*Original Research*

AMERICAN ACADEMY OF OTOLARYNGOLOGY–HEAD AND NECK SURGERY FOUNDATION

OTO Open
2021, Vol. 5(1) 1–7

DOI: 10.1177/2473974X21995453
http://oto-open.org
SAGE

# Head and Neck Paragangliomas: Patterns of Otolaryngology Referrals for Genetic Testing Over 2 Decades

**Joshua D. Smith, MD[1], Emily L. Bellile, MS[2], Tobias Else, MD[3], and Gregory Basura, MD, PhD[1]**

## Abstract

*Objective.* A large proportion of head and neck paragangliomas (HNPGLs) arise in patients with a genetic predisposition due to pathogenic variants in succinate dehydrogenase (*SDHx*) genes. Contemporary practice guidelines recommend consideration of referral for genetic testing for all patients with HNPGLs. We sought to assess adherence to these recommendations, factors associated with referral, and temporal trends in referral patterns by otolaryngologists over the past 2 decades.

*Study Design.* Retrospective cohort study.

*Setting.* Single tertiary care center.

*Methods.* All patients with newly diagnosed HNPGLs treated at a single academic center between 2000 and 2019 were included. Bivariable association of specific features of referral for genetic testing by treating surgeons were tested with $\chi^2$ and Wilcoxon rank-sum tests. Logistic regression was used to assess temporal trends in referral patterns overall and for specific clinical subgroups over time.

*Results.* Of 221 patients included, only 77 (34.8%) were referred for genetic testing. Factors associated with referral included young age, family history of paraganglioma, more recent year of diagnosis (ie, closer to study end date), tumor subsite (all $P < .0001$), and treatment by an otolaryngologist (vs vascular surgeon or neurosurgeon, $P = .009$). Overall, referral rates increased over time ($P = .0002$), but even in the most recent 5 years, only 51% of newly diagnosed patients were referred.

*Conclusion.* Our analysis suggests that referral rates for genetic testing in patients with HNPGLs are growing yet are still largely based on young age, family history, and tumor subsite.

## Keywords

paraganglioma, head and neck, succinate dehydrogenase, genetic testing

Received August 31, 2020; accepted January 27, 2021.

As many as half of all head and neck paragangliomas (HNPGLs) are caused by pathogenic variants in a known susceptibility gene.[1] The past 2 decades have seen tremendous advancement in our understanding of the genetic basis for inherited predisposition to HNPGLs, particularly with the discovery of pathogenic variants in the succinate dehydrogenase complex of mitochondrial membrane proteins (*SDHA*, *SDHB*, *SDHC*, *SDHD*, and *SDHAF2*) in the early 2000s.[2-4]

Confirmation of a hereditary basis for HNPGL development has critical implications for the managing health care provider. For instance, particular pathogenic *SDHx* variants correlate with risk of malignancy (*SDHB*),[5] tumor multifocality (*SDHD*),[6] and coincident pheochromocytoma and paraganglioma as well as other tumors.[7] In addition, treatment planning, surveillance patterns, and screening of at-risk family members are all guided by genetic testing.[8] Consequently, contemporary clinical practice guidelines (CPGs) recommend thoughtful consideration of referral for genetic counseling and testing in all patients with HNPGL diagnoses.[9-11]

Despite these recommendations, evidence suggests that a minority of patients presenting with HNPGLs are referred for genetic testing as part of their diagnostic evaluation and treatment plan.[12] The reasons for this are unclear but may include failure to recognize the prevalence and implications of *SDHx* pathogenic variants in patients with HNPGLs, a paradigm shift toward conservative (ie, nonsurgical) approaches to treatment, and/or inadequate institutional referral structures

[1]Department of Otolaryngology–Head & Neck Surgery, University of Michigan Medical School, Ann Arbor, Michigan, USA
[2]Center for Cancer Biostatistics, Department of Biostatistics, University of Michigan School of Public Health, Ann Arbor, Michigan, USA
[3]Department of Internal Medicine, Division of Metabolism, Endocrine, and Diabetes, University of Michigan Medical School, Ann Arbor, Michigan, USA

**Corresponding Author:**
Gregory Basura, MD, PhD, Department of Otolaryngology–Head and Neck Surgery, University of Michigan, 1500 E. Medical Center Dr, SPC 5312, Ann Arbor, MI 48109-5312, USA.
Email: gbasura@umich.edu

or resources.[13] Herein, we sought to explore factors associated with otolaryngology referrals for genetic testing in patients with HNPGLs and to report temporal trends in referral patterns over a 2-decade period.

