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PTEN, DICER1, FH, and Their Associated Tumor Susceptibility Syndromes: Clinical Features, Genetics, and Surveillance Recommendations in Childhood

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Abstract

PTEN hamartoma tumor syndrome (PHTS), *DICER1* syndrome, and hereditary leiomyomatosis and renal cell cancer (HLRCC) syndrome are pleiotropic tumor predisposition syndromes that include benign and malignant neoplasms affecting adults and children. PHTS includes several disorders with shared and distinct clinical features. These are associated with elevated lifetime risk of breast, thyroid, endometrial, colorectal, and renal cancers as well as melanoma. Thyroid cancer represents the predominant cancer risk under age 20 years. *DICER1* syndrome includes risk for pleuropulmonary blastoma, cystic nephroma, ovarian sex cord–stromal tumors, and multinodular goiter and thyroid carcinoma as well as brain tumors including pineoblastoma and pituitary blastoma. Individuals with HLRCC may develop multiple cutaneous and uterine leiomyomas, and they have an elevated risk of renal cell carcinoma. For each of these syndromes, a summary of the key syndromic features is provided, the underlying genetic events are discussed, and specific screening is recommended. *Clin Cancer Res; 23(12); e76–e82. ©2017 AACR.*

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Introduction

PTEN hamartoma tumor syndrome (PHTS), *DICER1* syndrome, and hereditary leiomyomatosis and renal cell cancer syndrome are pleiotropic tumor predisposition syndromes that include benign and malignant neoplasms affecting children and adults. As the clinical findings and surveillance recommendations vary by syndrome, each syndrome is considered separately here.

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PHTS

PHTS (OMIM +601728) encompasses several autosomal dominant disorders with both overlapping and distinctive features (1). Syndromes definitively classified within the PHTS spectrum are Cowden syndrome (CS) and Bannayan–Riley–Ruvalcaba syndrome (BRRS). Some would also include PTEN-related Proteus-like syndromes (PS; refs. 1–3) under this rubric. Clinical features shared among the different PHTS conditions include macrocephaly (CS/BRRS), gastrointestinal polyposis (CS/BRRS), lipomas (CS/BRRS/PS), vascular malformations (BRRS/PS), and intellectual disability/autism spectrum disorder (PHTS/CS/BRRS; ref. 4). In addition, there are significant lifetime risks for malignancy in affected individuals, including breast, endometrial, and colorectal cancer, renal cell carcinoma, and melanoma, with thyroid cancer representing the predominant risk in childhood (5). An overall prevalence for PHTS has not been established, but the prevalence of CS has been estimated to be at least one in 200,000 (6).

Epithelial differentiated thyroid cancer (DTC) occurs in as many as one third of patients with PHTS (5). It can be preceded by multinodular goiter. Papillary pathology is more common than follicular, although there is an excess of follicular carcinoma relative to the general population (7). The risk starts in childhood, with the earliest reported case occurring at 7 years of age (8). As many as 5% of individuals with PHTS under 20 years of age will develop DTC (5). Other PHTS-related cancers have rarely been reported in children (5, 9). There are no conclusively established genotype–cancer phenotype correlations (10). However, individuals with missense pathogenic variants in the *PTEN* gene may have a lower risk of thyroid cancer than other mutation types (11).

PHTS genetic summary

PHTS has an autosomal dominant mode of inheritance and is characterized by heterozygous germline pathogenic variants in the *PTEN* gene located on chromosome 10 at position q23.31 (1). The PI3K/AKT/mTOR pathway, which plays a central role in cell-cycle processes including cell proliferation, is negatively regulated by the *PTEN* gene (12). In this role, the *PTEN* gene can be considered a tumor suppressor. The penetrance of pathogenic variants is near complete, and almost all individuals possessing germline *PTEN* gene pathogenic variants develop at least one feature of PHTS by young adult years (1). Specific *PTEN* gene pathogenic variants do not predict particular PHTS disorders, but some potential correlations between the site of the mutation and the PHTS phenotype have been noted (1).

