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Von Hippel–Lindau and Hereditary Pheochromocytoma/Paraganglioma Syndromes: Clinical Features, Genetics, and Surveillance Recommendations in Childhood

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Abstract

Von Hippel–Lindau disease (vHL) is a hereditary tumor predisposition syndrome that places affected individuals at risk for multiple tumors, which are predominantly benign and generally occur in the central nervous system or abdomen. Although the majority of tumors occur in adults, children and adolescents with the condition develop a significant proportion of vHL manifestations and are vulnerable to delayed tumor detection and their sequelae. Although multiple tumor screening paradigms are currently being utilized for patients with vHL, surveillance should be reassessed as the available relevant clinical information continues to expand. We propose a new vHL screening paradigm similar to existing approaches, with important modifications for some tumor types, placing an emphasis on risks in childhood. This includes advancement in the timing of surveillance initiation and increased frequency of screening evaluations. Another neuroendocrine-related familial condition is the rapidly expanding hereditary paraganglioma and pheochromocytoma syndrome (HPP). The tumor spectrum for patients with HPP syndrome includes paragangliomas, pheochromocytomas, renal cancer, and gastrointestinal stromal tumors. The majority of patients with HPP syndrome harbor an underlying variant in one of the *SHDx* genes (*SDHA*, *SDHB*, *SDHC*, *SDHD*, *SDHA*, and *SDHAF2*), although other genes also have been described (*MAX* and *TMEM127*). Annual screening for elevated plasma or urine markers along with complete blood count and biennial whole-body MRI accompanied by focal neck MRI is recommended for older children and adults with HPP syndrome to detect tumors early and to decrease morbidity and mortality from HPP-related tumors. *Clin Cancer Res; 23(12); e68–e75. ©2017 AACR.*

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Von Hippel–Lindau Disease

Introduction

Von Hippel–Lindau disease (vHL; OMIM #193300) is a multisystemic tumor predisposition syndrome characterized by benign and malignant tumors, including central nervous system (CNS) and retinal hemangioblastomas, clear cell renal cell carcinoma (RCC), pheochromocytoma (PHEO), pancreatic neuroendocrine tumors (pancreatic NET), endolymphatic sac tumor (ELST), and epididymal and broad ligament cystadenoma, as well as visceral (renal and pancreatic) cysts (1). Originally described in 1936 in the context of familial retinal angiomatosis by von Hippel (2) and CNS hemangioblastomas by Lindau (3), the incidence of vHL is estimated at approximately one in 36,000 (based on data preceding the advent of molecular genetic testing), and the lifetime penetrance approaches 100% by age 75 (4).

A clinical diagnosis of vHL can be established in one of two scenarios: (i) in an individual with a family history of vHL and the presence of a CNS or retinal hemangioblastoma, PHEO, or RCC; or (ii) in a simplex case (an individual with no family history) with ≥2 hemangioblastomas or ≥2 visceral tumors or one hemangioblastoma and one visceral tumor (5). Clinically, vHL is subdivided into five subtypes based on tumor spectrum and

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Table 1. Clinical phenotypes of vHL are classified into four types

	Type I	Type IB	Type IIA	Type IIB	Type IIC
Clinical manifestations	• Retinal angioma • CNS HB • RCC • Pancreatic NETs • Low risk for PHEO	• Retinal angioma • CNS HB • Pancreatic NETs • Low risk for PHEO • Low risk for RCC	• PHEO • Retinal angioma • CNS HB • Low risk for RCC	• PHEO • Retinal angioma • CNS HB • Pancreatic cysts • Pancreatic NETs • RCC	• PHEO • CNS HB • Pancreatic NETs (rare)
Most common *VHL* variants	Truncating variants, exon deletions	Gene deletions encompassing *VHL*	Missense variants (e.g., p.Y98H, p.Y112H, p.V116F)	Missense variants (e.g., p.R167Q, p.R167W)	Missense variants (e.g., p.V84L, p.L188V)

NOTE: Based on ref. 6.
Abbreviation: CNS HB, central nervous system hemangioblastoma.

mutation type (Table 1). The clinical diagnosis is confirmed upon identification of a pathogenic variant in the *VHL* gene, the gold standard for vHL diagnosis (6).