## Methods

This study was approved by the University of Michigan Institutional Review Board (HUM 00120115). We conducted a retrospective medical record review of our previously published patient cohort[14] to identify all patients who presented with an index HNPGL between 2000 and 2019 and were treated at our institution. Eligible patients were identified using the Electronic Medical Record Search Engine (EMERSE), as described.[15] Only those patients with a known personal history of *SDHx* variant testing prior to presentation or who were known obligate carriers were excluded from our analysis. From individual patient records, a single author (J.D.S.) manually extracted and collated comprehensive data on patient demographics, tumor characteristics, treatment, and status and outcomes of referral for genetic testing.

Our primary outcome of interest was receipt of referral from the treating provider to our cancer genetics division for consideration of genetic testing as a component of the patient's diagnostic and treatment plan. Secondarily, we also collected and reported data on the percentage of referred patients with HNPGLs who were ultimately seen by our cancer geneticists and underwent genetic testing. Demographic and clinical variables were summarized with descriptive statistics (median, range, percentage) for the entire patient cohort and by referral (yes/no) for genetic testing. Bivariable associations with referral were tested by $\chi^2$ (categorical) or Wilcoxon rank-sum (continuous) test.

Logistic regression models were then used to (1) test referral pattern and initial treatment changes over time, (2) test associations of clinical variables with referral patterns over time, and (3) test whether the treatment pattern was associated with referral rates. For associations with clinical variables, separate logistic regression models were performed for each covariable (sex, age, family history, tumor type, etc) that contained the variable, time period, and their interaction (ie, variable x–time period) to test whether there were significant differences among subgroups in the time trends. Year of diagnosis (2000-2019) was categorized into 4 consecutive 5-year time periods and time period treated as a categorical variable in regression models. All statistical analyses were performed in SAS 9.4 (SAS Institute).

## Results

### Factors Associated With Referral for Genetic Testing

From 2000 to 2019, we identified 221 patients with HNPGLs treated at our institution (**Table 1**). In total, 201 (91%) of these patients presented with isolated paraganglioma of the following head and neck subsites: carotid body (n = 93, 42%), jugular fossa (n = 51, 23%), cranial nerve X (n = 27, 12%), tympanic cavity (n = 21, 10%), sympathetic chain (n = 7, 3%), cranial nerve VII (n = 1, 0.5%), or infratemporal fossa (n = 1, 0.5%). Conversely, 20 (9%) patients presented with multifocal HNPGL and/or thoracoabdominal region.

Overall, only 77 (34.8%) patients were provided a referral from their provider to our cancer genetics clinic for consideration of genetic counseling and testing. Factors associated with referral are presented in **Table 1**. Not surprisingly, referrals were much more prevalent in younger patients ($P < .0001$) and in those with a positive family history of paraganglioma ($P < .0001$). Similarly, referral rates significantly differed by anatomic subsite of HNPGL, with the highest rates of referral seen for multifocal tumors and isolated jugular paraganglioma in contrast to considerably lower referral rates for isolated carotid body and tympanic paraganglioma ($P < .0001$). Patients with measured catecholamine or metanephrine levels were similarly more likely to be referred ($P < .0001$). Finally, otolaryngologists were more likely than their neurosurgery and vascular surgery colleagues to refer for genetic testing ($P = .009$).

### Temporal Trends in Referral Patterns

From 2000 to 2019, there was a steady increase in the proportion of patients with HNPGLs referred for genetic testing per time period of diagnosis (**Figure 1A,B**). On average, the odds of referral increased by 1.15 (95% CI, 1.08-1.22) per year and 1.92 (95% CI, 1.42-2.60) per 5-year quartile of incident diagnosis. However, even in the most recent time period (2015-2019), the overall referral rate was just 51%.

