Ambry Genetics®

Research For Your Practice

Setting a new standard in clinical germline genetic testing: Paired DNA and RNA sequencing improves accuracy and detection

Increase in Pathogenic Variants

Concurrent DNA/ RNA leads to relative increase in detection of pathogenic variants.

Decrease in VUS rate

Generates functional evidence that helps resolve VUS

Equity

Reduces evidence gaps in non-White populations

Ripple Effect

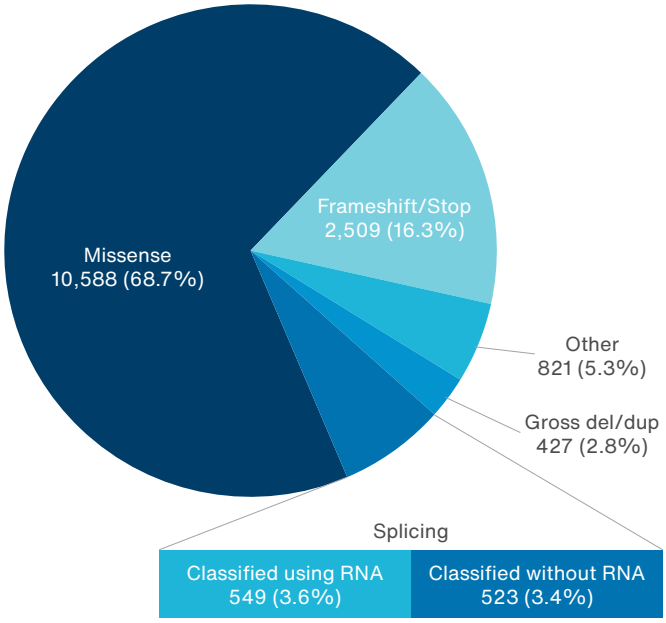
Extends clinical impact to thousands of patients

EXPERIENCE THAT MATTERS

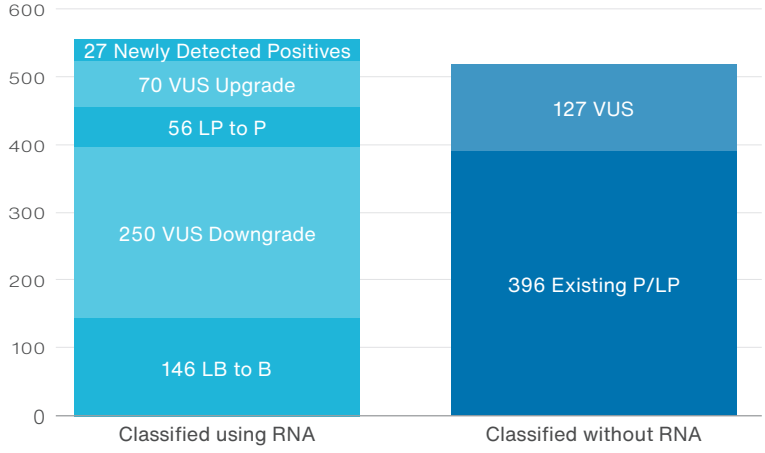
Here we review the two largest peer reviewed studies evaluating concurrent DNA-RNA genetic testing results.

In 2019, Ambry Genetics became the first clinical lab to introduce paired DNA-RNA testing. This extends analysis into introns normally missed by DNA-only testing.

The types of variants observed in our hereditary cancer cohort are shown on the right. We saw that splicing variants overall, and specifically splicing variants that required RNA for classification, were more common than gross deletions and duplications.



