Revisiting Germline SDHA-Related Tumor Risks: A Cohort of 558 *SDHA* Positive Patients from a Single Reference Laboratory

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BACKGROUND

- *SDHA* PVs are considered high risk for paragangliomas (PGLs), pheochromocytomas (PCCs), renal cell carcinomas (RCCs), & gastrointestinal stromal tumors (GISTs)
- Risk of PGL/PCCs estimates in *SDHA* PV carriers vary greatly dependent on methodology, from ~2%[1] (estimated lifetime penetrance) and ~90%[2] (age-related penetrance)
- *SDHA* variants are often identified incidentally on multi-gene panel testing (MGPT)[3]

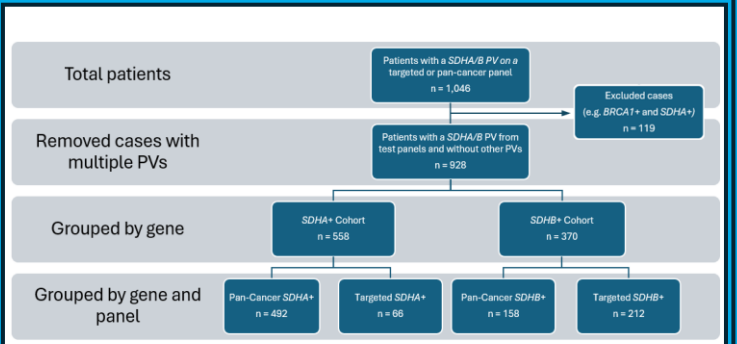
AIMS

- This study characterized *SDHA* PV tumor incidence in a cohort representative of current cancer genetics patient populations, i.e., those detected on pan-cancer MGPT, often incidentally

METHODOLOGY

- Retrospective review of de-identified individuals with a *SDHA* or *SDHB* PV from a single reference laboratory between 2013 and 2024 and a curated germline negative (pan-cancer panel) control group
- Four test cohorts were developed, grouped by testing panel type and gene
  - Targeted cohorts were defined as those identified by PGL/PCC-focused panels (12-14 genes)
  - Pan-cancer cohorts were defined as those identified by general cancer MGPT (49-71 genes)
  - The pan-cancer *SDHA*+ cohort was anticipated to be representative of the incidental *SDHA PV* population
  - *SDHB* serves as a comparison HPPGL gene, well established as highly penetrant
- Personal and family histories were reviewed for testing criteria eligibility as well as core cancers (e.g., PCL, PCC)
  - Personal histories were collected from ordering providers (i.e. submitted documentation, clinic notes, etc.)
  - Testing eligibility criteria based on published *SDHA*-specific genetic testing guidelines
- Hereditary Paraganglioma and Pheochromocytoma Syndrome (HPPGL) tumors were defined as PGLs, PCCs, GISTs, and renal tumors (RCC or unspecified pathology)
  - Additional tumor types, such as pituitary and thyroid, were included in tumor-specific penetrance estimates.
- Kaplan-Meier estimation analyses were used to estimate tumor specific and overall HPPGL tumor age-related penetrance. The survival time was considered the age of tumor onset for patients with the tumor. Tumor-free patients were censored at the age at time of their test

