SDHA Secondary Findings in Germline Testing: Counseling and Surveillance Considerations

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Abstract
This commentary explores the complexities faced by clinicians when encountering a secondary SDHA pathogenic variant (PV) in patients without a personal or family history of SDHA-related tumors. The increasing use of germline multi-gene panel testing has led to a rise in such secondary findings, necessitating a nuanced approach to counseling, surveillance, and decision-making. We aim to discuss the current data surrounding the penetrance of SDHA PVs, the spectrum of screening guidelines, recommendations for educating individuals and families about their secondary findings, and the need for future research to optimize care for these individuals. Practical recommendations for clinicians dealing with patients with secondary SDHA findings include acknowledging the limitations of existing guidelines, fostering shared decision-making, and considering specialist referrals. Overall, the evolving landscape of SDHA penetrance data warrants ongoing reassessment of surveillance approaches.

Introduction
A 44-year-old woman is diagnosed with breast cancer and undergoes germline multi-gene panel testing (MGPT). The results reveal no findings related to her breast cancer diagnosis, but a pathogenic variant (PV) in the SDHA gene. She has no personal or family history of SDHA-related tumors. The patient has four children ranging from age 8 to 20, who have not had genetic testing. After disclosure of the genetic testing results, this patient has many questions:

- What is my chance of developing an SDHA-related tumor?
- What screening is recommended for me?
- What are the next steps for my children?
- How do I juggle this new finding with my current healthcare needs?

For the clinician disclosing these results and evaluating this patient, the answers to these questions are complicated and continue to evolve based on current data and expert/consensus guidelines. This commentary aims to inform a clinician’s approach to a secondary SDHA finding.
by reviewing the current state of SDHA penetrance data, screening recommendations, and future research needs.

The advent of next-generation sequencing and the subsequent decrease in germline testing costs has led to an increase in MGPT for patients with a personal and family history of cancer (Schienda and Stopfer, 2020). As more genes are tested, the chances of discovering an unexpected, or secondary, finding increase (Zhang et al., 2015; Mandelker et al., 2017). The National Society of Genetic Counselors defines a secondary finding as a finding in a gene that is purposely analyzed as part of the test, but unrelated to the primary indication for testing (National Society of Genetic Counselors, 2023). This contrasts with an incidental finding, such as a discrepancy in sex chromosome composition detected during quality control, which is unrelated to the initial testing purpose. Though “secondary” and “incidental” are often used interchangeably, the term secondary finding will be used to describe an SDHA PV identified in a patient with no personal or family history of SDHA-related tumors.

SDHA-related Hereditary Paraganglioma Pheochromocytoma Syndrome

The SDHA gene encodes one of four subunits in the succinate dehydrogenase (SDH) complex, which function as tumor suppressors. Germline SDHA PVs are associated with an increased risk of paraganglioma (PGL), pheochromocytoma (PCC), gastrointestinal stromal tumor (GIST), and renal cell carcinoma (van der Tuin et al., 2018). This hereditary predisposition falls under the spectrum of hereditary paraganglioma-pheochromocytoma (PPGL) syndromes. Additional genes that cause hereditary PPGL include the other SDHx genes (SDHB, SDHC, SDHD, and SDHAF2), MAX, and TMEM127. PVs in RET, FH, VHL, NF1, and other genes are also known to increase the risk of PGL and/or PCC.

Although individuals with hereditary PPGL syndrome may develop any SDHx-related tumors, the penetrance and phenotype of hereditary PPGL syndrome differ significantly depending on the gene. PVs in MAX and TMEM127 most often cause PCC, whereas head/neck
PGL are more common in patients with PVs in SDHC, SDHD and SDHAF2. SDHB and SDHA PVs have been associated with PPGL across multiple locations, including abdominopelvic and head/neck PGLs. Pathogenic variants in each gene confer a specific risk for developing a related tumor (penetrance), with the highest risk associated with paternally inherited SDHD PVs (van der Tuin et al., 2018).

Approximately 4% of individuals with hereditary PPGL syndrome have an SDHA PV. A retrospective cohort study of 393 patients with prior negative genetic testing of SDHB, SDHC, SDHD, SDHAF2 identified 30 patients with an SDHA PV. The most common presentation was a single sympathetic PGL, followed by head/neck PGL, and PCC (van der Tuin et al., 2018). An additional series of 34 individuals, both probands and their family members, with an SDHA PV showed that head/neck PGL was the most common manifestation in 44% of affected patients. Four patients in this series also had metastatic disease (Bausch et al., 2017). In both studies, a vast majority of patients lacked a family history of SDHA-related tumors. The earliest reported tumor diagnosis in these studies occurred at age 8 and 15, respectively, but most patients were not diagnosed until their fifth decade of life.

