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Radiological Surveillance Screening in Asymptomatic Succinate Dehydrogenase Mutation Carriers

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There has been a significant increase in the availability of testing for pheochromocytoma and paraganglioma (PPGL) germline susceptibility genes. As more patients with genetic mutations are identified, cascade genetic testing of family members is also increasing. This results in identifying genetic predispositions at a much earlier age. With our current understanding of familial PPGL syndromes, lifelong surveillance is required. This review focuses on carriers of succinate dehydrogenase (*SDH*) mutations. For genetic testing to be proven worthwhile, the results must be used for patient benefit. For *SDHx* mutations, this should equate to a surveillance program that is safe and removes as much uncertainty around diagnosis as possible. Early identification of these tumors is the goal of any surveillance program, as surgical resection is the mainstay of treatment with curative intent to prevent the morbidity and mortality consequences associated with catecholamine excess, in addition to the risk of malignancy. Modality and frequency of surveillance imaging and how to engage individuals in the process of surveillance remain controversial questions. The data reviewed here and the cumulative advice supports the avoidance of using radiation-exposing imaging in this group of individuals that require lifelong screening.

Freeform/Key Words: succinate dehydrogenase, SDHB, surveillance, screening, paraganglioma, phaeochromocytoma

There has been an exponential increase in the number of pheochromocytoma and paraganglioma (PPGL) germline susceptibility genes identified in the last 16 years [1, 2]. Up to 40% of patients with a pheochromocytoma or paraganglioma (PGL) are now thought to carry an associated germline mutation [1], although inclusion criteria for genetic testing differ between regions and countries, and if a mutations is identified, subsequent cascade genetic testing is offered to relatives of mutation-positive patients. This review focuses on these carriers of succinate dehydrogenase (*SDH*) mutations. The clinical management of these asymptomatic, screen-detected relatives lags behind the genetic advances: For each gene, it takes time to establish the phenotype, the penetrance, and the malignancy risk, such that even now, 16 years after the identification of *SDHB* and *SDHD* genes, there are no clear evidence-based guidelines for the screening of asymptomatic carriers. There is, therefore, a danger that cascade genetic testing can take well, asymptomatic individuals

Abbreviations: ^{18}F-DOPA, [fluorine-18]-dihydroxyphenylalanine; ^{18}F-FDG, 2-deoxy-2-[fluorine-18]fluoro-D-glucose; CT, computed tomography; DOPA, dihydroxyphenylalanine; HNPGL, head and neck paraganglioma; MIBG, metaiodobenzylguanidine; MRI, magnetic resonance imaging; PET, positron emission tomography; PGL, paraganglioma; PPGL, pheochromocytoma and paraganglioma; SDH, succinate dehydrogenase; TAP, thoracic, abdominal, and pelvic.

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who may have a low risk of ever developing disease and create a health problem, both economic and personal.

There have been detailed studies and discussions looking at PPGL localization and subsequent management in symptomatic index patients. We will not reiterate these discussions in detail, but instead focus on the current dilemmas and controversies that arise in the management of the asymptomatic individuals detected through cascade genetic testing.

SDHB is the PPGL predisposing gene that has generated most discussion, as it accounts for 25% of familial PPGL cases and has the highest rate of malignant transformation. It also provides an ideal model for discussion as it highlights the clinical disparity between a condition that has a high malignancy rate (up to 30%) [3, 4] but a low penetrance (perhaps as low as 30%) [5]. Early identification of these tumors is the goal of screening, as surgical resection is the mainstay of treatment with curative intent to prevent the morbidity and mortality consequences associated with catecholamine excess, in addition to the risk of malignancy. There is currently no single clinical or biochemical test that reliably identifies *SDHB*-related disease and, as many PGLs are nonsecretory, biochemistry and clinical examination alone will miss operable tumors. In addition, there is no clinical or histological method of reliably identifying malignant disease, until metastatic deposits are present. Imaging is therefore currently the principal mode of surveillance.

We believe there are three important considerations relating to the management of carriers of an *SDHx* germline mutation that remain controversial: (1) modality of surveillance imaging, (2) frequency of surveillance imaging, and (3) how to engage and maintain individuals in the process of surveillance.