PHTS cancer screening/surveillance protocols and recommendations

Current National Comprehensive Cancer Network (NCCN) guidelines recommend annual thyroid ultrasounds starting at the time of PHTS diagnosis (Evidence: Category 2A; ref. 13). We advocate for modifying this guideline. The youngest reported case of PHTS-related thyroid cancer occurred in a 7 year old (8). Given the indolent nature of papillary thyroid carcinoma, we recommend initiation of ultrasound surveillance of the thyroid at age 7. If the baseline ultrasound is negative (i.e., no nodules with sonographic features suggestive of malignancy), ultrasound may be repeated every 2 years through childhood. Suspicious ultrasound findings should prompt referral to a provider with expertise in pediatric thyroid disease. There is currently no evidence that the outcome following DTC is different in PHTS than in the general population, but there are insufficient data to be certain. In addition, there is a high rate of benign nodules among carriers, and so there is an increased risk of false positive findings (e.g., benign nodules) that may lead to unnecessarily aggressive interventions such as thyroidectomy. As such, a balanced discussion about both benefits and risks of thyroid cancer screening should occur between the medical team and the family. Thyroid ultrasound should be preferably coordinated by a pediatric subspecialist with experience in managing patients with PHTS. If a family or medical provider opts against thyroid ultrasounds, physical examination of the thyroid gland should be presented as a less sensitive alternative. Children should also have annual health supervision visits, including a comprehensive physical examination with physicians primarily responsible for their PHTS care from diagnosis. Current NCCN guidelines also address surveillance of adult cancer risks in individuals with PHTS (13).

DICER1 Syndrome

DICER1 syndrome is an autosomal dominant hereditary tumor predisposition syndrome caused by pathogenic variants in the *DICER1* gene (OMIM *606241, #601200; ref. 14). Pleuropulmonary blastoma (PPB), the most common lung tumor of infancy and early childhood (15), was the first tumor described

Table 1. Key clinical phenotypes associated with germline *DICER1* pathogenic variants

Phenotype and relative frequency	Approximate ages of susceptibility range (peak)	Malignant (M) or benign (B)	Deaths associated in DICER1-mutated cases
Most frequent phenotypes			
PPB			
Type I (cystic) PPB	0–24 m (8 m)	M	y, if progresses to type II or III
Type II (cystic/solid) PPB	12–60 m (31 m)	M	y, ∼40%
Type III (solid) PPB	18–72 m (44 m)	M	y, ∼60%
Type Ir (cystic) PPB	Any age	B or M	None observed
Multinodular goiter[a]	5–40 y (10–20 y)	B	n
Cystic nephroma	0–48 m (undetermined)	B	n (see anaplastic sarcoma of kidney below)
Sertoli–Leydig cell tumor of ovary	2–45 y (10–25 y)	M	y, <5% of cases
Moderate frequency phenotypes			
Cervix embryonal rhabdomyosarcoma	4–45 y (10–20 y)	M	None observed
Rare frequency phenotypes			
DTC	5–40 y (10–20 y)	M	None observed
Wilms tumor	3–13 y (undetermined)	M	None observed
Juvenile hamartomatous intestinal polyps	0–4 y (undetermined)	B	n
Ciliary body medulloepithelioma	3–10 y (undetermined)	B or M	None observed
Nasal chondromesenchymal hamartoma	6–18 y (undetermined)	B	n
Pituitary blastoma	0–24 m (undetermined)	Undetermined	y, ∼50%
Pineoblastoma	2–25 y (undetermined)	M	y
Very rare phenotypes			
Anaplastic sarcoma of kidney	Estimated 2–20 y	M	y
Medulloblastoma	Undetermined	M	Unknown
ERMS bladder	Estimated <5 y	M	None observed
ERMS ovary	Undetermined	M	None observed
Neuroblastoma	Estimated <5 y	M	y
Congenital phthisis bulbi	Birth	B	n
Juvenile granulosa cell tumor	Undetermined	M	None observed
Gynandroblastoma	Undetermined	M	None observed
Cervix primitive neuroectodermal tumor	Undetermined	M	None observed

NOTE: The conditions in italic may not be sufficiently associated with *DICER1* mutations to warrant testing in the absence of other personal or family history suggestive of DICER1 syndrome.

Abbreviations: ERMS, embryonal rhabdomyosarcoma; m, months; y, years (approximate ages of susceptibility range); y, yes; n, no (deaths associated in DICER1-mutated cases).

[a]Multinodular goiter occurring below age 18 years may warrant *DICER1* testing, even if occurring in the absence of other syndromic features in the patient or family.

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in association with *DICER1* pathogenic variants (16), which are now known to confer increased risks for a myriad of benign and malignant conditions summarized in Table 1. *DICER1* pathogenic variants may also be associated with macrocephaly (17). An overgrowth syndrome has been reported in some children where the pathogenic variants are mosaic and affect the RNase IIIb domain (18).