Additional attention has recently been paid to the metastatic potential of SDHA-related PPGL and it is believed that these PPGLs have a higher propensity for spread than initially reported. A series of 10 patients with metastatic PPGL associated with an SDHA PV showed a similar disease course to SDHB-related tumors (Jha et al., 2019); additional studies have also identified a proportion of metastatic disease ranging from 10% to 33% (Bausch et al., 2017; Tufton et al., 2017; van der Tuin et al., 2018).

Both GIST and RCC have been reported for individuals with an SDHA PV. Among patients with SDH-deficient GISTs, an estimated 30% have a germline SDHA PV (Schipani et al., 2023). SDHB, SDHC, and SDHD PVs have also been reported in SDH-deficient GISTs, prompting the recommendation for germline testing of all four genes in individuals with wild-type
GIST. SDH-deficient RCC is likewise a relatively rare subset of kidney cancers, but has been associated with germline PVs in both SDHA and SDHB (McEvoy et al., 2018).

Penetrance of SDHA Pathogenic Variants

Optimizing SDHA surveillance options for patients requires consideration of penetrance and evaluation of the threshold at which screening is optimally beneficial for early tumor detection (Pinsky, 2015). The estimated lifetime tumor risk for individuals with an SDHA pathogenic variant continues to be revised as new data is disseminated. Penetrance estimates for individuals with SDHA PVs range from 0.1% (Maniam et al., 2018) to 10% (van der Tuin et al., 2018). As additional cases are identified with secondary SDHA PVs, this number is expected to evolve.

Multiple studies have attempted to evaluate penetrance through literature reviews and/or institutional cohorts. Benn et al. (2018) used a Bayesian approach to evaluate unrelated Australian and UK subjects with paragangliomas, estimating lifetime disease penetrance to be 1.7% in those with SDHA PVs. In contrast, a multi-center cohort study of patients with PPGL in the Netherlands calculated 10% penetrance by age 70, though the 95% confidence interval ranged from 0-21% (van der Tuin et al., 2018). Additional studies utilize literature review, with or without institutional cohorts, to derive SDHA penetrance values. Comparing available SDHA cases in the literature to GnomAD generates a penetrance range from 0.1% to 4.9% (Maniam et al., 2018). These estimates demonstrate wide variability due to the differences in methodology and ascertainment between studies. These studies are summarized in Table 1.

The penetrance of SDHA PVs appears to be significantly lower than PVs in SDHB and SDHD, the most studied of the SDHx genes, whose penetrance ranges from 22-43% in non-probands (Andrews et al., 2018; Benn et al., 2018). In the same studies, SDHC penetrance ranges from 8-25% in non-probands, which overlaps with both SDHA and SDHB/D. More research is necessary to understand the penetrance for SDHC PVs. Therefore, whether the
same SDHx surveillance guidelines should be applied across all SDHx genes is unknown. Although currently most guidelines include all SDHx genes in their recommendations, recent publications suggest modifying the surveillance approach for individuals with an SDHA PV (Hanson et al., 2023).

**SDHA PV as a Secondary Finding**

Recent years have demonstrated a rise in reports of SDHA PVs as a secondary finding. A 5-year retrospective review of hereditary PPGL at a single institution identified 83 patients with a PV in an SDHx gene or in TMEM127, 19 (23%) of which were secondary findings. Of the secondary findings, at least 30% were in SDHA (personal communication, Mersch 2023). A similar study identified 22 patients (12 SDHA) with SDHx secondary findings over the past five years (Buchanan et al., 2022). Regarding the SDHA gene specifically, a recent abstract described 37 patients with an SDHA PV, 33 (89%) of which were secondary findings (Kohlmann et al., 2023). One study from an academic cancer center investigated the frequency of germline SDHA PV (n=10) in a cohort of ~5000 patients with solid tumors (Dubard Gault et al., 2018). Two of the 10 patients had a GIST diagnosis, which falls within the SDHA tumor spectrum. The remaining eight patients had a variety of tumors not typically associated with an SDHA mutation. Follow-up testing revealed a somatic second hit in a GIST and a neuroblastoma, indicating an oncogenic role for SDHA in these tumors. Somatic findings were absent in the tumors not related to the SDHA phenotype.

