

# Moving in the Fast Lane: Test Design and Validation to Produce Up-to-Date Hereditary Breast and Gynecologic Cancer Tests

## Background

- Genetic testing has become more important to clinicians who monitor and treat patients with breast and gynecologic cancers.
- Testing for many genes at once using a panel can identify cancer syndromes and clinically significant gene variants that may not be suspected.
- Such panels must be kept up to date with the most current knowledge of cancer susceptibility genes and validated.
- **Objective:** In this study, the investigators designed and validated a 66-gene hereditary cancer panel.

## Methods

- The 66-gene hereditary cancer panel includes only genes that primarily confer a  $\geq 2$ -fold increased risk or 5% lifetime risk of developing cancer. Thirty of the 66 genes are related to breast cancer, gynecological cancer, or both.
  - The protein-coding exons, intron-exon splice sites, and clinically relevant noncoding regions (deep intronic regions, 5' UTR, and 3' UTR) were interrogated for single-nucleotide variants (SNVs) and insertions/deletions (indels).
  - Copy number variations (CNVs) were targeted in relevant regions.
- An NGS library was created from extracted genomic DNA using a probe panel designed to enrich 4,500 genes associated with inherited disease; this approach allows for adjustment in the future.
- The library was sequenced on an Illumina NovaSeq instrument, and the resulting data were analyzed using a bioinformatics variant analysis pipeline developed in house.
- The validation process used DNA from Coriell Repository specimens; >100 deidentified whole-blood and saliva specimens; Genome in a Bottle (NA12878); and Ashkenazim Trios specimens (NA24149, NA24385, NA24143). For blood and saliva specimens, 11,911 variants in 508 genes had been previously identified by Sanger sequencing, NGS, or microarray assays.
- The analytic sensitivity (positive percent agreement [PPA]) and specificity (technical positive predictive value [TPPV] and negative percent agreement, NPA) were assessed for each SNVs, indels, and CNVs.

## Results

- Analytical sensitivity: PPA was 100% for SNVs, 100% for indels, and 97.8% for CNVs.
- Analytical specificity: Overall specificity (SNVs, indels, and CNVs) was >99.0%.
  - TPPV was 100% for SNVs, 99.3% for indels, and 100% for CNVs.
  - NPA was 100% for all variants.

## Conclusions

- The 66-gene hereditary cancer panel demonstrated high analytical sensitivity and specificity.
- The ability of the assay to target 4,500 genes allows for expedited updates to the panel as more gene-cancer associations are identified.

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