Metastatic Pheochromocytoma/Paraganglioma Related to Primary Tumor Development in Childhood or Adolescence: Significant Link to *SDHB* Mutations

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A B S T R A C T

Purpose

To present data on the high rate of *SDHB* mutations in patients with metastatic pheochromocytoma/paraganglioma whose initial tumor presentation began in childhood or adolescence.

Patients and Methods

From 2000 to 2010, 263 patients with pheochromocytoma/paraganglioma were evaluated through the National Institutes of Health (NIH), Bethesda, MD. Of the 263 patients, 125 patients were found to have metastatic disease; of these 125 patients, 32 patients presented with a tumor before 20 years of age. An additional 17 patients presented with a tumor before 20 years of age but demonstrated no development of metastatic disease. Genetic testing for mutations in the *VHL*, *MEN*, and *SDHB/C/D* genes was performed on patients without previously identified genetic mutations.

Results

Of the 32 patients who presented with metastatic disease and had their primary tumor in childhood or adolescence, sequence analysis of germline DNA showed *SDHB* mutations in 23 patients (71.9%), *SDHD* mutations in three patients (9.4%), *VHL* mutations in two patients (6.3%), and an absence of a known mutation in four patients (12.5%). The majority of these 32 patients (78.1%) presented with primary tumors in an extra-adrenal location.

Conclusion

The majority of patients with metastatic pheochromocytoma/paraganglioma who presented with a primary tumor in childhood/adolescence had primary extra-adrenal tumors and harbored *SDHB* mutations. Except for primary tumors located in the head and neck where *SDHD* genetic testing is advised, we recommend that patients who present with metastatic pheochromocytoma/paraganglioma with primary tumor development in childhood or adolescence undergo *SDHB* genetic testing before they undergo testing for other gene mutations, unless clinical presentation or family history suggests a different mutation.

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INTRODUCTION

Pheochromocytomas, which are chromaffin-cell tumors that arise from the adrenal medulla, and paragangliomas, which are chromaffin-cell tumors that arise in extra-adrenal locations, are catecholamine-producing tumors. In approximately one-third of patients, pheochromocytomas and paragangliomas are associated with mutations in the following nine susceptibility genes: von Hippel-Lindau (*VHL*); *RET* in multiple endocrine neoplasia type 2 (*MEN2*); neurofibromatosis type 1 (*NF1*); recently discovered

SDHAF2^{1,2} and (5) *TMEM127*³; and mutations of the A, B, C, and D subunits of the mitochondrial succinate dehydrogenase (*SDH*) complex.⁴⁻⁷

Pheochromocytoma/paraganglioma in the pediatric/adolescent patient is exceedingly rare, with studies that showed only approximately 20% of all cases were pediatric/adolescent.⁸ The pediatric/adolescent patient appears to present with symptoms similar to those of the adult patient, although with a more frequent occurrence of sustained hypertension on clinical presentation.⁸ In addition, the pediatric/adolescent population with pheochromocytoma/paraganglioma appears

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Fig 1. Flow chart of study patient population. Statistical analysis that compared percentages of pediatric/adolescent patients in the metastatic versus nonmetastatic groups (26.7% and 12.7%, respectively) showed statistical significance ($P = .006$) in the metastatic group. Similarly, statistical analysis that compared the rate of *SDHB* mutations among pediatric/adolescent patients with metastatic disease with the pediatric/adolescent patients without metastatic disease demonstrated statistical significance ($P = .002$) in the metastatic group. (*) Statistically higher compared with the nonmetastatic tumor group. *MEN2*, multiple endocrine neoplasia type 2; *NF1*, neurofibromatosis type 1; *SDHB*, succinate dehydrogenase subunit B; *SDHD*, succinate dehydrogenase subunit D; Sporadic, no mutation identified; *VHL*, von Hippel-Lindau.

to have a higher predominance of males than does the adult population.⁹ The exact rate of metastatic disease in children is unclear, with metastatic rates between 9% and 47% cited.^{10,11} The reported prevalence of genetically related pediatric/adolescent pheochromocytoma/paraganglioma is poorly defined, with some studies citing the incidence of familial disease at 22%, and other studies citing the rate in the age group of 10 years and younger as high as 70%.^{8,12} Furthermore, the rate of metastatic disease as related to the type of genetic mutation remains unknown.

