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## Tumor Detection Rates in Screening of Individuals with *SDHx*-related Hereditary Paraganglioma-Pheochromocytoma Syndrome

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### Abstract

**Purpose:** Minimal data exist regarding the efficacy of screening protocols for individuals with *SDHx* germline pathogenic variants with Hereditary Paraganglioma-Pheochromocytoma

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Declaration of Conflicts of Interests:

SG received a one-time honorarium for consulting with Tempus Laboratories, outside of the scope and unrelated to this research study. TE received honoraria for serving on advisory boards for HRA Pharma and Corcept Pharmaceuticals outside the scope and unrelated to this research.

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Syndrome. This study aimed to evaluate the *SDHx*-related tumor detection rate in individuals undergoing clinical screening protocols.

**Methods:** A multi-center retrospective longitudinal observational study was conducted. Individuals with germline *SDHx* pathogenic variants underwent clinical whole-body imaging and biochemical testing.

**Results:** 263 individuals with *SDHx* germline pathogenic variants completed 491 imaging screens. Individuals with *SDHB* germline pathogenic variants were most common (n=188/263, 72%), followed by *SDHD* (n=35/263, 13%) and *SDHC* (n=28/263, 11%). *SDHx*-related tumors were found in 17% (n=45/263) of the cohort. Most *SDHx*-related tumors were identified on baseline imaging screen (n=39/46, 85%). Individuals with *SDHD* pathogenic variants had the highest tumor detection rate (n=14/35, 40%). Of imaging screens identifying *SDHx*-related paraganglioma/pheochromocytoma, 29% (n=12/41) had negative biochemical testing. Secondary actionable findings were identified in 15% (n=75/491) of imaging screens.

**Conclusion:** Current *SDHx* screening protocols are effective at identifying *SDHx*-related tumors. Tumor detection rates vary by *SDHx* gene and screening has the potential to uncover actionable secondary findings. Imaging is an essential part of the screening process as biochemical testing alone does not detect all disease.

## Keywords

*Succinate Dehydrogenase Subunit* genes (*SDHx*); Hereditary paraganglioma and pheochromocytoma syndrome; cancer predisposition; screening; pheochromocytoma

## Introduction

Paragangliomas (PGL) and pheochromocytomas (PCC) are tumors that arise from the sympathetic or parasympathetic ganglia and adrenal medulla, respectively. Many PGL/PCC are associated with catecholamine excess, leading to hypertension, stroke and even death if undiagnosed. Head and neck PGL (HN-PGL) often are non-secreting, yet cause symptoms due to mass effect. Although usually localized, PGL/PCC can become metastatic in 15% and 10% of cases, respectively<sup>1</sup>. The incidence of PGL/PCC is approximately 2-8 new cases per million per year<sup>2</sup>, the prevalence has recently been suggested to be as high as 1 in 3000<sup>3</sup>.

Expert recommendation is that all individuals with PGL/PCC undergo germline genetic testing to evaluate for an associated hereditary cancer predisposition syndrome because up to 40% of individuals with PGL/PCC will have a hereditary cause<sup>4-7</sup>. Fifty-percent of those are due to pathogenic variants (PV) found in the *Succinate Dehydrogenase Subunit* (*SDHx*) genes (*SDHA* (OMIM: 600857), *SDHB* (OMIM: 185470), *SDHC* (OMIM: 602413), *SDHD* (OMIM: 602690), and *SDHAF2* (OMIM: 613019))<sup>8,9</sup>. The SDH complex catalyzes the conversion of succinate to fumarate in the Krebs cycle and participates in the electron transport chain. Germline PVs in any *SDHx* gene lead to Hereditary Paraganglioma-Pheochromocytoma Syndromes (OMIM: 614165, 115310, 605373, 168000, 601650) in which individuals have an increased risk for multi-focal primary PGL/PCC, renal cell carcinoma (RCC), and gastrointestinal stromal tumors (GIST)<sup>7</sup>. PVs in each *SDHx* gene confer a different lifetime-risk for tumor development and predispose to different locations

