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

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Disclaimer:

ABSTRACT

Background

PTEN hamartoma tumour syndrome is a diverse multi-system disorder predisposing to the development of hamartomatous growths, increasing risk of breast, thyroid, endometrial, renal cancer, and possibly increasing risk of colorectal cancer and melanoma. There is no international consensus on cancer surveillance in PHTS and all current guidelines are based on expert opinion.

Methods

A comprehensive literature review was undertaken and guidelines were developed by clinicians with expertise from clinical genetics, gynaecology, endocrinology, dermatology, radiology, gastroenterology and general surgery, together with affected individuals and their representatives.

Results Recommendations were put forward for surveillance for breast, thyroid and renal cancers. Limited recommendations were developed for other sites including endometrial, colon and skin.

Conclusion

The proposed cancer surveillance recommendations for PHTS require a coordinated multidisciplinary approach and significant patient commitment. The evidence base for cancer surveillance in this guideline are limited, emphasising the need for prospective evaluation of the effectiveness of surveillance in the PHTS population.

GUIDELINE SUMMARY: CANCER SURVEILLANCE FOR INDIVIDUALS WITH *PTEN* HAMARTOMA TUMOUR SYNDROME (PHTS)

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. The expectation is that clinicians will follow this guideline unless there is a compelling clinical reason specific to an individual patient not to.

Table 1. Summary of the surveillance protocol

	Surveillance	Interval	From Age	Evidence
Breast cancer	MRI	Yearly	30	Strong
	Mammography	Every 2 yrs.	40	Moderate
	Risk reducing surgery offered	-	-	Moderate
Thyroid cancer	Ultrasound	Yearly	18*	Strong
Renal cancer	Ultrasound	Every 2 yrs.	40	Moderate
Colorectal cancer	Baseline colonoscopy	-	35-40	Moderate
Melanoma	baseline skin examination**		30	Weak
Endometrial cancer***	Not recommended	-	-	Weak

* Moderate evidence for age of commencement of surveillance

** Consider further surveillance as required

***Consider surveillance as part of clinical trial.

In addition to the tests listed above the guideline recommends that risk reducing breast surgery can be offered to affected women.

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1. INTRODUCTION

PTEN hamartoma tumour syndrome (PHTS), OMIM 158350, ORPHA:306498, is caused by pathogenic germline variants in the *PTEN* (phosphatase and tensin homolog) gene and encompasses Cowden syndrome (CS), Bannayan-Riley-Ruvalcaba syndrome (BRRS) and Proteus-like syndrome. It is a diverse multi-system disorder predisposing to the development of hamartomatous growths, increasing risk of breast, thyroid, endometrial, renal cancer, and possibly increasing risk of colorectal cancer and melanoma (Pilarski R. et al., 2019).

The reported average lifetime risks of cancer in PHTS patients 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 (Riegert-Johnson DL et al., 2010; Bubien V et al., 2013; Tan MH et al., 2012; Starink TM et al., 1986; Nieuwenhuis MH et al. 2014). These estimates and those given in the table 1 below are likely to be at the upper end of the true range because of some ascertainment bias in studies published to date. Ultimately, larger longitudinal studies, including those individuals diagnosed in childhood because of developmental problems, and asymptomatic relatives with *PTEN* mutations, will be needed to define the risk more accurately.

Cancer	Current Risk Estimates	Publications
Breast	Cancer – lifetime up to 85% Average age at diagnosis 38-46 years High incidence of fibrocystic breast disease	81% (Riegert-Johnson et al., 2010) 85.2% (Tan et al., 2012) 77% (Bubien et al., 2013)
Thyroid	Cancer – lifetime 35% (usually follicular, rarely papillary, never medullary) Median age at diagnosis 37 years Up to 75% risk of multinodular goitre, adenomatous nodules & follicular adenomas	21% (Riegert-Johnson et al., 2010) 35.2% (Tan et al., 2012) 38% (Bubien et al., 2013)
Endometrial	Cancer – lifetime up to 28% Risk starts late 30s – early 40s Benign uterine fibroids very common.	19% (Riegert-Johnson et al., 2010) 28.2% (Tan et al., 2012) 2.0% (Bubien V, 2013)
Renal	Cancer – lifetime up to 35% (mostly papillary) Risk starts late 40s	15% (Riegert-Johnson et al., 2010) 33.6% (Tan et al., 2012) 2.0% (Bubien V, 2013)
Colorectal	Cancer – lifetime up to 9% Risk starts late 30s More than 90% have polyps, which may be symptomatic	16% (Riegert-Johnson et al., 2010) 9.0% (Tan et al., 2012) 3.0% (Bubien V, 2013) 13% (Heald et al., 2010)

