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

Laboratory for Molecular Medicine
65 Landsdowne Street, Cambridge MA 02139
Phone: (617) 768-8500 Fax: (617) 768-8513
www.partners.org/personalizedmedicine/lmm

Unit Number(s):

Lab Accession: **PM-15-D00000**
Patient Name: **DOE, JANE**
Birth Date: **01/01/1950**
Age Sex: **65 year old Female**

MOLECULAR DIAGNOSTICS REPORT

Specimen Type: Blood, Peripheral
Related Accession(s):
Referring Physician: DR. JOHN SMITH
Copies To:

Received Date: 05/01/2015
Referring Facility: UNIV HOSP OF AMERICA
Referring Fac. MRN: 0123456789
Lab Control Number: 15-111-2222
Family Number: F000000

TEST DESCRIPTION - eMERGE gene panel (97 genes), **(CNV)**, Sequence Confirmation Test

TEST PERFORMED - PCM-pnlCv3; (**CNV code if applicable**); SeqConfirm

INDICATION FOR TEST - Clinical diagnosis and family history of HCM

RESULTS

DNA VARIANTS:

VARIANTS RELEVANT TO INDICATION FOR TESTING
Heterozygous c.1504C>T (p.Arg502Trp), Exon 17, MYBPC3, Pathogenic
Note (Birgit): This will read "N/A" if no indication is provided

OTHER VARIANTS OF MEDICAL SIGNIFICANCE (SECONDARY FINDINGS)
Heterozygous c.2339C>G (p.Ser611X), Exon 10, BRCA2, Pathogenic
Heterozygous c.1521_1523delCTT (Phe508del), Exon 11, CFTR Pathogenic

INTERPRETATION:
Positive. DNA sequencing (and copy number analysis) 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 (<100% of bases ≥20X) please see "Additional notes and disclaimers" section.

SUMMARY (VARIANTS RELEVANT TO INDICATION FOR TESTING):
This individual has a well established, pathogenic variant in the MYBPC3 gene. This variant causes HCM, which is consistent with this individual's reported diagnosis. The available information on this variant is described below.

SUMMARY (OTHER VARIANTS OF MEDICAL SIGNIFICANCE):
One pathogenic variant in the BRCA2 gene was identified. The available information on this variant is described below. Pathogenic variants in the BRCA2 gene are strongly associated with hereditary breast and ovarian cancer and this individual may be at risk for developing BRCA2-associated cancers.

In addition, this individual carries a heterozygous CFTR variant and is therefore at risk for having a child with cystic fibrosis. To determine the risk, the partner of this individual would need to be tested for variants in this gene.

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

For reports including VUSs:

- *Disclaimer that we cannot rule out that the variant may be common when race was not provided*
- *Testing of relatives, particularly those who are affected may help clarify significance of this/these variants*

The following genes are not fully covered: xxx (…%), YYY (…%), etc

DETAILED VARIANT INTERPRETATIONS:

The **p.Arg502Trp** variant in MYBPC3 (NM....) has been well reported in multiple individuals across multiple studies and is known to be pathogenic for HCM. This variant meets our criteria for pathogenicity (http://www.partners.org/personalizedmedicine/LMM) based upon extensive segregation studies and functional evidence (Richard 2003, Van Driest 2004, Carballo 2005, Ingles 2005, Maron 2008, Kaski 2009, Marston 2009, Saltzman 2010). It is also the most common pathogenic HCM variant identified by our laboratory.

The **p.Ser611X** variant in BRCA2 (NM....) has been previously reported in 1 individual with unspecified cancer and in 1 individual with breast cancer and was found to segregated with disease in 1 affected relative (Lubinski 2004, Tea 2014). It has not been identified in large population studies. This nonsense variant leads to a premature termination codon at position 611, which is predicted to lead to a truncated or absent protein. Heterozygous loss of BRCA2 function is an established disease mechanism in BRCA2-associated cancers. In summary, this variant meets our criteria to be classified as pathogenic for BRCA2-associted cancers in an autosomal dominant manner based upon the predicted impact to the protein.

The **p.Phe508del** variant in CFTR (NM....) (also known as ΔF508) is a deletion of a single amino acid a position 508 and is well-established as a pathogenic variant for cystic fibrosis in an autosomal recessive manner (Kerem 1989, Fuller 1992, Southern 1997, Grody 2001, Sosnay 2013). The p.Phe508del is the most common pathogenic variant reported in CFTR and is included in the ACMG Technical Standards and Guidelines for CFTR Mutation Testing (http://www.acmg.net/Pages/ACMG_Activities/stds-2002/cf.htm).