Although numerous studies have described pediatric and adolescent patients with a diagnosis of pheochromocytoma/paraganglioma, information on clinical and genetic characteristics of metastatic disease in the pediatric/adolescent population is lacking. We present what is to the best of our knowledge new data in this article that disclosed a high rate of *SDHB* mutations among patients who developed metastatic disease and who mainly presented with their primary extra-adrenal tumor in childhood or adolescence.

PATIENTS AND METHODS

Patients

This study included 32 patients (25 men and seven women) with histologically documented pheochromocytoma/paraganglioma who presented with their primary tumor before 20 years of age, which was defined as a pediatric or adolescent tumor, and had, or later developed, metastatic disease (defined as pheochromocytomas/paragangliomas in nonchromaffin-containing tissue: ie, lungs, bones, lymph nodes, and liver¹³). An additional 17 pediatric/adolescent patients did not develop metastatic disease. The patients included came from a larger group of 263 patients with pheochromocytoma/paraganglioma who were recorded on the NIH registry (ie, a referral center for patients with pheochromocytoma/paraganglioma) between November 2000 and July 2010 (Fig 1). This study was approved by the institutional review board of the Eunice Kennedy Shriver National Institute of Child Health and Human Development, NIH, and all patients gave written informed consent before testing.

Genetic Analysis

Of the 49 patients (both with and without metastatic disease) included in the current study, 39 patients were found to have a genetic mutation that was

previously recognized as pathogenic in the development of pheochromocytoma/paraganglioma. Of those 39 patients, 19 patients underwent genotyping before evaluation at the NIH, and 18 patients underwent genotyping through evaluation at the NIH; two patients were diagnosed with *NF1* on the basis of the clinical presentation. Genetic testing through the NIH involved an assessment for mutations or large deletions in *RET*, *VHL*, *SDHB*, *SDHC*, and *SDHD*. An investigation was not performed for more recently discovered *SDHA*, *SDHAF2*, and *TMEM127*. Genotyping was performed in collaboration with the Mayo Clinic, Rochester, MN, and the Department of Genetics, the European Georges Pompidou Hospital, Paris, France.

A mutation in the aforementioned genes was not found in 10 patients. None of these patients had any family or personal history of a syndromic presentation that would suggest the presence of *MEN2*, *VHL*, *NF1*, or a syndrome associated with *SDH* mutations (*SDHx*).

Biochemical Testing

On evaluation at the NIH, patients underwent a biochemical assessment for plasma catecholamines, metanephrines, and chromogranin A (Table 1). Methoxytyramine testing was not performed because of the unavailability of the test until 2007. Blood samples were collected by use of a forearm venous line, with patients supine for 20 minutes after catheter insertion before sampling as previously described.

Statistical Analysis

The following five end points were evaluated: age at initial symptoms, age of initial diagnosis, age at metastatic diagnosis, interval between initial diagnosis and occurrence of metastases (or last follow-up if no metastatic disease), and interval between initial diagnosis and death (or last follow-up if still surviving). For comparisons of ages or intervals in patients who developed metastatic disease, between those with a germline *SDHB* mutation and those with either an *SDHD* mutation or no evidence of a known mutation (sporadic), a standard two-sample *t* test was used. Although these values were survival-type data, none of the patients in these comparisons had censored values and, hence, the *t* test could be applied. For confirmation, both the nonparametric Wilcoxon rank sum test and the log-rank test for survival data were computed and gave similar results (results not shown). Means and standard deviations are listed in Table 1.

Fisher's exact test was used to compare the proportion of pediatric/adolescent patients between metastatic versus nonmetastatic groups (Fig 1).

For plotting metastases-free survival (ie, the time from initial diagnosis to development of metastases or last follow-up) of all patients included (both patients who developed and did not develop metastases), Kaplan-Meier plots

Table 1. Clinical Characteristics of 32 Pediatric/Adolescent Patients Who Developed Metastatic Disease

