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Patient Information

Name:	Doe, Jane	**Accession Number:**	BRCA 1/2_Screening
Date of Birth:	03/30/1989		
Gender:	Female	**Ordering Physician:**	John Smith, MD
Date Received:	01/31/2017	**Date Accessioned:**	01/31/2017
Date Collected:	01/30/2017	**Date Reported:**	02/14/2017

Review Status Final

Test Performed

BRCA1/2 Screening: Sequence analysis was performed on this sample of peripheral blood by means of targeted next-generation sequencing. See Test Details for more information.

Result Summary

Variants Detected	Classification	Zygosity
BRCA 1 p.C14G p.C61G	Pathogenic	heterozygous

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Clinically Relevant Results

BRCA 1 p.C14G p.C61G Pathogenic	*BRCA1* encodes a nuclear phosphoprotein that plays a role in maintaining genomic stability, and also acts as a tumor suppressor. Germline alterations in BRCA1 are associated with Hereditary Breast and Ovarian Cancer syndrome (PMID: 24116874). *A BRCA1* C61G missense mutation located in exon 5 is identified in this patient. This variant has been shown to be pathogenic in vivo (PMID: 19770520). BRCA1 C61G has been reported as a founder mutation specifically in Jewish individuals (PMID: 19594371) and in the European population (PMID:16168118; 20345474). The cancer-predisposing C61G mutation, which alters a conserved Zn2+-binding residue, abolishes metal binding to Site II of the RING finger motif, while Site I remains intact and functional. The C61G mutation also results in increased proteolytic susceptibility of the COOH-terminal portion of the NH2-terminal domain and perturbs the oligomerization properties of *BRCA1* (PMID: 9525870). This mutation located in the BRCA1 RING domain reduces BRCA1/BARD1 heterodimerization and abrogates its ubiquitin ligase activity (PMID: 22172724; 16403807; 11320250). In vivo analysis revealed that in contrast to BRCA1-deficient mammary carcinomas, tumors carrying the *BRCA1* C61G mutation responded poorly to platinum drugs and PARP inhibition and rapidly developed resistance (PMID: 22172724). Genetic counseling is recommended for individuals carrying the *BRCA1* C61G variant.

Other Results

Other variants: See "All Identified Variants Detailed Information" section.

Test Details

BRCA1 and BRCA2 Screeing: *BRCA1* and BRCA2 were subjected to targeted next generation sequencing analysis. Details available upon request.

Database Details: The versions/releases/builds/dates of the following databases were used to generate this report.

- Genomic Build: GRCh38.p7
- Genomic Anotation Sources: NCBI RefSeq v108
- ExAC: v0.3.1
- dbNSFP: 3.3c
- dbSNP: 149
- ClinVar: Feb 2017
- NHLBI ESP: v.0.0.30

Coding Exon Coverage Metrics: All exons of all genes in the ordered gene set achieved coverage of 10x or greater at least 90% of positions.

Methodology

General information: Hereditary cancer syndromes are thought to account for 5-10% of cancers. They are associated with an early age at diagnosis, multi-focal or bilateral disease, or multiple primary tumors. Individuals may have multiple family members across generations affected. More than 200 hereditary cancer syndromes have been identified but the best studied include primary cancers of the colorectum, stomach, breast, ovary, endometrium, and endocrine organs (thyroid, parathyroid, pancreas, and pituitary). The genes targeted in this panel are known to be associated with hereditary cancer syndromes.

Methodology: Genomic DNA (gDNA) is isolated from peripheral blood, quantified, and sheared. Following an amplification step, oligonucleotide probes are used for target sequence enrichment. The targeted library is then amplified and purified for loading on the Ion Torrent Next Generation Sequencing instrument. The targeted DNA fragments are sequenced in parallel and resultant data file is used for analysis.

Informatics Methodology: There are five informatics tools used. Novoalign is an alignment tool. Freebayes and Samtools (Mpileup) are variant callers used to identify substitutions. Pindel and GATK are a variant callers used to identify insertions, and deletions. Relevant versions and parameters used for each tool are detailed below:

1. Novoalign
Version 3_04_04
Parameters: -o SAM -r none --hlimit 7 -t 20,4 -i 230 140 --matchreward 3 --softclip 9999 -l 30 -e 100 -H -c 12

2. Freebayes
Version v1.0.2-29
Parameters: --min-alternate-count 10 --min-alternate-fraction 0.03 --min-coverage 10 --min-base-quality 20 --minmapping-quality 30 --min-supporting-allele-qsum 20 --min-supporting-mapping-qsum 30 --min-alternate-qsum 40

3. Pindel
Version 0.2.5b8
sam2pindel: Parameters: 270 sample 0 "Illumina-PairEnd"
pindel: Parameters: -c 1 -r false -t false -l false -k false -T 1

4. samtools (mpileup)
Version 0.1.19

5. GATK
Version 1.2
Parameters: -T UnifiedGenotyper -stand_call_conf 1.0 -stand_emit_conf 1.0 -dcov 5000 -G Standard -glm INDEL

Disclaimer

Rare diagnostic errors can occur due to primer or probe binding site mutations. Sensitivity to detect insertions and deletions smaller than a full exon may be reduced. Based on validation study results, this assay achieves >99% analytical sensitivity and specificity. Novel regulator region mutations and deep intronic mutations will not be detected by this assay. Other genes associated with hereditary breast and ovarian cancer are not evaluated. This test has components designated by the manufacturer as "For Research Use Only". The performance characteristics of this test were determined by Reference Laboratory. The components have not been cleared or approved by the U.S. Food and Drug Administration (FDA). The test results are not intended to be used as the sole means for clinical diagnosis or patient management.

All Identified Variants Detailed Information

Level 1 - Pathogenic Variant

Non-synonymous (Variants found : 1)

BRCA1 NM_007294.3:c.181T>G NM_007297.3:c.40T>G NM_007298.3:c.181T>G NM_007299.3:c.181T>G NM_007300.3:c.181T>G	(chr17:g.41258504A>C) NP_009225.1:p.C61G NP_009228.2:p.C14G NP_009229.2:p.C61G NP_009230.2:p.C61G NP_009231.2:p.C61G

No established biological impact, non-coding region (Variants found : 0)

Synonymous (Variants found : 0)

Level 2 - Likely pathogenic variant

Non-synonymous (Variants found : 0)

No established biological impact, non-coding region (Variants found : 0)

Synonymous (Variants found : 0)

Level 3 - Variant of uncertain significance

Non-synonymous (Variants found : 0)

No established biological impact, non-coding region (Variants found : 0)

Synonymous (Variants found : 0)

Level 4 - Likely benign variant

Non-synonymous (Variants found : 1)

No established biological impact, non-coding region (Variants found : 0)

Synonymous (Variants found : 0)

Level 5 - Benign variant

Non-synonymous (Variants found : 14)

No established biological impact, non-coding region (Variants found : 0)

Synonymous (Variants found : 19)

Report electronically reviewed and signed out by
Bryce Daines

Electronically signed by Bryce Daines