Skin & vascular system	Melanoma – ~5% Many non-malignant lesions	6.0% (Tan et al., 2012)
Brain	Lhermitte-Duclos disease – up to 32%	Lhermitte-Duclos disease 32% (Riegert-Johnson et al., 2010)

Table 1: Estimated Lifetime risks of tumours in individuals with PHTS

PHTS is rare and its clinical diagnosis relies on the presence of the characteristic signs and symptoms with variable expressivity, subsequently confirmed by genetic testing. Early identification of individuals and appropriate surveillance are key to the timely detection of lesions and can precede the development of advanced cancer by several years (Molvi, Sharma and Dash, 2015).

2. COMPOSITION OF THE GUIDELINE DEVELOPMENT GROUP

ERN Guidelines on Cancer Surveillance Guideline for Individuals PHTS consists of clinicians with expertise from clinical genetics, gynaecology, endocrinology, dermatology, radiology, gastroenterology, general surgery and affected individuals and their representatives.

The Guideline Development Group was led by a Core Writing Group of ERN GENTURIS HCP Members from different Member States and who are recognised experts in specialised clinical practice in the diagnosis and management of PHTS.

Approach to secure views and preference of target population

The ERN GENTURIS PHTS Guideline Development Group was supported by a Patient Advisory Group of four patient or parental representatives with experience of PHTS. The Patient Advisory Group identified one member of the group to be a formal member of the Guideline Development Group, acting as a bridge between the two groups.

Involving the community representatives in the development of these guidelines and in the Guideline Development Group helped to ensure that:

- the questions addressed are relevant to them and will make a positive impact on individual care;
- important aspects of the experience of illness are considered;
- critical clinical and patient important outcomes are identified and prioritised;
- the balance of benefits and harms of the intervention is appropriately considered when recommendations are formulated in conjunction with individual's values and preferences.

The Patient Advisory Group advised on the scope, target population and clinical questions the guideline aimed to address and rate the outcomes in terms of their importance.

The representatives mapped the needs of children and adults living with PHTS along a 'Patient Journey' which was used to inform the development of the guideline. The group also reviewed the findings of the literature review and recommendations and co-produced a 'Plain Language Summary' of the guideline.

3. CONFLICT OF INTERESTS

All members of the ERN GENTURIS *PTEN* Writing 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. This information is publicly accessible through the ERN GENTURIS website.

4. PURPOSE AND SCOPE OF THIS GUIDELINE

4.1. WHY WAS THIS GUIDELINE PRODUCED?

This guideline is intended to consider the cancer surveillance of individuals with PHTS. It 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.

4.2. WHO IS THE GUIDELINE FOR?

The *PTEN* hamartoma tumour syndrome (PHTS) Guideline Development Group have prepared this guideline document to assist healthcare professionals in the evidence-based surveillance of individuals with a confirmed germline pathogenic variant in *PTEN*.

Clinical guidelines are statements, based on systematically evaluated evidence, for a specified clinical circumstance to support decision making. Whilst clinical guidelines draw on and present the latest published evidence, care and treatment of affected individuals are first and foremost based on the clinical expertise of the responsible medical professional. Clinical guidelines should support clinical decision making, but decisions for treatment should be tailored to the individual needs, personal preferences and individual circumstances of each patient. 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.

4.3. WHAT IS THE GUIDELINE ABOUT?

4.3.1 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, renal, endometrial or colorectal cancers in PHTS. For melanoma, the risk is not sufficiently established to consider additional surveillance at present. There is clearly an increased risk of cancers in PHTS and this guideline seeks to clarify these risks, and to balance the risk of harm from the over-diagnosis of cancer with the potential benefits of early identification of cancers.

4.3.2 POPULATION

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

4.3.3 EPIDEMIOLOGY & AETIOLOGY

Epidemiology: The prevalence of PHTS was estimated to be 1 in 200-250,000 (Eng, 2000; Gammon et al., 2016) but is now thought to be more common than this.