of the PGL/PCC (HNPGGL versus thorax/abdomen PGL or PCC) and different risk for metastatic disease,<sup>10,11</sup> and these estimates are still evolving. Notably, risk estimates for *SDHx*-related tumors have decreased as more recent analyses of larger cohorts of family members exclude probands<sup>3,10</sup>. For example, unaffected individuals with *SDHB* PVs have a 25% risk of PGL/PCC by age 60<sup>10</sup>. *SDHB*-related PGL/PCC are primarily located in the abdomen, and have an increased risk for metastatic disease (~25%) compared to other *SDHx* genes (<5%)<sup>10,12–16</sup>. In contrast, individuals with *SDHD* PVs have a 43% risk for PGL/PCC by age 60 which are commonly multi-focal primary HNPGGL, with a low risk for metastatic disease<sup>10</sup>. Interestingly, *SDHD* (and *SDHAF2*) PVs only confer a risk for PGL/PCC if paternally inherited<sup>7</sup>. This differs from the biparental autosomal dominant inheritance of the other *SDHx* genes.

Given the risk of PGL/PCC as well as RCC and GIST, expert consensus guidelines recommend standard screening protocols for individuals with *SDHx* PVs<sup>17,18</sup>. A combination of serial imaging from the skull base to pelvis with annual biochemical testing (metanephrines, catecholamines) has been suggested to identify presymptomatic tumors in this at-risk population, and results in better outcomes<sup>19–22</sup>. Therefore, a consensus working group from the American Association of Cancer Researchers recommends whole-body MRI every two years starting at age 6–8 with annual biochemical testing for individuals with known *SDHx* PVs<sup>17</sup>.

This recommendation however, is based on limited data from very few small studies. The first published study evaluated whole-body MRI in 37 individuals with *SDHx* variants who underwent 45 whole-body MRIs. *SDHx*-related tumors were identified in 13.5% of individuals, with a sensitivity of 87.5% and a specificity of 94.7%<sup>19</sup>. A subsequent study evaluated 42 individuals with *SDHx* variants with 116 whole-body MRI, and 13 individuals (31 scans) had *SDHx*-related tumors<sup>23</sup>. They identified nine individuals with new PGL during the surveillance period (mean follow-up 6.4 years), with a false positive scan rate of 1.6%. A third investigation evaluated 92 individuals with *SDHB* variants, 27 of whom were probands<sup>24</sup>. Within the index patient group, four individuals had synchronous *SDHx*-related tumors identified at diagnosis, and five had metachronous *SDHx*-related tumors. In the 60 unaffected individuals undergoing whole-body MRI, 25% (n=15) had *SDHx*-related tumors identified on screening, most of which were PGL (n=11), followed by RCC (n=3), and GIST (n=1). A recent review of available literature on screening individuals with *SDHx* variants highlighted a wide range of screening rates amongst different studies, most of which include large numbers of probands<sup>25</sup>. Given the limited data on asymptomatic individuals and wide variation in tumor detection, we hypothesized that the tumor detection rate would be low overall and will vary by *SDHx* gene. Therefore, focusing on asymptomatic individuals screening, we performed a retrospective multi-center study of the largest cohort to date of individuals with *SDHx* PVs to evaluate the effectiveness of screening with whole-body imaging and biochemical testing.

## Materials and Methods

### Ethics Statement

Each institution had IRB approval for prospective data collection with informed consent or retrospective collection with waiver of consent for reporting de-identified data given feasibility for rare disease and minimal risk (Huntsman Cancer Institute protocol # 46740; University of Michigan protocol # HUM00091004, HUM00024461, HUM00043430; University of Pennsylvania protocol # 812495). All research was performed in accordance with relevant guidelines and regulation. No compensation was provided to subjects.

### Study population

A multi-center retrospective analysis was performed at the Primary Children's Hospital and Family Cancer Assessment Clinic at the Huntsman Cancer Institute at the University of Utah (Salt Lake City, UT, USA), the Michigan Medicine Rogel Cancer Center Cancer Genetics and Endocrine Oncology Clinics (Ann Arbor, MI, USA) and the University of Pennsylvania (Philadelphia, PA, USA) of all individuals with *SDHx* variants with at least one screen from the start of the screening protocol at each center through March 1, 2018. A subject was considered an individual with *SDHx* variant if they had germline clinical genetic testing identifying a known *SDHx* PV or likely PV (LPV) based on ClinVar or if they were an obligate carrier. All variants are reported as found in ClinVar. The Huntsman Cancer Institute and Michigan Medicine Rogel Cancer Center included children under 18 years of age. The University of Pennsylvania included only adults age 18 or older. Subjects from the previous research cohort published by the Huntsman Cancer Institute (n=37) were included in this study to allow for longer follow-up times from this small subgroup<sup>19</sup>.

