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Patient Information	Accession:	Physician:	Report Date: **Aug 23, 2019**
DOB:	FD Test#:		
Sex:	Order#:	Phone:	
MR#	Ext Test#:	Fax:	
FD Patient#:	Ext Order#:		
	Specimen Type: Blood (EDTA)		
	Collected:		
	Received Date:		
	Authorized Date:		

FINAL Report

TEST PERFORMED

ASPiRA GenetiX BRCA1, BRCA2 reflex to Targeted Breast and Ovarian 24
(24 Gene Panel; gene sequencing with deletion and duplication analysis)

INDICATIONS FOR TESTING:

Personal History: None **Family History:**

RESULTS:

A heterozygous pathogenic variant consistent with a molecular diagnosis of an increased risk for *ATM*-related cancers was identified.

Actionable Variants

Gene Info		Variant Info		
GENE	INHERITANCE	VARIANT	ZYGOSITY	CLASSIFICATION
ATM NM_000051.3	Autosomal Dominant & Autosomal Recessive	c.7327C>T p.Arg2443*	Heterozygous	**Pathogenic**

Additional Variants

None

CLINICAL INTERPRETATIONS AND RECOMMENDATIONS:

ATM

Variant: A nonsense variant, predicted to result in the loss of function of the *ATM* gene was detected.
Cancer Risk: Heterozygous carriers of *ATM* mutations are estimated to have an overall 4-fold increased risk for developing cancers, primarily for breast cancer with an estimated risk of 9% by age 50 and, depending on the study, 17%-52% by age 80 (PubMed: 15928302, 16998505, 1961222).
Cancer Spectrum: Individuals with heterozygous *ATM*-mutations primarily have an increased risk of developing breast cancer. However, pancreatic cancer, leukemia and lymphoma have also been reported (PubMed: 22585167, 20301790).
More frequent screening for breast cancer in individuals with heterozygous *ATM* mutations may be warranted. The effect of impaired DNA repair on treatment options for this individual should be taken into account. For further information on cancer risk, spectrum and possible management options, see PubMed: 20301790.

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Other variants, notes, and recommendations:

- The above analysis was ordered as reflex testing for this sample. Testing was initiated following nondiagnostic primary test results, reported separately.
- As requested, this report only includes variants classified as Pathogenic, Likely Pathogenic, or Risk Allele at the time of analysis. If detected, this report does not include variants classified as uncertain significance.
- This individual is a carrier for an autosomal recessive *ATM*-related condition. This individual's offspring may be at risk of being affected by this condition. Targeted testing may be warranted for family planning purposes.
- Guidelines for the management of various cancer syndromes can be found at nccn.org
- Where available, clinical trials may be found under clinicaltrials.org
- Children, siblings, and each parent of this individual have up to a 50% chance of being a carrier of the pathogenic variant reported. Testing of at risk family members for this variant is available.
- Gene specific limitations are present, see Test Summary.
- These results should be interpreted in the context of this individual's clinical findings, biochemical profile, and family history.
- Genetic counseling is recommended.

TEST SUMMARY:

24 genes tested (99.99% of coding bases at >50x).

ATM, *BARD1*, *BRCA1*, *BRCA2*, *BRIP1*, *CDH1*, *CHEK2*, *DICER1*, *EPCAM*, *MLH1*, *MRE11*, *MSH2*, *MSH6*, *NBN*, *NF1*, *PALB2*, *PMS2*, *PTEN*, *RAD50*, *RAD51C*, *RAD51D*, *SMARCA4*, *STK11*, *TP53*

Gene Specific Notes and Limitations

- *EPCAM* gene testing is limited to deletion and duplication analysis (PubMed: 23264089).
- Inversion of *MSH2* exons 1-7 ("Boland" inversion) is assessed for Lynch Syndrome, Colorectal, and Endometrial Cancer Panel testing (for both Focus and Comprehensive Panels) as well as Comprehensive Gastric Cancer Panel testing. Unless otherwise specified, this testing is not performed for other cancer panels, but is available upon request.
- The ordered testing method does not guarantee the detection of potentially causative somatic changes in *NF1*.
- The whole *PMS2* gene is assessed for both sequence and copy-number variants (if del/dup is ordered). Variants located in the region homologous to the pseudogene *PMS2CL* (exons 12-15) will be confirmed by long range PCR. Exception: a specific variant, NM_000535.6:c.2186_2187del (p.Leu729Glnfs*6), may not be detected due to pseudogene interference unless there is clinical suspicion for Lynch Syndrome. Potential copy number variants located in the region homologous to the pseudogene *PMS2CL* will be tested by LR-PCR with NGS. The sensitivity of this approach may not be as high as for copy number variants in other genes.
- The *PTEN* promoter region is analyzed for both sequencing and copy number variants.
- Copy-number analysis of the *RAD50* gene is limited to variants encompassing at minimum two consecutive exons.

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INTERPRETATION:

About *ATM*

Heterozygous pathogenic mutations in *ATM* have been associated with an increased risk for breast and pancreatic cancer (PubMed: 15928302, 22585167, 20301790). Of note: genotype-phenotype studies suggest the cancer risk for heterozygous carriers may be dependent on the type of mutation detected (PubMed: 20301790). Biallelic mutations in *ATM* have been associated with ataxia-telangiectasia (A-T), which is characterized by a severe sensitivity against ionizing radiation, such as x-rays, and an increased risk for leukemia and lymphoma, as well as other cancers (PubMed: 20301790; OMIM: 607585).

The gene product of the *ATM* gene is a protein called ATM serine/threonine kinase. See OMIM gene entry for *ATM* (OMIM: 607585) for further information.

