PARTNERS HEALTHCARE | PERSONALIZED MEDICINE
MASSACHUSETTS GENERAL HOSPITAL | BRIGHAM AND WOMEN'S HOSPITAL

Laboratory for Molecular Medicine
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Unit Number(s):

Lab Accession: **PM-16-A07001**
Patient Name: **68282000, 10038000**
Birth Date: **1/1/1800**
Age Sex: **215 Year old Female**

MOLECULAR DIAGNOSTICS REPORT

Specimen Type:	DNA, Isolated - Blood, Peripheral (edit)	**Received Date:**	9/1/2016
Related Accession(s):		**Referring Facility:**	HARVARD
Referring Physician:	EMERGE-CLINIC-TEST	**Referring Fac. MRN:**	
Copies To:	GENEINSIGHT	**Lab Control Number:**	10038000_68282000-0_SM-B3ZZZ
	EMERGE-HUB GENEINSIGHT	**Family Number:**	FAB123

TEST DESCRIPTION - Copy Number Variation Analysis
Sequence Confirmation Test eMERGE III Sequencing Panel

TEST PERFORMED - CNV-a; SeqConV2; EMERGE-pnlC

INDICATION FOR TEST - Not selected for trait

RESULTS

DNA VARIANTS:
Heterozygous c.338C>A (p.Ser113X), Exon 4, PMS2, Pathogenic

INTERPRETATION:
Positive. DNA sequencing of the coding regions and splice sites of 97 genes (see methodology section below) identified the variants listed above. Copy number analysis using NGS could not be completed because data did not meet quality standards for CNV detection. For a list of exons that are incompletely covered please see "Additional notes and disclaimers" section below.

SUMMARY:
This individual carries a Pathogenic variant in the PMS2 gene. The available information on this variant is described below. Disease-causing variants in the PMS2 gene are strongly associated with Lynch syndrome and this individual may be at risk for developing colorectal cancer / polyps.

ADDITIONAL NOTES AND DISCLAIMERS:
Disease penetrance and severity can vary due to modifier genes and/or environmental factors. The significance of a variant should therefore be interpreted in the context of the individual's clinical manifestations

DETAILED VARIANT INTERPRETATIONS:
p.Ser113X, c.338C>A (PMS2; NM_000535.5; Chr7g.6043336G>T; GRCh37):
The p.Ser113X variant in PMS2 has not been previously reported in individuals with Lynch syndrome and was absent from large population studies. This nonsense variant

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leads to a premature termination codon at position 113, which is predicted to lead to a truncated or absent protein. Heterozygous loss of function of the PMS2 gene is an established disease mechanism in Lynch syndrome (http://www.ncbi.nlm.nih.gov/books/NBK1211/). In summary, this variant meets our criteria to be classified as pathogenic for Lynch syndrome (http://www.partners.org/personalizedmedicine/LMM) based upon predicted impact to the protein and absence in controls.

RECOMMENDATION:
Genetic counseling is recommended for this individual and their relatives. Familial variant testing is available for other relatives if desired. For assistance in locating genetic counseling services or disease specialists, please call the laboratory at 617-768-8500 or email at LMM@partners.org.

Please note that variant classifications may change over time if more information becomes available. Please contact us at 617-768-8500 or LMM@partners.org.

TEST INFORMATION

BACKGROUND:
The eMERGE (electronic MEdical Records and GEnomics) network combines DNA biorepositories with electronic health record (EHR) systems for large-scale discovery and clinical implementation research in genomic medicine. A main goal is the return of genomic testing results to patients in a clinical care setting. In phase III, participating sites are sequencing 109 clinically relevant genes in ~25,000 participants using a custom next generation sequencing panel.

METHODOLOGY:
Test content (target region): This test includes 109 genes (including the ACMG56 genes; PMID: 23788249, and additional genomic positions for known variants. For reference sequences exons/positions covered see http://personalizedmedicine.partners.org/Laboratory-For-Molecular-Medicine/).

Note that this test may not detect variants in regions with difficult sequence contexts (e.g. high or low GC content) and is generally not designed to detect deep intronic variants as well as variants in the 5' and 3'UTR. Regions with high sequence homology are only included in this test if a unique Sanger sequencing assay can be designed to rule out false positive calls.