### Screening protocol

At each site, screening protocols included biennial whole-body imaging from skull base to pelvis and annual biochemical testing. Given the retrospective nature of the study, not all subjects followed this protocol and imaging or biochemical screening may have occurred more or less frequently. Most imaging studies were MRIs, but CT and PET/CT imaging was also included. In some cases, subjects did not have full-body imaging but were included in the analysis if at least two body sections were imaged (a body section was considered imaging of the 1. neck, 2. chest or 3. abdomen/pelvis). Biochemical testing included either plasma metanephrines and/or plasma catecholamines or 24-hour urine metanephrines/catecholamines. There were only five screens with plasma catecholamines only. Individuals with a history of intrathoracic or abdominopelvic PGL/PCC were excluded unless the patient had resumed screening rather than surveillance for prior tumors. Individuals with known HNPGL were included as they were still in screening protocols for other associated tumors.

Imaging screens that found at least one *SDHx*-related tumor (PGL/PCC, RCC or GIST) were considered a positive screen. The clinical radiology reports were used to determine findings. Secondary findings were classified as "actionable" meaning follow-up required, versus "non-actionable" meaning no follow-up required.

Biochemical testing was included with the imaging screen if it occurred within four months of the imaging date. Biochemical testing was considered positive if any result was above the reference range since this was a high-risk population being screened for early detection.

### Data abstraction

Clinic notes and imaging and pathology reports were reviewed from the center's respective medical record for the established timeframe. Abstracted information included gene affected and likely PV or PV (L/PV), kindred, age at end of study, sex, personal history of *SDHx*-related tumor or any cancer, type of imaging screen, imaging results including *SDHx*-related tumor and secondary findings, as well as biochemical testing results.

### Statistical analyses

Summary statistics were calculated including mean and standard deviation ( $\pm$ SD), unless otherwise stated. The number and proportion of *SDHx*-related tumors identified were calculated, along with the rate of true negative, true positive, false negative, and false positive screens. Stata (IC12.1) was used to calculate case-control odds ratio and 95% confidence interval with p value calculation using a two-sided Fisher's Exact test.

### Role of the funding source

There was no involvement of the funding source in decisions regarding study design, data collection or analysis, interpretation, and publication submission.

## Results

### Patient demographics

A total of 473 individuals with *SDHx* L/PVs existed across the three sites. Of these, 263 (55.6%) met the inclusion criteria of being in screening and not surveillance mode and having whole body imaging or imaging of at least 2 body sites. Of the 263 individuals with *SDHx* L/PVs, 56% (n=146) were females (Table 1). The cohort ranged in age from 6 to 90 years with a median of 41 years. The subjects were from 124 kindreds, 89 of which (72%) had more than one family member in the cohort.

The majority of subjects had germline L/PVs in *SDHB* (n=188, 71%), followed by *SDHD* (n=35, 13%) and *SDHC* (n=28, 11%). Though individuals with *SDHA* and *SDHAF2* L/PVs were included in the study, they represented a small subset (n=9 and 3, 3% and 1%, respectively).

A majority of the cohort (n=194/263, 74%) had never been diagnosed with an *SDHx*-related tumor (Table 2). Sixty-nine individuals had a prior history of a PGL/PCC (26%), three (4%) had a history of RCC, and four (6%) had a history of GIST. Notably, 22 individuals (8%) had a prior history of a non-*SDHx*-related cancer (Table S1).

### Patient screening summary

The 263 subjects had 491 imaging screens, with a mean of  $1.9\pm 1.2$  studies per person, ranging from 1 to 7 (Table 2). The mean follow-up time was  $1.81\pm 2.75$  years and ranged

from 0 to 24 years. Almost half of the cohort had two or more imaging screens (n=123, 47%) with a mean follow-up time of  $3.87\pm 2.86$  years, and 22% of subjects (n=59) had three or more imaging screens with a mean follow-up time of  $5.5\pm 3.17$  years. A majority of the imaging screens (n=343, 70%) included biochemical testing (Table 2). Most subjects had complete whole body imaging (n=198/263; 75%) with each screen, with the chest/thorax being the most commonly left out area. The thorax is the most uncommon site for PGL occurrence, compared with the abdomen/pelvis and neck.