Although many of the lesions associated with vHL present in the third and fourth decades of life, the age range of initial manifestations is wide (Table 2), and children are particularly vulnerable, as pediatric patients are at risk of developing hemangioblastomas and PHEO that can remain clinically occult until symptoms become severe. Moreover, when vHL-related tumors do occur, these malignancies can cause profound and lasting consequences (6–11).

Although most vHL-related tumors are histologically benign, morbidity due to mass effect can be significant (e.g., vision loss due to retinal hemangioblastoma; ref. 12). In addition, surgical intervention for tumors may be associated with operative/postoperative complications, such as hemorrhage from a large CNS hemangioblastoma (13). Historically, substantial mortality was attributable to RCC, pancreatic NET, and CNS hemangioblastoma (11). Fortunately, these risks have been mitigated in recent years by the institution of comprehensive surveillance paradigms, leading to early recognition of tumors and their multidisciplinary management (14–16).

Molecular genetics of vHL

VHL results from pathogenic variants in the *VHL* gene (6). vHL is inherited in an autosomal dominant pattern. Approximately 80% of individuals with vHL disease have an affected parent, and about 20% result from a *de novo* pathogenic variant. Genetic testing is indicated in first-degree relatives of individuals with pathogenic variants in *VHL*, as well as any child diagnosed with any of the following:

- Retinal angioma (hemangioblastoma)
- CNS hemangioblastoma
- Clear cell RCC
- PHEO or paraganglioma
- ELST
- Epididymal or adnexal papillary cystadenoma
- Multiple pancreatic cysts or pancreatic NET
- Multiple renal cysts

The type of variant identified in the *VHL* gene has been shown to account for differences in PHEO risk, with a strong genotype–phenotype correlation (Table 1; ref. 17). Truncating variants or exon deletions in the *VHL* gene are identified among individuals with vHL type I and confer a relatively low risk of PHEO (17, 18). In contrast, vHL type II is associated with missense variants that generally do not affect the protein structure and are associated with a relatively higher risk of PHEO (17).

The risk for RCC and hemangioblastoma in affected individuals may reflect the ability of the variant protein to regulate the hypoxia-inducible factor (HIF) pathway (19, 20). Higher HIF expression appears to result in lower risk of RCC and hemangioblastoma. In addition, specific missense variants in *VHL* are also associated with hereditary polycythemia. Most of these variants lead solely to the polycythemia phenotype; however, a few variants (L188V, G104V, V130I, and Y175C) have been associated with both polycythemia and PHEO (21, 22).

Table 2. Lifetime risks of VHL-associated tumors

Tumor[a]	Risk	Youngest/mean age of diagnosis (years)
CNS hemangioblastoma	60%–80%	9/30
Cerebellar	44%–72%	9/31
Brainstem	10%–25%	12/32
Spinal	13%–50%	8/33
Retinal angioma/hemangioblastoma	25%–60%	0/25
Renal	25%–75%	12/39
Cyst	42%	12/37
RCC[b]	17%–70%	13/44
PHEO[c]	10%–25%	2/27
ELST[d]	10%–15%	6/22
Pancreatic	35%–75%	5/36
Cyst	21%	5/33
NET[e]	10%–17%	16/35
Papillary cystadenoma		
Epididymis	25%–60%	17/24
Broad ligament[f]	10%	16/unknown (16–46)

[a] References 6, 23, and 24.
[b] References 7, 11, 31, and 70.
[c] Reference 10.
[d] Reference 8.
[e] Reference 9.
[f] Reference 6.

Cancer screening/surveillance protocols

Early recognition and testing of at-risk individuals is key to the prevention of morbidity and mortality in vHL. Families with a history of vHL should be counseled regarding the importance of identifying at-risk children, performing genetic testing to identify mutation carriers, and initiating periodic surveillance. For example, children are susceptible to visual loss as result of retinal hemangiomas that, in the absence of surveillance, may go unnoticed until retinal damage becomes severe. CNS hemangioblastomas, if detected early, may be surgically excised with minimal damage to surrounding tissue.