Much of the literature to date has focused on the follow-up of index patients after the identification and resection of a PPGL. However, as stated in recent European guidelines [6], there have been no longitudinal studies looking at the long-term follow-up of these patients. There are several suggested algorithms in the literature [6–9], many of which adopt a genotype-specific approach to localizing PPGLs or tend to focus on identification of synchronous, metachronous, and metastatic disease in patients known to have tumors and their follow-up imaging [10]. Numerous studies report on the different imaging options available to confirm diagnosis and tumor localization in patients with unequivocal biochemical evidence of disease [6, 11–13]. Fewer papers have focused on the three considerations noted previously, and there is no widely agreed consensus on the frequency or modality of surveillance in asymptomatic carriers of these underlying genetic mutations. We review the current literature with relevance to *SDHx* mutations, discussing the risks of the radiation burden from some imaging protocols and debating the advantages and disadvantages of magnetic resonance imaging (MRI)– vs computed tomography (CT)–based imaging.

1. Methods

Relevant literature was identified using search criteria for publications indexed in PubMed up to December 2016. The following search terms were used in a variety of combinations: *SDHB*, succinate dehydrogenase, asymptomatic carriers, asymptomatic relatives, surveillance, screening, PGL, and pheochromocytoma. Identified publications were then reviewed for content. Additional relevant publications were identified from the references included in the publications reviewed (Table 1).

A. How Often Should Surveillance Assessments Be Carried Out?

One of the first studies to look at surveillance in *SDHx* carriers [14] included 38 asymptomatic carriers of *SDHB* or *SDHD* mutations. On first surveillance screening, they found 4 out of 33 individuals with *SDHB* mutations had disease (two extra-adrenal PGLs and two head and neck PGLs [HNPGLs]), but they did not publish longer-term outcomes. They suggested a surveillance protocol that included annual clinical review with metanephrines and two yearly imaging scans with either CT or MRI of neck, thorax, abdomen, and pelvis as a minimum

Table 1. Summary of Current and Historical Surveillance Recommendations and Numbers of Patients Included, in Chronological Order

Reference	Year	Clinical Review and Biochemical Tests	Total No. of *SDHB* Patients	No. of *SDHB* Asymptomatic Carriers	Anatomical Imaging	Functional Imaging
Kirmani and Young	1993	Annual	NA; review article	NA	HN CT/MRI every 2 years and TAP MRI every 4 years	^{123}I-MIBG every 4 years
Neumann *et al.*	2004		53	28		
Benn *et al.*	2006	Annual	33	33	Neck and TAP CT/MRI every 2 years	Consider ^{18}F-DOPA-PET
Srirangalingam *et al.*	2008	Annual	32	11	Neck and TAP MRI annually	
Neumann *et al.*	2009	Annual	NA; review article	NA	Serial MRI of skull base to pelvis (frequency not stated)	Consider ^{123}I-MIBG and ^{18}F-DOPA-PET
European Association of Nuclear Medicine guidelines	2012		NA; guideline	NA		Choice of nuclear imaging depends on genetic diagnosis and tumor site
Gimenez-Roqueplo *et al.*	2013		124	85	First screen with HN MRI + TAP CT (frequency for follow-up surveillance imaging not stated)	First screen with somatostatin receptor scintigraphy
Taieb *et al.*	2014	Annual	NA; review article	NA	HN MRI every 3 years	Consider PET on individual case basis
Endocrine Society clinical practice guidelines	2014	Annual	NA; guideline	NA	Periodic MRI (frequency not stated)	Reserved for further characterization of detected tumors
Jasperson *et al.*	2014	Annual	33	28		
Favier *et al.*	2015	Annual	NA; review article	NA	Initial HN and TAP CT/MRI and, if negative, 2 to 3 yearly whole-body MRIs	First screen with ^{111}In-pentetreotide scintigraphy or ^{18}F-FDG-PET/CT
Tufton *et al.*	2016	Annual	92	65	Abdomen MRI annually; HN, thorax, and pelvis MRI every 2 years	
European Society clinical practice guidelines	2016	Annual	NA	NA	TAP MRI every 1 to 2 years for follow-up of resected biochemically silent tumors	
Kornaczewski *et al.*	2016		20	14	Whole-body CT every 5 years	^{18}F-FDG PET/CT every 5 years
Daniel *et al.*	2016	Annual	36	27	2 yearly neck and TAP MRIs	
Eijkelenkamp *et al.*	2017	Annual	93	72	TAP MRI every 2 years; HN MRI every 3 years	

