

Invitae hereditary cancer validation study:

A SYSTEMATIC COMPARISON OF TRADITIONAL AND MULTI-GENE PANEL TESTING FOR HEREDITARY BREAST AND OVARIAN CANCER GENES IN MORE THAN 1000 PATIENTS

OVERVIEW

A study comparing Invitae's panel test to traditional BRCA1 and BRCA2 tests in more than 1000 patients was undertaken in collaboration with the Stanford University School of Medicine and Massachusetts General Hospital. The study demonstrated 100% analytic sensitivity and specificity for Invitae's panel compared to traditional genetic test results for both sequence alterations and deletions/duplications. Variant classifications were also highly (99.8%) concordant.

BACKGROUND

Multi-gene panels for hereditary breast and ovarian cancer risk assessment are gaining acceptance, not only as additions to but also as replacements for traditional BRCA1/2 testing. To help determine which tests are appropriate for any given patient, it is important to understand the analytic and clinical performance of these tests by comparison with traditional testing.

METHODS

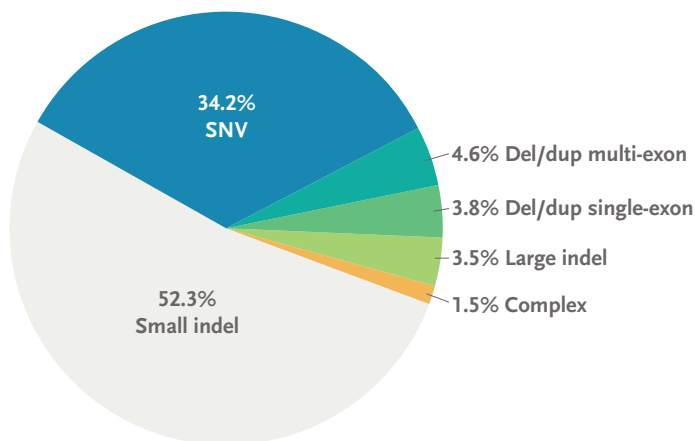
A total of 1105 individuals were tested using an Invitae 29-gene hereditary cancer panel. Sequence alterations and copy number deletions/duplications were determined by next-generation sequencing (NGS) using Invitae's custom biochemical and bioinformatics methodologies. For these 1105 individuals, high-quality reference and confirmatory data were available for direct comparison. Variants were classified using a framework (Sherloc) based on the American College of Medical Genetics and Genomics 2015 guidelines using only publicly available and not proprietary data resources. Classifications were compared for 975 individuals for whom traditional BRCA1/2 test results from Myriad Genetics were available.

RESULTS

- 100% analytic sensitivity and specificity was observed across all 750 comparable variant calls in the 1105 individuals (Table 1).
- These 750 variants included 48 technically challenging examples of sequence and/or copy number variation that together represented a significant fraction (13.4%) of the pathogenic variants in the prospective cases (Figure 1).
- Considering variant classifications for BRCA1/2, 99.8% report concordance was observed (Table 2).
- The rates of variants of uncertain significance for BRCA1/2 testing were comparable, albeit slightly higher, in the Invitae test versus the traditional tests (4.1% vs. 3.2%).
- Consistent with other studies of comparable populations, 4.5% of the BRCA1/2-negative patients had a mutation uncovered in another cancer risk gene.

Table 1: Analytic concordance

		Previous testing or independent confirmation		
		Variant present	Variant not present	Result
29-gene NGS panel	Variant detected	750 true positives	0 false positives	100% sensitivity (CI sequence: 100%–99.7%) (CI del/dup: 100%–91.8%)
	Variant not detected	0 false negatives	Sequence: 15.0m true negative base pairs Del/dup: 22.2k true negative exons	100% specificity (CI sequence: 100%–99.99998%) (CI del/dup: 100%–99.989%)

Figure 1: Types of pathogenic variants observed

Table 2: Interpretation concordance for BRCA1/2

		Previous BRCA1/2 testing			
		Positive	Uncertain	Negative	Total
BRCA1/2 results from 29-gene panel	Positive	188			188 (19.3%)
	Uncertain	2	30	8	787 (80.7%)
	Negative		1	746	
Total		190 (19.5%)	785 (80.5%)		975

DISCUSSION

Invitae's NGS panel test can provide analytic and clinical results highly comparable to those of traditional BRCA1/2 testing. For both sequence and deletion/duplication variants across many genes, 100% sensitivity and specificity was observed, as well as high interpretation concordance (99.8%). Panel tests can also uncover potentially actionable findings that may be otherwise missed. A detailed study of the clinical actionability of non-BRCA1/2 variants observed in these and other patients is reported separately.

PUBLICATION

This study is published in the *Journal of Molecular Diagnostics*, the official journal of the Association for Molecular Pathology (AMP).

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Learn more about this and other Invitae validation studies at www.invitae.com/validation-studies.