Lifelong surveillance is, therefore, mandated given ongoing risks for tumor development and malignant growth with increasing age, and evidence that longitudinal surveillance in vHL limits morbidity and mortality (14–16). Multiple groups have developed surveillance guidelines (Table 3). Historically, these guidelines were based on expert consensus, with early screening targeted to tumor spectrum, risk levels, and typical ages of presentation (7, 23–25). Recent efforts have employed mathematical modeling methodologies, informed by the available clinical data,

Table 3. Existing paradigms for vHL tumor surveillance

Tumor	VHL Alliance 2015[a]	Binderup et al. 2013[b] (Denmark)	Hes et al. 2001[c] (the Netherlands)	Kruizinga et al. 2014[d]
Retinal HB	Annual eye exam ≥1 y	Annual eye exam ≥0 y	Annual eye exam ≥5 y	Biennial eye exam ≥7 y
PHEO	Annual PFM or UFM ≥5 y	Annual PFM ≥5 y	Annual PFM and UFM ≥10 y (serum and 24-h urine)	Every 4 y screen ≥0 y
	Annual abd U/S 8–15 y Annual abd imaging ≥16 y (alternate U/S and MRI)		Q 1 y abd U/S 10–14 y Q 1 y abd imaging ≥15 y (alternate U/S and MRI)	
ELST	Q 2–3 y audiology eval 5–15 y Q 2 y audiology eval ≥16 y	Q 1 y audiology eval ≥5 y	None specified	None specified
CNS HB	Biennial MRI b/s ≥16 y	MRI b/s once 8–14 y Biennial MRI b/s ≥15 y	Biennial MRI b/s ≥15 y	Annual MRI b/s ≥14 y
RCC	Annual abd U/S 8–15 y	Annual abd imaging ≥15 y (U/S or MRI)	Annual abd U/S 10–14 y	Annual screen ≥18 y
	Annual abd imaging ≥16 y (alternate U/S and MRI)		Annual abd imaging ≥15 y (alternate U/S and MRI)	
Pancreatic NET	Annual abd U/S 8–15 y	Annual abd imaging ≥15 y (U/S or MRI)	Annual abd U/S 10–14 y	Biennial screen ≥16 y
	Annual abd imaging ≥16 y (alternate U/S and MRI)		Annual abd imaging ≥15 y (alternate U/S and MRI)	

Abbreviations: abd, abdominal; eval, evaluation; h, hour; HB, hemangioblastoma; MRI b/s = MRI brain/spine; PFM, plasma-free metanephrines; Q, every; UFM, urinary fractionated metanephrines; U/S, ultrasound; y, year/years.

[a] Reference 23.

[b] Reference 24.

[c] Reference 7.

[d] Reference 26.

to predict the ideal ages to initiate surveillance and the most appropriate frequency for ongoing screening (26).

Our current consensus recommendations for screening of vHL-related tumors incorporate the elements of existing paradigms into a new surveillance regimen, with an emphasis on pediatric patients (Table 4). Broadly, the age-specific tumor risk, the youngest reported ages of occurrence, presumed growth rate, and the potential clinical impact of tumor progression were all considered in developing these new surveillance recommendations based on risk in children and adolescents.

Regardless of age, every individual with vHL should undergo an annual history and physical examination, including blood pressure assessment and a comprehensive neurologic evaluation, assessing for deficits including evidence of visual disturbance or hearing impairment. Ideally, these visits would be conducted by a medical provider experienced in caring for individuals with vHL, who has access to a multidisciplinary team with expertise in managing vHL-associated tumors. At these visits, education should also be provided on the signs and symptoms that could raise concern.

Beginning from birth, ophthalmology exams should be performed annually, with particular attention to the retina to monitor for retinal hemangioblastomas. This is consistent with most current screening paradigms. These exams should be conducted by an ophthalmologist experienced in pediatric retinal evaluation. In addition, starting at 2 years of age, PHEO surveillance should commence with blood pressure checks at every medical visit (using standard tables based on age and height; ref. 27), and with annual plasma or urine metanephrine levels. This screening interval is in agreement with standard practices, but the youngest age to initiate PHEO screening advocated in existing screening protocols is 5 years of age. There are multiple reports of PHEO occurring in children at younger ages, driving the impetus to advance the onset of screening (10, 26). We note that younger patients with PHEO bore missense variants (type II/III) rather than truncating or deletion variants (type I). This may inform future iterations of recommendations with respect to the age to initiate PHEO surveillance. In the course of surveillance, attention should be given to avoiding potentially interfering foods and medications that may confound interpretation of biochemical testing (Supplementary Table S1).