### Imaging results

Forty-seven individuals (of 263, 18%) had *SDHx*-related tumors identified on imaging across 49 imaging screens (of 491, 10%) (Table 3). Two of these individuals had a recurrence of a PGL/PCC from prior diagnosis, and were removed from further analyses, resulting in 45 subjects (17%) with new *SDHx*-related tumors identified across 46 imaging screens (9%) (i.e. one subject had additional tumors found on a subsequent imaging screen). The majority of *SDHx*-related tumors identified were PGL/PCC (n=41) and five were RCCs (Table 3). There was a false positive rate of 0.81% (n=4 imaging screens had indeterminate adrenal nodules or lymph nodes removed or biopsied and pathology confirmed adenomas and benign lymph nodes). Three imaging screens (0.61%) had inconclusive findings requiring additional follow-up, including  $^{68}\text{Ga}$ -DOTATATE PET/CT imaging or endoscopy.

Given that tumor penetrance may differ between index individuals and unaffected individuals, the cohort was separated into those with a prior PGL/PCC (n=69/263, 26%) and those without a prior history of PGL/PCC (n=194/263, 74%). In the previously unaffected cohort, 19% (n=36/194) had a true positive imaging screen for an *SDHx*-related tumor (Table 4). In addition, there were two false positive imaging screens (adrenal cortical adenoma and benign lymph nodes confirmed by pathology), one indeterminate finding (subcentimeter mass near the carotid body area, with the patient subsequently lost to follow-up) and over time, one recurrent tumor identified. The rate of *SDHx*-related tumor detection in subjects with a prior history of PGL/PCC was lower at 13% (n=9/69) (Table 4). In addition, two subjects had a recurrent tumor identified, two subjects had false positive scans (adrenal cortical adenoma and a benign lymph node confirmed by pathology) and one subject had indeterminate findings (positive  $^{68}\text{Ga}$ -DOTATATE PET/CT but lack of anatomic correlate on cross-sectional imaging; after the study period this was determined to be a small-bowel neuroendocrine tumor on endoscopy).

Of the 45 subjects with an *SDHx*-related tumor identified on imaging screens, only nine of them had a prior history of PGL/PCC. Of the nine subjects, one had a prior extra-adrenal PGL diagnosed 33 years earlier and had a known HNPGL not resected. This subject was placed back in the standard screening protocol and was found to have two additional HNPGLs. The other eight subjects had prior HNPGLs. Of the eight patients, four were found to have extra-adrenal PGLs and the other four had additional HNPGLs identified on imaging screening. Of the 46 imaging screens that identified an *SDHx*-related tumor, 85% of them (n=39) were baseline scans. Seven *SDHx*-related tumors were identified on subsequent imaging screens after baseline imaging, including four on the second and three on the third imaging screens. These individuals' previous scans were re-reviewed. Three tumors were not

seen on prior imaging at all. One tumor was initially called indeterminate and on repeat imaging was definitively reported as an *SDHx*-related tumor. Notably, the remaining three subsequently positive imaging screens had tumors seen retrospectively on prior scans (false negative rate of 0.61%). One tumor reported on the second imaging screen was present on the baseline screen in retrospect, and two tumors reported on the third imaging screen were present in retrospect on the second but not on the baseline imaging screen (Table S2).

Of the 41 subjects with PGL/PCC found on imaging screening, 13 of these subjects (32%) had multiple PGL/PCC identified simultaneously (Table S2). The rate of any *SDHx*-related tumor detection (PGL/PCC and RCC) differed by gene [40% of individuals with *SDHD* L/PVs (n=14/35), 15% of *SDHB* (n=29/188), 11% of *SDHA* (n=1/9) and 4% of *SDHC* (n=1/28)] (Table 5). Only *SDHD* L/PVs were associated with a significantly higher rate of tumor detection (OR 4.24, 95% CI 1.78–9.76, p=0.0004) when compared to non-*SDHD* L/PVs.

### Secondary imaging findings

Secondary actionable findings were identified in 15% (n=75/491) of imaging screens scans, and included breast and thyroid nodules, breast cysts, and cancers outside of the *SDHx* spectrum (Table S3). Secondary non-actionable findings included sinusitis, liver or renal cysts, and spondylolithiasis.