Sample preparation, sequencing, variant calling and confirmation: This test is performed by next generation sequencing using sonicated genomic DNA (Covaris) followed by target enrichment (Illumina Rapid Capture Custom Kit), Illumina HiSeq sequencing (76 bp paired-end reads) and alignment/variant calling (BWA/GATK). A custom script is used to generate calls for the individual genomic positions. Sample identity is confirmed by comparing NGS derived genotypes of a custom set of SNPs to results generated for the same specimen using a fingerprinting genotype array. Samples with ≤95% of the target region covered at ≥20X are failed and repeated. Copy number variants (CNVs) of ≥3 exons are detected by an in-house developed tool (VisCap, PMID: 26681316). This assay is 99.33% sensitive to detect single nucleotide variants (95% CI = 96.30-99.88%), 100% sensitive to detect indels (95% CI = 79.61-100.00%) and 100% sensitive to detect CNVs (n=4). All variants included on this report are confirmed (SNVs and indels: Sanger sequencing, CNVs: ddPCR).

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Variant annotation and filtration: All variants within the coding sequence of the included genes (default: exons +/- 5 bp) are subjected to the following process: Variant annotations are derived from ExAC (vs 0.3), ClinVar (April 2016 release), HGMD (2016.1), 1000 Genomes (Phase 3), Alamut Batch (vs 1.4.4), (dbnsfp vs 3.1), and LMM's GeneInsight knowledge base (vs 5.3.2). The following variant types are further analyzed: a) Loss of function variants with a minor allele frequency (MAF)<1%, b) Variants previously classified as pathogenic or likely pathogenic regardless of MAF, c) ClinVar pathogenic or likely pathogenic and HGMD DM variants with a MAF<5%.

Variant interpretation and clinical reporting: Variants assessment is based on in-house developed expert criteria and the most recent ACMG classification framework (PMID: 25741868) with disease and gene-specific modifications when applicable. Please note that variant classifications can change over time. Reporting is restricted to pathogenic and likely pathogenic variants in a subset of eMERGE network genes and variants consisting of 62 genes and 1 variant in an additional gene: ACTA2, ACTC1, APC, APOB, BRCA1, BRCA2, CACNA1C, CACNA1S, COL3A1, DSC2, DSG2, DSP, FBN1, GLA, HNF1A, KCNE1, KCNH2, KCNJ2, KCNQ1, LDLR, LMNA, MEN1, MLH1, MSH2, MSH6, MUTYH, MYBPC3, MYH11, MYH7, MYL2, MYL3, MYLK, NF2, OTC, PCSK9, PKP2, PMS2, PRKAG2, PTEN, RB1, RET, RYR1, RYR2, SCN5A, SDHAF2, SDHB, SDHC, SDHD, SMAD3, SMAD4, STK11, TGFBR1, TGFBR2, TMEM43,
TNNI3, TNNT2, TP53, TPM1, TSC1, TSC2, VHL, WT1 and HFE (rs1800562). Carrier status for autosomal recessive conditions will not be reported.

This test was developed and its performance characteristics determined by the Laboratory for Molecular Medicine at Partners HealthCare Personalized Medicine (LMM, 65 Landsdowne St, Cambridge, MA 02139; 617-768-8500; CLIA#22D1005307). It has not been cleared or approved by the U.S. Food and Drug Administration (FDA). The FDA has determined that such clearance or approval is not necessary.

REFERENCES:

Hendriks YM, Jagmohan-Changur S, van der Klift HM, Morreau H, van Puijenbroek M, Tops C, van Os T, Wagner A, Ausems MG, Gomez E, Breuning MH, Bröcker-Vriends AH, Vasen HF, Wijnen JT. 2006. Heterozygous mutations in PMS2 cause hereditary nonpolyposis colorectal carcinoma (Lynch syndrome). Gastroenterology. 130(2):312-22.

REPORT by Matthew Lebo Ph.D., on Friday September 09, 2016 at 04:22:23PM
Final Diagnosis by **Matthew Lebo Ph.D.,** Electronically signed on Monday September 12, 2016 at 10:56:03AM