syndrome. These diagnoses, the prospects and implications of surveillance can be psychologically impactful lifelong. Also, individuals diagnosed with genetic tumour risk syndromes (whether or not they have cancer at the time of diagnosis) may experience a period of depression-like symptoms. It is important for clinicians (irrespective of their specialty) to address potential psychological implications of surveillance and to check whether psychological support or an intervention is needed throughout the patient's life and on multiple occasions. Psychological support should be tailored to individual needs.

11. WHAT DO OTHER GUIDELINES STATE?

Recently an international guideline was published on PHTS (Dhawan et al. 2025). The differences between the international guideline and the revised European ERN GENTURIS are listed in the table below. The differences between the current European ERN GENTURIS guideline and the international guideline first of all are a result of interpretation by experts in case of weak or no evidence of surveillance recommendations. Secondly the international guideline was written by a group that included mainly experts from the USA with a different health care system than the European healthcare system. In European guidelines the cost effectiveness and availability of a recommendation for every citizen is a relatively larger driver for decision making. Thirdly the literature search had a different time period. Where the international guideline stopped at January 2023, the ERN guideline had 20 more months as it included publications up to September 2024. And last but not least, the Delphi group had different members and slightly different procedure. The last explanation of course also relates to the first argument, in case of weak evidence the expert opinion is important

Topic	Surveillance method	Updated ERN GENTURIS guideline	International PHTS consensus guidelines	Difference
Breast cancer (women only)	MRI	Start age 25, interval as for *BRCA1* (most national guidelines for *BRCA1* recommend yearly surveillance)	Start age 25, yearly	None
	Mammography	as for *BRCA1* (most national guidelines for *BRCA1* recommend mammography every 1-2 years, start age 40)	Start age 40, yearly	Minor
	Risk reducing surgery	Offered from age 25 years	Offered from age 25 years	None
	Risk reducing medication	**No**	**Consider reducing medication (e.g. tamoxifen, raloxifene, exemestane or anastrozole)**	**Major**
	General	-	Consider stopping surveillance at age 75 – 80 years	Minor

Thyroid cancer	**Ultrasound**	Start between age 10-18 years	Start age 12 years	Minor
		Yearly, frequency decreased to every 2-3 years after 2 ultrasounds with no suspicious findings	**Ultrasound without nodules: every 3-5 years, ultrasound with nonactionable nodules every 2-3 years, ultrasound with actionable nodules with benign findings on cytology every 1-2 years**	**Major**
	TSH (blood)	**No**	**Start age 19 years, considered yearly**	**Major**
Endometrial cancer	Ultrasound	Can be considered from age 35 – 40 years, every year	Only considered as part of a clinical trial	Minor
	Endometrial biopsy	Can be considered	Only considered as part of a clinical trial	Minor
	Risk reducing surgery	Not recommended	Not recommended	None
Renal cancer	**Imaging**	**Baseline imaging between age 35 -40 years**	**Ultrasound: Start at 35 – 40 years every 2 years**	**Major**
		No further surveillance unless required by baseline outcome	**MRI instead of ultrasound may be considered**	**Major**
	Urine	No	No	None
Colorectal cancer	Colonoscopy	Baseline between age 35 – 40 years preferably in expert centre	Baseline between age 35 – 40 years	None
		Further surveillance based on baseline outcome and CRC family history. No further colonoscopy in those with only hamartomas and no first-degree relatives with CRC.	In high polyp burden or at least 1cm with high-grade dysplasia, 1 – 3 years.	Minor
	Risk reducing surgery	No	No	None

Skin melanoma	**Skin exam**	**Baseline age 30 years by dermatologist or expert.** No further surveillance unless required by baseline outcome.	**At time of diagnosis, general physical examination by primary care provider.**	**Major**
General		**None**	**At time of diagnosis, general physical examination by primary care provider**	Major

12.SUGGESTIONS FOR FUTURE RESEARCH

The evidence base for cancer surveillance in this guideline has increased, as is the quality, since the last version of the ERN GENTURIS guideline in 2020 (Tischkowitz et al. 2020) but still is limited. A better understanding of the age-related penetrance and the extent of the risk increase of cancer is critical to improve risk counselling and risk-based recommendations for cancer prevention and treatment. Our recommendation remains that national and international registries (such as the GENTURIS registry) are established to collect prospective data on PHTS individuals undergoing surveillance.