Characteristic	SDHB	SDHD	VHL	No Mutation Identified	Total
No. of patients	23	3	2	4	32
AOI, years					
Mean	10.8*	16.3	7.00	14.5	11.6
SD	4.43	4.62	2.83	3.70	4.68
Range	3-18	11-19	5-9	10-18	3-19
AOD, years					
Mean	12.3*	16.7	7.00	15.5	12.8
SD	3.81	4.04	2.83	3.32	4.17
Range	7-18	12-19	5-9	11-18	5-19
AOM, years					
Mean	19.9*	31.0	18.5	28.5	21.9
SD	7.89	17.5	6.36	7.00	9.35
Range	9-40	13-48	14-23	18-32	9-48
MI, years					
Mean	7.57	14.3	11.5	13.0	9.13
SD	7.62	14.0	9.19	9.13	8.45
Range	0-25	1-29	5-18	0-21	0-29
Primary tumor, No. of patients†					
Retroperitoneal	19	0	0	3	22
Adrenal	4	0	2	1	7
Head and neck	0	3	0	0	3
Biochemistry, No. of patients‡					
NE	17	2	2	3	24
EPI	2	0	0	0	2
DA	5	2	0	0	7
No. of patients with data unavailable	3				3
NMN	19	2	0	3	24
No. of patients with data unavailable			1		1
MN	3	0	0	1	4
No. of patients with data unavailable			1		1
CgA	14	2		2	18
No. of patients with data unavailable	3		2	1	6

NOTE: Statistical analysis revealed statistically lower ages at initial symptoms, initial diagnosis, and initial diagnosis of metastatic disease among SDHB-mutation patients with metastatic disease compared with the combination of SDHD-mutation patients with metastatic disease and patients with metastatic disease but with no identifiable mutation ($P = .024$, $P = .031$, and $.016$, respectively).

Abbreviations: AOD, age at initial tumor diagnosis; AOI, age at report of initial tumor-related symptoms; AOM, age at initial diagnosis of metastatic disease; CgA, chromogranin A; DA, dopamine; EPI, epinephrine; MI, metastatic interval (years between initial tumor diagnosis and diagnosis of metastatic disease); MN, metanephrine; NE, norepinephrine; NMN, normetanephrine; SDHB, succinate dehydrogenase subunit B; SDHD, succinate dehydrogenase subunit D; VHL, von Hippel-Lindau.

*Statistically lower age compared with SDHD-mutation patients and patients with no identifiable mutation.

†Data are presented as the number of patients who presented with a primary tumor in the given location.

‡Data are presented as the number of patients who presented with increase of the given catecholamine or MN/NMN at diagnosis of metastatic disease. Interfering peaks or unavailability of a test was the reason for missing CgA results in six metastatic patients, missing DA results in three metastatic patients, and missing plasma MN/NMN results in one metastatic patient. Biochemical testing in three metastatic patients was performed outside the National Institutes of Health under recommended testing guidelines.

for censored survival data were calculated along with their associated confidence bands; small vertical tic marks on the Kaplan-Meier curves showed the follow-up times for patients who did not develop metastases. All P values were two sided.

RESULTS

Patient Characteristics

Of the 263 patients with pheochromocytoma/paraganglioma evaluated through the NIH pheochromocytoma/paraganglioma registry, 49 patients were diagnosed with pheochromocytoma/paraganglioma before 20 years of age, and 32 of these patients were known to have developed metastatic disease (Fig 1). The percentage of pediatric and adolescent patients among those with a history of metastases (32 of 120 patients; 26.7%) was found to be significantly higher ($P = .006$) than the percentage of such patients with no history of metastases (17 of 134 patients; 12.7%). Nine of the 263 patients who presented with symptoms of pheochromocytoma/paraganglioma before 20 years of age were not officially diagnosed until adulthood. Although we believe these patients had pheochromocytoma/paraganglioma in childhood/adolescence, they were not analyzed in this study.

The average age of initial symptom onset for these 32 pediatric/adolescent patients who developed metastatic disease was 11.6 ± 4.7 years (range, 3 to 19 years). The average age at the time of initial diagnosis was 12.8 ± 4.2 years (range, 5 to 19 years), whereas the average age at the time metastases were confirmed was 21.9 ± 9.4 years (range: 9 to 48 years). The interval between diagnosis of a primary tumor and of metastatic disease was 9.1 ± 8.5 years (range, 0 to 29 years).

The average age of initial symptom onset for the 17 pediatric/adolescent patients who did not develop metastatic disease was 11.1 ± 4.8 years (range, 3 to 18 years). The average age at the time of initial diagnosis was 12.5 ± 5.1 years (range, 4 to 19 years).

Genetics

Of the 32 patients with metastatic disease studied, 23 patients (71.9%) were found to have germline SDHB mutations; three patients (9.38%) had SDHD mutations; VHL mutations were found in two patients (6.25%); in four patients (12.5%), a mutation could not be found, although in some patients, not all testing was performed (Table 1).