Each variable in **Table 1** was measured using unique logistic regression models containing the variable, time period of diagnosis, and the interaction term, ''variable x–time period,'' to assess temporal trends in referral patterns for unique clinical subgroups. We found that while referral rates by otolaryngologists increased significantly over time, the same was not true of treating neurosurgeons or vascular surgeons ($P$ value for interaction = .01, **Figure 1C**). Furthermore, referral rates increased more steeply for patients presenting with isolated non–carotid body paraganglioma and multifocal tumors ($P$ value for interaction = .25, **Figure 1D**). Of note, no patients presenting with isolated tympanic paraganglioma (n = 21) were referred for genetic testing over the entire study period (**Figure 1D**). Finally, while referral rates were consistently higher for younger patients longitudinally, we saw a clear trend toward increased frequency of referral in our more elderly patient population ($P$ value for interaction = .25, **Table 1**).

### Outcomes of Referral for Genetic Testing

Of the 77 patients with HNPGLs referred by their provider, 63 (81.8%) were seen in our cancer genetics clinic and 60 (77.9%) elected to receive genetic testing. The 3 patients who declined genetic testing had significant anxiety and distress related to their diagnosis (n = 2) or were rapidly lost to follow-up (n = 1). Ultimately, a pathogenic mutation was identified in 43 of 60 (71.7%) patients (**Table 2**).[16]

## Discussion

Routine diagnostic evaluations for HNPGLs have recently undergone considerable change.[17] The frequency of underlying

**Table 1.** Referral Rates for Genetic Testing by Demographic, Tumor, and Clinical Variables.[a]

| Variable | Entire cohort (n = 221) | Not referred (n = 144) | Referred (n = 77) | *P* value |
|---|---|---|---|---|
| Age, median (range), y | 53 (13-85) | 57 (16-85) | 44 (13-82) | *<.0001* |
| Sex | | | | .20 |
| Male | 82 (37) | 49 (34) | 33 (43) | |
| Female | 139 (63) | 95 (66) | 44 (57) | |
| Family history | 34 (15) | 10 (7) | 24 (31) | *<.0001* |
| Year of diagnosis, median (range) | 2012 (2000-2019) | 2010 (2000-2019) | 2014 (2002-2019) | *<.0001* |
| Time period of diagnosis | | | | *.0006* |
| 2000-2004 | 31 (14) | 27 (19) | 4 (5) | |
| 2005-2009 | 54 (24) | 42 (29) | 12 (16) | |
| 2010-2014 | 62 (28) | 39 (27) | 23 (30) | |
| 2015-2019 | 74 (33) | 36 (25) | 38 (49) | |
| Tumor status | | | | .21 |
| Benign | 214 (97) | 141 (98) | 73 (95) | |
| Malignant | 7 (3) | 3 (2) | 4 (5) | |
| Tumor type | | | | *<.0001* |
| Isolated CBP | 93 (42) | 68 (47) | 25 (32) | |
| Isolated TP | 21 (10) | 21 (15) | 0 | |
| Isolated JP | 52 (24) | 26 (18) | 26 (34) | |
| Isolated VP | 27 (12) | 18 (13) | 9 (12) | |
| Isolated other | 11 (5) | 5 (3) | 6 (8) | |
| Multiple paragangliomas | 17 (8) | 6 (4) | 11 (14) | |
| Labs drawn[b] | 111 (50) | 51 (35) | 60 (78) | *<.0001* |
| Surgeon | | | | *.009* |
| Otolaryngologist | 184 (83) | 113 (78) | 71 (92) | |
| Other[c] | 37 (17) | 31 (22) | 6 (8) | |
| Initial treatment | | | | .17 |
| Surgical | 144 (65) | 100 (69) | 44 (57) | |
| Nonsurgical | 77 (35) | 44 (31) | 33 (43) | |

Abbreviations: CBP, carotid body paraganglioma; JP, jugular paraganglioma; TP, tympanic paraganglioma; VP, vagal paraganglioma.

