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

Authors: Elyse Ryan, Devon Thrush, Jamie Weyandt, Colin Young, Laura Hudish, Noriko Yokoyama, Jessica Laprise, Jessica Grzybowski

Introduction: Known gene-cancer risk associations are constantly evolving. The content of hereditary cancer panels should evolve with this knowledge to ensure maximum clinical utility and limit rates of incidental findings. Here we present an examination of the inclusion and utility of *DICER1* and *SMARCA4* on multigene panel tests (MGPT).

Historically, *DICER1* and *SMARCA4* have been included in expanded-phenotype gynecologic cancer MGPTs due to specific, rare ovarian cancer associations. *DICER1*-Tumor Predisposition Syndrome (DTPS) is associated with ovarian Sertoli-Leydig cell tumors, and *SMARCA4*-related Rhabdoid Tumor Predisposition Syndrome (RTPS) with small cell carcinoma of the ovary, hypercalcemic type (SCCOHT). These genes have also appeared on comprehensive hereditary cancer panels for ovarian and broader cancer phenotypes (DTPS: various findings of the lung, thyroid, and more, RTPS: rhabdoid tumors throughout the body).

Methods: From a cohort of individuals undergoing hereditary cancer MGPT prior to March 2024, we retrospectively curated clinical data for carriers of pathogenic *DICER1* or *SMARCA4* alterations. We analyzed overall positive rates and utilized available clinical data (from test request forms, clinic notes, etc.) to estimate the rate of incidental findings. Cases in which the presumed reason for testing was not explained by the *DICER1/SMARCA4* variant were considered incidental. Three MGPTs were studied: an expanded-gynecologic cancer panel, a common hereditary cancer panel, and an expanded comprehensive hereditary cancer panel.

Results: *DICER1/SMARCA4* positive rates were low across MGPTs (<0.02%) and rates of incidental findings were significant. The highest rate of incidental findings, where the result did not explain the personal or family cancer history, was seen on the common hereditary cancer MGPT. Cancer screening/management was not expected to change for these patients due to their age/other history. Across MGPTs, positive rates were highest in cases of Sertoli-Leydig cell tumor, SCCOHT, or a known familial variant.

Conclusions: This analysis supports testing for *DICER1*/*SMARCA4* in cases with specific ovarian findings or known familial mutation. We also support the inclusion of these genes on panels indicated for rare cancer types. However, these genes lack utility on MGPTs for general gynecologic or common cancer indications. By prioritizing the inclusion of genes with higher diagnostic yield and clinical applicability on targeted-phenotype panels, the overall impact and usefulness of MGPTs is maximized for patients and providers.