Of the 17 patients without a history of metastatic disease, four patients (23.5%) harbored SDHB mutations, one patient (5.9%) harbored an SDHD mutation, four patients (23.5%) harbored a VHL mutation, and two patients (11.8%) harbored an NF1 mutation. A mutation was not identified in six (35.3%) patients. At the most recent follow-up, none of these patients showed signs of metastatic disease.

Statistical analysis that compared the rate of SDHB mutations in this pediatric/adolescent population showed a significantly higher ($P = .002$) rate of SDHB mutations in the group with a history of metastatic disease (23 of 32 patients; 71.9%) compared with patients without such a history (four of 17 patients; 23.5%).

Biochemistry

Patients with metastatic disease were tested for plasma catecholamines, metanephrines, and chromogranin A at evaluation of metastatic disease (Table 1). In a high percentage of patients, these data showed increased plasma norepinephrine (75%), normetanephrine (75%), and chromogranin A (69.2%) levels. The percentage of

patients with *SDHB* mutations whose tumors secreted norepinephrine (73.9%), normetanephrine (82.6%), and chromogranin A (70.0%) was comparable with the percentage of patients without an *SDHB* mutation (77.8%, 62.5%, and 66.7%, respectively).

Tumor Location

Of the 32 patients with metastatic disease studied, 22 patients presented with a primary tumor in the retroperitoneum, seven patients presented with primary adrenal tumors, and three patients presented with primary tumors in the head and/or neck (Table 1). The majority of patients with *SDHB* mutations (19 of 23 patients; 82.6%) presented with primary tumors in the retroperitoneum. All three patients with *SDHD* mutations presented with primary tumors in the head and/or neck. The location of the primary tumor in patients without an identifiable mutation was the retroperitoneum in three patients and the adrenal gland in one patient; the two patients with *VHL* mutations presented with primary tumors in the adrenal gland. Three patients with *SDHB* mutations were found to have cystic nodules in the thyroid gland, and one patient with an *SDHD* mutation was reported to have had esophageal leiomyosarcoma.

Metastases were found in the bones (in 87.5% of patients), liver (in 21.9% of patients), lungs (of 25% of patients), and lymph nodes (in 46.9% of patients), and some patients had more than one site of metastases. The majority of patients presented with metastatic lesions to bones, and all patients with metastatic disease whose tumors harbored either *SDHB* or *SDHD* mutations presented with at least one metastatic lesion to the bones. A total of 96.9% of patients had metastatic lesions in either bones or lymph nodes, and only one of the 32 patients presented with no metastatic lesions in these locations.

Outcomes

A comparison of patients with an *SDHB* mutation (23 patients) with the combined group of patients with metastatic disease with the *SDHD* mutation (three patients) and patients without an identified mutation (four patients), we found that ages of initial symptom onset, initial diagnosis of disease, and initial diagnosis of metastatic disease for patients with *SDHB* mutations were significantly lower ($P = .024$, $P = .031$, and $P = .016$, respectively). The interval between initial diagnosis and detection of metastases was not significantly different between groups, although patients with metastatic disease with an *SDHB* mutation tended to have a shorter interval ($P = .10$; Table 1).

All five deceased patients harbored *SDHB* mutations and had metastatic disease. These patients survived an average of 6.4 ± 7.6 years after the initial diagnosis of metastatic disease (2, 3, 3, 4, and 20 years) and an average of 18.0 ± 9.62 years after the initial diagnosis of disease. The remaining 27 patients with metastatic disease have been followed an average of 6.7 ± 7.0 years after the initial diagnosis of metastatic disease and an average of 15.4 ± 12.1 years after the initial diagnosis of disease. The 17 patients without metastatic disease have survived an average of 4.82 ± 8.17 years after the initial diagnosis of disease.

Among all 49 patients, the Kaplan-Meier estimate of the 5-year survival rate was 97.6% (95% CI, 84.3% to 99.7%), of the 10-year survival rate was 97.6% (no deaths occurred between 5 and 10 years), and of the 20-year survival rate was 83.7% (95% CI: 54.5% to 94.9%). Among the group of patients with *SDHB* mutations, the 5-, 10-, and 20-year survival rates were 95.8%, 95.8%, and 71.9%, respectively. Among the 22 patients with non-*SDHB* mutations, survival estimates were all 100%.

