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

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

• Variant A
  - DNA: Exon 1 → intron → Exon 2
  - RNA: Normal RNA
  - Protein: Normal Protein Functional
  - Evidence for Pathogenicity

• Variant B
  - DNA: Exon 1 → intron → Exon 2
  - RNA: Missing Exon 3
  - Protein: Truncated Protein Inactive

• Variant C
  - DNA: Exon 1 → intron → Exon 3
  - RNA: Longer Exon 3
  - Protein: Longer Protein Inactive
  - Evidence for Pathogenicity
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.

**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*).

<table>
<thead>
<tr>
<th>Variants Impacted by RNA</th>
<th>Classification Impact</th>
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<tbody>
<tr>
<td>BRCA1 c.5152+6T&gt;G</td>
<td>New alteration detected (Pathogenic mutation)</td>
</tr>
<tr>
<td>BRCA1 c.81-9C&gt;G</td>
<td>New alteration detected (Pathogenic mutation)</td>
</tr>
<tr>
<td>ATM c.3065T&gt;G</td>
<td>Initial VLP classification</td>
</tr>
<tr>
<td>ATM c.8418+5G&gt;A</td>
<td>Variant reclassified (VUS to VLP)</td>
</tr>
<tr>
<td>BRCA2 c.475+4DELT</td>
<td>Variant reclassified (VUS to VLP)</td>
</tr>
<tr>
<td>PMS2 c.11C&gt;G</td>
<td>Variant reclassified (VUS to VLP)</td>
</tr>
<tr>
<td>MUTYH c.577-5A&gt;G</td>
<td>Variant reclassified (VUS to VLP)</td>
</tr>
</tbody>
</table>

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**