PPB presents in four main forms (19). Type I PPB is a purely cystic lesion presenting at a median age of 8 months at diagnosis. Type II is a mixed cystic and solid tumor with a median age of 35 months at diagnosis. type III PPB is a purely solid, aggressive primitive neoplasm with a median age of 41 months at diagnosis. The fourth type of PPB, type Ir, is a purely cystic tumor devoid of malignant cells and thought to represent regressed or nonprogressed type I PPB (19). Type I PPB has a 5-year overall survival (OS) of 89%, but it may progress to type II or III PPB. Types II and III PPB are treated with aggressive chemotherapy and often radiation. Despite aggressive therapy, these are associated with an OS of only 74% and 53%, respectively (19). The median age of diagnosis for type Ir PPB is 47 months, with an OS of 100% (19). The pathophysiology of PPB presents an opportunity for surveillance and early diagnosis of PPB in its earliest and most curable form (20).

Similar to PPB, other *DICER1*-related tumors, including Sertoli–Leydig cell tumor (SLCT) and Wilms tumor, are most curable when found in their earliest forms. SLCT and gynandroblastoma may present with signs of virilization, abdominal distension, and/or abdominal mass. Unlike PPB, however, the age range of risk for ovarian tumors is wide (2 to 40 years; ref. 21). In contrast with computed tomography (CT), pelvic ultrasound is not associated with radiation but may be complicated by higher rates of false positives. SLCT and gynandroblastoma may be associated with elevated alpha-fetoprotein and testosterone. If ultrasound reveals a mass, evaluation with tumor markers and additional imaging should be offered. Whole-body MRI is under consideration in some centers as a mode of surveillance of children with *DICER1* pathogenic variants who do not need anesthesia.

Multinodular goiter is common in individuals with *DICER1* pathogenic variants. In a recent study from the United States, the cumulative incidence of multinodular goiter or thyroidectomy by age 20 years was 32% in women and 13% in men (22). Risk of DTC is elevated compared with the general population and usually associated with an indolent course. No deaths from DTC have been reported in *DICER1* mutation carriers. Evaluation and consideration of treatment in childhood should consider the American Thyroid Association (ATA) pediatric risk levels (23).

DICER1 syndrome genetic summary

DICER1, located on chromosome 14q32.13, encodes an RNase III endonuclease that processes miRNA precursor hairpins into mature miRNAs, in addition to other roles. Most neoplasms in the syndrome have been shown to harbor biallelic pathogenic variants in *DICER1*, usually a germline loss-of-function pathogenic variant in one allele that can occur in any domain and a tumor-specific pathogenic somatic variant in exons encoding the RNase IIIb domain of the second allele. Rarely, an individual will have mosaicism for an RNAse IIIb pathogenic variant, and the tumor-specific "second hit" will be a loss of function pathogenic variant (24–26). These individuals may display earlier diagnosis of *DICER1*-related conditions, have a higher number of sites of disease, and warrant more intensive surveillance. Mosaic RNase IIIb domain pathogenic variants are the likely basis of GLOW syndrome (Global developmental delay, Lung cysts, Overgrowth and Wilms tumor), which is a more severe form of *DICER1* syndrome (18).

DICER1 syndrome cancer screening/surveillance protocols and recommendations

Indications for consideration of *DICER1* gene testing include a new diagnosis of most, if not all, the conditions in Table 1, or any childhood tumor in association with a personal or family history of *DICER1*-related conditions. In 2016, the International *DICER1* Symposium convened to establish recommendations for testing and surveillance guidelines for individuals with *DICER1* pathogenic variants (K.A.P. Schultz; article in preparation). Consensus recommendations from the 2016 AACR Childhood Cancer Predisposition Workshop are summarized here.

PPB may present with respiratory distress, chest pain or systemic symptoms, including fever and weight loss. Cystic lung disease may be associated with risk for pneumothorax in addition to oncologic risks. As PPB is most curable in its earliest form, we recommend screening with initial chest CT between 3 and 6 months of age, and follow-up interval to be determined on the basis of initial findings. If the initial chest CT is normal, a second chest CT is recommended between 2.5 and 3 years of age. Intermittent chest radiograph should also be considered, with frequency more often in early childhood. Consideration should be given to every-6-month chest radiographs until 8 years of age and annual chest radiograph from age 8 to 12 years.