**Surveillance Guidelines**

Table 2 summarizes existing surveillance guidelines relevant to individuals with SDHA PVs. Guidelines are largely written by and for providers within a specific country (United States, United Kingdom, Sweden, or Australia/New Zealand). One publication represents the main source of international guidance (Amar et al., 2021). Most guidelines broadly address
hereditary PPGL surveillance, while the UK guideline is written specifically for individuals with SDHA PV (Hanson et al., 2023). This UK guideline is also unique in that it recommends neither surveillance in individuals with SDHA found as a secondary finding nor cascade testing for their family members.


Biochemical assessment: Most guidelines recommend biochemical analysis (such as plasma metanephrines) annually, but international guidelines recommend pediatric biennial surveillance and annual surveillance in adults. The guidelines vary in the preference of metanephrines evaluation via plasma or urine.

Imaging: All guidelines recommend full-body imaging, with most recommending MRI (preferably full-body or skull base to pelvis) as the preferred imaging modality. However, multiple guidelines suggest the consideration of positron emission tomography/computed tomography (PET/CT) and 68Ga-Dotatate imaging options.

Surveillance cessation: Recommendations vary, with multiple suggesting that after age 70, surveillance tests should be prolonged to every 5 years and follow-up should be stopped at age 80 (Amar et al., 2021).

It should be acknowledged that the guidelines for hereditary PPGL surveillance above require regular clinical follow-up, with specialized testing protocols, and are largely written by individuals who work at large, well-resourced, academic centers. Additionally, the authors of this commentary likewise work in such centers and acknowledge that patients and providers outside...
of these settings will face greater barriers to accessing specialty care. Regardless of expertise, the discrepancies in the guidelines raise challenges for any provider to determine appropriate surveillance as secondary SDHA PVs become commonplace. In other hereditary cancer syndromes, there is a shift from broad condition surveillance guidelines to gene-specific recommendations. It is possible that SDHA is in the middle of this shift, and guidelines will be standardized soon. In the meantime, multiple considerations should be incorporated to identify the best approach for the individual and their family given resources available and patient-specific concerns.

Counseling a Patient with a Secondary SDHA Finding

It is imperative to engage in shared decision-making regarding surveillance and cascade testing when providing care to someone with a secondary SDHA PV. Providers unaccustomed to managing patients with hereditary PPGL syndromes should consider referral to a physician/center familiar with this indication after initial discussion with the patient. Several resources exist to identify experts in the field. Examples include utilizing a provider search through the Pheo-Para Alliance (pheopara.org) or Endocrine Society’s Find an Endocrinologist feature [https://www.endocrine.org/patient-engagement/find-an-endocrinologist-directory - search term “Endocrine Cancer and Neoplasia”].

Despite recent efforts to standardize gene-specific recommendations, discrepancies between guidelines can be challenging for providers to navigate. Hanson et al. (2023) is the only guideline that suggests no surveillance or predictive testing in families with secondary SDHA finding. Hanson et al. also suggest SDHA/SDHB IHC analysis in tumors not associated with SDHA PV (such as breast cancer) to determine if probands should be included in surveillance recommendations, despite a lack of data to suggest that IHC analysis is effective across non-SDHx tumor types. The recommendations by this group are likely influenced by sentiment in the cancer genetics community that, given the penetrance, patients with SDHA-
associated hereditary PPGL are being over-screened. Only offering surveillance in patients/families with known SDHA-associated tumors falsely implies that data suggest the tumor risk is different based on family history, even though an absence of family history of related tumors is not overly reassuring since the majority of probands with an SDHA-related tumor likewise have no associated family history. Limiting surveillance in this way could lead to inequalities in access or false reassurance for patients with limited family contact or information about their medical history.

In contrast, acknowledging and discussing the penetrance of SDHA PVs and the broad array of acceptable surveillance guidelines allows patients to take ownership in determining a surveillance plan that addresses their needs and concerns. Ultimately, patients and their families should understand that at this time there is no “one size fits all” surveillance recommendation for SDHA-related hereditary PPGL syndrome. As multi-gene panel testing identified an increasing volume of SDHA PV carriers, standardized screening based on evolving evidence will be required. Any surveillance plan put into action should be open to change as our understanding of the penetrance and clinical course of this condition evolves.

