Abstract # 10603: Clinically Significant Variant Classification Resulting from the Addition of RNA Sequencing: Experience at High-Volume Cancer Genetics Center

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Background

- Germline genetic testing plays an important role in cancer risk assessment leading to clinical interventions allowing for cancer prevention, early detection, and targeted therapies[1]
- Use of multi-gene panel testing (MGPT) has increased, underscoring the importance of accurate variant classification
- The addition of RNA sequencing has been reported to contribute to variant classification and clinical care by:[2]
  - Reducing the rate of variants of uncertain significance (VUS)
  - Increasing diagnostic yield
  - Improving the accuracy of cancer risk assessment[1]
- This study reports the impact of RNA sequencing in a high volume Cancer Genetics Center

Methods

- 6343 patients underwent MGPT at a single testing laboratory from 2019-2023 at the Nancy & James Grosfeld Cancer Genetics Center
- Genetic testing was completed via standard DNA technology with added RNA sequencing
- Patients whose result was clinically impacted by RNA sequencing were identified and characterized according to:
  - Upgrades from non-actionable/VUS to likely pathogenic/pathogenic variants (LPV/PV)
  - Downgrades from LPV/PV to non-actionable VUS

Results

- RNA sequencing impacted variant interpretation in 2.8% (179/6343 patients) (Figure 1)
- Of those 179 patients, 26.3% (47 patients) had a clinically significant reclassification (Figure 2)
- 31 patients were upgraded to actionable results of LPV/PV
  - *BRCA1* (1), *BRCA2* (4), *MSH2* (4), *MSH6* (1), *PMS2* (1), *ATM* (5), *C HEK2* (5), *RAD51C* (5), *CDH1* (2), *PALB2* (3) (Figure 2)
- 16 patients were downgraded from LPV/PV to non-actionable VUS
- *BRCA2* (7), *RAD50* (1), *RAD51D* (8) (Figure 2)

RNA sequencing allows for more accurate cancer risk assessment for individuals undergoing MGPT.

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Figure 1

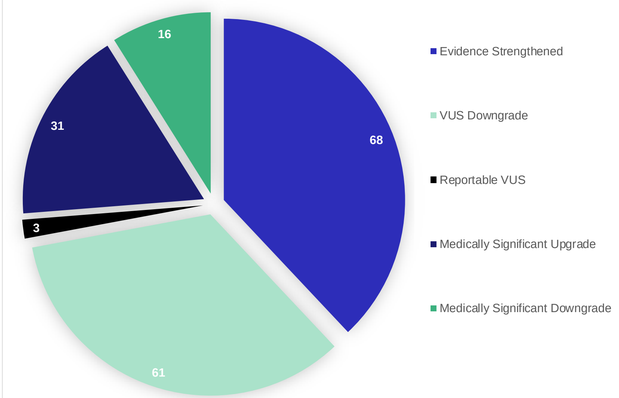
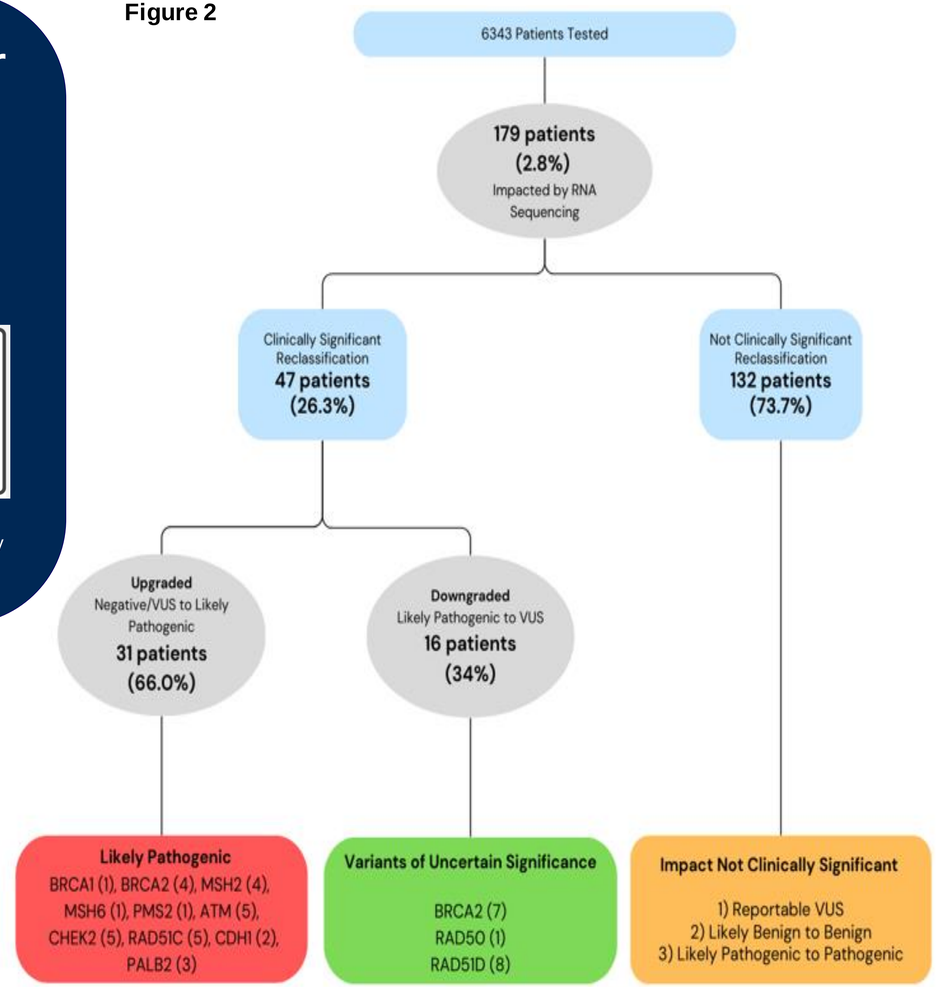


Figure 2



References:

1. Horton C, Hoang L, Zimmermann H, et al. Diagnostic Outcomes of Concurrent DNA and RNA Sequencing in Individuals Undergoing Hereditary Cancer Testing. JAMA Oncol. 2024;10(2):212–219. doi:10.1001/jamaoncol.2023.5586
2. Karam R, et al. Assessment of Diagnostic Outcomes of RNA Genetic Testing for Hereditary Cancer. JAMA Netw Open. 2019 Oct 2;2(10):e1913900. doi: 10.1001/jamanetworkopen.2019.13900. PMID: 31642931; PMCID: PMC6820040.