Abbreviations: HN, head and neck; NA, not applicable.

monitoring program, with additional consideration of the use of 6-[^{18}F]fluorodopamine positron emission tomography (PET).

Neumann *et al.* [4] started to unravel the different genotype-phenotype correlations within the different *SDH* subgroups. Their observations were subsequently validated by others [14, 15], suggesting that surveillance protocols need to be subunit specific. Heesterman *et al.* [16] looked specifically at a cohort of asymptomatic carriers with *SDHx* mutations and found that on first surveillance imaging, 28 of the 47 asymptomatic *SDHD* mutation carriers had HNPGLs, but only 2 out of 17 *SDHB* mutation carriers had a PGL, supporting the difference in penetrance in the different *SDH* subunits. In a later review analyzing these previous studies, Neumann and Eng [17] suggested individuals carrying *SDHx* mutations should be followed up clinically on an annual basis and additionally undergo serial imaging with MRI of the complete autonomic nervous system (skull base to pelvis), with consideration of preoperative metaiodobenzylguanidine (MIBG) or dihydroxyphenylalanine-PET functional imaging. However, it does not specify the frequency of surveillance imaging.

A recent review of hereditary HNPGLs [9] highlights that mutations in *SDHD* are currently the leading cause of hereditary HNPGLs (>50%), followed by *SDHB* (20% to 35%) and *SDHC* (15%). They highlight that the optimal follow-up algorithm has not yet been validated in hereditary HNPGLs but recommend annual clinical and biochemical assessments of *SDHx* mutations carriers with head and neck MRI at three yearly intervals. The authors support the use of MRI for surveillance imaging to minimize the radiation exposure and advocate that indications for use of PET imaging studies should be reviewed on an individual basis.

A review by Favier *et al.* [1] concluded that *SDHx* mutation carriers, on first review, should undergo clinical examination and metanephrine levels, plus head and neck and thoracic, abdominal, and pelvic (TAP) contrast MRI or CT, with either ^{111}In-pentetreotide scintigraphy or 2-deoxy-2-[fluorine-18]fluoro-D-glucose (^{18}F-FDG)-PET/CT (for *SDHB* mutation carriers) and [fluorine-18]-dihydroxyphenylalanine (^{18}F-DOPA)-PET/CT (for *SDHD* mutation carriers). If these first multiple investigations are negative, the authors suggest an annual clinical and biochemical review with two to three yearly whole-body MRIs. They argue that all potential sites of disease need to be thoroughly investigated on first surveillance screening, but once reassuring negative results are found, exposure to radiation should be limited in the follow-up of these individuals.

The Endocrine Society clinical practice guidelines [6] state that all PPGL mutation carriers should be considered for annual clinical and biochemical surveillance for PPGL. The guidelines suggest carriers of *SDHB* mutations require special attention and should additionally receive "periodic" MRI surveillance to detect biochemically silent tumors, but it does not specify the frequency of this imaging. The guidelines state that CT and nuclear medicine imaging modalities should be reserved for further characterization of detected tumors to avoid ionizing radiation exposure.

The European Society of Endocrinology's recent clinical practice guidelines on the long-term follow-up of patients that have required previous surgery [18] state that it is unknown which is the best imaging modality and frequency to use and therefore suggests TAP imaging one to two times yearly for patients that had biochemically silent tumors, with use of MRI if avoidance of radiation exposure is desired. However, it does not provide any guidance on surveillance of asymptomatic carriers.

