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

LABORATORY FOR MOLECULAR MEDICINE
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http://pcpgm.partners.org/lmm

Name: DOE, JOHN **Accession ID: PM-XX-12345**

DOB: **12/31/1976**
Sex: **Male**
Race/Ethnicity: **White**
Family #: **F012345**

MRN: **0123456789**
Referring facility: **Double Helix Hospital**
Referring physician: **Dr. DNA**
Copies to: **CGC**

Specimen: **semen**
Lab Control Number: **ABC123**
Received: **01/24/2014**
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Test(s) performed: **Whole exome sequencing**
Indication for test: **Clinical diagnosis and family history of DCM with arrhythmia**

RESULT: Positive
Findings explain patient phenotype, Incidental findings identified

VARIANTS RELEVANT TO INDICATION FOR TESTING

One pathogenic variant in FGFR3 gene was identified in the semen of this individual. A spermiogram of the patient was mandated after the abort of the fetus of his wife. No other variants of relevance to the indication were identified. Please see below for more detailed variant information.

Gene & Transcript	Polymorphism	Allele State	Phenotype OMIM Number	Classification
FGFR3	rs78311289	Heterozygote	187601	Pathogenic

METHODOLOGY

Exome sequence is generated from extracted DNA that is fragmented, adapted, barcoded, and subjected to a solution phase hybridization with the Agilent SureSelect Human All Exon V5 Plus probe set. Next generation sequencing is performed on the Illumina HiSeq2500 platform (rapid mode). Exomes are sequenced to an average target coverage of 125X with 90-95% of bases sequenced to at least 20X coverage. Paired-end reads are aligned to the NCBI reference sequence (GRCh37) using the Burrows-Wheeler Aligner (BWA), and variant calls are made using the Genomic Analysis Tool Kit (GATK). Variants are filtered to identify: (1) variants with a minor allele frequency ≤5% in NHLBI Exome Sequencing Project (http://evs.gs.washington.edu/EVS/) in the patient-specific phenotype-driven gene list (see supplement); (2) variants classified as disease causing mutations in public databases; and (3) predicted loss-of-function variants with a minor allele frequency ≤1%. The evidence for phenotype-causality is then evaluated for each variant resulting from the filtering strategies above and variants are classified according to LMM criteria (http://pcpgm.partners.org/LMM). Only those variants with evidence for causing or contributing to disease are reported. All variants on this report have been confirmed via Sanger sequencing or another orthogonal technology.

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). This test 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.

VARIANT ASSESSMENT PROCESS

Each variant is evaluated based on the available information from the following: databases (including HGMD, ClinVar, LSDBs, NHLBI Exome Sequencing Project, 1000 Genomes, and dbSNP), published literature, clinical correlation, segregation analysis, functional studies, and its predicted functional or splicing impact using evolutionary conservation analysis and computational tools (including AlignGVGD, MAPP, MutationTaster, PolyPhen-2, SIFT, and SNAP). Please see our website (www.partners.org/personalizedmedicine/lmm) or publication (Duzkale 2013; PubMed ID 24033266) for details on variant classification. Variants are reported according to HGVS nomenclature (www.hgvs.org/mutnomen).

LIMITATIONS

It should be noted that this test does not sequence all bases in a human genome, not all variants have been identified or interpreted, and this report is limited only to variants with evidence for causing or contributing to disease. Triplet repeat expansions, translocations and large copy number events are currently not reliably detected by genome sequencing. Furthermore, not all disease-associated genes have been identified and the clinical significance of variation in many genes is not well understood. It is recommended that genomic sequencing data is periodically reinterpreted, especially when new symptoms arise.