Aetiology: In 1997, the mutations in the *PTEN* gene, located on 10q23.3, were first confirmed to be the cause of Cowden Syndrome (Nelen et al. 1997). *PTEN* (phosphatase and tensin homolog) is a tumour suppressor gene, the loss of which results in the increased cell proliferation and survival leading to tumorigenesis (Hansen-Kiss et al., 2017; Gammon, Jasperson and Champine, 2016; Bubien et al., 2013; Eng, 2000). Approximately 80% of the PHTS cases are due to the germline predicted pathogenic variants in the *PTEN* with almost 45% arising de novo or due to mosaicism (Mester J et al, Genet Med 2012; Mester J et al, Handb Neurol 2015; Gammon et al., 2013).

5. KEY FINDINGS & RECOMMENDATIONS

5.1. RECOMMENDATIONS & EVIDENCE FOR BREAST EVIDENCE

There is direct evidence of an increase in breast cancer in women with germline pathogenic variants in *PTEN* (Bubien et al., 2013; Nieuwenhuis et al., 2014; Tan et al., 2012). However, there was no direct evidence to address the questions of which modality should be used for screening and if, in PHTS early breast cancers can be identified through screening and if there are benefits from early identification. The limited evidence suggests that the breast cancer risk in PHTS is similar to that in women with germline pathogenic variants in BRCA1/BRCA2 so many of the recommendations are derived from the much larger evidence base which exists for those hereditary breast cancer predisposition syndromes.

For those centres that wish to use mammography there is no evidence of additional incremental benefit in performing mammography more frequently than every two years with screening in the intervening years being better performed by MRI.

Breast		Evidence
Recommendation 1	Women **should** be Screened for Breast Cancer.	**Strong**
Recommendation 2	Screening for Breast Cancer in *PTEN* **should** use MRI. (MRI should be conducted between day 5 and day 12 of the menstrual cycle).	**Strong**
Recommendation 3	Surveillance for breast cancer with MRI **should probably** start at 30.	**Strong**
Recommendation 4	Women **should** be screened for breast cancer annually.	**Strong**
Recommendation 5	If screening for breast cancer in *PTEN* additionally uses Mammography this **should** be undertaken no more frequently than every 2 years.	**Moderate**
Recommendation 6	If surveillance for breast cancer with Mammography is offered this **should probably** start at 40.	**Moderate**

Recommendation 7	Risk reduction surgery **should** be offered using the same considerations as for women with germline *BRCA1/BRCA2* pathogenic variants.		**Moderate**
Paper	**Design**	**Quality**	**Directness**
(Nieuwenhuis et al., 2014)	Observational	Large Sample (180),	Direct
(Bubien et al., 2013)	Observational	Large Sample (154),	Direct
(Tan et al., 2012)	Observational	Large Sample (368),	Direct
(Riegert-Johnson et al., 2010)	Observational	Large Sample (211),	Indirect (includes non-*PTEN* predicted pathogenic variants)
(Mann et al., 2019)	Systematic Review	11 studies	MRI for Breast Ca
(Vreemann et al., 2018)	Observational	Large Sample (2026)	MRI for Breast Ca (+/-*BRCA*)

5.2. RECOMMENDATIONS & EVIDENCE FOR THYROID

There is direct evidence of an increase in thyroid carcinoma in PHTS with evidence that these can occur relatively young (Bubien et al., 2013; Nieuwenhuis et al., 2014; Plamper et al., 2018; Riegert-Johnson et al., 2010; Smith et al., 2011; Smpokou et al., 2015; Tan et al., 2012), however there was no direct evidence to address the questions of which modality should be used for screening and whether, early thyroid carcinoma can be identified through screening or if there are benefits from early identification. Although there are occasional reported cases of children with PHTS developing thyroid carcinoma (Plamper et al., 2018; Smith et al., 2011), the evidence does not appear to support this being common enough to justify the significant additional screening burden that would be required to screen all individuals throughout childhood.

There is evidence that identification of early stage thyroid carcinomas in other populations leads to better outcomes (Riegert-Johnson et al., 2010). There is evidence, in other populations that US is an appropriate modality for screening for thyroid carcinomas.