[a]Data presented as number (%) unless otherwise indicated. *P* values were derived from $\chi^2$ test (categorical) or Wilcoxon rank-sum test (continuous). Italics represent significance for *P* values was $P < .05$.

[b]Plasma or urine catecholamines and/or metabolites.

[c]Vascular surgeon or neurosurgeon.

genetic predisposition coupled with the clinical implications of such findings has led some to support uniform referral for genetic testing in all patients with HNPGLs.[18] In recent years, a plethora of studies have emerged detailing the pathogenesis, clinical manifestations, and natural history of hereditary paraganglioma-pheochromocytoma syndromes associated with *SDHx* variants. However, our dedicated literature search failed to identify any published articles examining rates of, and factors associated with, referral for genetic testing by otolaryngologists. Our current study fills a crucial gap in this regard.

Over the past 2 decades, the treating providers at our institution referred for genetic testing only a minority (34.8%) of patients with incidentally identified HNPGLs. Our providers tended to base their clinical decision making on traditional ''high-risk'' patient features, referring a significantly higher proportion of younger patients and those with a positive family history.[19] Tumor subsite was also important, as our providers tended to refer a significantly higher proportion of patients with isolated non-CBP or multifocal tumors (**Table 1**). Referral was also more common in patients whose plasma and/or urine catecholamine/metanephrine levels were assessed at time of diagnosis, potentially indicative of a more comprehensive and protocolled diagnostic evaluation by certain providers.

Based on our findings, it is evident that providers still elect to refer their patients for genetic testing on an individualized case-by-case basis guided by the presence of certain risk factors, perceived clinical impact of positive *SDHx* pathogenic variants, and/or accessibility and cost of genetic testing. However, the wide phenotypic manifestations of *SDHx*-related hereditary paraganglioma syndrome are well documented, and failure to refer patients nondiscriminately at first presentation may lead to delayed or missed genetic diagnoses for patients and their at-risk relatives.[20] The cost-effectiveness of sequential genetic testing algorithms and resources for financial assistance in academic medical centers where patients with HNPGLs are treated may motivate surgeons to refer

