MEDICAL DIAGNOSTIC LABORATORIES L.L.C.
2439 KUSER ROAD, HAMILTON, NJ 08690-3303
TL: 609-570-1000, FX: 609-570-1050, TF: 877-269-0090
www.mdlab.com

Preliminary

MDL#: 6522138 **Test Results** **Physician Copy**

Genetic Counselor Information:

Specimen Type:	Mouthwash
Date Collection:	2/9/2016
Date Processed:	2/10/2016
Date Reported:	

Patient Information: **SSN:** XXX-XX-1111 **DOB:** 1/1/1987 (Age: 29)

MRS.DOE, JANE M
56 LIBERTY DRIVE
ABC
DAYTON, NJ 08810

Home: **(732) 555-6666** **Patient ID:** TEST123

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

JOHN DOE, MD

202 ANY STREET
DAYTON, NJ 08810

Tel: 609-570-1005
Fax: 609-570-1017

BRCAcare™ 1235:Breast Cancer High Risk Extended Panel Plus: 14 genes

Interpretation Summary:

POSITIVE FOR LIKELY PATHOGENIC MUTATION

Test Performed	Gene Transcript	Variant	Zygosity	Location	Disease	Inheritance	Parental Origin	Reference	Classification
BRCA1 Sequencing								-	NO ANOMALIES DETECTED
BRCA1 Deletion / Duplication Analysis								-	NO ANOMALIES DETECTED
BRCA2 Sequencing								-	NO ANOMALIES DETECTED
BRCA2 Deletion / Duplication Analysis								-	NO ANOMALIES DETECTED
ATM Sequencing	NM_000051.3	g.108203474G>T	Heterozygous	Exon52	Cancer (Breast, Ovarian,other)	Autosomal recessive	Unknown	-	VARIANT OF UNCERTAIN SIGNIFICANCE
ATM Sequencing	NM_000051.3	g.108151708_108151709insTA	Heterozygous	Exon23	Cancer (Breast, Ovarian,other)	Autosomal recessive	Unknown	-	VARIANT OF UNCERTAIN SIGNIFICANCE
CDH1 Sequencing	NM_004360.3	c.-285C>A (Non protein-coding)	Homozygous	Exon5	Cancer (Breast, HDGC Gastric)	Autosomal dominant	Unknown	1-2	LIKELY PATHOGENIC
CHEK2 Sequencing	NM_007194.3	c.1461+1897A>G	Homozygous	Exon17	Cancer (Breast,Prostate,other)	Autosomal dominant	Unknown	-	VARIANT OF UNCERTAIN SIGNIFICANCE
PALB2 Sequencing	NM_024675.3	c.2903C>G (p.Ala968Gly)	Heterozygous	Exon5	Cancer (Breast, Ovarian,other)	Autosomal dominant	Unknown	-	VARIANT OF UNCERTAIN SIGNIFICANCE
PALB2 Sequencing	NM_024675.3	g.23635422insA	Heterozygous	Exon6	Cancer (Breast, Ovarian,other)	Autosomal dominant	Unknown	-	VARIANT OF UNCERTAIN SIGNIFICANCE

View: M

Mail:	Yes	Overnight
	All	Yes

Fax:	Yes	***Manual***
	All	No

Medical Director, Dante A. Ragasa, MD.

BR

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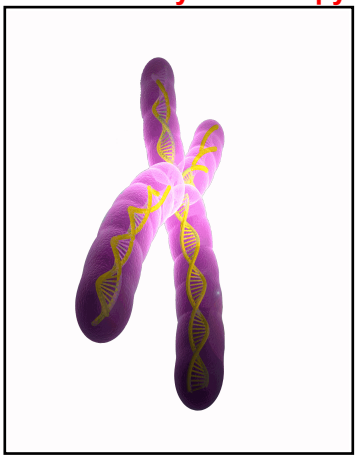

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BARD1,BRIP1,MUTYH,PTEN,RAD51C,RAD51D,STK11,TP53 Sequencing — **NO ANOMALIES DETECTED**

The following Likely Benign variants were also detected:

Gene	Gene Transcript	Variant	Zygosity	Location	Disease	Inheritance	Parental Origin	Ref.
BARD1	NM_000465.2	c.1977A>G (p.Arg659=)	Heterozygous	Exon2	Cancer (Breast, Ovarian)	Autosomal dominant	Unknown	-
STK11	NM_000455.4	c.374+24G>T	Heterozygous	Exon2	Cancer (Breast, Ovarian,other)	Autosomal Dominant	Unknown	-

Comprehensive Interpretation:

Test Interpretation:
Sequencing of the coding regions and splice junction sites of the CDH1 gene was done and was **POSITIVE for the c.-285C>A (Non protein-coding)** change in the CDH1 gene. This change has been identified as having strong likelihood of causing Hereditary Breast Ovarian Cancer Syndrome and is considered **LIKELY PATHOGENIC**. This change was identified by NGS and classified based on the MDL variant classification system. This change has strong evidence implicating it as a cause of increasing risk for development of breast and/or ovarian cancers.

Sequencing of the coding regions and splice junction sites of the ATM,CHEK2,PALB2 genes were completed and determined to be NEGATIVE for any pathogenic changes predicted to cause an increased risk of breast and/or ovarian cancers. However, genetic variants g.108151708_108151709insTA(ATM),g.108203474G>T(ATM),c.1461+1897A>G(CHEK2),c.2903C>G (p.Ala968Gly) (PALB2),g.23635422insA(PALB2) were identified. These variants are classified as **Variants of Uncertain Significance (VUS)** by the MDL variant classification system based on public database resources and In Silico analysis using PROVEAN, SIFT and MutationTaster. Variants of these types **may or may not** affect the function of the protein encoded by the genes in which they are found. Therefore, the contribution of these variants to the relative risk of breast, ovarian, pancreatic, or other cancers cannot be established solely from this testing. Comprehensive testing of selected first-degree relatives and family members affected with cancer is available to assist in the categorization of the VUS.