Cystic nephroma is seen in up to 10% of families presenting with PPB, typically occurring by age 4 years. Rare progression to anaplastic sarcoma of the kidney may occur. *DICER1* syndrome also includes an elevated risk of Wilms tumor, which is not a consequence of a prior cystic nephroma. Wilms tumor may present with abdominal mass or hematuria. Surveillance abdominal ultrasound is recommended, but the age at which this should be stopped or reduced in frequency has not been established. Surveillance for Wilms tumor in patients with Beckwith–Wiedemann syndrome or hemihypertrophy is until age 8 years [see the article by Kalish and colleagues (27) in this *CCR* Pediatric Oncology Series], but the oldest age of diagnosis of Wilms tumor in a *DICER1* mutation carrier thus far reported is 13 years (28). Consideration should be given to biannual abdominal ultrasound until age 8 and annually thereafter.

Pineoblastoma may present with symptoms of pineal or pituitary mass, or ophthalmologic changes. Pituitary blastoma typically presents with Cushing syndrome, ophthalmoplegia, or diabetes insipidus. The role of surveillance brain MRI is controversial. We suggest urgent brain MRI if there are symptoms of intracranial pathology. Surveillance brain MRI may be considered, but the risk–benefit ratio is not yet known, and these tumors are rare (<1% incidence), even within this syndrome.

Gonadal tumors seen within the spectrum of *DICER1* include ovarian sex cord–stromal tumors, especially SLCT and gynandroblastoma and embryonal rhabdomyosarcoma (ERMS; Table 1). The wide age range of risk (early childhood through age ~45 years) complicates screening algorithms. As with all tumor predisposition syndromes, individuals should be counseled

regarding possible presenting symptoms. For ovarian sex cord–stromal tumors, these include abdominal mass or distention, menstrual irregularities and signs of virilization (voice changes, hirsutism, or premature acne). Cervical ERMS may present with vaginal spotting or a polypoid mass extending from the vagina. We recommend consideration of annual or semiannual pelvic ultrasound throughout early and late childhood and adulthood. Abdominal ultrasound could be performed at the same time to look for cystic nephroma or renal tumor, as discussed above (in conjunction with biannual to annual ultrasound starting at birth but extending pelvic ultrasound into adulthood to account for wider age of risk).

Thyroid nodules, multinodular goiter, and well-differentiated thyroid carcinoma may present with palpable nodules or rarely, local compressive symptoms, including dysphagia, dysphonia or stridor. Consideration should be given to thyroid ultrasound with assessment for regional adenopathy starting at age 8 years. If normal, repeating every 3 years is justified by the risk for thyroid cancer, which is generally indolent but is curative with surgery alone when found in its earliest form. If nodules are seen, routine follow-up per standard pediatric endocrinology guidelines is recommended (23, 29).

Families and health care providers should be counseled regarding risks and possible presenting symptoms of eye and nasal tumors, and gastrointestinal polyps. Ear, nose, and throat (ENT) evaluation with nasal endoscopy is suggested for persistent symptoms of nasal obstruction. Symptoms of intestinal obstruction in a young child with germline *DICER1* pathogenic variant requires prompt evaluation and possible surgical consultation because hamartomatous polyps are a likely diagnosis (Table 1).

Hereditary Leiomyomatosis and Renal Cell Cancer

Hereditary leiomyomatosis and renal cell cancer (HLRCC; OMIM #150800) is an autosomal dominant syndrome caused by pathogenic variants in the fumarate hydratase (*FH*) gene, which leads to the development of multiple cutaneous and uterine leiomyomas as well as an increased risk of developing renal cell carcinoma (RCC). Although these manifestations typically occur in adulthood, childhood presentations have also been reported. Reed and colleagues (30) described two families with inherited susceptibility for cutaneous and uterine leiomyomas and leiomyosarcomas. Subsequently, the association with papillary RCCs was also made, and the genetic locus was mapped to chromosome 1q42-44 (31). Clinical criteria for HLRCC have not been fully established, but criteria have been proposed based on 14 families with pathogenic germline *FH* variants (32). The presence of multiple histopathologically confirmed leiomyomas of the skin are thought to indicate a likely diagnosis of HLRCC, and the clinical syndrome is suspected with the presence of two or more of the following: clinically severe uterine leiomyomas requiring surgery before the age of 40, often with characteristic histological findings; type II RCC before the age of 40; or a first-degree relative with any of the above (32). Diagnostic molecular testing should be considered for individuals who do not meet full clinical criteria, as syndromic features may not have manifested, or family history may not be fully known (33). Additional tumors have been reported among individuals with *FH* pathogenic variants, although more data are needed to understand the true extent of association with HLRCC (34). Interestingly, a recent report found five individuals with germline *FH* pathogenic variants among a cohort of 598 patients with paragangliomas/pheochromocytomas (35).