Fig 2. Kaplan-Meier survival curve and 95% confidence band: Metastases-free survival for all patients (N = 49). The two main characteristics of this estimated survival curve were (1) an early set of failures within 2 years (the 2-year estimate was 79.2%, which indicated that approximately 20% of patients would develop metastatic disease within 2 years of diagnosis) and (2) a slow but steady decrease in the curve from 2 to 30 years, with a 30-year estimate of 4.5%. Small tic marks indicate follow-up times for patients who did not develop metastases.

The time to the development of metastatic disease after initial diagnosis (ie, metastases-free survival) is shown in Figure 2 along with its 95% confidence band. A comparison of metastases-free survival between *SDHB* patients and non-*SDHB* patients is shown in Figure 3.

DISCUSSION

In this study, we found that patients with metastatic pheochromocytoma/paraganglioma who presented with tumors in childhood or adolescence were at high risk for harboring an *SDHB* mutation. In addition, these patients far more frequently presented with sympathetic paraganglioma than with pheochromocytoma. Specifically, of 32 pediatric/adolescent patients, 23 patients (71.9%) were found to have *SDHB* mutations, and all three patients (9.4%) with metastatic head and neck paragangliomas harbored *SDHD* mutations.

Fig 3. Comparison of metastases-free survival between succinate dehydrogenase subunit B (*SDHB*) patients (n = 27) and non-*SDHB* patients (n = 22). Although both groups showed an early set of failures (within 2 years) followed by a steady stream of patients who developed metastases over the next two to three decades, *SDHB* patients fared substantially worse ($P = .005$). Small tic marks indicate follow-up times for patients who did not develop metastases.

Pheochromocytomas and paragangliomas in childhood and adolescence are rare, and although recent reviews¹⁴ have described this disease in the pediatric/adolescent population, much knowledge is lacking. As reported in the literature, in the majority (56%) of pheochromocytomas/paragangliomas in patients under the age of 18 years, a germline mutation (reported only in the *VHL*, *SDHD*, and *SDHB*) could be identified, which was a much higher percentage than in the adult population.¹² The available data for pediatric/adolescent pheochromocytomas/paragangliomas also suggested that the rate of malignancy was as high as 12%, but the reported cohort had few patients with only paragangliomas and had no mutation analysis.⁸ In our adult patient cohort, metastatic disease was previously seen in 24% to 48% of *SDHB*-related pheochromocytoma/paraganglioma cases.^{16,17} In this study, of 27 pediatric/adolescent patients with *SDHB* mutations, 23 patients (85.2%) developed metastatic disease. As noted, of 32 pediatric/adolescent patients who developed metastatic disease, 23 patients (71.9%) were found to harbor an *SDHB* mutation. Furthermore, all five deceased patients had *SDHB* mutations, and all of these patients had at least a 10-fold increase in one of the measured plasma catecholamines or metanephrines. Thus, our data demonstrated a rate of development of metastatic disease that was much higher than previously thought, with *SDHB* mutations as the most significant risk factor for the development of metastatic disease in this population.

With an additional analysis of patients with metastatic disease (32 patients) presented in this study, we found that the age of symptom onset, age of initial diagnosis, and age of initial diagnosis of metastatic disease were significantly lower in metastatic patients with *SDHB*-related tumors compared with patients with *SDHD*-related tumors or with pheochromocytomas/paragangliomas in which a germline mutation could not be identified. Not only is the presence of an *SDHB* mutation in pediatric/adolescent patients with pheochromocytoma/paraganglioma a risk factor for the development of metastatic disease, but it may also indicate a risk for the development of disease at an extra-adrenal location and at an early age compared with other patients. However, the age of onset did not differ much between patients with *SDHB* mutations who developed metastatic disease and patients who did not develop metastatic disease, which indicated that the early age of onset alone may not increase the risk of metastatic development.