By 5 years of age, biennial audiology evaluations should be commenced to screen for ELST. This is in agreement with current screening paradigms. By 8 years of age, biennial MRI of the brain and spine should begin to monitor for CNS hemangioblastomas. Our recommendation to start this longitudinal surveillance at 8 years is significantly younger than dictated by other guidelines. Although the risk of CNS hemangioblastomas prior to adolescence is relatively low, multiple instances have been reported earlier in childhood (6, 23, 24). Moreover, these tumors may cause substantial morbidity with progression, particularly those lesions associated with peritumoral cysts that are more commonly found in younger individuals with vHL and that may progress more rapidly (28). As the risk of CNS hemangioblastomas rises in adolescence, and given the approximately 7% risk of hemangioblastomas developing in the interval between every-other-year MRIs, consideration may be given to increasing the screening frequency to annually starting in mid-adolescence, in contrast to the biennial surveillance recommended in established guidelines (4). The risk of rapidly growing hemangioblastomas, however, needs to be better quantified before this approach can be formally recommended. Cranial imaging should include thin cuts through the internal auditory canals, as a complement to audiology evaluations for ELST screening due to the possibility of ELST detection prior to development of audio-vestibular symptoms (29). Because spinal hemangioblastomas can occur at any segment of the spinal cord, it should be emphasized that spinal imaging should extend the entire length of the cord and not be restricted to only the cervical cord (30).

Our proposed surveillance for visceral manifestations of vHL diverges significantly from established recommendations. Primary screening for PHEO with imaging is not advocated given the high sensitivity of biochemical screening measures. Therefore, the characteristics of RCC (31) and pancreatic NET (6, 9, 23, 24)

Table 4. Proposed vHL tumor surveillance regimen with an emphasis on the pediatric age range

Tumor	Recommended surveillance	Age to begin	Interval
Retinal HB	Eye exam including retina[a]	Birth	Annual
PHEO	Blood pressure at all medical visits[b]	2 years	
	PFM[c,d,e,f] or 24-h urine fractionated metanephrines[g]	2 years	Annual
ELST	Audiogram	5 years	Biennial
CNS HB	MRI brain with and without contrast[h] MRI spine with contrast	8 years	Biennial[i]
RCC	MRI abdomen[j]	10 years	Annual
Pancreatic NET	MRI abdomen	10 years	Annual

Abbreviations: HB, hemangioblastoma; PFM, plasma-free metanephrines.

[a] During childhood, ophthalmologic examination should be performed by an ophthalmologist with experience in pediatric retinal examination.

[b] Blood pressure in children should be assessed using age- and height-specific normative ranges (https://www.nhlbi.nih.gov/files/docs/guidelines/child_tbl.pdf).

[c] Reference to pediatric reference intervals for plasma (71, 72) and urine (73) metanephrines should be considered.

[d] Ideally, to limit false positive results, PFMs should be collected from an indwelling venous catheter after patient has been lying supine for $\geq$30 minutes. Clinicians may elect to bypass this approach, but marginally elevated results should prompt repetition of testing under ideal conditions.

[e] Several foods and medications may interfere with metanephrine analysis and should be avoided prior to testing. These are summarized in Supplementary Table S1.

[f] Recommended action based on plasma metanephrines:
- Confirm interfering agents were avoided prior to testing (Supplementary Table S1).
- If $\geq 4\times$ upper limit of reference range: consistent with disease, proceed with imaging to localize lesion.
- If $2\times$–$4\times$ upper limit of reference range: repeat testing in 2 months.
- If marginally elevated: repeat testing in 6 months or consider clonidine suppression test to exclude false positivity (74, 75).

[g] Twenty-four–hour urine fractionated metanephrines are an acceptable alternative to plasma metanephrines once patients are continent of urine.

[h] Including thin cuts through internal auditory canals.

[i] Some providers may choose to advance the frequency of CNS imaging to annually starting in adolescence due to retrospective data describing relatively quick growing hemangioblastomas in between every-2-year scans.