RNA EVIDENCE IS A POWERFUL TOOL IN SPLICING VARIANTS

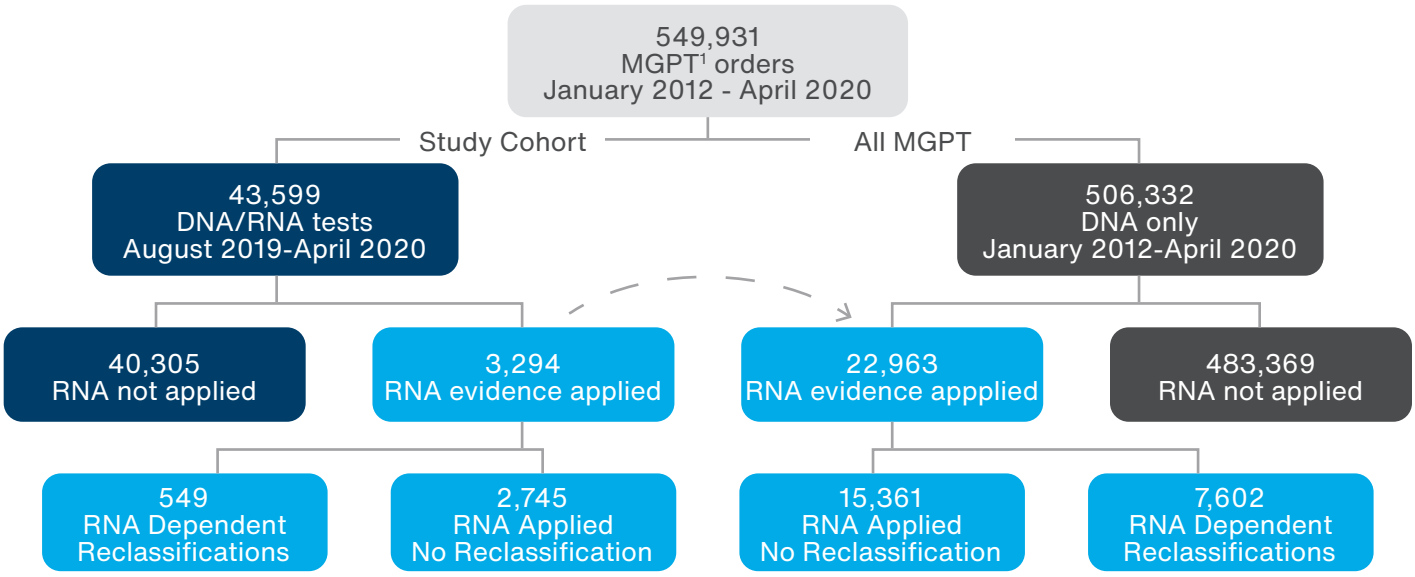


Reclassifications were made in half of individuals with splicing variants.

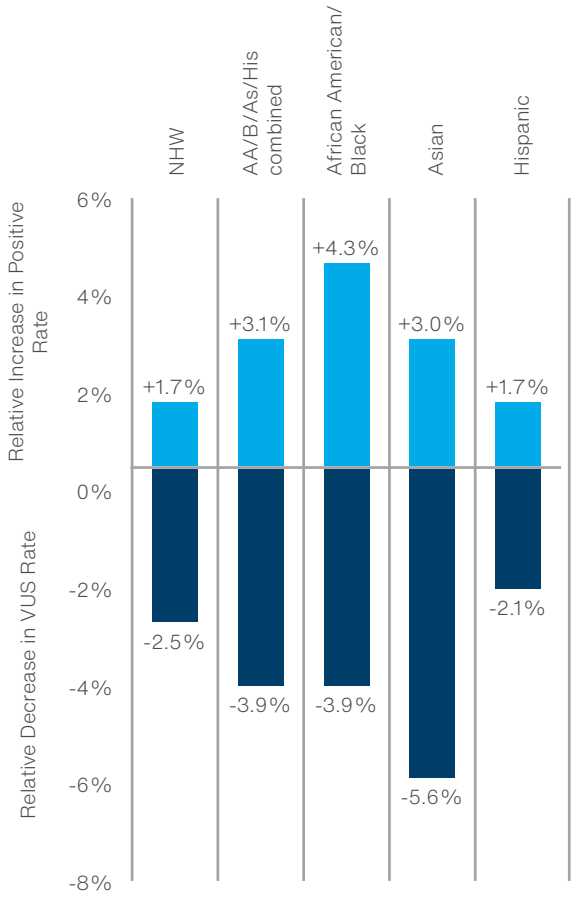
In over one quarter of individuals with an RNA-impacted result, reclassifications to likely pathogenic/pathogenic were made. Individuals with newly detected positive results would have been reported as negatives using DNA-only testing.

Resolution of VUS to likely benign/benign occurred in nearly half of individuals with an RNA-impacted result.

THE RIPPLE EFFECT OF RNA EVIDENCE



Based on expert guidelines, functional evidence from individuals who had RNA sequencing within the study period can be used in individuals with the same variant even if their test was ordered before RNA sequencing was available. Therefore, evidence generated from the first year of testing alone was applied to 26,000 individuals (5% of all tested), leading to reclassification that were dependent on RNA in 8,000 individuals (1.5% of all tested).



MITIGATING HEALTH DISPARITIES IN VARIANT CLASSIFICATION

Genetic data are typically derived from European cohorts, so there are evidence gaps in underrepresented populations. Generating novel functional evidence helps close those gaps and leads to a preferential improvement in accuracy among non-White populations, in which a larger increase in positive rate and decrease in VUS rate were recorded. Paired DNA and RNA sequencing may therefore play an important role in improving equity of genetic testing results.

TAKE HOME POINTS

The functional evidence provided by paired DNA and RNA sequencing can:

- increase accuracy of variant interpretation
- improve detection of pathogenic variants
- help resolve variants of uncertain significance
- address evidence gaps in non-White populations
- inform classification even in patients with DNA-only testing

Horton C, Hoang L, Zimmermann H, et al. Diagnostic Outcomes of Concurrent DNA and RNA Sequencing in Individuals Undergoing Hereditary Cancer Tesing.JAMA Oncol. 2023 Nov 4:e235586. doi:10.1001/jamaoncol.2023.5586.

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