Enhancing Clinical Relevance in Hereditary Cancer Panels: An Evidence-Based Approach for *DICER1* & *SMARCA4*

Elyse Ryan, MS, CGC[1]; Devon Thrush, MS, CGC[1]; Jamie Weyandt, PhD[1]; Colin Young, PhD[1]; Laura Hudish, PhD[1]; Noriko Yokoyama, PhD[1]; Carolyn Horton, CGC[1]; Jessica Laprise, MS, CGC[1]; Jessica Grzybowski, MS, CGC[1]

[1]*Ambry Genetics. 1 Enterprise, Aliso Viejo, CA 92656*

BACKGROUND

- Genetic testing laboratories are relied upon to thoughtfully curate their Multi-Gene Panel Tests (MGPTs) to ensure maximum utility for patients and healthcare providers. Curation is not a one-and-done process: as our knowledge of gene-disease relationships evolves with new scientific studies, the content of MGPTs should also evolve to maximize clinical utility.
- *DICER1* and *SMARCA4* have historically been included on gynecologic cancer MGPTs due to their associations with tumor predisposition syndromes that include rare ovarian cancers.
  - *DICER1* (*DICER1*-Tumor Predisposition Syndrome): Sertoli-Leydig cell tumors of the ovary
  - *SMARCA4* (Rhabdoid Tumor Predisposition Syndrome)*:* small cell carcinoma of the ovary, hypercalcemic type (SCCOHT)
- *DICER1* & *SMARCA4* have also appeared on larger, comprehensive hereditary cancer panels that are intended to cover expanded gynecologic phenotypes beyond epithelial ovarian cancer.
- This study examined the utility of these genes on MGPTs and showed their usefulness to be limited.

METHODS

All cases with pathogenic or likely pathogenic variants identified in *DICER1* and *SMARCA4* prior to March 2024 on three MGPTs were reviewed. The three panels were 1) an expanded-gynecologic cancer panel, 2) a common hereditary cancer panel, and 3) an expanded-comprehensive hereditary cancer panel. All available clinical information about the patient &/or their family history was reviewed from test request forms, clinic notes, pedigrees, &/or written communications between the laboratory and the ordering provider.

Each case was then coded as either Likely Diagnostic, Potentially Diagnostic, or Incidental:

- **Likely Diagnostic**: Cases where *DICER1* or *SMARCA4* could be suspected prior to genetic testing being complete (e.g. a history of Sertoli-Leydig cell tumor of the ovary or SCCOHT).
- **Potentially Diagnostic**: Not enough clinical information was known or provided to the laboratory to be able to determine if the presentation could indicate a *DICER1* or *SMARCA4* phenotype (e.g. ovarian cancer NOS, dx 10y).
- **Incidental**: The personal &/or family history was not explained by the *DICER1* or *SMARCA4* finding (e.g. history of breast or colon cancers). The positive finding was not expected to have an impact on patient management.

RESULTS

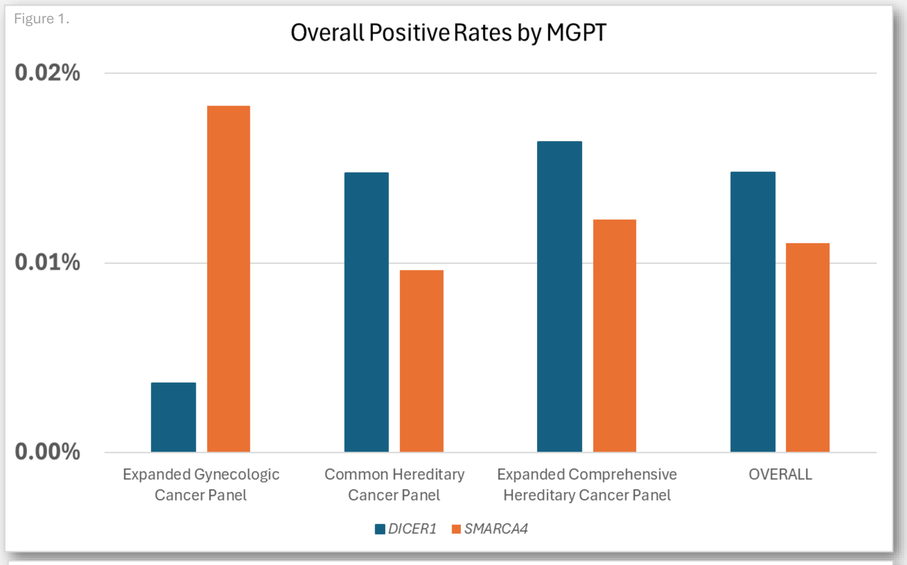
Table 1.