The European Association of Nuclear Medicine guidelines [19] discuss the use of radionuclide imaging in PPGL investigation and management. The guidelines state that nuclear imaging may be helpful to confirm diagnosis and for staging and is especially useful when planning targeted radionuclide therapy. The guidelines suggest that preoperative functional imaging is probably not necessary in patients that are >40 years, with no family history, with a small pheochromocytoma of <3 cm and with negative genetics if available. They recommend a clinical algorithm for the use of different types of nuclear imaging depending on the genetic diagnosis and site of tumor.

B. At What Age Should Surveillance Commence?

Some authors have addressed the uncertainty about the optimal age to begin screening carriers of *SDHB* mutations. Eijkelenkamp *et al.* [20] adopted the Dutch clinical guideline recommendations of annual clinical and biochemical review with MRI of the TAP regions every 2 years and MRI of the head and neck every 3 years to prospectively investigate the occurrence of PGLs in 93 *SDHB* mutation carriers (21 index patients and 72 asymptomatic carriers) over a median follow-up period of 3 years. They identified six new HNPGLs in the *SDHB* asymptomatic carriers and calculated an optimal age to start imaging for HNPGL as 27 years with three yearly surveillance scans, but they were unable to assess the optimal age to begin surveillance for sympathetic PPGLs due to the low number of patients with these tumors. Kirmani and Young [21] suggest beginning surveillance at age 10 years or at least 10 years before the earliest age of diagnosis within each family, based on the earlier analysis of Benn *et al.* [14], with MRI being the preferable choice for whole-body imaging. Kimani and Young divide their surveillance regimen suggestions by genotype with two yearly imaging scans of skull base and neck and four yearly whole-body imaging scans in *SDHD* or *SDHC* mutation carriers and two yearly TAP imaging scans in *SDHB* mutation carriers, using either MRI or CT, and additionally with four yearly ^{123}I-MIBGs to detect PGLs or metastatic disease [21].

The youngest patients we can identify with PPGL disease in the context of an *SDHB* mutation are aged 6 years with an abdominal PGL [22], 9 years with an pheochromocytoma [14] or HNPGL [23], 15 years with a thoracic PGL [14], and 5 years with *SDHD* mutations [4]. The youngest patient reported to develop metastatic disease was 9 years old [24]. In our own practice, rather than relying on the family history, we commence clinical annual review from age 5. This approach limits parental anxiety, and screening of children is tailored to each family, taking into account which type of imaging modality individual children will tolerate [25].

C. What Are the Best Modalities for Surveillance Assessment?

C-1. Cross-sectional and functional imaging

Functional imaging has been demonstrated to have a higher sensitivity for detecting metastases [1, 7, 19, 26, 27], and specifically ^{68}Ga-Dodecanetetraacetic acid-Octreotate (DOTATATE) PET/CT is superior in the localization of *SDHB*-associated metastatic PPGL [27, 28]. The recommendation for the use of functional imaging to exclude metastatic disease is reviewed in detail elsewhere [6, 7, 29]. Cross-sectional imaging has been shown to have higher sensitivity for the diagnosis of a primary PPGL tumor compared with functional imaging, although, of note, CT rather than MRI was used in some studies [26]. MRI is already the gold standard for the diagnosis of HNPGLs [16]. It has been previously recommended that CT or MRI is sufficient to detect an adrenal lesion and have similar sensitivities for detection of PPGLs [11, 21, 30]. It is argued that CT may offer better spatial resolution detecting smaller lesions, but MRI provides better soft tissue contrast and thus offers unique information for tumor characterization and delineation [7]. MRI is considered more favorable for localizing extra-adrenal PGLs in pregnant and pediatric patients and in patients whom radiation exposure should be limited [11, 30]. We would argue that asymptomatic carriers of *SDHx* mutations fall in this latter category, and therefore MRI, rather than CT, should be the imaging of choice for surveillance in this group.

Several studies have looked at prevalence of tumors in asymptomatic carriers of *SDHx* mutations using different imaging modalities. Although some studies make suggestions for long-term follow-up of these individuals, long-term data are lacking.