Fig. A: Cohort Design



RESULTS

Fig. B: HPPGL Published Test Criteria Eligibility

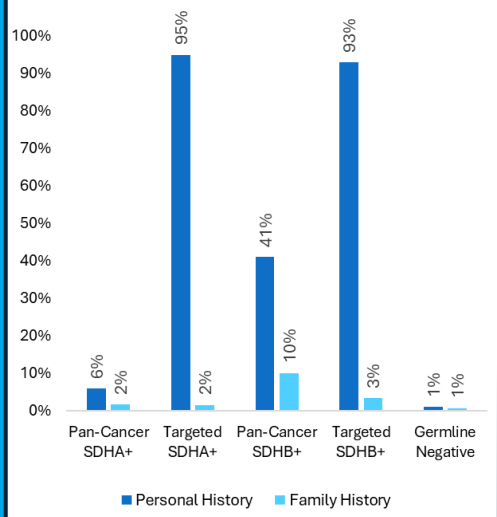


Fig. C: HPPGL Kaplan Meier Curves

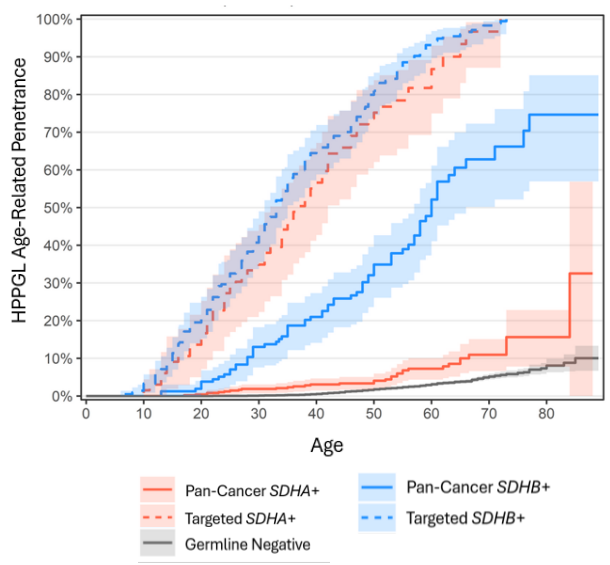
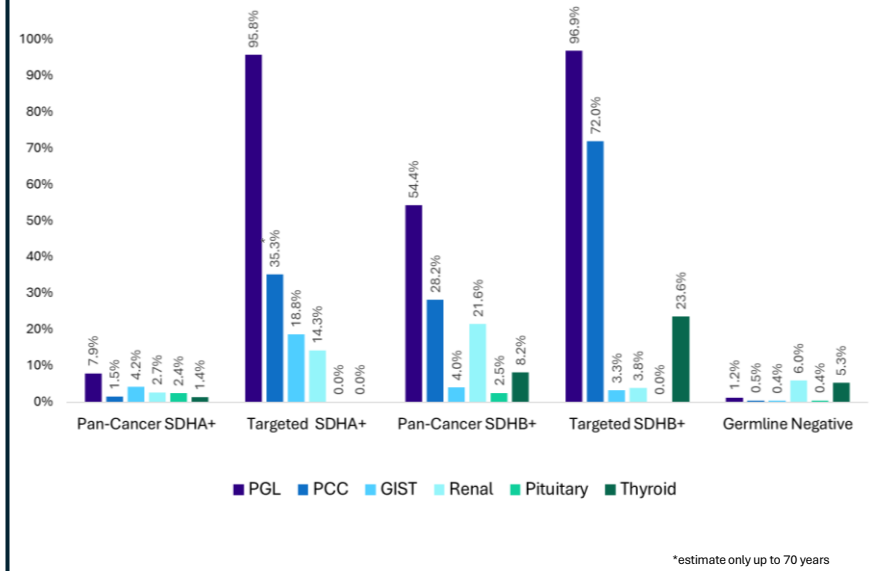


Fig. C: Tumor-Specific Penetrance Estimates (80 yrs)



*estimate only up to 70 years

TAKE-HOME POINTS

- Among *SDHA*+ patients, only 6% had a personal and 2% a family history meeting published testing criteria, suggesting that *SDHA* PVs are typically incidental findings MGPT
- Few pan-cancer *SDHA*+ patients met HPPGL published testing criteria, highlighting a gap between real-world MGPT detection and existing guidelines
- GISTs were present in a higher proportion of *SDHA*+ cohorts than *SDHB*+ cohorts
- The pan-cancer *SDHA*+ cohort showed lower age-related penetrance than the targeted *SDHA*+ cohort, yet remained above the general hereditary cancer clinic baseline
- Patients with incidental *SDHA* PVs may benefit from tailored management guidelines based on their personal and family histories

CITATIONS

1. Benn, D. E., et al., 2018. Journal of Medical Genetics
2. Bausch, B., et al., 2017. JAMA Oncology
3. Kohlmann, W., et al., 2023. Genetics in Medicine Open