MGPT	Total Test Count	DICER1 Number of Positive Cases	DICER1 POSITIVE RATE	DICER1 Case Types	SMARCA4 Number of Positive Cases	SMARCA4 POSITIVE RATE	SMARCA4 Case Types
Expanded Gynecologic Cancer Panel	27,318	1	**0.004%**	Dx: 1 Potentially Dx: 0 Incidental: 0	5	**0.018%**	Dx: 2 Potentially Dx: 0 Incidental: 3
Common Hereditary Cancer Panel	311,899	46	**0.015%**	Dx: 11 Potentially Dx: 9 Incidental: 26	30	**0.010%**	Dx: 6 Potentially Dx: 2 Incidental: 22
Expanded Comprehensive Hereditary Cancer Panel	195,125	32	**0.016%**	Dx: 12 Potentially Dx: 8 Incidental: 12	24	**0.012%**	Dx: 4 Potentially Dx: 3 Incidental: 17
COMBINED	534,342	79	**0.015%**	Dx: 24 Potentially Dx: 17 Incidental: 38	59	**0.011%**	Dx: 12 Potentially Dx: 5 Incidental: 42

↑ Table 1.
Positive rates were low across MGPTs, regardless of case type. The Expanded Gynecologic Cancer Panel data is sparse; a single *DICER1* positive, only 5 *SMARCA4* positives. Looking at individual MGPTs or the data overall, there are a significant number of incidental cases.

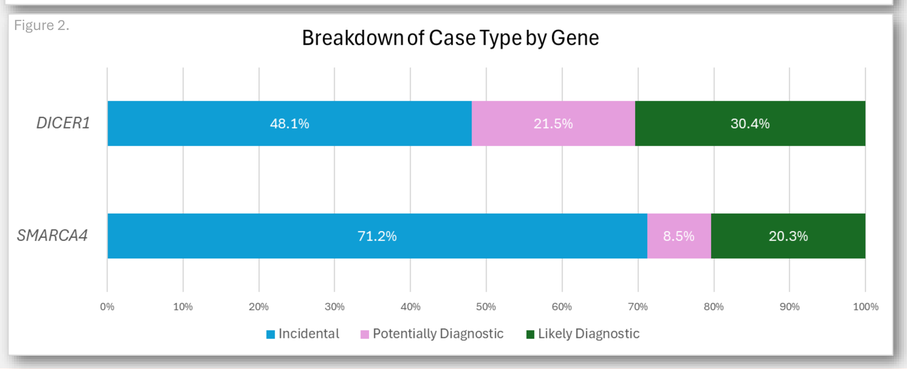
Case Types: Likely Diagnostic (Dx), Potentially Diagnostic (Potentially Dx) , Incidental.

Figure 1.



←Figure 1.
The positive rate for both *DICER1* and *SMARCA4* on any panel does not exceed 0.018%.

Figure 2.



←Figure 2.
A significant proportion of positive cases are incidental. The personal &/or family history in these cases were not explained by the positive finding, and it is expected that the finding would not impact patient management.

TAKE HOME POINTS

- *DICER1* & *SMARCA4* lack clinical utility on MGPTs, with overall positive rates under 0.02% and high rates of incidental findings (up to 73%; for *SMARCA4* findings on the Common HC panel).
- *DICER1* & *SMARCA4* should be suspected and included in testing for patients with a personal &/or family history indicative of *DICER1*-Tumor Predisposition Syndrome or Rhabdoid Tumor Predisposition Syndrome.
- For patients who present with vague or unclear gynecologic histories, providers should consider more comprehensive testing to include rare ovarian predisposition genes.
- In the setting of epithelial ovarian cancer, *DICER1* & *SMARCA4* have limited clinical utility.

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Contact Information:

Elyse Ryan
Genetic Counselor II, Product Development
eryan@ambrygen.com
949.900.5500

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