[j] MRI surveillance for RCC and pancreatic NET may be part of the same study, provided that dedicated renal sequences are included.

should drive the timing of screening initiation and the interval of ongoing surveillance. We recommend that surveillance for visceral manifestations of vHL should be implemented at 10 years of age, with annual MRI of the abdomen to maximize the sensitivity and maintain the consistency of the screening methodology for RCC and pancreatic NET detection. To ensure optimal detection for RCC, this abdominal MRI should be performed per institutional protocol used for renal evaluation. Ultrasound may be considered to complement the MRI, whereas CT is reserved for rare circumstances where biochemical abnormalities are detected and MRI is contraindicated. The latter places high value on reduction of exposure to ionizing radiation, in accordance with the position of the VHL Alliance (23).

Although longstanding evidence supports genotype–phenotype correlations in vHL, these are generally not considered in tailoring screening recommendations, as the correlations are still being characterized. This may change as data accrued from systematic surveillance become available. It should be recognized that the tumor surveillance in vHL is time-consuming and may incur substantial financial and psychosocial burdens (32), as discussed further in the genetic counseling article in this *CCR* Pediatric Oncology Series (33). However, these burdens may be diminished by experienced multidisciplinary teams through care coordination and enhanced education.

Conclusions

We propose a tumor surveillance paradigm for individuals with vHL based on specific risks in childhood and adolescence. Although these recommendations derive from existing paradigms, in considering screening onset and intervals, we placed high priority on the earliest ages of tumor onset, potential tumor growth rates, and the clinical impact of delayed detection of these tumors in children and adolescents. We have not made specific recommendations for adults with VHL, and practitioners should rely on the existing screening regimens for adults with VHL (Table 3).

Despite our reliance on available data, these guidelines remain largely based on expert opinion. The next logical step would incorporate a prospective assessment of clinical outcomes of individuals with vHL, screened according to these proposed guidelines. In addition, future advances in early detection methodologies may be realized through identification of reliable biomarkers for the aberrant vascular proliferation occurring in vHL. Finally, no measures are currently available to prevent individuals from developing vHL manifestations. Future investigations, however, could include the identification and application of strategies to inhibit aberrant vascular growth (34). The main impediments to all of these avenues of future study are the relatively low prevalence of vHL and the prolonged duration over which associated tumors may arise. These characteristics of the condition make accrual of sufficient numbers of affected patients, and/or samples, for these studies challenging and will depend on collaborative multi-institutional efforts.

Hereditary PHEO/Paraganglioma Syndromes

Introduction

Hereditary paraganglioma and PHEO syndromes (HPP) are characterized by rare and usually benign tumors of neural crest origin that are symmetrically distributed along the paravertebral axis from the base of the skull and neck to the pelvis. In addition to paraganglioma/PHEOs, patients with HPP syndromes can develop renal cancers, gastrointestinal stromal tumors (GIST), pituitary adenomas, and other rare tumor types. The genes in which pathogenic variants are known to cause HPP syndromes collectively include the *SDHx* genes, a group of multiple nuclear genes encoding subunits of the succinate dehydrogenase (SDH) enzyme complex. This enzyme complex catalyzes the conversion of succinate to fumarate in the Krebs cycle and serves as complex II of the electron transport chain. *SDHx* genes include SDH subunits A to D and SDH assembly factor 2 (SDHAF2), which is a stabilizing protein required for the flavination of SDHA (35). Other non-*SDHx* genes associated with hereditary paraganglioma/PHEOs include the *MAX* gene encoding a member of the helix-loop-helix leucine zipper family of transcription factors that regulates cell proliferation, *TMEM127* that encodes a transmembrane protein that negatively regulates mTOR (36, 37). Recently HIF2α, EGLN1, and KIF1β have been implicated in the development of PHEO/paraganglioma (38, 39). It should also be borne in mind that PHEO/paraganglioma are components of other hereditary tumor predisposition syndromes associated with the *RET*, *VHL*, *NF1*, and *FH* genes, described elsewhere.

As with vHL, although the tumors associated with HPP syndrome are most frequently histologically benign, they can result in significant clinical morbidity related to mass effect, cranial nerve palsies, or hypertension/tachycardia resulting from catecholamine excess. If left untreated, a subset of these tumors will metastasize. A high malignant potential has been specifically recognized for *SDHB*-related tumors and is associated with tumor size at the time of diagnosis (40, 41). The increased metastatic potential and aggressive nature of *SDHx*-related paragangliomas compared with *de novo* paragangliomas without underlying germline predisposition must be taken into account when developing early tumor surveillance in patients with HPP.