Thyroid			**Evidence**
Recommendation 1	Individuals **should** be offered surveillance thyroid cancer.		**Strong**
Recommendation 2	Surveillance for thyroid cancer in PHTS **should** be by US.		**Strong**
Recommendation 3	Surveillance for thyroid cancer **should probably** start at 18 years following the **TiRADS criteria**[1, 2].		**Moderate**
Recommendation 4	Individuals **should probably** be screened for thyroid cancer annually.		**Moderate**
Paper	**Design**	**Quality**	**Directness**
(Smpokou et al., 2015)	Observational	Small Sample(34), single centre	Direct
(Plamper et al., 2018)	Observational	Small Sample(16), single centre	Direct

[1] J Am Coll Radiol. 2015 Dec; 12 (12 Pt A):1272-9. doi: 10.1016/j.jacr.2015.07.011. Epub 2015 Sep 26. *Thyroid Ultrasound Reporting Lexicon: White Paper of the ACR Thyroid Imaging, Reporting and Data System (TIRADS) Committee.* Grant EG, Tessler FN, Hoang JK, Langer JE, Beland MD, Berland LL, Cronan JJ, Desser TS, Frates MC, Hamper UM, Middleton WD, Reading CC, Scoutt LM, Stavros AT, Teefey SA.

[2] Nuklearmedizin. 2015;54(3):144-50. doi: 10.3413/Nukmed-0712-14-12. Epub 2015 Apr 13. *TIRADS for Sonographic Assessment of Hypofunctioning and Indifferent Thyroid Nodules.* Schenke S1, Rink T, Zimny M.

(Smith et al., 2011)	Observational	Tiny Sample (7), single centre	Direct
(Nieuwenhuis et al., 2014)	Observational	Large Sample (180), single centre	Direct
(Bubien et al., 2013)	Observational	Large Sample (154), single centre	Direct
(Tan et al., 2012)	Observational	Large Sample (368), single centre	Direct
(Riegert-Johnson et al., 2010)	Observational	Large Sample (211), single centre	Indirect (includes non-*PTEN* predicted pathogenic variants)

5.3. RECOMMENDATIONS & EVIDENCE FOR RENAL

There is direct evidence of an increase in renal cell carcinoma (RCC) in individuals with PHTS, however there was no direct evidence to address the questions of which modality should be used for screening and if, in PHTS, early RCCs can be identified through screening and if there are benefits from early identification. There is strong evidence that identification of early stage RCCs in other populations leads to significantly better outcomes (Fiori et al., 2016). There is evidence, in other populations that US is an appropriate modality for screening for RCCs (Chiarello et al., 2018; Vogel et al., 2018). There is no evidence to suggest that RCCs in PHTS behave differently to sporadic RCCs.

Renal			**Evidence**
Recommendation 1	Individuals **should** be offered surveillance for RCC.		**Moderate**
Recommendation 2	Surveillance for RCC in *PTEN* **should** be by US.		**Moderate**
Recommendation 3	Surveillance for RCC **should probably** start at 40.		**Moderate**
Recommendation 4	Surveillance for RCC **should probably** be at least every 2 years.		**Moderate**
Paper	**Design**	**Quality**	**Directness**
(Mester et al., 2012)	Observational	Moderate sample Small effect size	Direct
(Smpokou et al., 2015)	Observational	Small Sample	Direct
(Choyke et al., 1990)	Observational	Small Sample	Indirect (vHL)
(Mihara et al., 1999)	Observational	Huge Cohort	Indirect (General Pop^{n})
(Filipas et al., 2003)	Observational	No serious limitations	Indirect (General Pop^{n})
(Fiori et al., 2016)	Observational	No serious limitations	Indirect (Surgery RCC)
(Ishikawa et al., 2004)	Observational	No serious limitations	Indirect

			(RCC - Dialysis)
(Malaeb et al., 2005)	Observational	No serious limitations	Indirect (Elderly Pop^{n})
(Chiarello et al., 2018)	Systematic review	13 Studies	Indirect (Diagnostic accuracy)
(Vogel et al., 2018)	Systematic review	40 Studies	Indirect (Diagnostic accuracy)

5.4. RECOMMENDATIONS & EVIDENCE FOR COLORECTAL

There is conflicting evidence regarding colorectal cancer risk in PHTS (Pilarski R. et al 2019). Therefore, the recommendations for screening should be those that apply to the general population.