The multicenter PGL.EVA study [26] is a large study that compared four methods of radiological screening in 238 subjects (113 index patients and 125 asymptomatic carriers) with mutations in all *SDH* subunits (124 *SDHB,* of which 85 were carriers), with a follow-up

period of 3 years. They compared head and neck gadolinium-enhanced magnetic resonance angiography together with contrast-enhanced TAP CT to functional imaging using ^{123}I-MIBG scintigraphy and somatostatin receptor scintigraphy with ^{111}In-labeled pentetreotide scintigraphy. They demonstrated a 91.7% sensitivity of tumor detection with the combined use of cross-sectional imaging using head and neck gadolinium-enhanced magnetic resonance angiography plus TAP CT and functional imaging with somatostatin receptor scintigraphy when centrally reported and concluded that initial screening of patients should be with this combination. This conclusion, however, does not factor in the requirement for lifelong screening, often from a young age, through reproductive years and the potential cumulative lifetime radiation exposure. A retrospective subanalysis of the PGL.EVA cohort evaluated the use of a rapid contrast-enhanced angio-MRI, which has a much shorter duration of scanning of 5 to 10 minutes, in detecting HNPGL in *SDHx* mutation carriers and found no difference in performance with standardized MRI [31].

A recent study by Kornaczewski *et al.* [32] provides an excellent overview of the use of different functional imaging modalities in *SDHB* mutation carriers. Previous work has suggested superiority of [fluorine-18]-dihydroxyphenylalanine (^{18}F-FDOPA) PET to CT/MRI or any other functional imaging modalities for detection of *SDHx*- and non-*SDHx*-related primary skull base and neck PGLs [33]. In the Kornaczewski *et al.* study, they showed no inferiority in using ^{18}F-FDG PET/CT for surveillance imaging in asymptomatic carriers and argue for the use of this functional imaging with paired CT every 5 years in screening due to the risk of MRI missing a proportion of HNPGL [26, 34]. They argue that modalities that use increase glucose uptake (*e.g.*, ^{18}F-FDG PET) can identify additional dedifferentiated tumors due to hypermetabolic activity, whereas functional imaging that relies on specific attributes of PPGL processing pathways (*e.g.*, MIBG, 6-[18F]-fluorodopamine (^{18}F-FDA), and ^{18}F-DOPA techniques) are susceptible to missing lesions when there is tumor dedifferentiation [32]. Overall, ^{18}F fluorodopamine PET is thought to be the most sensitive method in the evaluation of non–head and neck primary PPGLs [34] but availability is limited [6]. Both MIBG [16] and ^{111}In-diethylene triamine pentacetic acid-pentetreotide scintigraphy (octreoscan) [6] have been shown to be inferior in localizing PPGLs in *SDHx* mutation carriers and therefore are less useful in surveillance imaging.

Although sensitivities of the different imaging modalities are important, this argument is only valid for very small lesions [35–38]. In asymptomatic carriers, very small lesions may not be clinically relevant or may result in a management change. In most clinical scenarios, lesions would need to be greater than 1 cm (where sensitivities are similar) for consideration of surgical resection, and therefore we would argue that multiple imaging modalities to identify very small lesions are unnecessary. If one accepts this premise, it allows the use of radiation-free modalities for surveillance in individuals that will require imaging screening from childhood.

Non–contrast-enhanced MRI of the chest, abdomen, and pelvis for surveillance can be acquired in 60 minutes. Although lengthy, the time penalty is offset by MRI's lack of radiation exposure. The risks of cumulative medical radiation exposure from CT and functional scintigraphy to children and young adults are higher than when averaged over the entire population [39]. Both clinicians and radiologists need to be aware of the increased risks of this cumulative radiation dose when justifying lifelong surveillance with the high-dose examinations increasingly being carried out on children [39–41]. The total lifetime risk of cancer induction is highest in the young. The cumulative lifetime cancer risk for a young female < 20 years of age having a single CT scan of the chest, abdomen, and pelvis is over 1 in 1000 additional cancers. Females remain at higher risk than males (by 27% to 44%) at all ages [40]. When considering risks of radiation-induced heritable effects, the risks are again highest for young female patients undergoing CT examinations of the abdomen and pelvis [42–44].