Paragangliomas in the skull base, neck, and upper mediastinum are primarily associated with the parasympathetic nervous system and generally do not hypersecrete catecholamine or other hormones, although a subset can secrete dopamine. In contrast, paragangliomas in the lower mediastinum, abdomen, and pelvis are typically associated with the sympathetic nervous system and usually hypersecrete catecholamines. PHEOs are catecholamine-secreting paragangliomas confined to the adrenal medulla.

The most current studies suggest that up to 35% of PHEO/paraganglioma are hereditary (42). The diagnosis of HPP syndrome is based on molecular genetic testing, which should be offered to all patients with paraganglioma or PHEO. However, recognition of bilateral paraganglioma/PHEO and/or a strong autosomal dominant familial presentation of paraganglioma/PHEO may also lead to a clinical diagnosis of HPP. Assessment of the family history should include specific inquiry regarding relatives with sudden death, and it should detail the spectrum of tumors associated with HPP syndrome, some of which are known by different names (paragangliomas, e.g., may be called glomus tumors or extra-adrenal PHEOs). The medical history should include symptoms of catecholamine excess, such as elevation in blood pressure, headaches, diaphoresis, and palpitations, and also symptoms attributable to mass effect, such as dysphagia, hearing loss, and dysarthria. The exam should include assessment for arrhythmias and palpable masses (35).

GISTs occurring in the setting of pathogenic *SDHx* germline variants have distinct clinical features. The *SDHx*-related GISTs are almost always located in the stomach, arising from the interstitial cells of Cajal in a submucosal location. Multifocal gastric tumors are common. Because of their gastric location, by far the most common presentation for *SDHx*-related GISTs is gastric bleeding.

Molecular genetics of HPP syndromes

Pathogenic missense and truncating variants in *SDH B*, *C*, and *D* underlie the majority of patients with HPP syndromes (after excluding other syndromes such as vHL, multiple endocrine neoplasia and, less frequently, neurofibromatosis and hereditary leiomyomatosis and RCC). Variants in *SDHA* and *SDHAF2*, albeit rare, have also been reported. Although SDHx-related GISTs can be due to many of the different *SDH* genes (including *SDHC* epimutations), the *SDHA* germline mutations seem to be the most common germline mutations associated with GISTs (43). In the setting of tumor susceptibility, the *SDHx* genes act as tumor suppressors. The tumorigenesis mediated by mutated *SHDx* genes is thought to result from elevations in cellular succinate concentrations that stabilize the HIFα transcription factor by inhibiting prolyl hydroxylases, thus preventing HIFα degradation by ubiquitination (44). High levels of HIFα are strongly implicated in promoting tumor growth and metastasis through the role of HIFα in initiating angiogenesis and regulating cellular metabolism to overcome hypoxia (45). In addition, several reports suggest that *SDHx*-related tumors display a hypermethylator phenotype associated with downregulation of key genes involved in neuroendocrine differentiation (46, 47). *TMEM127* and *MAX* also function as tumor suppressors, and loss of heterozygosity has been demonstrated in PHEO/paraganglioma tumor tissue.

Susceptibility to paraganglioma/PHEO, as well as other associated tumors, is either inherited in a strict autosomal dominant fashion (*SDHA*, *SDHB*, *SDHC*, and *TMEM127*) or in an autosomal dominant fashion modified by parent of origin. *SDHD*, *SDHAF2*, and *MAX* variants present with this parent-of-origin–dependent tumorigenesis, wherein tumor formation occurs almost exclusively in the context of paternal transmission of the variant due to maternal imprinting (i.e., affected children of carrier fathers will present with disease, but affected children of carrier mothers will not).