Colorectal			Evidence
Recommendation 1	Individuals **probably should not** be screened for colorectal cancer at any greater frequency or earlier age then the general population.		**Moderate**
Recommendation 2	Baseline colonoscopy should be undertaken at 35-40 yrs to assess polyp load.		**Moderate**
Paper	**Design**	**Quality**	**Directness**
(Nieuwenhuis et al., 2014)	Observational	Large Sample (180)	Direct
(Bubien et al., 2013)	Observational	Large Sample (154)	Direct
(Tan et al., 2012)	Observational	Large Sample (368)	Direct
(Riegert-Johnson et al., 2010)	Observational	Large Sample (211)	Indirect (includes non-*PTEN* predicted pathogenic variants)
(Yurgelun et al., 2015)	Observational	Sample (457)	Indirect (considers all colorectal cancers, 6 with potential *PTEN*)

5.5. RECOMMENDATIONS & EVIDENCE FOR DERMATOLOGIAL

There is conflicting evidence regarding skin cancer risk in PHTS (add reference). Therefore, the recommendations for screening should be those that apply to the general population.

Dermatology			Evidence
Recommendation 1	Individuals **probably should** have a baseline skin examination at age 30, further surveillance as required (consider every 2 years)		**Weak**
Paper	**Design**	**Quality**	**Directness**
(Tan et al., 2012)	Observational	Large sample (368)	Direct
(Bubien et al., 2012)	Observational	Large sample (546)	Direct

5.6. RECOMMENDATIONS & EVIDENCE FOR ENDOMETRIAL

There is conflicting evidence regarding endometrial cancer risk in PHTS. The limited evidence suggests that if they occur, they behave similarly to endometrial cancers in other cancer syndromes. So that the clinical consideration of screening and risk-reduction surgery should be tailored to and focused on the individual risks and circumstances of each person.

Endometrial			Evidence
Recommendation 1	Women **should probably not** be screened for endometrial cancer.		**Moderate**
Recommendation 2*	If surveillance for endometrial cancer in *PTEN* **should** be by US, as part of a clinical trial.		**Strong**
Recommendation 3*	If surveillance for endometrial cancer is offered, it **should probably** start at 40.		**Weak**
Recommendation 4*	If screening, women **should** be screened for endometrial cancer at least annually.		**Weak**
Recommendation 5*	There is no clinical indication for endometrial risk reduction surgery.		**Weak**
Paper	**Design**	**Quality**	**Directness**
(Nieuwenhuis et al., 2014)	Observational	Large Sample (180),	Direct
(Bubien et al., 2013)	Observational	Large Sample (154),	Direct
(Tan et al., 2012)	Observational	Large Sample (368),	Direct
(Riegert-Johnson et al., 2010)	Observational	Large Sample (211),	Indirect (includes non-*PTEN* predicted pathogenic variants)
(Moller et al., 2018)	Observational	Huge Sample (3119)	Indirect (Lynch Syndrome, PMS2 predicted pathogenic variants considered analogous)
(Moller et al., 2017)	Observational	Huge Sample (1942)	Indirect (Lynch Syndrome, PMS2 predicted pathogenic variants considered analogous)

(Moller et al., 2017)	Observational	Huge Sample (1273)	Indirect (Lynch Syndrome, PMS2 predicted pathogenic variants considered analogous)

*NB: Recommendation 2-5, should be undertaken as part of a clinical trial.

5.7. PSYCHOLOGICAL NEEDS

There are wider issues to consider when engaging with people regarding a diagnosis of a potential cancer related syndrome and about potential surveillance than simply the technical aspects. These diagnoses, the prospects and implications of surveillance are psychologically impactful. People diagnosed with genetic cancer related syndromes (whether or not they have cancer at the time of diagnosis) experience a period of depression-like symptoms for 6-12 months before reversion to baseline. These people and their families have on-going informational and support needs. As these appear to be best met through peer-support interventions, support groups and secure online group and not through formal psychological intervention, services that deliver these diagnoses and the subsequent surveillance are encouraged to support the formation and continuation of support groups whether face-to-face or online for the facilitation of peer-support.

