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Quantitative evaluation of methods designed to improve the accuracy and quality of multi-gene panel testing for hereditary cancer

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BACKGROUND

- Germline genetic testing for hereditary cancer syndromes is increasingly performed using multi-gene panel testing (MGPT) via next-generation sequencing (NGS).
- Various methods can increase accuracy and quality of MGPT, such as those designed to mitigate inherent limitations of NGS-based assays and improve results interpretation.
- Few efforts have been made to quantify the effect these methods have on genetic test results at the patient level.
- We aim to determine the clinical impact of enhancements to assay design and variant interpretation.

METHODS

- A consecutive series of patients undergoing hereditary cancer MGPT for 2-81 genes between January 2019 and December 2019 (n=107,258) were retrospectively reviewed.
- We identified the number of individuals with a germline pathogenic/likely pathogenic variant (gPV) identified by one of the following MGPT supplementary methods: 1) bioinformatics enhancements; 2) implementation of orthogonal assays; 3) variant classification tools.

TAKE-HOME POINTS

Improved accuracy and clinical fitness of MGPT can be derived in a variety of ways.

These improvements are especially vital at a high-volume laboratory offering clinical-grade testing that directly impact patient care.

Aspects of test quality outlined here can be used to facilitate laboratory selection by clinicians and consensus building for technical standards.

Quality Area	Description of Test Improvement	Purpose
Bioinformatics	Pipeline Customizations: Enhanced accuracy in regions that are technically challenging for NGS variant calling	Prevent false positives and negatives
	Protected Intronic Variants: Integration of clinically significant variants from published literature that reside outside standard detection range	Increase clinical sensitivity
Orthogonal assays	Specialized MLPA probes are used to distinguish between gross deletions in the *PMS2* pseudogene versus the expressed gene	Prevent false positives and negatives
Variant classification	RNA sequencing for improved interpretation and detection of splicing variants	Increase clinical sensitivity and reduce inconclusive rate
	Protein structural modeling for improved interpretation of missense variants	

Figure 1. Opportunities for Accuracy Improvement

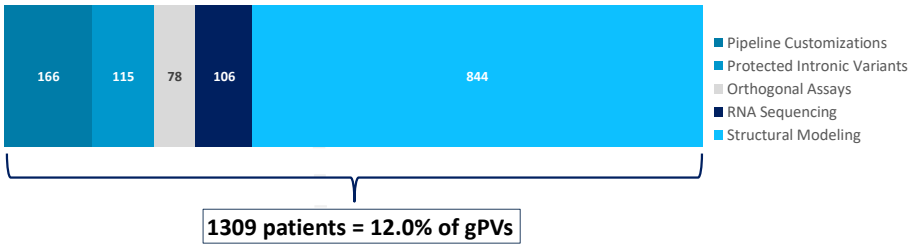


Figure 2. Spotlight on Variant Interpretation Improvements

Figure 2a. RNA Sequencing Resolves VUS

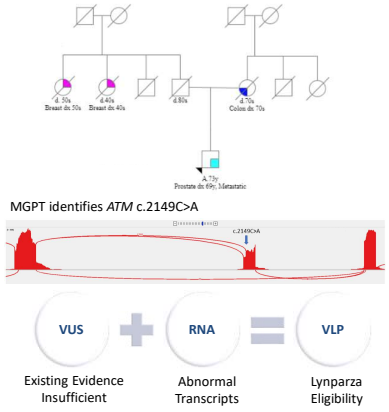
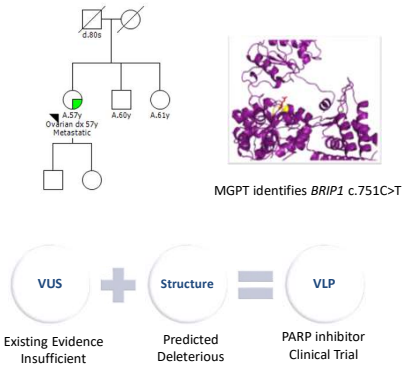


Figure 2b. Structural Modeling Resolves VUS



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