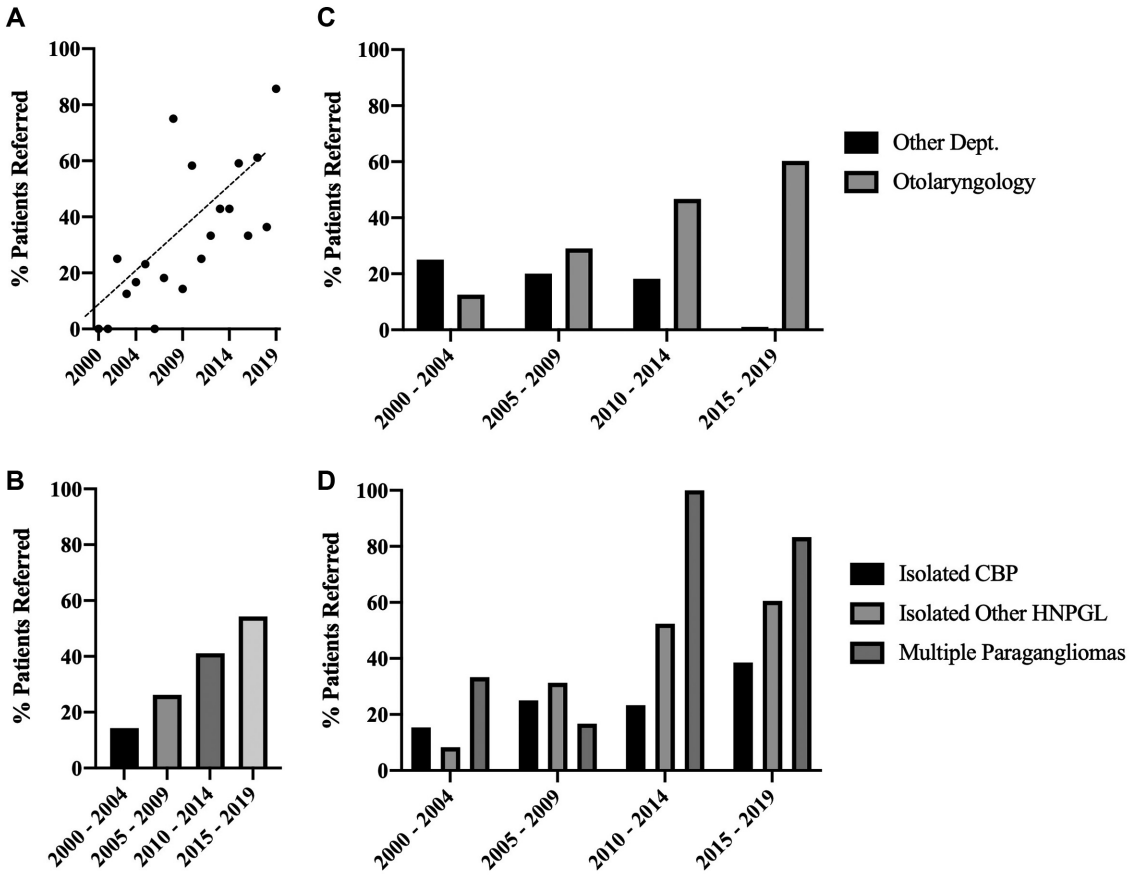


**Figure 1.** Yearly (A) and 5-year quartile (B) referral rates. Referral trends by specialty (C), and subsite (D). Rates for isolated tympanic paraganglioma excluded from D as none were referred over the entire study. CBP, carotid body paraganglioma; HNPGL, head and neck paraganglioma.

freely.[21] Perhaps at minimum, a referral could be offered to the patient, thus leading to a shared decision-making process between the patient and genetics provider regarding the pros and cons of pursuing genetic testing.

We saw a significant overall trend toward increased referral rates in patients with HNPGLs over the past 2 decades (**Figure 1**). This improvement was particularly notable in certain clinical subgroups, namely, in those patients treated by otolaryngologists and in those with solitary jugular, vagal, or sympathetic chain paragangliomas or multifocal tumors. In addition, we saw a rise in referral rates for older patients over the past 2 decades (**Table 1**), potentially indicative of increased awareness of the possibility of *SDHx*-related HNPGL presentations at advanced ages. However, even in the most recent time period of 2015 to 2019, the overall referral rate to genetics had just barely surpassed 50%, leaving much room for progress in optimal care of these complex patients. Publication and dissemination of studies such as these are helpful to increase awareness of the heritable bases of HNPGLs among otolaryngologists and surgeons in related disciplines.

Optimal care of patients with HNPGLs is often a multidisciplinary effort among otolaryngologists, vascular surgeons, and neurological surgeons owing to frequent vascular and intracranial tumor involvement. In our series, an otolaryngologist was consulted on each HNPGL patient who first presented to our vascular or neurosurgical colleagues for treatment. Because the latter was the patient's primary provider, they ultimately made the decision on whether to refer for genetic testing. As we saw a clear disparity in overall and longitudinal referral patterns favoring otolaryngologists, there is an opportunity for cross-disciplinary discussion and education regarding the frequency and clinical impact of genetic predisposition in patients with HNPGLs.

The value of referral for genetic testing in all patients with HNPGLs should be determined primarily by the impact of a positive *SDH* mutation on care delivery and patient outcomes. In our series, 63 of 77 (81.8%) referred patients were seen in person in our cancer genetics clinic. Of those, only 3 declined genetic testing. Ultimately, a susceptibility mutation was identified in 71.7% of patients with HNPGLs who had genetic testing (**Table 2**), a number that may support universal referral for all patients with HNPGLs at our institution. In accordance with our institutional practice, all were recommended to undergo biannual whole-body magnetic resonance imaging and annual plasma metanephrine screening for life.[22] In addition, all were provided with resources for notifying at-risk family members to obtain expedited screening. Importantly, the recommended standard of genetic testing for patients with HNPGLs demands a shared decision-making approach between patient