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.

COMMENTS:

Variants of unlikely clinical significance are not included on this report but can be derived from the raw data (deposed on DNAnexus - - details here - -).

TEST INFORMATION (to be replaced by eMERGE specific methods)

METHODOLOGY:

The DCM/Arrhythmogenic Cardiomyopathy Panel includes the following 53 genes: ABCC9, ACTC1, ACTN2, BAG3, CASQ2, CHRM2, CRYAB, CSRP3, DES, DMD, DOLK, DSC2, DSG2, DSP, DTNA, EMD, GATAD1, GLA, JUP, LAMP2, LDB3, LMNA, MURC, MYBPC3, MYH6, MYH7, MYL2, MYL3, MYOZ2, MYPN, NEBL, NEXN, PKP2, PLN, PRDM16, PRKAG2, PTPN11, RAF1, RBM20, RYR2, SCN5A, SGCD, TAZ, TCAP, TMEM43, TNNC1, TNNI3, TNNT2, TPM1, TRDN, TTN, TTR, VCL. For reference

sequences and exons covered, please visit our website (www.partners.org/personalizedmedicine/lmm).

This test is performed by next generation sequencing using Agilent SureSelect capture followed by Illumina MiSeq sequencing of the coding regions and splice sites. Variant calls are generated using the Burrows-Wheeler Aligner followed by GATK analysis. Sanger sequencing is used to fill in regions with insufficient coverage and to confirm clinically significant variants, excluding variants classified as likely benign or benign. Detection of copy number variants (CNVs) encompassing 1 or more exons is performed using VisCap™ analysis followed by confirmation using an alternate assay. This test is highly sensitive to detect variants changing a single base (100% of 466 substitution variants tested were detected). Its ability to detect large insertions or deletions is reduced (13 out of 13 indels ranging from 1-10 bases were detected, while 2 out of 9 indels >10 bases were missed).

This test does not detect variants in non-coding regions, aside from the splice junctions, that could affect gene expression and a few exons have been excluded due to technical difficulties. CNV analysis is only performed when data meets necessary quality standards and may not be available for all cases. Single exon level resolution for CNV analysis may not be available for all genes. Please see our website for additional information.

Each variant is evaluated based on the available information from the following: databases (including HGMD, ClinVar, LSDBs, Exome Aggregation Consortium and other large population studies), published literature, clinical correlation, segregation analysis, functional studies, and its predicted functional or splicing impact using evolutionary conservation analysis and computational tools (including PolyPhen-2, SIFT, and other prediction software programs). Please see our website or publication (Duzkale 2013; PubMed ID 24033266) for details on variant classification. Variants are reported according to HGVS nomenclature (www.hgvs.org/mutnomen).

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:

Ackerman MJ, Priori SG, Willems S, Berul C, Brugada R, Calkins H, Camm AJ, Ellinor PT, Gollob M, Hamilton R, Hershberger RE, Judge DP, Le Marec H, McKenna WJ, Schulze-Bahr E, Semsarian C, Towbin JA, Watkins H, Wilde A, Wolpert C, Zipes DP. 2011. HRS/EHRA Expert Consensus Statement on the State of Genetic Testing for the Channelopathies and Cardiomyopathies This document was developed as a partnership between the Heart Rhythm Society (HRS) and the European Heart Rhythm Association (EHRA). Heart Rhythm. 8(8):1308-39.

Askanas V, Engel WK, McFerrin J, Vattemi G. 2003. Transthyretin Val122Ile, accumulated Abeta, and inclusion-body myositis aspects in cultured muscle. Neurology. 61(2):257-60.

Beckermann TM, McLeod K, Murday V, Potet F, George AL. 2014. Novel SCN5A mutation in amiodarone-responsive multifocal ventricular ectopy-associated cardiomyopathy. Heart Rhythm. 11(8):1446-53.

Birdwell KA, Decker B, Barbarino JM, Peterson JF, Stein CM, Sadee, W, Wang D, He Y, Swen JJ, Leeder JS, van Schaik R, Thummel KE, Klein TE, Caudle KE, MacPhee I. 2015. Clinical Pharmacogenetics Implementation Consortium (CPIC) Guidelines for CYP3A5 Genotype and Tacrolimus Dosing. Clin. Pharmacol. Ther. 98(1):19-24.