Research should focus on understanding factors affecting the risk of each type of cancer and translate this into more accurate and personalised cancer risk estimates. Furthermore, research is needed to gain insights into the cancer treatment and prognosis of individuals with PHTS. At present, cancer treatment of individuals with PHTS is similar to that for sporadic cancers. Understanding the relation between the individual with PHTS, tumour and treatment characteristics would be the first step towards developing a tailored treatment for individuals with PHTS. As PHTS is a rare disease, collaboration and coordination through a common/central PHTS registry infrastructure is essential to underpin this. Ideally, surveillance of PHTS individuals should be performed as part of a clinical trial in order to gather more prospective evidence for future guideline improvement. In addition, the role of risk reducing breast surgery has not extensively been evaluated for this syndrome and requires further research.

Early detection and surveillance of hereditary cancers relies on established imaging methods such as US and MRI. It is imperative that new surveillance techniques are developed, that are not only more specific in their detection ability, but also more easily available and affordable for the health care systems. Utilisation of non-invasive "liquid biopsy" technologies able to identify the presence of genetic material from cancer cells in the blood or molecular markers in urine, saliva or cervical smears that can identify precursor lesions or cancer at its earliest stages are being evaluated in a research setting and individuals with PHTS are a good target population to trial these. Another area of need is the identification of the relation between genotype and phenotype. The question whether individuals with PHTS with a truncating *PTEN* variant are at higher risk of cancer needs further investigation. Above all, it will be important to prospectively evaluate the effectiveness of surveillance in the PHTS population and to foster global collaborations with data sharing to enhance clinical care and research opportunities for this group of high-risk individuals.

The evidence base for surveillance for organ systems in this guideline are limited. The quality of the evidence regarding baseline risk has been rated as weak as it is non-randomised and based on small numbers. We therefore recommend that national and international registries are established to collect prospective data on PTHS individuals undergoing surveillance. Specifically, the evidence for surveillance recommendation for renal cancer, colorectal cancer, skin cancer and endometrial cancer is weak and needs more research.

A better understanding of the age-related penetrance and the extent of the risk increase of cancer is critical to improve risk counselling and risk-based recommendations for cancer prevention and treatment. Research should focus on understanding factors affecting the risk of each type of cancer and translate this into more accurate and personalised cancer risk estimates. Furthermore, research is needed to gain insights into the cancer treatment and prognosis of individuals with PHTS. At present cancer treatment of individuals with PHTS is similar to sporadic cancer. Understanding the relation between individual, tumour and treatment characteristics would be the first step towards developing a tailored treatment for individuals with PHTS. As PHTS is a rare disease, multidisciplinary collaboration reaching out to many nations is essential to realise the best prognosis for individuals with PHTS.

13.ABBREVIATIONS AND DEFINITIONS

BRRS	Bannayan-Riley-Ruvalcaba syndrome
CI	Confidence interval
CS	Cowden syndrome
CRC	Colorectal cancer
EB	Endometrial biopsy
ERN	European Reference Network
ERN GENTURIS	European Reference Network on Genetic Tumour Risk Syndromes
genturis	Genetic tumour risk syndrome
IQR	Interquartile range
MRI	magnetic resonance imaging
NR	Non-resident
PHTS	*PTEN* hamartoma tumour syndrome
RCC	renal cell carcinoma
SIR	Standardised incidence ratio
TVUS	transvaginal ultrasound
US	ultrasound

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15.APPENDIXES

APPENDIX 1

Highlight of changes in the new guidelines

Most of the recommendations are unchanged or have minor changes, some have been simplified. Taking new evidence into account, the core of the recommendations for breast cancer, thyroid cancer, colorectal cancer, and skin cancer remains the same, but specifics of timing, modality and frequency have been updated. The recommendations for renal cancer and endometrial cancer have changed. Notable changes include a lowering of the age range for commencing thyroid cancer (the wide age range to commence reflects limited evidence and uncertainty), the addition of surveillance for endometrial cancer and a reduction in the intensity of surveillance for renal cancer. See the table below for a comparison of the new and previous recommendations:

	New recommendation (current guideline)	Previous recommendation (2020 guideline)
Breast cancer	**Women should be offered surveillance for breast cancer.**	Women should be screened for breast cancer.
	Surveillance for breast cancer in PHTS should include MRI.* * **Most national guidelines for *BRCA1* surveillance recommend yearly surveillance with MRI and mammography every 1-2 years.**	Screening for breast cancer in PTEN should use MRI. (MRI should be conducted between day 5 and day 12 of the menstrual cycle).
	Surveillance for breast cancer with MRI should probably start at age 25. In post-menopausal women, an individual assessment of the need for continued MRI surveillance is recommended.	Surveillance for breast cancer with MRI should probably start at 30.
	Surveillance for breast cancer should be performed as for *BRCA1* and *BRCA2*. * **Most national guidelines for *BRCA1* surveillance recommend yearly surveillance with MRI and mammography every 1-2 years.**	Women should be screened for breast cancer annually. / If screening for breast cancer in PTEN additionally uses Mammography this should be undertaken no more frequently than every 2 years. / If surveillance for breast cancer with Mammography is offered this should probably start at 40.
	Risk reduction surgery should be offered as an alternative to intensive surveillance in an individual risk management discussion.	Risk reduction surgery should be offered using the same considerations as for women with germline *BRCA1/BRCA2* pathogenic variants.

Thyroid cancer	**Individuals should be offered surveillance for thyroid cancer.**	Individuals should be offered surveillance thyroid cancer.
	Surveillance for thyroid cancer in PHTS should be by ultrasound.	Surveillance for thyroid cancer in PHTS should be by ultrasound.
	Surveillance for thyroid cancer should probably start between 10 and 18 years of age.	Surveillance for thyroid cancer should probably start at 18 years following the TiRADS criteria.
	Individuals should be offered surveillance for thyroid cancer annually initially. Individuals with two ultrasound examinations with no suspicious findings should probably be re-scanned at an increased interval of two to three years as clinically indicated.	Individuals should probably be screened for thyroid cancer annually.
Endometrial cancer, increased	**Women should probably have surveillance for endometrial cancer.**	Women should probably not be screened for endometrial cancer.
	If surveillance for endometrial cancer is offered, it should probably start at 35–40 years.	If surveillance for endometrial cancer is offered, it should probably start at 40.
	If surveillance for endometrial cancer is offered, it should probably be via transvaginal ultrasonography done at least annually. Endometrial biopsy can be considered.	If surveillance for endometrial cancer in PTEN should be by US, as part of a clinical trial. / If screening, women should be screened for endometrial cancer at least annually.
	There is no clear clinical indication for endometrial cancer risk reduction surgery (hysterectomy). It can be considered in an individual risk management discussion.	There is no clinical indication for endometrial risk reduction surgery (hysterectomy).
Renal cancer, reduction	**Individuals should be offered a baseline imaging exam at age 35-40 years for renal cell carcinoma (RCC).##** **## Where renal baseline imaging is normal, further regular surveillance is not recommended, just follow-up based on signs and symptoms.**	Individuals should be offered surveillance for RCC. / Surveillance for RCC in PTEN should be by US. / Surveillance for RCC should probably start at 40. /Surveillance for RCC should probably be at least every 2 years.
Colorectal cancer	**Baseline colonoscopy should be undertaken at 35-40 years to assess polyp load preferably in an expert centre. Interval of monitoring is guided by the number, size and pathology of resected polyps. In individuals with a family history of early-onset colorectal cancer, earlier colonoscopy may be warranted.**	Baseline colonoscopy should be undertaken at 35-40 yrs to assess polyp load.
	In individuals with only hamartomas or no polyps at baseline colonoscopy, colorectal cancer surveillance may follow general population guidelines. However, a repeat colonoscopy after 5 to 10 years can be considered.	Individuals probably should not be screened for colorectal cancer at any greater frequency or earlier age then the general population.

Skin melanoma	**Individuals probably should have a baseline skin examination performed by a doctor with expertise in this condition at age 30, further surveillance as required.###** **### In case of a normal dermatological baseline examination, further regular surveillance is not recommended, just follow-up based on signs and symptoms.**	Individuals probably should have a baseline skin examination at age 30, further surveillance as required (consider every 2 years)

APPENDIX 2

(Baran et al. 2020, Jonker et al. 2020, Smith et al. 2021, Drissen et al. 2022, Hoxhaj et al. 2022, Khare et al. 2022, Pena-Couso et al. 2022, Plitt et al. 2022, Teramae et al. 2022, Drissen et al. 2023, Hendricks et al. 2023, Kwinten et al. 2023, Yehia et al. 2023, Liu et al. 2024, Martinez-Rios et al. 2024, Bormans et al. 2025)