**Table 2.** Catalog of Mutations Identified in Our Patient Cohort With Head and Neck Paraganglioma.[a]

| Gene | Mutation | Patient age, y | Tumor number | Tumor location |
|---|---|---|---|---|
| *SDHA* | c.91C>T;p.Arg31ter | 53 | Single | CBP |
| | c.733C>G;p.His245Asp | 56 | Single | JP |
| *SDHB* | c.268C>T;p.Arg90ter | 18 | Single | SCP |
| | c.574T>C;p.Cys192Arg | 57 | Single | JP |
| | c.649C>T;p.Arg217Cys | 29 | Single | CBP[b] |
| | c.689G>T;p.Arg230Leu | 26 | Single | JP |
| | c.724C>T;p.Arg242Cys | 71 | Single | CBP |
| | c.725G>A, p.Arg242His | 36 | Single | CBP |
| | c.725G>A, p.Arg242His | 56 | Single | VP |
| | c.72+1G>T | 45 | Single | JP |
| | c.72+1G>T | 36 | Single | CBP |
| | c.423+1 G>A | 54 | Single | CBP |
| | c.EX7_3′UTRdel | 30 | Single | SCP |
| *SDHC* | c.43C>T;p.Arg15ter | 39 | Single | CBP[b] |
| | c.43C>T;p.Arg15ter | 33 | Multiple | CBP, MP |
| | c.214C>G;p.Arg72Gly | 33 | Single | SCP |
| | c.379C>T;p.His127Tyr | 60 | Single | CBP |
| | c.21-?_77 + ? Del;pDEL2 | 30 | Multiple | JP, CBP |
| | c.21-?_77 + ? Del;pDEL2 | 40 | Multiple | JP, MP |
| | c.405+1G>C | 15 | Single | JP |
| *SDHD* | c.242C>T;p.Pro81Leu | 55 | Single | CBP |
| | c.242C>T;p.Pro81Leu | 48 | Single | JP |
| | c.242C>T;p.Pro81Leu | 44 | Single | SCP |
| | c.242C>T;p.Pro81Leu | 54 | Multiple | CBP, VP |
| | c.242C>T;p.Pro81Leu | 64 | Single | CBP |
| | c.242C>T;p.Pro81Leu | 47 | Single | JP |
| | c.242C>T;p.Pro81Leu | 49 | Single | CBP |
| | c.242C>T;p.Pro81Leu | 14 | Single | CBP |
| | c.242C>T;p.Pro81Leu | 41 | Single | CBP |
| | c.242C>T;p.Pro81Leu | 17 | Single | VP[b] |
| | c.242C>T;p.Pro81Leu | 53 | Single | CBP |
| | c.242C>T;p.Pro81Leu | 22 | Single | VP |
| | c.242C>T;p.Pro81Leu | 18 | Single | VP |
| | c.242C>T;p.Pro81Leu | 33 | Single | CBP[b] |
| | c.242C>T;p.Pro81Leu | 42 | Multiple | CBP, CBP |
| | c.94_95del;p.Ala33Ilefs | 32 | Single | CBP |
| | c.94_95del;p.Ala33Ilefs | 16 | Single | JP |
| | c.337_340del;p.Asp113fs | 65 | Multiple | CBP, CBP |
| | c.5′UTR_3′UTRdel | 48 | Multiple | CBP, CBP, VP |
| *SDHAF2* | c.347G>A;p.Trp116ter | 30 | Single | CBP |
| *MUTYH* | c.1147del;p.Ala385fs | 64 | Single | VP |
| *NF1* | c.8479G>A;p.Ala2827Thr | 36 | Single | JP |
| | c.4986C>G;p.Asn1662Lys | 52 | Single | SCP |

Abbreviations: CBP, carotid body paraganglioma; JP, jugular paraganglioma; MP, mediastinal paraganglioma; SCP, sympathetic chain paraganglioma; VP, vagal paraganglioma.