Sequencing of the coding regions and splice junction sites of the BARD1,BRCA1,BRCA2,BRIP1,MUTYH,PTEN,RAD51C,RAD51D,STK11,TP53 gene was completed and was determined to be NEGATIVE for any pathogenic changes predicted to cause an increased risk of breast and/or ovarian cancers.

In addition to the gene sequencing assay, a multiplex ligation-dependent probe amplification (MLPA) analysis which detects deletions and/or duplications involving one or more exon, including those that affect the entire BRCA1 and BRCA2 gene, was completed. No deletions or duplications were detected.

In coordination with the healthcare provider and genetic counselors, MDL provides complimentary testing of the gene variants of unknown significance (VUS) for blood relatives with hereditary breast and ovarian cancer syndrome (HBOC) according to the National Comprehensive Cancer Network HBOC Guidelines (version 2.2014). This is offered to patients which primary detection of the VUS was by the MDL Breast Cancer High Risk Extended Panel Plus Analysis. This information will aid in variant classification and will be made publically available through deposition into the ClinVar and BIC databases.

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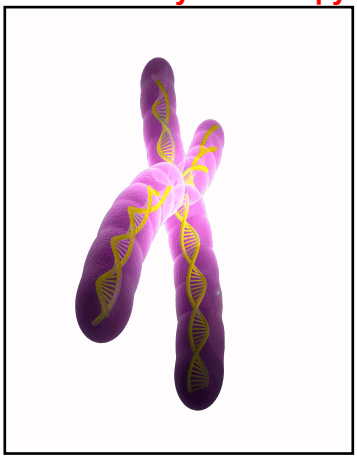

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Comprehensive Interpretation (continued):

The classification and interpretation of all genetic variants identified as a result of this genetic testing is based on the current scientific information available. As new scientific information becomes available, in some circumstances, the classification and interpretation of the genetic variants may change.

Genetic counseling is advised to learn the full meaning of the test results and to discuss risks to other family members. Relatives should consider genetic counseling and testing. All test results should be interpreted by physician or genetic counselor in the context of the personal/family cancer history, and clinical and laboratory data.

Methods and Variant Classification:
The entire gene coding region of the BRCA1, BRCA2, ATM, BARD1, BRIP1, CDH1, CHEK2, MUTYH, PALB2, PTEN, RAD51C, RAD51D, STK11 and TP53 genes, as well as all flanking non-coding regions, were analyzed by Next Generation Sequencing. The multiple-ligation-probe amplification assay (MLPA) was also performed to detect copy number variations (gross deletions and duplications) in the BRCA1 and BRCA2 genes. The MDL variant classification system is based on the 5-tier system recommendations for the interpretation of sequence variants proposed by the American College of Medical Genetics and Genomics (ACMG) complies with the standards and guidelines for the interpretation of sequence variants by the American College of Medical Genetics and Genomics (ACMG) and the Association for Molecular Pathology (AMP)*.

To classify each variant, MDL assigns weight to each piece of available evidence, including literature review, reputable database reports, population frequencies, and computational evidence and prediction. Each identified variant is classified as Benign, Likely Benign, a Variant of Unknown Significance, Likely Pathogenic, or Pathogenic. Variants determined to be benign are not reported, but are available upon request. MDL 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 BRCA1(NM_007294.3), BRCA2(NM_000059.3), ATM(NM_000051.3), BARD1(NM_000465.2), BRIP1(NM_032043.2), CDH1(NM_004360.3), CHEK2(NM_007194.3), MUTYH(NM_025077.3), PALB2(NM_024675.3), PTEN(NM_000314.4), RAD51C(NM_058216.1), RAD51D(NM_002878.3), STK11(NM_000455.4) and TP53(NM_000546.5).

Test Limitations:
This assay cannot detect mutations affecting gene regions not examined in the assay. Intronic regions are analyzed up to 20 nucleotides before and 10 nucleotides after each intron/exon boundary.

Disclaimer:
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/Footnotes:

1 Jonsson et al. (2004) genotyped 1,036 patients with sporadic, familial (2 close relatives), or hereditary (3 or more close relatives) prostate cancer (176807) and 669 controls for the -160C/A promoter polymorphism (rs16260). The risk of hereditary prostate cancer was increased among CA carriers (odds ratio = 1.7) and AA carriers (odds ratio = 2.6) compared to controls; genotype frequencies did not differ between sporadic or familial cases and controls. Jonsson et al. (2004) concluded that CDH1 is a low-penetrant prostate cancer susceptibility gene that might explain a proportion of familial and particularly hereditary prostate cancer.

View: M

Mail:	Yes	Overnight
	All	Yes

Fax:	Yes	***Manual***
	All	No

Medical Director, Dante A. Ragasa, MD.

Ver. 11.27

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References/Footnotes (continued):

Source: PubMed PMID: 14961571

2 In an independent replication study population consisting of 612 patients with sporadic prostate cancer and 211 patients with at least 2 relatives with prostate cancer in a nuclear family (so-called FH+ cases) and 540 controls, Lindstrom et al. (2005) found strong evidence of an association between the -160C-A promoter polymorphism and risk of prostate cancer (p = 0.003) when comparing FH+ cases and controls. In the total study population, CA and AA carriers had an increased risk compared to CC carriers (odds ratio = 1.5 and 2.6, respectively). No significant difference in genotype frequency was observed between sporadic cases and controls.
Source: PubMed PMID: 16189707

3 * Sue Richards 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 2015 May;17(5):405-24.