ATM NM_000051.3:c.7327C>T (p.Arg2443*)

Classification: **Pathogenic**

Zygosity and Inheritance	• This heterozygous pathogenic variant is consistent with autosomal dominant inheritance of a *ATM*-related condition. • This heterozygous pathogenic variant is consistent with this individual being a carrier for an autosomal recessive *ATM*-related condition.
Variant Type	• Genomic change: Chr11(GRCh37):g.108200960C>T. • This variant is predicted to result a stop gain (nonsense) change of the wild type Arg at codon 2443 in exon 50 of the *ATM* gene product. • This variant is predicted to result in a premature truncation of the *ATM* gene product.
Variant in Cases	• This variant has been reported as heterozygous in individuals with breast cancer (PubMed: 15101044, 26822949), as well as as homozygous or compound heterozygous in at least two individuals with ataxia-telangiectasia (PubMed: 30198223, 8808599). • Other truncating variants in the *ATM* gene have been reported as pathogenic (PubMed: 12810666, 15880721, 28779002, 30287823). • This variant is classified as a "Disease Mutation" (DM) in the Human Gene Mutation Database (HGMD).
Variant in Controls	• This variant has been observed at a frequency of less than 0.01% (1/245842 alleles). • The highest allele frequency that this variant has been observed at in any sub-population with available data is less than 0.01% (European (Non-Finnish) population). • There are 0 homozygous control individuals for this variant. • The Broad Institute database was used for this analysis.

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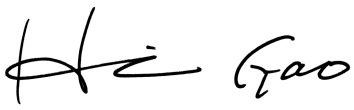
METHODS:

Genomic DNA from the submitted sample is barcoded and enriched for the coding exons of targeted genes using hybrid capture technology. Prepared DNA libraries are sequenced using a Next Generation Sequencing (NGS) technology. Sequencing results are aligned to the human genome reference sequence (assembly GRCh37 / hg19) and variants are detected in regions with sufficient coverage. In general, 100% of coding regions and splicing junctions are covered to at least 50x by NGS or by Sanger sequencing. Locus specific databases, literature searches, and other molecular biological principles are used to classify variants. To minimize false positive results, any variants that do not meet internal quality standards are confirmed by Sanger sequencing. Only variants classified as pathogenic, likely-pathogenic, or unknown significance which are located in the coding regions and nearby intronic regions (+/- 20bp) of the genes listed above are reported. Likely benign and benign variants (including intronic and synonymous variants which are not predicted to impact splicing) are not included in this report, but are available upon request. All genes listed were evaluated for large deletions and/or duplications. Deletions or duplications identified by NGS are confirmed by an orthogonal method (qPCR or MLPA). New York patients: diagnostic findings are confirmed by Sanger sequencing for variants in genes for which confirmation of NGS results has been performed <10 times. Bioinformatics: Fulgent Germline Pipeline v2019.1 was used to generate variant calls for this test.

LIMITATIONS:

Test results and variant interpretation are based on the proper identification of the submitted specimen and use of correct human reference sequences at the queried loci. In very rare instances, errors may result due to mix-up or co-mingling of specimens. Positive results do not imply that there are no other contributions, genetic or otherwise, to the patient's phenotype, and negative results do not rule out a genetic cause for the indication for testing. Official gene names change over time. Fulgent uses the most up to date gene names based on HUGO Gene Nomenclature Committee (https://www.genenames.org) recommendations. If the gene name on report does not match that of ordered gene, please contact the laboratory and details can be provided. Result interpretation is based on the collected information and Alamut annotation available at the time of reporting. This assay is not designed or validated for the detection of mosaicism. DNA alterations in regulatory regions or deep intronic regions (greater than 20bp from an exon) will not be detected by this test. There are technical limitations on the ability of DNA sequencing to detect small insertions and deletions. Our laboratory uses a sensitive detection algorithm, however these types of alterations are not detected as reliably as single nucleotide variants. Rarely, due to systematic chemical, computational, or human error, DNA variants may be missed. Although next generation sequencing technologies and our bioinformatics analysis significantly reduce the confounding contribution of pseudogene sequences or other highly-homologous sequences, sometimes these may still interfere with the technical ability of the assay to identify pathogenic variant alleles in both sequencing and deletion/duplication analyses. Deletion/duplication analysis can identify alterations in genomic regions and is evaluated at a single exon resolution level in relevant genes associated with the patient's clinical presentation. For custom added genes and applicable genes that may be of interest, deletion/duplication analysis is evaluated at a resolution of two or more contiguous exons. When novel DNA duplications are identified, it is not possible to discern the genomic location or orientation of the duplicated segment, hence the effect of the duplication cannot be predicted. Where deletions are detected, it is not always possible to determine whether the predicted product will remain in-frame or not. Unless otherwise indicated, in regions that have been sequenced by Sanger, deletion/duplication analysis has not been performed.

SIGNATURE:



Dr. Harry Gao, DABMG, FACMG on **Aug 23, 2019 13:20**
Electronically signed

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DISCLAIMER:

This test was developed and its performance characteristics determined by Fulgent Genetics CAP #8042697 CLIA #05D2043189; 4978 Santa Anita Ave., Suite 205, Temple City, CA 91780. It has not been cleared or approved by the FDA. The laboratory is regulated under CLIA as qualified to perform high-complexity testing. This test is used for clinical purposes. It should not be regarded as investigational or for research. Since genetic variation, as well as systematic and technical factors, can affect the accuracy of testing, the results of testing should always be interpreted in the context of clinical and familial data. For assistance with interpretation of these results, healthcare professionals may contact us directly at 844.277.4721 or aspirasupport@vermillion.com. It is recommended that patients receive appropriate genetic counseling to explain the implications of the test result, including its residual risks, uncertainties and reproductive or medical options.