MEDICAL DIAGNOSTIC LABORATORIES L.L.C.

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MDL#: 9752081

Physician Copy

Final - Corrected (v1) 11-8-2023

Test Results

Patient Information: **SSN:** XXX-XX-5555 **DOB:** 1/1/1993 (Age: 22)

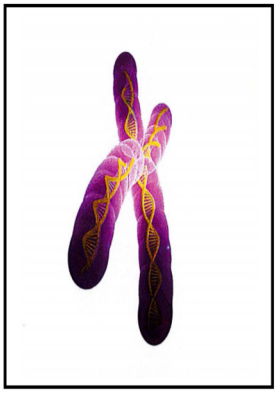
DOE, JANE
90 TRENTON ROAD
DAYTON, NJ 08690

Home: (142) 141-4113 **Patient ID:** 4444444

Genetic Counselor Information:

Genetic counseling was waived.

Tel: 661-322-4902
Fax: 661-322-4904



Ordering Physician/Lab: **NPI:** 2121212121

JOHN DOE MD
JOHN DOE, MD
202 ANY STREET
DAYTON, NJ 08810

Tel: 555-555-5551
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Results Faxed To:
JANE DOE HOSPITAL

Specimen Type:	Saliva
Date Collected:	2/3/2020
Date Processed:	2/5/2020
Date Reported:	11/8/2023

BRCAcare™ 2600: Breast Cancer High Risk Extended Panel Plus

RESULT: Positive for Variant of Unknown Significance

AFFECTED GENES

ATM **(1)**	*BARD1* (0)	*BRCA1* (0)	*BRCA2* (0)	*BRIP1* (0)	*CDH1* (0)	*CHEK2* (0)	*NBN* (0)	*NF1* (0)	*PALB2* (0)
PTEN (0)	*RAD51C* (0)	*RAD51D* (0)	*STK11* (0)	*TP53* (0)					

VARIANTS RELEVANT TO INDICATION FOR TESTING

One uncertain significance variant in ATM was identified in this individual. No other variants of relevance to the indication were identified. Please see below for more detailed variant information.

Gene & Transcript	Variant	Allele State	Location	Disorder or Phenotype	Inheritance	Classification
ATM NM_000051.3	c.7390T>C p.Cys2464Arg	Het.	Exon 50,Exon 7	Breast Cancer	Autosomal Recessive / Heterozygous	Uncertain Significance

RECOMMENDATIONS

The interpretation of these results should be done in the context of a patient's medical record and family history. Please note that interpretation and classification of the variants reported here may change over time. Please see a genetic counselor for services regarding the implications of these results in the context of understanding the implications of incidental findings, family planning and the informing of family members of potentially shared genetic outcomes.

APPROACH

Sequencing of the coding regions and flanking non-coding regions of select genes was performed using Next Generation Sequencing and the data was analyzed to identify both previously classified and novel variants in targeted genes. The select gene panel including targeted genes with previous implications of association with breast cancer, ovarian cancer, and/or Lynch syndrome were covered with a minimum read depth of 20X. A multiplex ligation-dependent probe amplification (MLPA) analysis which detects deletions and/or duplications involving one or more exons of ***BRCA1*** *and* ***BRCA2*** *genes,* was completed.

DETAILED VARIANT INFORMATION (VARIANTS RELEVANT TO INDICATION FOR TESTING)

Gene & Transcript	Variant	Inheritance	Disorder or Phenotype	Criteria	Classification
ATM NM_000051.3	c.7390T>C p.Cys2464Arg	Autosomal Recessive / Heterozygous	Breast Cancer		Uncertain Significance

Location	Allele State	Allelic Read Depths
Exon 50,Exon 7	Het.	Ref(T): 243, Alt(C): 190, VAF: 43.88%

Genomic Position	Variant Frequency
NC_000011.9:g.108201023T>C	0.091% max frequency observed in gnomAD Non Finnish European

VARIANT INTERPRETATION: The missense variant p.C2464R in ATM (NM_000051.3) has not been reported previously as a pathogenic variant nor as a benign variant, to our knowledge. There is a large physicochemical difference between cysteine and arginine, which is likely to impact secondary protein structure as these residues differ in polarity, charge, size and/or other properties. For these reasons, this variant has been classified as Uncertain Significance.

