Ambry Genetics®
A Konica Minolta Company

RESEARCH FOR YOUR PRACTICE

# RNA Genetic Testing Increases Diagnostic Yield of Hereditary Cancer Multigene Panel Tests

FEBRUARY 2020

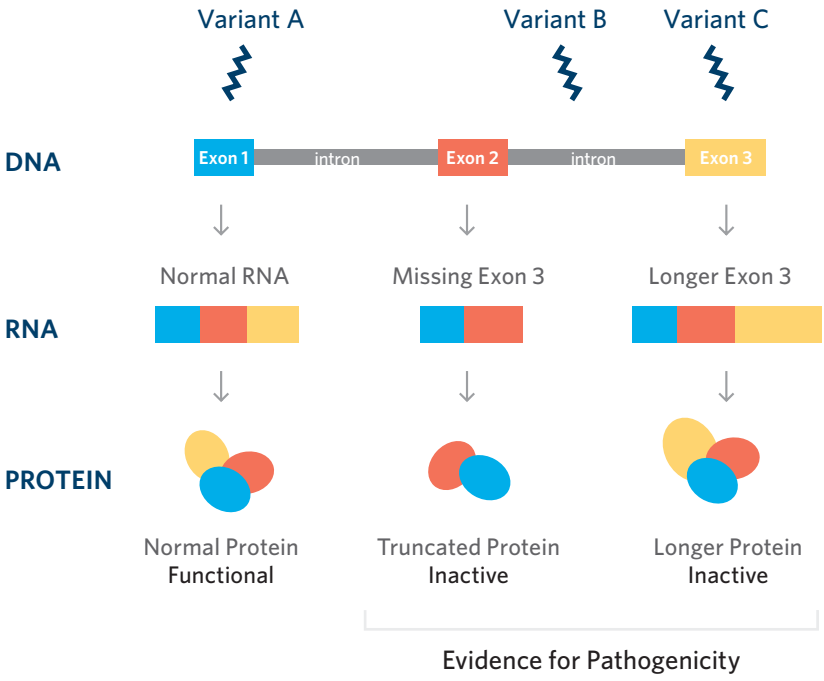
## Paired DNA and RNA genetic testing identifies more patients with hereditary cancer than DNA testing alone

Our study, recently published in *npj Precision Oncology*, demonstrated how paired DNA and RNA sequencing of 18 cancer predisposition genes improves the diagnostic yield of genetic testing and reduces variants of unknown significance, enhancing a clinician's ability to inform medical management.[1]

### Background

- Splicing is the removal of non-coding sequences (introns) from an RNA molecule followed by the ligation of exons, the protein coding regions of genes.[2,3]
- RNA genetic testing (RGT) generates data that can be used as a strong line of evidence to help determine if a DNA variant is pathogenic or benign.[4]
- RGT also enables the identification of pathogenic intronic variants in regions not typically captured by DNA testing alone.[3]
- This study described a scalable and targeted approach to RGT performed in parallel with DNA multi-gene panels and evaluated the change in diagnostic yield for 1,000 patients undergoing genetic testing for hereditary cancer to assess the clinical utility of this model.

FIGURE 1: VARIATION IN DNA CAN CAUSE ERRORS IN SPLICING RESULTING IN A PROTEIN THAT IS NOT PROPERLY EXPRESSED



# RNA Genetic Testing Identified Disease-Causing Variants that Would Not Have Been Resolved with DNA-Only Testing

## Increase in Diagnostic Yield

- 84 individuals received positive results from paired DNA and RNA genetic testing compared to 77 individuals, if only DNA testing was performed.
- The addition of RNA genetic testing resulted in a 9.1% relative increase in diagnostic yield.


- For 6 of 7 RNA-related positive cases, changes to medical management would be recommended based on current guidelines.

## Variants Impacted by RNA Genetic Testing

- Results of testing identified disease-causing variants in genes associated with breast and ovarian cancer (*BRCA1, BRCA2, ATM*), polyposis (*MUTYH*), and Lynch syndrome (*PMS2*).

| Variants Impacted by RNA | Classification Impact |
|---|---|
| *BRCA1* c.5152+6T>G | New alteration detected (Pathogenic mutation) |
| *BRCA1* c.81-9C>G | New alteration detected (Pathogenic mutation) |
| *ATM* c.3065T>G | Initial VLP classification |
| *ATM* c.8418+5G>A | Variant reclassified (VUS to VLP) |
| *BRCA2* c.475+4DELT | Variant reclassified (VUS to VLP) |
| *PMS2* c.11C>G | Variant reclassified (VUS to VLP) |
| *MUTYH* c.577-5A>G | Variant reclassified (VUS to VLP) |

VUS: Variant of Unknown Significance
VLP: Variant, Likely Pathogenic

## Key Benefits of +RNAinsight®

Identifies clinically actionable variants that may otherwise be inconclusive or missed by DNA-only testing

Reduces variants of unknown significance in real-time

Gives healthcare providers clearer, more accurate results to inform medical management


**REFERENCES**

1. Landrith T *et al.* Splicing profile by capture RNA-seq identifies pathogenic germline variants in tumor suppressor genes. *npj Precision Oncology* 2020
2. Rivas, M. A. *et al.* Human genomics. Effect of predicted protein-truncating genetic variants on the human transcriptome. *Science* 348, 666–669 (2015).
3. Scotti, M. M. & Swanson, M. S. RNA mis-splicing in disease. *Nat. Rev. Genet.* 17,19–32 (2016).
4. Richards, S. *et al.* Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. *Genet. Med.* 17, 405–424 (2015).




One Enterprise, Aliso Viejo, CA 92656 USA | Toll Free +1.866.262.7943 | Fax +1.949.900.5501 | ambrygen.com