Paired DNA and RNA sequencing from 450,000 consecutive individuals: Impact on yield in hereditary breast, ovarian, pancreatic, and prostate (HBOP) cancer genes

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Paired DNA and RNA sequencing has shown promise in improving detection and interpretation of DNA variants identified across a variety of clinical indications. Here we report preliminary outcomes of a study in progress evaluating paired DNA and RNA sequencing among 450,000 individuals undergoing hereditary cancer multigene panel testing, focusing on hereditary breast, ovarian, and related cancer genes.

Results from concurrent DNA and RNA sequencing performed between April 2019-December 2023 were retrospectively reviewed. The positive rate calculated excludes monoallelic variants in genes associated with recessive conditions and moderate risk pathogenic variants (PVs) (e.g., APC p. I1307K and CHEK2 p.I157T). Variant classifications were compared before and after application of RNA evidence to calculate positive yield. Medically significant upgrades were those resulting from a newly detected germline intronic PV and reclassifications from uncertain significance to PV. Positive yield will be calculated for the 20 genes in NCCN's Breast, Ovarian, Pancreatic, and Prostate Guidelines (v.2.2025; HBOP genes), and specifically those with breast surgical recommendations that were included in an urgent/STAT order.

A total of 455,379 cases were included. The overall positive rate was 9.9% (46,027 PVs in 45,202 individuals). Medically significant upgrades based on RNA evidence were made to 1,838 variants, resulting in a 4.2% (1:25) relative increase in positive yield. The increase in positive yield for HBOP genes as well as those with surgical recommendations is underway.

In this study, 1 in 25 PVs, were dependent on RNA evidence. Differences in yield based on gene and clinical indication may help estimate the residual risk of a positive result following an initial STAT DNA-only report. In this way, identifying genes in which RNA sequencing is especially impactful can provide useful insights to aid providers in risk assessment and test selection, including when RNA data may be important for real-time breast cancer surgical decision-making.