Paired DNA and RNA Genetic Testing Improves Variant Detection and Classification Independently of Personal History of Cancer

S. Campian, K. Burgess, C. Horton, L. Hoang, R. Pilarski, J. Profato, H. Zimmermann, E. Chao, R. Karam; Ambry Genetics, Aliso Viejo, CA

BACKGROUND

- Concurrent mRNA genetic testing (RGT) and DNA genetic testing (DGT) results in fewer variants of uncertain significance (VUS) and increased detection of deep intronic pathogenic/likely pathogenic variants (PVs) than DGT alone.
- It is currently unclear whether concurrent DGT/RGT testing benefits all patients equally.
- **Study Aim:** To determine whether personal cancer history impacts the rate of detection of PVs that would have been misclassified or undetected with DGT alone.

METHODS

- Clinical histories were reviewed for patients undergoing concurrent DGT/RGT in our lab.
- PVs found in individuals meeting stand alone personal history NCCN criteria[1,2] for genetic testing (Table 1) and those not meeting criteria were compared for RNA impact.

RESULTS

- Clinical information was provided for 43,145 individuals undergoing DGT/RGT.
- Of these, 4,807 had a pathogenic variant in one of the 18 genes analyzed with RNA, consisting of 13.1% of those who met NCCN criteria and 10.5% of those who did not.
- RNA impact amongst those who did and did not meet NCCN criteria for testing are described in Figure 1.

REFERENCES

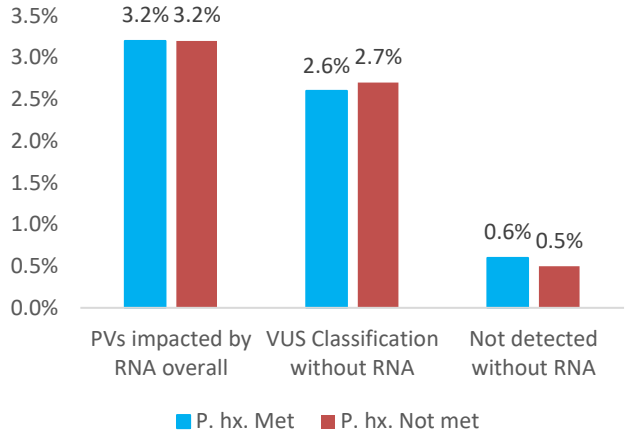
1. NCCN Clinical Practice Guidelines in Oncology: NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian and Pancreatic. Version 2.2021. 2. NCCN Clinical Practice Guidelines in Oncology: NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal. Version 1.2021. Available at NCCN.org.

Table 1. Proband Personal History

Individuals with stand-alone personal history meeting NCCN criteria*	10,882 (25.2%)
Breast cancer ≤45y	4,749 (11.0%)
Triple negative breast cancer ≤60y	1,380 (3.2%)
Two primary breast cancers with the first ≤50y	897 (2.0%)
Colorectal cancer ≤50y	1,109 (2.6%)
Endometrial cancer ≤50y	463 (1.1%)
Ovarian cancer	1,926 (4.5%)
Pancreatic cancer	1,433 (3.3%)
Male breast cancer	169 (0.4%)
Individuals with stand-alone personal history not meeting NCCN criteria*	32,263 (74.8%)
Breast cancer	10,607 (24.6%)
Colorectal cancer	924 (2.1%)
Endometrial cancer	660 (1.5%)
Other cancer	5,215 (12.1%)
No personal history of cancer	15,195 (35.2%)

*includes individuals who meet multiple criteria and/or have multiple cancer types

Figure 1. Percent of PVs Impacted by RNA



TAKE-HOME POINTS

- PVs in both groups were equally impacted by RNA.
- These results suggest that RGT is equally beneficial in patients undergoing genetic testing regardless of personal history.
- Additional studies are needed to determine if these findings also apply to individuals with a family history of cancer.