[a]Mutation nomenclature follows the Human Genome Variation Society guidelines.[16]

[b]Malignant tumor.

and provider, cost-effectiveness of genetic testing, and an established, streamlined process for referral to maximize patient retention. We recognize that there may be systems-based challenges to attaining these goals at some institutions. However, an optimal scenario might involve a "consultation phone line" in which patients and providers are able to seek immediate, albeit preliminary, recommendations from a geneticist regarding genetic testing at first presentation to limit patients lost to follow-up.

Moving forward, confirmation of a genetic basis for HNPGL development will only become more important to the managing otolaryngologist in an era of personalized and multidisciplinary therapy for these tumors. Emerging evidence suggests that specific *SDHx* variants are characterized by recurring clinical phenotypes,[23] unique sensitivity to functional imaging and potential treatment modalities (ie, [$^{68}$Ga]Ga-DOTA-SSA, [$^{18}$F]FDG PET/CT),[24,25] and prognosis for recurrence and metachronous tumor development.[26] Our data imply that referral rates must continue to improve in order to optimally leverage emerging data and technologies in the care of these complex patients.

Our single-center analysis limits our ability to generalize our findings to the practices of other academic medical centers in the United States and abroad. A multi-institutional or national database study examining predictors and patterns of referral in patients with HNPGLs across the United States would be a valuable follow-up to the present study. We limited our primary outcome variable to include only those referrals placed within 6 months from date of diagnosis. For our statistical analysis of referral patterns over time, we chose to use 4 equal 5-year time periods starting in the year 2000, as the first reports of causative *SDHx* variants emerged then.[2,3] The first referrals for genetic testing in our series occurred in early 2001, so we believe this to be an appropriate and statistically robust categorization. However, it is quite evident that referral was exceedingly rare in the first few years of the 21st century.

## Conclusions

Our analysis suggests that referral rates for genetic testing in patients with HNPGLs are growing yet are still largely based on young age, family history, and tumor subsite.

### Author Contributions

**Joshua D. Smith**, substantial contributions to the conception or design of the work, drafting the work, final approval of the version to be published, and agreement to be accountable for all aspects of the work; **Emily L. Bellile**, revising this work critically for important intellectual content, final approval of the version to be published, and agreement to be accountable for all aspects of the work; **Tobias Else**, revising this work critically for important intellectual content, final approval of the version to be published, and agreement to be accountable for all aspects of the work; **Gregory Basura**, revising this work critically for important intellectual content, final approval of the version to be published, and agreement to be accountable for all aspects of the work.