Penetrance estimates have been defined for variants in *SDHD* and *SDHB*. For *SDHD* variants, the penetrance is about 90% for probands and relatives identified through variant testing (48). Penetrance estimates for *SDHB* variant carriers have been more variable due to ascertainment and analytic differences between studies. Early studies estimated an approximately 77% risk for paraganglioma by age 70 (49); however, more recent estimates based on testing of extended families have estimated the lifetime risk to be between 30% and 50% (50) and may be even as low as 14% by age 60 (51). Variants in *SDHA*, *SDHAF2*, and *SDHC* are rare, and specific penetrance estimates have not been calculated. A single-center review of eight probands identified with *SDHC* variants noted that none of them had a family history of paraganglioma, suggesting that the penetrance is likely incomplete (52). *SDHAF2* variants have been described in a large Dutch family. In this kindred, 11 of 16 individuals (69%) who had paternally inherited the variant were found to have paraganglioma (50, 53). Cumulative penetrance of *TMEM127*-associated PHEOs has been estimated to be 32% from a large family with 34 members (54).

Patients with *SDHB* variants have a positive family history in 33% of cases, present with single tumors at a mean age of 25 to 30 years (range, 6–77), and are strongly associated with extra-adrenal sympathetic paragangliomas, mainly in the abdomen and pelvis. About 20% may also have PHEOs, and, as discussed, paragangliomas in these patients have a substantial propensity to metastasize (25, 55–59). Paraganglioma development in *SDHB* variant carriers is generally associated with higher morbidity and mortality than pathogenic variants in the other *SDHx* genes due to the greater risk for malignancy and metastasis. In comparison with individuals with sporadic, malignant paraganglioma, those with malignant disease and a germline *SDHB* variant have shorter survival (55). Although less common than malignant extra-adrenal sympathetic paragangliomas, malignant PHEOs do occur and may be more common among individuals with a germline variant in *SDHB* compared with other PHEO-predisposing loci.

Patients with *SDHD*, *SDHC*, and *SDHAF2* variants are more frequently associated with parasympathetic skull-base and neck paragangliomas (49, 52, 53). Individuals with *SDHD* variants present at a mean age of 28 to 31 years (range, 12–70) with multiple tumors, whereas those with *SDHC* variants most commonly develop a solitary tumor (about 77%), with a mean age of

Table 5. Proposed HPP surveillance regimen

Tumor	Recommended surveillance	Age to begin	Interval
PGL/PHEO	Blood pressure at all medical visits[a]	6–8 years	Annual (at minimum)
	Plasma methoxytyramine	6–8 years	Annual
	PFM[b,c,d,e] or 24-h urine fractionated metanephrines[f]	6–8 years	Annual
	Optional: serum chromogranin A	6–8 years	Annual
	Whole-body MRI (skull base to pelvis)[g]	6–8 years	Biennial
	Optional: neck MRI ± contrast[h]	6–8 years	Biennial
GIST	Complete blood count (w/RBC indices)	6–8 years	Annual

Abbreviations: PFM, plasma-free metanephrines; RBC, red blood cell.

[a] Blood pressure in children should be assessed using age- and height-specific normative ranges (https://www.nhlbi.nih.gov/files/docs/guidelines/child_tbl.pdf; ref. 27).

[b] Reference to pediatric reference intervals for plasma (71, 72) and urine (73) metanephrines should be considered.

[c] Ideally, to limit false positive results, PFMs should be collected from an indwelling venous catheter after patient has been lying supine for ≥30 minutes. Clinicans may elect to bypass this approach, but marginally elevated results should prompt repetition of testing under ideal conditions.

[d] Several foods and medications may interfere with metanephrine analysis and should be avoided prior to testing. These are summarized in Supplementary Table S1.

[e] Recommended action based on plasma metanephrines:
- Confirm interfering agents were avoided prior to testing (Supplementary Table S1).
- If ≥4× upper limit of reference range: consistent with disease, proceed with imaging to localize lesion.
- If 2×–4× upper limit of reference range: repeat testing in 2 months.
- If marginally elevated: repeat testing in 6 months or consider clonidine suppression test to exclude false positivity (74, 75).

[f] Twenty-four–hour urine fractionated metanephrines are an acceptable alternative to plasma metanephrines once patients are continent of urine.

[g] Specific attention also paid to the kidneys due to rare risk of RCC.