### Biochemical testing results

Associated biochemical testing was available for 343 of the 491 imaging screens (70%). Four of these biochemical tests were negative in conjunction with imaging that identified renal cell carcinoma. These were excluded from further analysis. From the cohort of 339 biochemical tests, 61 (18%) were elevated and 20 of the 61 had PCC/PGL on imaging (33% true positive; n=20/61). In contrast, 41 positive biochemical tests had no corresponding imaging finding, and 19 of these were from individuals with a known prior PGL/PCC or HNPGL. Importantly, 12 positive imaging screens for PGL/PCC had negative biochemical testing (4% false negative; n=12/278). Of these 12 with negative biochemical testing, eight imaging screens found HNPGLs and four found abdominal/pelvic extra-adrenal PGLs. The sensitivity of biochemical testing for PGL/PCC detection is 54.29%, and specificity is 62.50%. Using a higher cut off for biochemical positivity (2x the upper limit of normal), 34 of 339 screens (10.03%) were positive for biochemical testing, and 15 of the 34 (44.12%) had a PGL/PCC identified on corresponding imaging.

### Discussion

Here, we report the largest study to date of screening individuals with *SDHx* L/PVs with imaging and biochemical testing, most of whom were previously unaffected. Our study found that 17% of subjects had new *SDHx*-related tumors identified on imaging screens, the majority of which were seen on baseline imaging. The rate of tumor detection varied by gene, with individuals with *SDHD* L/PVs having the highest positive imaging screening rate, followed by those with *SDHB* L/PVs. These data confirm that imaging is an effective tool for identifying *SDHx*-related tumors in an asymptomatic population. Furthermore, given

13% of individuals with a prior history of PGL/PCC had new tumors identified, longitudinal screening of affected populations is warranted. Notably, no GISTs were identified, prompting the question of whether or not whole-body imaging is the optimal strategy to identify these tumors. Rednam et al. suggest laboratory evaluation for anemia as a proxy for *SDHx*-related GIST<sup>17</sup>; however, it remains to be determined whether the detection rate for GIST would justify the risks and costs of additional diagnostic procedures (e.g. endoscopy) for all adults with anemia. Novel imaging such as <sup>68</sup>Ga-DOTATATE PET/CT has high sensitivity for PGL/PCC<sup>21,26</sup>, but the sensitivity for GIST remains unclear<sup>27</sup> and it would likely not detect RCC. Considerations for cumulative radiation exposure and cost prohibit the regular use of <sup>68</sup>Ga-DOTATATE PET/CT for continuous screening; however, more data is needed to determine if it could be an effective baseline screening for individuals with *SDHx* variants. Of note, 31 individuals in our cohort had cancers outside the *SDHx*-related tumor spectrum (22 prior to screening initiation and 9 discovered by screening). *SDHx* L/PVs might contribute to a wider range of cancers, but molecular analysis was not completed on the majority of these tumors.

Given the rate of tumor identification is lower in certain *SDHx* genes than others, we suggest potentially tailoring imaging screening in a gene-specific manner, while maintaining annual biochemical testing. For example, only 4% of individuals with *SDHC* variants had tumors identified. Therefore, following a negative baseline imaging screening in those with *SDHC* variants, one might consider extending the interval of repeat imaging. It must be noted that the current study had an overall short follow up time. On the other hand, given the high rate of tumors detected in individuals with *SDHD* variants (40%), keeping a biennial screening protocol is likely optimal to ensure early detection. Another potential screening strategy for those with *SDHD*L/PVs is to alternate whole-body and neck-specific imaging, to account for the fact that most *SDHD*-related tumors are HNPGL.

One aim of this study was to evaluate if the currently recommended screening interval of two years was appropriate. Most tumors were identified on initial workup; however, there also were subsequent positive imaging screens. This highlights the importance of initial screening for all individuals with *SDHx* L/PVs and also argues for continuous screening. Some tumors found on subsequent scans were retrospectively seen on prior imaging even in our expert centers with considerable experience in whole-body MRI imaging.

Our and other prior analyses are largely limited to the adult population. The natural history of tumor development in individuals with *SDHx* L/PVs is largely unknown given a majority are identified as adults. When PGL/PCCs are identified, it is unknown how long they were present. Given the indolent nature of PGL/PCC<sup>28-30</sup>, it is likely that the age of onset is significantly earlier than the age at diagnosis. Therefore, any consideration of adjusting surveillance recommendations would not be generalizable to the pediatric population. Research dedicated to pediatric individuals with *SDHx* L/PVs, focusing on longitudinal screening outcomes, will provide additional insight into optimal protocols for this population.