METHODOLOGY

The individual's DNA was extracted and fragmented, with fragments from the coding regions and flanking non-coding regions of the select gene panel targeted for amplification and sequencing. Reads from the sequence output were aligned to the human reference genome (GRCh37) and variants to the reference were called using Sentieon DNAseq (vs. 2018.08.07). The variants were annotated and filtered using the Golden Helix VarSeq (vs 2.3.0) analysis workflow implementing the ACMG guidelines for interpretation of sequence variants. This includes comparisons against the gnomAD population catalog of variants in 123,136 exomes, the 1000 Genomes Project Consortium's publication of 2,500 genomes, the NCBI ClinVar database of clinical assertions on variant's pathogenicity and multiple lines of computational evidence on conservation and functional impact.
The variant results are reported using numbering and nomenclature recommended by the Human Genome Variation Society (HGVS http://hgvs.org). Nucleotide and codon number are based on the gene transcript: ***ATM*** (NM_000051.3), ***BARD1*** (NM_000465.3), ***BRCA1*** (NM_007294.3), ***BRCA2*** (NM_000059.3), ***BRIP1*** (NM_032043.2), ***CDH1*** (NM_004360.3), ***CHEK2*** (NM_007194.3), ***NBN*** (NM_002485.4), ***NF1*** (NM_000267.3), ***PALB2*** (NM_024675.3), ***PTEN*** (NM_000314.6), ***RAD51C*** (NM_058216.2), ***RAD51D*** (NM_002878.3), ***STK11*** (NM_000455.4) and ***TP53*** (NM_000546.5).

In addition to the gene sequencing assay, a MLPA analysis which detects deletions and/or duplications involving one or more exons, including those that affect the entire ***BRCA1*** *and* ***BRCA2*** *genes*, was completed.

VARIANT ASSESSMENT PROCESS

The following databases and *in silico* algorithms are used to annotate and evaluate the impact of the variant in the context of human disease: 1000 genomes, gnomAD, ClinVar, OMIM, dbSNP, NCIB RefSeq Genes, ExAC Gene Constraints, VS-SIFT, VS-PolyPhen2, PhyloP, GERP++, GeneSplicer, MaxEntScan, NNSplice and PWM Splice Predictor. Analysis was reported using the HGVS nomenclature (www.hgvs.org/mutnomen) as implemented by the VarSeq transcript annotation algorithm. The reported transcript matches that used most frequently by clinical laboratories submitting to ClinVar.

LIMITATIONS

It should be noted that this test is performed on a limited number of genes and does not include all intronic and non-coding regions. This assay cannot detect mutations affecting gene regions not examined in the assay. Intronic regions are analyzed up to 10 nucelotides before and 10 nucleotides after each intron/extron boundary. This report only includes variants that meet a level of evidence threshold for cause or contribution to disease. Certain classes of genomic variants are also not covered using the NGS testing technology, including triplet repeat expansions, copy number alterations, translocations and gene fusions or other complex structural rearrangements. More evidence for disease association of genes and causal pathogenic variants are discovered every year, and it is recommended that genetic variants are re-interpreted with updated software and annotations periodically.
This test was developed and its performance characteristics have been determined by Medical Diagnostic Laboratories, LLC. Performance characteristics refer to the analytical performance of the test. It is not been reviewed by the US Food and Drug Administration (FDA). The FDA has determined that such clearance or approval is not necessary.

REFERENCES

Richards, Sue, 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." Genetics in Medicine 17.5 (2015): 405.
Exome Aggregation Consortium et al. "Analysis of Protein-Coding Genetic Variation in 60,706 Humans." Nature 536.7616 (2016): 285–291. PMC. Web. 13 May 2018.
The 1000 Genomes Project Consortium. "A Global Reference for Human Genetic Variation." Nature 526.7571 (2015): 68–74. PMC. Web. 13 May 2018.

** CORRECTIONS:

11-8-2023 10.58 (v1) Saliva

RAD51C variant (NM_058216.2 c.790 G>A, p.G264S) initially reported as variant of unknown significance was re-evaluated and classified as Benign based upon recent clinical and experimental studies.