6. METHODS FOR GUIDELINE DEVELOPMENT

6.1. ESTABLISHMENT OF THE GUIDELINE DEVELOPMENT GROUP

The ERN GENTURIS PHTS Guidelines Development Group was established to provide assistance and general guidance by following leads as honorary member of the PHTS Guidelines Development Group:

Name	Speciality / Role	Hospital, Member State
Dr. Marc Tischkowitz	Clinical Genetics	Cambridge University Hospital NHS Foundation Trust, Cambridge, UK
Prof. Nicoline Hoogerbrugge	Clinical Genetics	Radboud university medical center, Nijmegen, The Netherlands
Dr. Chrystelle Colas	Clinical Genetics	Institut Curie, Paris, France
Dr. Janet Vos	Clinical Genetics	Radboud university medical center, Nijmegen, The Netherlands
Prof. Nathalie Chabbert-Buffet	Gynaecologist & Endocrinologist	Hôpital Tenon, APHP, Paris, France
Prof. Frederic CAUX	Dermatology	Hôpital Avicenne, APHP, Bobigny France
Dr. Virginie Bubien & Dr. Michel Longy	Genetics – Clinical & Molecular/lab	Cancer Genetics Unit, Institut Bergonié Bordeaux, France
Prof. Dr. Leo Schultze Kool	Radiology	Radboud university medical center, Nijmegen, The Netherlands
Dr. Marleen Kets	Clinical Genetics	Dutch Cancer Institute, Amsterdam, The Netherlands
Prof. Dr. Thera Links	Endocrinology	University Medical Center Groningen, The Netherlands
Dr. Ritse Mann	Radiology and Nuclear Medicine	Radboud university medical center, Nijmegen, The Netherlands
Prof. Dr. Martin Gotthardt	Radiology	Radboud university medical center, Nijmegen, The Netherlands
Dr. Tanya Bisseling	Gastroenterology	Radboud university medical center, Nijmegen, The Netherlands
Dr. Katherine Lachlan	Clinical Genetics	University Hospitals Southampton, United Kingdom
Prof. Rob Semple	Endocrinology	University of Edinburgh, United Kingdom
Mr. Ian Stock	Patient Representative	*PTEN* UK

Ms. Sophie Da Mota Gomes	Patient Representative	France
Dr. Sjaak Pouwels	Surgery & Patient Representative	Haaglanden Medical Center, The Hague, The Netherlands

6.2. RATING THE QUALITY OF THE EVIDENCE FOR EACH OUTCOME ACROSS STUDIES (IN ACCORDANCE WITH GRADE)

The ERN GENTURIS *PTEN* Guidelines Development Group used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach for assessment of quality of evidence and grading of recommendations. GRADE quality assessment, that is applied to the body of evidence is reported under four distinct levels - high, moderate, low, and very low – to reflect the level of confidence and certainty in the published evidence. The final quality rating of the evidence was assessed under the following areas:

- limitations in study design or implementation (risk of bias)
- imprecision of estimates (wide confidence intervals)
- inconsistency (variability in results)
- indirectness of evidence
- publication bias.

GRADE, however, is not appropriate for making guidelines recommendations when there is limited, low-quality and conflicting evidence, and consensus statements are more appropriate in these scenarios.

In day-to-day practice, clinicians will not have the time to explore the evidence as thoroughly as a guideline panel, nor devote as much thought to the trade-offs, or the possible underlying values and preferences in the population. Therefore, the Core Writing Group has made recommendations even when confidence in effect estimate is low and/or desirable and undesirable consequences are closely balanced. Such recommendations have been classified as 'weak' and been qualified. The recommendations have been graded on the quality of evidence; balance between benefits and harms; include the values and preferences of patients; and consider the feasibility, equity & acceptability of implementation and use.

Strength of recommendation has been determined through a consensus-based approach and through active engagement of affected individuals and parent 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.

6.3. FORMULATING AND GRADING STATEMENTS

The guidelines were elaborated on the basis of 131 published articles extracted from Pubmed, using the following terms: (screening[title/abstract] OR surveillance[title/abstract]) AND (PTEN[title] OR Cowden[Title]) AND "humans"[MeSH Terms].

Additional articles were requested from experts in the field and references of all the articles were considered. As is typical for many rare diseases, the volume of peer-reviewed evidence available to consider for these guidelines was small and came from a limited number of articles, which typically reported on small samples or series. To balance the weight of both published evidence and quantify the wealth of expert experience and knowledge, we have used for evidence grading the following scale: (i) strong evidence: consistent evidence and new evidence unlikely to change recommendation and expert consensus; (ii) moderate evidence: expert consensus or majority decision but with inconsistent evidence or significant new evidence expected and (iii) weak evidence: inconsistent evidence AND expert agreement.