The cutaneous leiomyomas associated with HLRCC are firm, flesh-colored to reddish brown papules or nodules that occur on the extremities, trunk, and less commonly, the head and neck region. They can occur as scattered lesions or in segmental clusters. These lesions are often painful, and pain may be elicited by cold, heat, or touch (36). The majority of individuals with HLRCC present with cutaneous leiomyomas, with an increase in prevalence with age (32, 34). These can occur in childhood, but they usually develop during the second decade of life (36). Management includes surgery or cryoablation for isolated lesions, or pharmacologic management of multiple symptomatic lesions (37).

Uterine leiomyomata occur among approximately 80% of female carriers of germline *FH* pathogenic variants and are clinically distinct from sporadic cases in that they present at an early age and are often multiple and aggressive, leading to myomectomy or hysterectomy, with surgical intervention occurring at a mean age of 35 years old (32). Younger women from the mid-teens to early 20s may already note gradually worsening symptoms that may include menorrhagia, abdominal pain, and abnormal bleeding (34, 36). The significant morbidity caused by the presence of these aggressive uterine leiomyomata has led to about 80% of individuals reporting a moderate to severe impact on quality of life (36).

Type II papillary RCC has been most commonly described in the setting of HLRCC, although other renal cancers, including collecting duct carcinoma as well as clear cell carcinoma, have also been described (33, 34, 38). In contrast with renal tumors seen in other cancer predisposition syndromes such as Von Hippel Lindau and Birt–Hogg–Dubé, in which the acquisition of metastatic potential is thought to occur only in the setting of larger primary tumors, the RCCs in HLRCC are generally of an exceptionally aggressive type, with a distinct histologic phenotype (38, 39). Although they can occur in both kidneys, RCCs in the setting of HLRCC are more likely to be unilateral and unifocal, and even small lesions (<3 cm) are often associated with metastatic disease (31, 40). Thus, early detection and surgical intervention is critical for improved outcomes in HLRCC (40). Although a favorable prognosis has been seen with early resection, poor clinical outcome is likely to occur in the absence of early detection, because metastatic disease is often found on presentation (33, 40).

HLRCC genetic summary

Germline pathogenic variants in *FH* lead to HLRCC (41). Missense pathogenic variants have predominantly been reported, but other mutation types including frameshift, nonsense, in/dels, and splice-site mutations as well as whole gene deletions have also been demonstrated among individuals with HLRCC (33, 38, 41, 42). *FH* normally functions to catalyze the conversion of fumarate to malate in the Krebs cycle. The abnormal accumulation of fumarate is thought to lead to the activation of hypoxia inducible factor (HIF) with downstream activation of cellular survival and proliferation genes (43). FH is thought to act as a classic tumor suppressor with somatic inactivation seen in tumors (31). Pathogenic variants in *FH* can lead to significantly low or absent FH enzyme levels in tumors (41). Thus, immunohistochemical studies have been proposed

for identification of HLRCC-associated tumors. Although loss of staining for FH is specific, positive staining for 2-succinocysteine (2SC), which accumulates in the setting of FH deficiency, has been shown to be more sensitive for detection of HLRCC-associated tumors.

HLRCC is inherited in an autosomal dominant fashion with incomplete penetrance. There has been much interest in understanding whether genotype–phenotype correlations can be identified, particularly for the identification of individuals with higher risk of developing RCC. Thus far, however, such genotype–phenotype correlations have not been convincingly demonstrated, and individuals with and without RCC in the family are thought to have comparable risks of developing renal cancers (33, 44).

Germline pathogenic variants in both copies of *FH* lead to an autosomal recessive syndrome, FH deficiency. Children with this syndrome often survive only months or a few years, and have a severe metabolic deficiency and neurologic impairment (OMIM #606812; ref. 45). Although cancers have not been reported among individuals with FH deficiency, the relatively short lifespan among these individuals may preclude such observations. Parents of individuals with FH deficiency have been noted to develop cutaneous leiomyomas (41), and known carriers of heterozygous mutations in *FH* may be offered reproductive counseling, but the population minor allele frequency is exceptionally low outside of certain founder populations.

HLRCC cancer screening/surveillance protocols and recommendations

There has been wide variability in recommendations for the timing of predictive *FH* germline testing for HLRCC and subsequent surveillance guidelines. Cancer screening guidelines generally focus on the early detection of RCC in the setting of HLRCC, given the particularly aggressive nature of this tumor and the suggestion that early detection may significantly improve morbidity and mortality.