[h] Depending on preferences of local radiologists, dedicated MRI of the neck may be preferred to inclusion in whole-body MRI. If this is the case, it should be performed concomitant with WBMRI.

diagnosis of 38 years of age (range, 15–40; refs. 25, 57, 58). Eighty percent of reported *SDHC*-related paragangliomas originate in the head and neck, and malignant disease has been rarely reported (2%; ref. 52). Only head and neck tumors, predominantly carotid body tumors (70%), have been reported in *SDHAF2* variant carriers, with an average age of onset of 33 years (range, 22–47). However, all descriptions of the *SDHAF2* phenotype are based on a single family (53, 60). Germline *SDHA* variants have been observed in association with both PHEOs and paragangliomas (sympathetic and parasympathetic; ref. 60).

Screening/Surveillance

Tumorigenesis is rare in the first decade of life among individuals predisposed to HPP. The youngest patient that we have identified with paraganglioma was 6 years at diagnosis (59). After reviewing the literature and clinical practice across many different institutions and countries, we recommend initiating tumor surveillance at 6 to 8 years of age. Although we acknowledge specific genetic lesions drive varying clinical presentations, we do not think that the genotype–phenotype relationships are currently well enough defined to justify distinct surveillance paradigms based on genotype. Therefore, we advocate a single regimen for all carriers of variants associated with HPP syndromes, with a need to accumulate enough data over time to make more gene-specific recommendations.

Surveillance recommendations for HPP syndromes resemble those for vHL with respect to PHEO/paraganglioma screening (Table 5). However, we recognize the existence of silent (nonsecretory) paragangliomas, particularly those occurring in the head and neck, which occur with greater frequency than in vHL and, thus, emphasize the importance of radiologic surveillance in HPP syndrome in addition to biochemical screening. This screening will also facilitate identification of RCCs, which have rarely been associated with germline *SDHx* variants. Although limited data exist, whole-body imaging was recently studied among individuals with SDH-associated paraganglioma syndromes and identified six tumors among asymptomatic carriers. Sensitivity and specificity of whole-body imaging were 87.5% and 94.7%, respectively, whereas biochemical surveillance yielded sensitivity and specificity of 37.5% and 94.5%, respectively (61). Although there is increasing interest in the use of contrast-enhanced ultrasound (CEUS; ref. 62), there are insufficient data to recommend CEUS over MRI for routine surveillance. As some paragangliomas are predominantly dopaminergic (particularly those associated with *SDHB, C, D*), plasma methoxytyramine analysis is advocated in addition to metanephrines (63–65). Finally, chromogranin A, a NET marker, has been demonstrated to enhance detection of PHEO/paragangliomas by 22%, with minimal impact on specificity, and can be included in annual surveillance (66).

There are currently no data to support routine imaging for GISTs in at-risk patients. Formal studies of the sensitivity of whole-body MRI for submucosal gastric masses have not been performed, but one would anticipate that the sensitivity will be relatively low for small GISTs. Imaging approaches more likely to detect submucosal gastric GISTs include CT with oral and intravenous contrast, with or without FDG-PET. Both of these imaging modalities carry the risk of exposure to radiation. Given the relatively low incidence of GIST in HPP, the benefits are unlikely to outweigh the risks of exposure to radiation and follow-up of false positives. On the basis of this information, we do not advocate imaging surveillance specifically for GIST detection in patients with HPP syndrome. Because essentially all GISTs in HPP patients are gastric (in some series, 95% of patients present with gastric bleeding and/or anemia, and in some cases, GISTs can present with rapid bleeding and significant anemia; refs. 67–69), based solely on a consensus of opinion, we recommend an annual complete blood count to screen for incident anemia during surveillance. The effectiveness of this approach and the frequency of incidental findings requiring further evaluation with hematology referral or endoscopy are not known. There are insufficient data to define the typical age of onset of GIST in this population, so we propose that the age of onset and the interval for surveillance is the same as for PHEO/paraganglioma (at least until such time as future evidence dictates otherwise).

Conclusions

The identification of the genetic basis of the HPP syndromes has led to significant advances in clinical care for these patients, providing prognostic insights as well as opportunities for early detection and treatment of component tumors. Further research is needed to clarify how individual genotypes can more reliably predict phenotypic behavior, and whether and how surveillance should differ based on genotype. In addition, there remains an urgent and unmet clinical need to develop improved therapies for patients with metastatic PHEO/paragangliomas.

Disclosure of Potential Conflicts of Interest

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