The quantification of strength of evidence for a recommendation is a composite of harm and benefit. As a general note for these recommendations, the harms a recommendation seeks to address are often clear, however the magnitude of the benefit of a specific recommendation are often not as clear. Therefore, the published evidence for a recommendation can be often classified 'weak', even when experts are convinced that the recommendation is correct.

The evidence available to consider this guideline came from a limited number of papers, which typically reported on small samples or cohorts. Indirect evidence from analogous conditions was often needed to address the clinical questions that form this guideline.

Indirect evidence was specifically necessary when considering:

Which modality to use for screening for Renal Cell carcinoma;

The benefit of screening for Renal Cell carcinoma; and

The role of risk reduction surgery for Breast or Endometrial cancer.

Method for formulating recommendations.

List the papers considered in each the topic for the recommendations:

Note was made of the **Design** of each study (RCT, Observational, Systematic Review, Expert Opinion)

Note was made of the **Quality** of each study with any particular limitation with respect to the topic or recommendations

Note was made of the **Directness** of the study to the topic or recommendations

Write recommendations 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

6.4. Internal and External review

ERN GENTURIS has actively involved external experts from different speciality areas that are relevant to the scope of the guideline to review the findings and recommendations developed in this guideline.

In addition, the PHTS Guideline Development Group engaged with the European Journal of Human Genetics as an independent review of the guideline.

ERN GENTURIS first published the Guidelines for Cancer Surveillance in individuals with *PTEN* hamartoma tumour syndrome (PHTS) in 2019.

6.5. Timeline and procedure for updating the guideline

Any new evidence that has been published will be updated to the Network clinical leads, on an annual basis and consideration for updating the guideline thereafter. New versions will be published on the Network's website and circulated through the ERN GENTURIS Members.

6.6. FUNDING AND FINANCIAL SUPPORT

All members of ERN GENTURIS *PTEN* Core Writing 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. This information is publicly accessible through the ERN GENTURIS website.

This guidelines document was developed with the financial support of the European Commission. No external sources of funding and support have been involved. ERN GENTURIS is one of the 24 European Reference Networks (ERNs) approved by the ERN Board of Member States. The ERNs are co-funded by the European Commission. EU funding is limited to administrative assistance and travel and meeting expenses. No honoraria or other reimbursements have been provided. For more information about the ERNs and the EU health strategy, please visit http://ec.europa.eu/health/ern

Below is a summary of the funding organisations for the members of the Core Writing Group.

LEAD	ROLE	FUNDING ORGANISATION
Dr. Marc Tischkowitz	Core Writing Group Chair	Cancer Research UK (CanGene-CanVar Catalyst Award C61296/A27223) and *PTEN* Research
Dr. Chrystelle Colas	Core Writing Group Clinical Member	Institut Curie, Paris, France
Dr Sjaak Pouwels	Core Writing Group Community Representative Member	Voluntary support
Prof Nicoline Hoogerbrugge	Core Writing Group Clinical Member	Radboud University Medical Center, Nijmegen, The Netherlands

7. DISCUSSION

The goal of cancer surveillance is to detect cancer at an earlier stage than symptomatic presentation, when interventions have a better chance of being curative. The proposed surveillance recommendations for PHTS require a coordinated multidisciplinary approach and significant patient commitment. As this is a very rare condition there is unlikely to be a large health economic burden for the health service if these guidelines are implemented. However, surveillance in each individual is complex and additional resources may need to be put in place for those health service providers that are planning to offer surveillance at a local and regional level. PHTS-related cancers are predominately adult onset and no specific recommendations have been made for non-malignant manifestations in adults or for the paediatric PHTS population whose management has been addressed elsewhere (Macken WL et al. 2019).

The evidence base for cancer surveillance 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. 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. We therefore recommend that national and international registries 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 PHTS patients. At present cancer treatment of PHTS patients is similar to that for sporadic cancers. Understanding the relation between patient, tumour and treatment characteristics would be the first step towards developing a tailored treatment for PHTS patients. As PHTS is a rare disease, collaboration supported by a common/central PHTS registry infrastructure is essential to underpin this. In addition, the role of prophylactic surgery has not 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 or saliva that can identify precursor lesions or cancer at its earliest stages are still being evaluated in a research setting and individuals with PHTS would be a good target population to trial these. Another area of need is the identification and validation of

biomarkers that may distinguish aggressive, life-threatening cancers from more indolent types. 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.