Although diagnosis of RCC in the setting of HLRCC has been described to occur at a mean age of 41 years, several cases among children have been reported (46). Alrashdi and colleagues reported an 11 year old with an RCC, which was discovered via ultrasound surveillance, with a palpable renal mass (47), and Menko and colleagues (46) reported a case occurring in a 10-year-old child. Nevertheless, the estimated risk of developing RCC before age 20 is estimated to be only around 1% to 2% (46), whereas the lifetime risk of RCC among *FH* pathogenic variant carriers is estimated to be around 15%. Therefore, some groups have recommended testing and screening only after the individual is 18 years of age (32, 34), although others have recommended screening to start as early as 5 years old given the youngest reported case (47). In 2014, consensus guidelines from an international HLRCC symposium recommended annual renal MRI starting at age 8 to 10 years, as also recommended by the HLRCC Family Alliance and the French National Cancer Institute (46, 48, 49). Importantly, Menko and colleagues (46) acknowledge the importance of making the decision regarding predictive testing and screening on an individual basis. Most groups have recommended annual renal MRI as a surveillance imaging modality (34, 37, 46), but others have also suggested every-6-month renal ultrasound screening for younger children with or without a baseline CT scan (34, 47, 50). Others have recommended semiannual imaging with alternating annual MRI and ultrasound (32, 50). However, it is generally accepted that although ultrasound may help to clarify cystic lesions, as some RCC lesions have been shown to be isoechoic, ultrasound is unlikely to be an appropriate singular imaging modality to achieve ongoing, robust surveillance (40). Some screening plans also incorporate skin checks and gynecologic exams in adulthood for early detection of leiomyosarcomas (32, 37, 48).

Table 2. Recommended surveillance protocol for HLRCC

Screening modality	Age to begin surveillance	Frequency
MRI with renal protocol	At age 8	Annual
Skin checks by pediatrician, dermatology as needed	At time of diagnosis	Annual
Gynecologic exam, ultrasound as needed	Age 20 or at the time of first gynecologic exam, earlier if symptoms	Annual

We recommend predictive germline testing of at-risk family members from the age of 8 years. If a familial mutation has not yet been identified, diagnostic testing using both sequencing as well as deletion/duplication testing (e.g., with multiplex ligation-dependent probe amplification) should be performed in an affected individual to guide subsequent targeted testing for at-risk family members. For individuals found to be carriers of pathogenic *FH* germline variants, we recommend surveillance for RCC with annual renal MRI from the age of 8 years old (Table 2). This age precedes the youngest reported case of RCC in the setting of HLRCC and also balances the risks of needing sedation if MRI were to be pursued at an earlier age. MRI also allows for the avoidance of radiation and is recommended to be performed using a targeted renal protocol for increased lesion detection, including diffusion-weighted imaging, adding chemical shift (in and out of phase) and gadolinium-based contrast enhanced sequences for improved characterization if lesions are demonstrated (51).

We also recommend annual full skin exams by a pediatrician from the time of diagnosis, with referral to dermatology as needed to assess for the presence of leiomyomas and to be evaluated for changes suggestive of leiomyosarcoma, although this occurs rarely (38). Annual gynecologic examination is also recommended from the age of 20 years (or earlier) to assess for uterine fibroids and for any changes such as significant growth that could be suggestive of leiomyosarcoma, with the addition of imaging as necessary. Awareness of potential manifestations in adolescence may also help to reduce morbidity.

As with many emerging cancer syndromes, the phenotypic spectrum of HLRCC is likely to expand as the *FH* gene becomes incorporated on more multiplex germline panels, which will also help to clarify the potential involvement of other tumor types in HLRCC. Surveillance guidelines proposed above should be prospectively vetted in the setting of large multicenter studies, and they may change to accommodate new data as our understanding of HLRCC expands. Further data will also help to guide management of symptomatic leiomyomas to reduce the significant morbidity often experienced from young adulthood. Moreover, the weight of cancer risks in patients with HLRCC grows in adulthood, which highlights the importance of transition into adult cancer genetics care for ongoing surveillance.

Conclusions

Given the heterogeneity of cancer development in individuals with PHTS, *DICER1* syndrome, and HLRCC, additional studies are needed to more precisely understand the types and frequencies of cancer risks. These studies will also lead to the development of biomarkers and clinical algorithms to provide optimal care for these patients. As in all rare diseases, international collaboration is encouraged.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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