Counseling of individuals with *SDHx* L/PVs should highlight the importance of initial imaging workup with the likelihood of identifying an *SDHx* tumor or a secondary finding



that requires additional follow-up. The frequency of follow-up imaging screening can be individually tailored in shared decision making with the patient, taking into account family history, affected gene, and patient preferences. Moreover, utilizing multi-disciplinary care teams including radiologists, genetic counselors, and subspecialty physicians with an expertise in *SDHx* and PGL/PCC can ensure that individuals have a comprehensive approach to their screening management.

This study has some limitations. First, despite the wide range, the mean follow-up time and number of screens per subject are low. As this cohort continues to undergo screening and additional individuals with *SDHx* L/PVs are identified, further analyses should be performed. Second, the imaging screens did not undergo central review. This does, however, reflect a real world experience in interpretation of radiology reports at expert centers. Third, although our cohort is one of the largest reported, the population of individuals with *SDHA* and *SDHAF2* L/PVs was small, limiting the ability to derive screening recommendations for this population.

Overall, whole-body imaging and biochemical testing is a beneficial screening tool that identifies *SDHx*-related tumors in individuals with *SDHx* L/PVs. Screening is essential at the time of initial *SDHx* germline L/PV identification. Further research should focus on the pediatric population, as well as identifying gene-specific protocols that are tailored to gene penetrance, primary location of tumor development, and metastatic risk. Ultimately, continued data collection and analysis of large *SDHx* cohorts can result in personalized *SDHx* screening protocols to optimize management of this patient population.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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**Table 1.**Demographics of total cohort with *SDHx* pathogenic variants.

	HCI	U of M	Penn	Total	Percent
<b>Cohort</b>					
<b>Total Subjects (n)</b>	100	95	68	263	..
<b>Families (n)</b>	25	48	51	124	..
<b>Families with &gt;1 member (n)</b>	17	38	34	89	..
<b>Sex</b>					
<b>Females (n)</b>	48	54	44	146	56%
<b>Males (n)</b>	52	41	24	117	44%
<b>Age at end of study</b>					
<b>Mean age (y)</b>	38	43	47	42	..
<b>Median age (y)</b>	39	42	47	41	..
<b>Age min (y)</b>	8	6	20	8	..
<b>Age max (y)</b>	77	90	76	90	..
<b>Adults and Children</b>					
<b>Age &lt;18 (n)</b>	17	9	0	26	10%
<b>Age 18 (n)</b>	83	86	68	237	90%
<b>Germline Genetics</b>					
<b><i>SDHA</i> (n)</b>	1	4	4	9	3%
<b><i>SDHB</i> (n)</b>	72	62	54	188	71%
<b><i>SDHC</i> (n)</b>	12	13	3	28	11%
<b><i>SDHD</i> (n)</b>	15	13	7	35	13%
<b><i>SDHAF2</i> (n)</b>	0	3	0	3	1%

HCI: Huntsman Cancer Institute; U of M: University of Michigan; Penn: University of Pennsylvania

**Table 2.**

Total cohort screening history.

	<b>HCI</b>	<b>U of M</b>	<b>Penn</b>	<b>Total</b>
<b>Total cohort</b>				
Total subjects (n)	100	95	68	263
Imaging screens (n)	180	186	125	491
Screens per subject (mean±SD)	1.80±1.17	1.96±1.24	1.84±1.23	1.87±1.22
Range screens per subject (n)	1-6	1-6	1-7	1-7
Screens including biochemistry (n (% screens))	117 (65%)	135 (73%)	91 (73%)	343 (70%)
Follow-up time, years (mean±SD)	1.58±2.42	2.04±2.69	1.82±3.22	1.81±2.75
Subjects with 2 screens (n (%))	44 (44%)	47 (49%)	32 (47%)	123 (47%)
Follow-up time, years (mean±SD)	3.60±2.47	4.13±2.45	3.86±3.75	3.87±2.86
Subjects with 3 screens (n (%))	20 (20%)	24 (25%)	15 (22%)	59 (22%)
Follow-up time, years (mean±SD)	5.22±2.21	5.72±2.34	5.53±4.91	5.50±3.17
<b>No prior history of PGL/PCC</b>				
Subjects (n (% of total subjects))	83	59	52	194 (74%)
Imaging Screens (n (% of total screens))	149	98	87	334 (68%)
<b>Prior history of PGL/PCC</b>				
Subjects (n (% of total total))	17	36	16	69 (26%)
Imaging Screens (n (% of total screens))	31	88	38	157 (32%)