8. WHAT DO OTHER GUIDELINES STATE?

Screening	Dutch	UK	NCCN
Breast			
Clinical breast exam	Annual beginning at age 25 years	No recommendation	Annual Age 25 or 5 – 10 years before earliest known breast cancer in the family.
Mammogram and breast MRI	Annual MRI with contrast and mammogram beginning at age 25 years	Annual MRI from age 30 years mammography from 40 years	Annual Age 30 – 35 or 5 – 10 years before earliest known breast cancer in the family.
Uterine			
Endometrial biopsy	Annual uterine biopsies and/or ultrasound beginning at age 30 years	Refer to specialist Gynaecologist age 35-40 years for discussion regarding screening options. Consider risk reducing hysterectomy	annual Age 30 – 35 or 5 years before earliest diagnosis of endometrial cancer in family until menopause
Endometrial ultrasound	Annual uterine biopsies and/or ultrasound beginning at age 30 years	No recommendation	annual Post-menopause
Renal			
Urinalysis	No recommendation	No recommendation	annual
Ultrasound	No recommendation	Annual renal USS/MRI from 40 years	every 1-2 years starting at age 40 years
Thyroid			
Thyroid ultrasound	Annual beginning at age 18 years	annual screen from 16 years Younger as guided by family history or after informed discussion with family.	annual Age 18 years
Colon			

Colonoscopy	every 5 years beginning age 40	Ascertainment colonoscopy at age 35 and 55 Polyp f/u as required	Colonoscopy every 5 years beginning age 35 or earlier based on family colon cancer history
Melanoma			
Dermatologic exam	No recommendation	Baseline dermatological review & appropriate f/u	Consider Every 12 months
Lhermitte-Duclos disease			
Brain MRI	No recommendation	only if symptomatic	No recommendation

9. SUGGESTIONS FOR FUTURE RESEARCH

The evidence base for screening and 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.

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 PHTS patients. At present cancer treatment of PHTS patients is similar to sporadic cancer. Understanding the relation between patient, tumour and treatment characteristics would be the first step towards developing a tailored treatment for PHTS patients. As PHTS is a rare disease, collaboration supported by a common/central PHTS registry infrastructure is essential to realise this.

In addition, the role of prophylactic surgery has not been evaluated for this syndrome and requires further research.

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APPENDIX – PLAIN LANGUAGE SUMMARY

ERN GENTURIS Plain Language Summary:

Cancer Surveillance Guideline for individuals with *PTEN* hamartoma tumour syndrome (PHTS)

(Based on final version – 01.11.2019)

INTRODUCTION

PTEN hamartoma tumour syndrome (PHTS), is caused by a change in the *PTEN* (phosphatase and tensin homolog) gene. PHTS increase the risk of breast, thyroid, endometrial, renal and colorectal cancers. PHTS is rare and its diagnosis relies on genetic testing. Surveillance is considered key to detecting early cancers and being able to treat people.

GUIDELINE AIMS

The *PTEN* hamartoma tumour syndrome (PHTS) Guideline has been created to assist healthcare professionals give the most up-to-date surveillance for individuals with PHTS. This guideline has been drawn from the best available evidence and the consensus of experts in caring for people with PHTS and it is regularly updated to reflect changes in evidence. The expectation is that clinicians will follow this guideline unless there is a compelling clinical reason specific to an individual patient not to.

SCOPE & PURPOSE OF THE GUIDELINE

The guideline is intended for the cancer surveillance of individuals with PHTS. For each type of cancer, the guideline states what test should be used for surveillance, what age to start surveillance and how often to repeat investigations.

KEY RECOMMENDATIONS

	What Test	How often	Starting at
Thyroid cancer	Ultrasound	Every year	18 yrs.
Breast cancer	MRI Mammography	Every year Every 2 yrs.	30 yrs.
Renal cancer	Ultrasound	Every 2 yrs.	40 yrs.
Endometrial cancer	Not recommended	*if screened then: Ultrasound: yearly	(40)*
Colorectal cancer	Follow general population screening guidelines	-	-

In addition to the tests listed above the guideline recommends that risk reducing breast surgery can be offered to affected women.

***Disclaimer**: The content of this summary is based on the GENTURIS Cancer surveillance guideline for individuals with PTEN Version 14 (05.09.2019)*

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