### Disclosures

**Competing interests:** None.

**Sponsorships:** None.

**Funding source:** None.

### References

1. Else T, Fishbein L. Discovery of new susceptibility genes: proceed cautiously. *Genet Med*. 2018;20(12):1512-1514.
2. Baysal BE, Ferrell RE, Willett-Brozick JE, et al. Mutations in SDHD, a mitochondrial complex II gene, in hereditary paraganglioma. *Science*. 2000;287:848-851.
3. Niemann S, Muller U. Mutations in SDHC cause autosomal dominant paraganglioma, type 3. *Nat Genet*. 2000;26:268-270.
4. Else T. Pheochromocytoma, paraganglioma and genetic syndromes: a historical perspective. *Endocr Relat Cancer*. 2015;22: T147-T159.
5. McCrary HC, Babajanian E, Calquin M, et al. Characterization of malignant head and neck paragangliomas at a single institution across multiple decades. *JAMA Otolaryngol Head Neck Surg*. 2019;145(7):641-646.
6. Boedeker CC, Hensen EF, Neumann HPH, et al. Genetics of hereditary head and neck paragangliomas. *Head Neck*. 2014;36: 907-916.
7. Fishbein L, Nathanson KL. Pheochromocytoma and paraganglioma: understanding the complexities of the genetic background. *Cancer Genet*. 2012;205:1-11.
8. Moore MG, Netterville JL, Mendenhall WM, Isaacson B, Nussenbaum B. Head and neck paragangliomas: an update on evaluation and management. *Otolaryngol Head Neck Surg*. 2016; 154(4):597-605.
9. Lenders J, Duh Q, Eisenhofer G, et al. Pheochromocytoma and paraganglioma: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab*. 2014;99:1915-1942.
10. Hampel H, Bennett RL, Buchanan A, Pearlman R, Wiesner GL. A practice guideline from the American College of Medical Genetics and Genomics and the National Society of Genetic Counselors: referral indications for cancer predisposition assessment. *Genet Med*. 2015;17:70-87.
11. Muth A, Crona J, Gimm O, et al. Genetic testing and surveillance guidelines in hereditary pheochromocytoma and paraganglioma. *J Intern Med*. 2019;285:187-204.
12. Fishbein L, Merrill S, Fraker DL, Cohen DL, Nathanson KL. Inherited mutations in pheochromocytoma and paraganglioma: why all patients should be offered genetic testing. *Ann Surg Oncol*. 2013;20:1444-1450.
13. Gupta N, Strome SE, Hatten KM. Is routine genetic testing warranted in head and neck paragangliomas. *Laryngoscope*. 2019; 129:1491-1493.
14. Smith JD, Harvey RN, Darr OA, et al. Head and neck paragangliomas: a two-decade institutional experience and algorithm for management. *Laryngoscope Investig Otolaryngol*. 2017;2(6): 380-389.
15. Hanauer DA, Mei Q, Law J, Khanna R, Zheng K. Supporting information retrieval from electronic health records: a report of University of Michigan's nine-year experience in developing and using the Electronic Medical Record Search Engine (EMERSE). *J Biomed Inform*. 2015;55:290-300.
16. den Dunnen JT, Dalgleish R, Maglott DR, et al. HGVS recommendations for the description of sequence variants: 2016 update. *Hum Mutat*. 2016;37:564-569.
17. Taieb D, Kaliski A, Boedeker CC, et al. Current approaches and recent developments in the management of head and neck paragangliomas. *Endocr Rev*. 2014;35(5):795-819.
18. Plouin PF, Amar L, Dekkers OM, et al. European Society of Endocrinology Clinical Practice Guidelines for long-term

follow-up of patients operated on for a phaeochromocytoma or a paraganglioma. *Eur J Endocrinol*. 2016;174:G1-G10.
19. Neumann NPH, Erlic Z, Boedeker CC, et al. Clinical predictors for germline mutations in head and neck paraganglioma patients: cost reduction strategy in genetic diagnostic process as fall-out. *Cancer Res*. 2009;69(8):3650-3656.
20. Burnichon N, Rohmer V, Amar L, et al. The succinate dehydrogenase genetic testing in a large prospective series of patients with paragangliomas. *J Clin Endocrinol Metab*. 2009;94(8): 2817-2827.
21. Martins R, Bugalho MJ. Paragangliomas/pheochromocytomas: clinically oriented genetic testing. *Int J Endocrinol*. 2014;2014: 794187.
22. Else T, Greenberg S, Fishbein L. Hereditary paraganglioma-pheochromocytoma syndromes. In: Adam MP, Ardinger HH, Pagon RA, et al, eds. *Gene Reviews*. Seattle: University of Washington, Seattle; 2008.
23. Nolting S, Ullrich M, Pietzsch J, et al. Current management of pheochromocytoma/paraganglioma: a guide for the practicing clinician in the era of precision medicine. *Cancers*. 2019;11: 1505.
24. Janssen I, Blanchet EM, Adams K, et al. Superiority of [$^{68}$Ga]-DOTATATE PET/CT to other functional imaging modalities in the localization of SDHB-associated metastatic pheochromocytoma and paraganglioma. *Clin Cancer Res*. 2015;21:3888-3895.
25. Timmers HJ, Chen CC, Carrasquillo JA, et al. Staging and functional characterization of pheochromocytoma and paraganglioma by $^{18}$F-fluorodeoxyglucose ($^{18}$F-FDG) positron emission tomography. *J Natl Cancer Inst*. 2012;104:700-708.
26. Sen I, Young WF Jr, Kasperbauer JL, et al. Tumor-specific prognosis of mutation-positive patients with head and neck paragangliomas [published online February 5, 2020]. *J Vasc Surg*.