HCI: Huntsman Cancer Institute; U of M: University of Michigan; Penn: University of Pennsylvania

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**Table 3.**

Total cohort tumor detection rates using imaging screening

	HCI	U of M	Penn	Total
<b>Total cohort imaging scans, n</b>	180	186	125	491
<u>Including recurrences</u>				
Scans with positive screens, n (%)	26 (14%)	8 (4%)	15 (12%)	49 (10%)
Percent true positive tumor screen found on first screen	77%	100%	87%	84%
Scans with recurrence of PGL/PCC, n (%)	1 (0.56%)	0 (0%)	2 (1.6%)	3 (0.61%)
<u>Excluding recurrences</u>				
Scans with positive screens, n (%)	25 (14%)	8 (4%)	13(10%)	46 (9%)
Percent true positive tumor screen found on first screen	76%	100%	92%	85%
<i>SDHx</i> -related tumors identified on scans, n				
PGL/PCC	24	6	11	41
GIST	0	0	0	0
RCC	1	2	2	5
<b>Total cohort subjects, n</b>	100	95	68	263
<u>Including recurrences</u>				
Subjects with true positive screens, n (%)	25 (25%)	8 (8%)	14 (21%)	47 (18%)
<u>Excluding recurrences</u>				
Subjects with true positive screens, n (%)	24 (24%)	8 (8%)	13 (19%)	45 (17%)
<b>Additional information</b>				
Total cohort imaging scans, n	180	186	125	491
Scans with false positive, n (%)	0 (0%)	4 (2%)	0 (0%)	4 (0.81%)
Scans with incidental actionable, n (%)	24 (13%)	26 (14%)	25 (20%)	75 (15%)
Scan with inconclusive finding, n (%)	2 (1%)	1 (0.54%)	0 (0%)	3 (0.61%)

HCI: Huntsman Cancer Institute; U of M: University of Michigan; Penn: University of Pennsylvania

True positive means tumor was *SDHx*-related including PGL/PCC, RCC or GIST

**Table 4.**

Total cohort tumor detection rates using imaging screening by history of prior PGL/PCC.

	HCI	U of M	Penn	TOTAL	Percent
<b>Subjects without prior history of PGL/PCC, n</b>	83	59	52	194	74% (194/263)
Subjects with screen positive SDHx-related tumor, n	18	7	11	36	19% (36/194)
Subjects with recurrence of SDHx-related tumor on screen, n	0	0	1	1	..
Subjects with false positive screen for SDHx-related tumors, n	0	2	0	2	..
Subjects with indeterminate finding for SDHx-related tumors, n	1	0	0	1	..
<b>Subjects with prior history of PGL/PCC, n</b>	17	36	16	69	26% (69/263)
Subjects with screen positive SDHx-related tumor, n	6	1	2	9	13% (9/69)
Subjects with recurrence of SDHx-related tumor on screen, n	1	0	1	2	..
Subjects with false positive screen for SDHx-related tumors, n	0	2	0	2	..
Subjects with indeterminate finding for SDHx-related tumors, n	0	1	0	1	..
<b>Total subjects with positive screen for SDHx-related tumor, n</b>	24	8	13	45	17% (45/263)

HCI: Huntsman Cancer Institute; U of M: University of Michigan; Penn: University of Pennsylvania

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**Table 5.**

Gene-specific rates of tumor detection using imaging screening for the total cohort.

	Subjects with true positive screens (excluding recurrence) (n)	Total subjects (n)	Percent positive subjects
<i>SDHA</i>	1	9	11%
<i>SDHB</i>	29	188	15%
<i>SDHC</i>	1	28	4%
<i>SDHD</i>	14	35	40%
<i>SDHAF2</i>	0	3	0.00%
<b>Total</b>	<b>45</b>	<b>263</b>	<b>17%</b>

True positive means tumor was *SDHx*-related including PGL/PCC, RCC or GIST

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