**Predictive testing**

Apart from Hanson et al. (2023), a majority of guidelines recommend predictive testing for at-risk relatives in the setting of a secondary SDHA PV. Patients undergoing predictive testing should be aware of the benefits and limitations of the Genetic Information and Nondiscrimination Act. Discrepancies between guidelines also raise the question of whether to test minors for familial SDHA PVs. In contrast to high penetrance genes, no clear data exist to demonstrate the benefit of screening during childhood for SDHA PV carriers. Providers and families must balance the possible benefits of surveillance with the ethical tenant of autonomy, or whether the future adult should be allowed to make their own decisions about knowing their genetic status (Dondorp et al., 2021). Shared decision-making between providers and patients
considering predictive testing for themselves or their children should include a discussion regarding the evolving SDHA penetrance data as well as the impact of rigorous surveillance on children and families.

Key Takeaways

For providers who see the patients with an SDHA secondary finding as described in the opening vignette, we recommend the following takeaways:

● Acknowledge that existing guidelines addressing hereditary PPGL were written primarily in the context of SDHB and SDHD research.

● Consider discussing the following with the patient and family: reduced penetrance, variability between guidelines, range of acceptable surveillance recommendations, and symptom awareness.

● Encourage shared decision-making regarding surveillance and cascade testing.

● Highlight the evolving data and guidelines in order to provide anticipatory guidance that recommendations may change over time. Encourage patients to follow up with surveillance as mutually determined and re-evaluate surveillance recommendations and decisions at subsequent appointments.

● If a patient chooses not to pursue surveillance, encourage them to re-engage if concerns arise and to check in periodically for updated recommendations.

● Consider referral to a physician/center familiar with hereditary PPGL.

As evidenced in this commentary, it is clear that current and future research will dictate shifts in these recommendations over time.

Future Directions

The growing rate at which SDHA PVs are identified in apparently unaffected individuals warrants additional research. Larger studies are needed to rule out possible associations of
SDHA PVs with other cancer types beyond what is currently described. Furthermore, determining optimal surveillance guidelines requires clarifying if tumor risks differ for families with an SDHA PV based on family history. Subsequently, standardizing guidelines across specialties and countries ensures that individuals with the same SDHA findings receive similar care. Further research must seek to understand the patient perspective and resource needs in secondary cancer genetic findings. Although no studies have specifically looked at reactions to secondary findings in SDHA, data from secondary findings in exome/genome sequencing reveals that patients typically do not report long-term, negative impacts after being told of a secondary finding (Cheung et al., 2022). Whether response may differ when a secondary finding has low penetrance, like an SDHA mutation, is yet to be determined. Overall, current evidence regarding the low penetrance associated with SDHA PVs may not justify the same rigorous surveillance approach as in other hereditary PPGL syndromes. Consideration should be given to the development of gene-specific clinical management recommendations for individuals with hereditary PPGL.

Declaration of interest

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Author contribution statement

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patients, who are affected by these secondary findings and have shared their stories, questions, and experiences that helped shape this commentary.