Previously published data demonstrated a difference in the expression of hypoxia inhibitory factor expression and activation of the Warburg effect among different genetic phenotypes.^{18,19} Specifically, data suggested a higher degree of (pseudo)hypoxia and hypoxia inhibitory factor 2 α expression in patients with *SDHB* mutations compared with other pheochromocytomas and paragangliomas. The higher degree of (pseudo)hypoxia may have been associated with a greater activation of angiogenesis and tumor-cell growth.¹⁸ These results may explain the lack of pediatric/adolescent *RET* and *NF1* patients who developed metastatic disease in the recent cohort and, in turn, the low percentage of patients with germline mutations in either *VHL* or *MEN2* compared with *SDHx* patients. It is not known whether a younger age at initial diagnosis and subsequent development of metastatic disease are additional consequences of abnormal immune function, differences in microenvironment, resistance to apoptosis, or the degree of mitochondrial dysfunction in children/adolescents compared with adults. Nevertheless, some data are available that compared pediatric and adult experimental animals. For example, different tumor characteristics in gliomas between pediatric and adult

rats, especially in regard to tumor invasiveness and growth patterns, have been demonstrated.²⁰ Therefore, the possibility of tumor differences between our adult and pediatric/adolescent populations was plausible. Additional studies may clarify these apparent differences.

Among our cohort, we found that the majority of patients with metastatic disease presented with a noradrenergic phenotype. *SDHB*-related metastatic pheochromocytomas/paragangliomas, in particular, were likely (in 91.3% of patients with metastatic disease) to present with increases in norepinephrine or normetanephrine, consistent with previous reports.¹⁶ This study also demonstrated increases of norepinephrine and dopamine in 21.7% of *SDHB* and 33.3% of *SDHD* patients with metastatic disease as reported previously.^{17,21-23} As a result of the unavailability of the test for most patients, methoxytyramine analysis was not performed, but the presence of increased dopamine emphasized the need for testing plasma methoxytyramine in patients with germline *SDHx* mutations.^{21,24} Although silent (catecholamines and metanephrines within normal limits) or solely dopaminergic biochemical phenotypes are gaining importance for *SDHx*-related pheochromocytoma/paraganglioma, in this study, we found that almost all patients who developed metastatic disease presented with increased catecholamine/metanephrine levels.

The majority of patients (23 of 27 patients; 85.2%), both with and without metastatic disease, with germline *SDHB* mutations presented with primary tumors in the retroperitoneum, which was consistent with previous reports^{17,25}; all patients with germline *SDHD* mutations had primary tumors in the head and neck. The present data further supported previous studies that *SDHB* mutations were often associated with extra-adrenal tumor location, and these two risk factors were highly associated with metastatic disease in children.

Despite the fact that the NIH Pheochromocytoma/Paraganglioma Research Program represents a tertiary center-level program, it was not designed as, and does not function as, a hereditary disease-oriented program but, rather, as an all-inclusive clinical program for advanced diagnostic assessment and clinical management of these patients. Although the likelihood of referral bias toward more complicated familial cases was recognized, it is noteworthy that in our pediatric/adolescent cohort, 48.6% of patients (18 of 37 patients) were unaware of their genetic status at the time of the NIH evaluation. Of the 31 patients who presented with *SDHx*-related pediatric/adolescent disease, 17 patients (54.8%) had no knowledge of a genetic mutation on initial evaluation at the NIH.

Recent discoveries and advances in studies of pathophysiology, genetics, and biochemistry of pheochromocytoma/paraganglioma have dramatically changed approaches to this disease, with an emphasis on tailoring clinical care to specific genetic backgrounds. For example, the recently described imaging flip-flop phenomenon has revolutionized the localization of metastatic pheochromocytoma/paraganglioma lesions in patients with germline *SDHB* mutations²⁶; and prophylactic thyroidectomy is now recommended for pediatric/adolescent patients with certain mutations to the *RET* proto-oncogene.^{27,28} Despite these recent discoveries, we are unable to reliably predict the outcome in any given patient. In this study, we began the process of understanding the natural history and can say that a child/adolescent who harbors a germline mutation in an *SDHx* subunit who develops a primary pheochromocytoma/paraganglioma in an extra-adrenal location has a high likelihood of developing metastatic disease. Because development of metastatic disease can occur during the transition from childhood to adulthood and pediatric to

adult care, there is a need for diligent follow-up and counseling by pediatric care providers and a proper transition into adult care. Although we agree with the clinical standard to genetically test all patients with pheochromocytoma/paraganglioma, we recommend that all patients who present with metastatic pheochromocytoma/paraganglioma and a history of the development of a primary extra-adrenal or head and neck tumor in childhood/adolescence be initially tested for mutations in the *SDHB* or *SDHD* genes, respectively. Finally, these patients may also be considered for screening for GIST stromal tumors (GISTs, Carney-Stratakis syndrome).²⁹

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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