CT-based modalities are more sensitive for the detection of small intrapulmonary nodules than MRI, which explains the reluctance of many surveillance protocols to use MRI of the chest [45, 46]. However, in this patient cohort, the anticipated primary PGLs are mediastinal lesions, and MRI has equivalent sensitivity to CT in detecting mediastinal disease.

Theoretically, small subcentimeter intrapulmonary lesions may be missed on MRI, but in the context of asymptomatic carriers with no known current or previous primary tumor, such lesions are extremely unlikely to be metastatic deposits.

In our center, most children undergoing MRI receive oral sedation if requested, use audio-visual aids during the MRI (music and video) and have a parent in the room. This culminates in a well-tolerated procedure. In addition to the advantages of MRI, the imaging appearances of *SDHx*-associated tumors are now well characterized [35, 36, 38]. We therefore recommend MRI as the most suitable and safest modality of choice for surveillance.

C-2. MRI-only surveillance studies

As we identify more patients with genetic mutations, cascade screening of family members will also increase. This will result in identifying mutation status in individuals at a much earlier age. Lifelong surveillance is required, as current evidence suggests each decade of life presents the same risk of developing a tumor and each tumor has the same risk of malignant transformation, and therefore cumulative radiation doses must be taken into account [18].

Very few studies have solely used MRI for surveillance imaging. A previous study in Utah [47] evaluated the results of 45 rapid sequence MRIs in 37 *SDHx* carriers, of whom 28 were asymptomatic. Patients had one to three MRI scans to assess tumor pickup rate. They identified six new *SDH*-related tumors in five patients. In this small study, they identified one true PGL that was not identified on initial MRI reading and one PGL that was later deemed not a PGL. Both of these results were altered at the second MRI reading. The authors concluded a sensitivity of MRI for surveillance of 87.5% and specificity of 97.7% and highlighted the importance of double reporting of MRIs.

A recent study in the United Kingdom [48] reported on the use of rapid-sequencing MRI for the long-term monitoring of individuals with *SDHx* mutations. They analyzed a cohort of 47 patients (of whom 35 were asymptomatic carriers) with known *SDH* mutations over a 10-year follow-up period. Patients underwent two yearly surveillance MRIs, and they identified six PPGLs in the asymptomatic carriers. The authors concluded that biannual rapid-sequence noncontrast MRI is effective to monitor individuals with *SDHx* mutations.

We recently published our *SDHB* cohort data [25], which included the clinical outcomes of 65 asymptomatic carriers identified through genetic cascade screening of an index patient. Fifteen asymptomatic carriers were identified as having *SDHB*-related disease: 11 PGLs, 3 renal cell carcinomas, and 1 gastrointestinal stromal tumor (GIST). Ten of these were identified on the first surveillance scan (five abdominal, three thoracic, one HNPGL, and one gastrointestinal stromal tumor) and five on subsequent surveillance scans (one abdominal, one pelvic PGL, and three renal cell carcinomas) following a negative initial screen. Only two of these asymptomatic carriers had raised metanephrine levels. In our cohort, the youngest age at which an index patient was diagnosed was 10 years, and the youngest age at which an asymptomatic carrier has been identified with a tumor *in situ* was 16 years. Three of the asymptomatic carriers were diagnosed with malignant disease, and these tumors were all identified on the first surveillance scan; one of these patients has subsequently died of the burden of metastatic disease.

Cumulatively, these three cohorts provide data on 181 individuals with *SDHx* mutations (161 *SDHB*), including 128 asymptomatic carriers (120 *SDHB*), which supports the use of nonionizing imaging for surveillance in the form of rapid-sequence MRI as a safe and reliable modality for monitoring and identifying new disease. The importance of reviewing images in a specialist center on more than one occasion is highlighted throughout all studies to ensure no disease is missed. All the MRIs at our center are double reported by specialist radiologists to avoid missing small *SDH*-related lesions. On diagnosis of a new lesion, previous imaging is re-evaluated to ensure this lesion was not visible on the preceding imaging. As a result of increasing confidence of our surveillance program, and the data available, we have now increased the imaging intervals to 18 monthly scans for abdominal MRI (and head and neck in *SDHD* carriers) and three yearly scans for whole-body MRI.

