Supplemental information

Recommended counseling guidelines

Susceptibility to all PGL syndromes is inherited in an autosomal dominant manner with incomplete age-dependent penetrance (Table 2). Table 3 summarizes tumor characteristics for each mutation. The lifetime risk of developing a renal tumor is higher in *SDHB* carriers (as is neuroblastoma), and mutations in all three genes can be associated with GIST (20, 24–26, 32, 33).

Surveillance guidelines for surveillance and screening of mutation positive patients exist but have yet to be validated. In general, the management of this patient population is best achieved through a combination of frequent physical exams, imaging [in pediatric patients preferably magnetic resonance imaging (MRI)] and biochemical testing (plasma or urine metanephrines and plasma methoxytyramine) (34, 35). The frequency and modality of the combination of all three varies among centers and specialists but it is recommended that such screening be initiated around age 7 (36). More importantly, it should be personalized to the particular needs of the individual and families. Our recommendations include the following:

– **Biochemical tests** In this method, plasma and/or 24-h urine concentrations of *O*-methylated metabolites of catecholamines, metanephrine, and normetanephrine are initially measured. The majority of *SDHB*-related tumors, or extra-adrenal metastatic tumors, secrete either normetanephrine or both normetanephrine and methoxytyramine (34, 35). However, some *SDHB*-related PGLs exclusively overproduce dopamine, but not other catecholamines (34). Therefore, measurement of plasma levels of *O*-methylated metabolite methoxytyramine should be considered in *SDHB*-related PGL. In addition, serum concentrations of chromogranin A should be added to the screening panel. Measuring plasma levels of methxytyramine (if available) is a very promising and effective way to differentiate between metastatic (elevated) and non-metastatic patients (34). Approximately 10% of *SDHB*-positive patients have biochemically silent tumors; thus, in this population, tyrosine hydroxylase expression in a tumor sample or the measurement of chromogranin A may be used to help to further characterize the phenotype (37).
– **Imaging studies** Several imaging modalities are used in the surveillance and screening of patients with *SDH* mutations. Each has specific indications depending on type of tumor, location, size, stage, and/or patient's clinical presentation. We discussed our approach in using imaging studies in our surveillance of mutation carriers. As stated above this information was selectively shared with patient and/or physicians according to the patient's needs.
– **Anatomical imaging** In general, the sensitivity of CT or MRI for these types of tumors is high but the specificity is low. Therefore, we recommend

functional imaging, especially with clinical or biochemical findings confirming the presence of a tumor, or in patients with large extra-adrenal tumors and *SDHB* mutations where the likelihood of metastatic spread at the initial diagnosis is high.

- **Functional imaging, i.e., ^{18}F-fluorodopamine positron emission tomography (^{18}F-FDA-PET) or ^{18}F-dihydroxyphenylalanine positron emission tomography (^{18}F-FDOPA-PET)** This imaging method is best used in patients with established biochemical diagnosis of PGL, and is especially useful in initial localization of tumor and identification of metastases (38–40).
- **^{18}F fluoro-2-deoxy-D-glucose position emission tomography (^{18}F-FDG-PET)**, or PET using other imaging compounds, can also assist in detecting metastatic disease. In patients with *SDHB* mutations, the preferred modalities are ^{18}F-FDG-PET and ^{18}F-FDA-PET; in patients where *SDHB* has been ruled out ^{18}F-FDA-PET or ^{18}F-FDOPA-PET should be used (41).

If PET imaging is not available, several options can be considered, such as those listed below.

- **^{123}I-metaiodobenzylguanidine (MIBG) scintigraphy** is best used to evaluate a patient as a potential candidate for treatment, or to further characterize masses that have been previously detected. In our experience, MIBG scintigraphy has shown suboptimal sensitivity compared witho newer compounds (above). This modality also has lower sensitivity in extra-adrenal and malignant PGLs. In addition, several medications may interfere with MIBG uptake (tricyclic antidepressants, calcium channel blockers, Labetalol) (42).
- **Octreotide scintigraphy** can be performed to measure uptake of a somatostatin analog; some MIBG-negative tumors are positive with octreotide scintigraphy.
- **Counseling for pediatric patients** Surveillance should start at approximately 5–7 years. The general guidelines for pediatric surveillance recommend that it should begin at age 10 or at least 10 years before the earliest age at diagnosis in the family; but we have seen a significant number of patients (i.e., 16) below age 10 who have presented with tumors. The majority of pediatric patients with metastatic PCC/PGL have *SDHB* mutations (43). Although those with primary tumors located in the head and neck predominantly have *SDHD* mutations. Children harboring *SDHB/C/D* mutations should begin screening at age 5–7 years with biochemical testing (43) and whole body MRI every 1–2 years if all results are negative. The use of radiation for surveillance should be minimized in children, unless MRI findings are equivocal, or biochemical tests are abnormal or inconclusive.