References


<table>
<thead>
<tr>
<th>First Author, Year, and Country</th>
<th>Title</th>
<th>Sample and Ascertainment</th>
<th>Study Design</th>
<th>Penetrance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benn, Diana, et al. 2018 Australia, UK</td>
<td>Bayesian approach to determining penetrance of pathogenic SDH variants</td>
<td>575 Australian and 1275 UK individuals with PPGL and genetic testing</td>
<td>Comparing allelic frequencies in cases versus controls from ExAC</td>
<td>1.7%</td>
</tr>
<tr>
<td>Casey, Ruth, et al. 2017 UK</td>
<td>SDHA related tumorigenesis: a new case series and literature review for variant interpretation and pathogenicity</td>
<td>Literature review: 47 individuals with PPGL and SDHA variant UK cohort: 15 PPGL cases and SDHA variant</td>
<td>Found in healthy individuals at frequency between 1/1000 and 1/10,000</td>
<td></td>
</tr>
<tr>
<td>Maniam, Pavithran, et al. 2018 N/A</td>
<td>Pathogenicity and Penetrance of Germline SDHA Variants in Pheochromocytoma and Paraganglioma (PPGL)</td>
<td>PubMed: PPGL with heterozygous germline SDHA variants GnomAD: All reported SDHA variants in GnomAD</td>
<td>Comparison of SDHA variant frequency in PPGL literature and GnomAD cohorts</td>
<td>0.1%-4.9%</td>
</tr>
<tr>
<td>Van der Tuin, Karin, et al. 2018 Netherlands</td>
<td>Clinical Aspects of SDHA-Related Pheochromocytoma and Paraganglioma: A Nationwide Study</td>
<td>393 individuals with PPGL; 30 variant carriers and 56 non-index carriers</td>
<td>Nationwide retrospective cohort study</td>
<td>10% at age 70 years</td>
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</tbody>
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Table 1. Summary of literature analyzing penetrance in individuals with SDHA PVs
PPGL: pheochromocytoma and paraganglioma; ExAC: Exome Aggregation Consortium; GnomAD: Genome Aggregation Database
<table>
<thead>
<tr>
<th>Guideline author/group</th>
<th>Origin/contributors</th>
<th>Age to start BP/biochem surveillance (interval)</th>
<th>Age to start imaging (interval) and special recommendations (if not recommending MRI)</th>
<th>Comments/ distinguishing features</th>
</tr>
</thead>
<tbody>
<tr>
<td>AACR Childhood Cancer Predisposition Workshop Redman et al 2017</td>
<td>International cohort of leading pediatric cancer experts from the US and Canada</td>
<td>6-8 years (annual)</td>
<td>6-8 years (every 2 years)</td>
<td>The guideline is targeted for the pediatric population, so recommendations may not apply to adults. Biochem assessment also includes plasma methoxytyramine</td>
</tr>
<tr>
<td>Amar et al 2021</td>
<td>International panel of 29 PPGL experts from 12 countries. Delphi method for consensus building.</td>
<td>10-15 years, (biennial in children and annual in adults)</td>
<td>10-15 years (every 2–3 years) PET–CT for initial surveillance in adults</td>
<td>Analyzed each gene separately but resulted in similar recommendations for all the SDHx genes, except regarding the age to start surveillance.</td>
</tr>
<tr>
<td>eviQ SDHA, SDHB, or SDHC-related risk management (version 3) <a href="http://www.eviq.org.au">www.eviq.org.au</a></td>
<td>Consensus guideline from committee of genetic counselors, geneticists, and cancer genetics researchers from Australia and New Zealand. Updated every 2 years.</td>
<td>18 years (annual)</td>
<td>18 years (every 5 years) 68Ga-Dotatate PET-CT/MRI once with initial imaging</td>
<td>Age to start surveillance differs based on SDHx gene. SDHA-specific statement: SDHA PV demonstrate low penetrance. Particular care should be taken in formulating follow-up plans for asymptomatic individuals with SDHA pathogenic variants to avoid over-surveillance.</td>
</tr>
<tr>
<td>Hanson et al 2023 on behalf of UK Cancer Genetics Centres</td>
<td>Survey of 24 regional genetics centers in UK</td>
<td>10, only if positive family history (annual)</td>
<td>15, only if positive family history (every 3–5 years)</td>
<td>Only SDHA-specific guideline. Cascade testing and surveillance only recommended for probands (or FDR of probands) with an associated tumor.</td>
</tr>
<tr>
<td>Muth et al 2019</td>
<td>Panel of 9 PPGL experts from Sweden</td>
<td>5 years before age of diagnosis in family</td>
<td>5 years before age of diagnosis in family (every 2 years, increase to every 3 if normal)</td>
<td>Does not address the scenario of incidental SDHA but only recommend ongoing surveillance in FDR and one time assessment in SDR</td>
</tr>
<tr>
<td>National Comprehensive Cancer Network (NCCN) Version 1.2023</td>
<td>Consensus guideline from expert panel with representation from 33 US-based cancer centers. Updated annually.</td>
<td>10-15 years (annual)</td>
<td>10-15 years (every 2–3 years)</td>
<td>SDHA-specific statement: Consideration can be given to modified surveillance intervals given low penetrance.</td>
</tr>
</tbody>
</table>

Table 2. Summary of current SDHx related surveillance recommendations
AACR: American Association for Cancer Research; PPGL: pheochromocytoma and paraganglioma; PET-CT: positron emission tomography - computed tomography; MRI: magnetic resonance imaging; PV: pathogenic variant; FDR: first-degree relative; SDR: second-degree relative