D. When Is It Safe to Cease Surveillance?

Current guidelines recommend lifelong surveillance is required for patients with familial PGL syndromes [6, 18]. In *SDHB* mutations, current evidence suggests each decade of life presents the same risk of developing a tumor and each tumor has the same risk of malignant transformation. Given there is also a lack of data about rate of growth and time to malignant transformation, when to cease surveillance should be made on clinical grounds, factoring in other comorbidities.

E. How to Engage and Maintain Individuals in the Process of Surveillance

Clearly another important consideration is to maintain patient engagement to allow accurate surveillance, and it falls on us to minimize inconvenience and anxiety in this group of individuals. They are asymptomatic and otherwise healthy, aside from the genetic diagnosis with which they have recently been labeled. This could understandably generate anxiety, not only regarding the implications of the genetic diagnosis, where the future course of disease is not predetermined and has no predictable pattern, but also guilt about the risk of "passing on" the mutation to their offspring. To address some of these aspects of dealing with genetic conditions, we review individuals in a dedicated specialist clinic, in family groups if desired, to reduce the inconvenience of multiple appointments for different family members on different days. They have direct contact with a specialist endocrine nurse, who coordinates investigations to be performed on the same day, and subsequent clinic reviews. This minimizes the number of visits to the hospital for the individuals/families, thereby both minimizing inconvenience and ensuring there is minimal delay between investigations and discussing findings.

2. Conclusion

If genetic testing is to be proven worthwhile, then the results must be used for patient benefit. For *SDHx* mutations, this should equate to a surveillance program that is safe and removes as much uncertainty around diagnosis as possible. For *SDHB*, with its higher malignancy risk, this is especially relevant, as any screening program should have, as its aim, the prevention of metastatic disease or the detection of disease at an early and correctable stage. If one cannot provide a successful surveillance strategy to reassure these otherwise well individuals, without causing further harm, we have failed to realize any benefit of genetic identification.

As further genotype-phenotype data comes to light, it is likely that surveillance protocols can be better tailored to specific *SDH* subtype mutations. The question of frequency of surveillance remains even harder to answer than the question of modality. Where double reporting occurs and radiology expertise is high, we now believe a protocol for *SDHB* carriers of an abdominal MRI every 18 months and an MRI of the neck, thorax, and pelvis every 3 years is unlikely to miss a significant lesion. However, protocols need to take into account the difference in phenotype and penetrance of the different *SDH* subunits, with less frequent imaging protocols generally accepted for *SDHD* carriers, due to their lower risk of malignancy, although recognizing the higher penetrance. It remains, as yet, unclear how asymptomatic carriers of *SDHA* and *SDHC* mutations fit into these protocols. In our center, we currently use the protocol described previously for *SDHB* mutation carriers.

Functional imaging undoubtedly has its place in the management of PPGLs, especially in the detection of occult functioning tumors, the further characterization of identified lesions, and the assessment of the overall metastatic tumor burden. We feel these investigations should be reserved for follow-up of known tumors and detection of metastatic disease and not for surveillance in the well patient where MRI has the important advantage of being radiation free.

The data reviewed here and the cumulative advice supports the avoidance of radiation-exposing imaging in this group of individuals that require lifelong screening [6, 9, 21, 30]. When functional imaging and CT-based protocols were established, it was thought that the penetrance and likely malignancy risk was much higher than it has now proven to be. It is

possible that concerns over missing small tumors or metastatic disease and the possible subsequent consequences of this has also resulted in enthusiastic imaging protocols using functional studies, but the cost of this is high radiation exposure to these asymptomatic individuals. In our center, over years of follow-up with MRI, radiologist confidence has increased with respect to the detection of significant disease, and we are confident significant tumors will not be missed with this method of imaging. The theoretical possibility of missing very small intrapulmonary lesions is balanced by the fact that at such small volume, no surgical resection or management change would be considered. We believe, therefore, that MRI sensitivity is sufficient to avoid even the initial radiation-based surveillance suggested in some protocols.

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