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: 12/31/1999
Sex: Male
Race/Ethnicity: White
Family #: F012345

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

Specimen: Blood, Peripheral
Lab Control Number: ABC123
Received: 01/24/2014

Test(s) performed: Whole genome sequencing
Indication for test: Clinical diagnosis and family history of DCM with arrhythmia

RESULT: Positive
Findings explain patient phenotype, Incidental findings identified

APPROACH
Sequencing of this individual's genome was performed and the data was analyzed to identify previously reported and novel variants in (1) 335 genes that have been previously implicated in various cardiac diseases and myopathies (see Supplement for a list of genes and coverage information); and (2) variants classified as disease-causing in public databases that have a minor allele frequency <5% in European American or African American chromosomes from the NHLBI Exome Sequencing Project (ESP; http://evs.gs.washington.edu/EVS/); (3) nonsense, frameshift, and +/-1,2 splice-site variants in disease-associated genes that have a minor allele frequency <1% in European American or African American chromosomes from the NHLBI ESP; and (4) previously reported and novel variants in 56 genes predicted to be of medical significance by the American College of Medical Genetics (Green 2013), which may be unrelated to the patient phenotype (incidental findings). All genes relevant to the indication had adequate coverage (>95% at 8X). Please note that the presence of pathogenic variants in genes not analyzed or with incomplete coverage cannot be fully excluded.

VARIANTS RELEVANT TO INDICATION FOR TESTING
One pathogenic variant in LMNA was identified in this individual. The LMNA gene is strongly associated with DCM, which is consistent with the reported clinical diagnosis. No other variants of relevance to the indication were identified. Please see below for more detailed variant information.

Gene & Transcript	Variant	Allele State	Location	Disease or Phenotype	Inheritance	Classification
LMNA NM_00112233.5	c.244G>A p.Glu82Lys	Het.	Exon 1	Dilated Cardiomyopathy	Autosomal dominant	Pathogenic

OTHER VARIANTS OF MEDICAL SIGNIFICANCE (INCIDENTAL FINDINGS)
Incidental findings are variants of medical significance that are not associated with the individual's reported indication. Please note that the presence of pathogenic variants in genes with incomplete coverage or in genes not examined cannot be fully excluded. Please contact the Laboratory for Molecular Medicine for coverage information on genes analyzed for incidental findings.

Monogenic Disease Risk
This test did NOT identify genetic variants that may be responsible for other diseases unrelated to this individual's clinical presentation. Please see limitations for more detail.

Carrier Status
This individual is a carrier of 1 heterozygous pathogenic variant in a gene associated with a recessive disorder that is unrelated to this individual's reported phenotype. In the heterozygous state, this variant is not known to play a role in disease. Please see below for more detailed variant information.

Gene & Transcript	Variant	Allele State	Location	Disease or Phenotype	Inheritance	Classification
MUTYH NM_012222	c.1428_1430del p.Glu477del	Het.	Exon 14	MUTYH-associated adenomatous polyposis	Autosomal recessive	Pathogenic

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RECOMMENDATIONS

These results should be interpreted in the context of the patient's medical evaluation, family history, and racial/ethnic background. Please note that variant classification and/or interpretation may change over time if more information becomes available. Reinterpretation of exome sequencing data is recommended on an annual basis and may be requested by a medical provider. For questions about this report, or for assistance in locating nearby genetic counseling services, please contact the Laboratory for Molecular Medicine at: lmm@partners.org or 617-768-8500.

DETAILED VARIANT INFORMATION (VARIANTS RELEVANT TO INDICATION FOR TESTING)

Gene & Transcript	Variant	Allele State	Location	Disease or Phenotype	Inheritance	Classification
LMNA NM_00112233.5	c.244G>A p.Glu82Lys	Het. (Mat.)	Exon 1	Dilated Cardiomyopathy	Autosomal dominant	Pathogenic
Genomic Position			**Variant Frequency**			
GRCh37 Chr11: g.47364249G>A			Not identified in large population studies			

VARIANT INTERPRETATION: The Glu82Lys variant in exon 14 of LMNA has been reported in at least 2 families with DCM and conduction system abnormalities, and segregated with disease in 8 affected relatives (Wang 2006, Wu 2010). It has not been identified in large population studies. Functional studies (in vitro) suggest an effect on protein function and mice carrying the variant exhibited clinical features of DCM (Wang 2006, Lu 2010, Sun 2010). In summary, this variant meets our criteria to be classified as pathogenic (http://pcpgm.partners.org/LMM) based upon segregation studies, absence from controls, and functional evidence.

DISEASE INFORMATION: *LMNA*-related dilated cardiomyopathy (DCM) is characterized by left ventricular enlargement and reduced systolic function frequently accompanied by significant conduction system disease and/or myopathy. Adapted from GeneReviews: http://www.ncbi.nlm.nih.gov/books/NBK1674/

PREVALENCE: ~1/2500

FAMILIAL RISK: Cardiomyopathy due to pathogenic variants in the LMNA gene is typically inherited in an autosomal dominant pattern. Each first-degree relative has a 50% (or 1 in 2) chance of inheriting a variant and its risk for cardiomyopathy. 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 INFORMATION (INCIDENTAL FINDINGS)

Monogenic Disease Risk

This test did NOT identify genetic variants that may be responsible for other diseases unrelated to this individual's clinical presentation. Please see limitations for more detail.

Carrier Status

Gene & Transcript	Variant	Allele State	Location	Disease or Phenotype	Inheritance	Classification
MUTYH NM_012222	c.1428_1430del p.Glu477del	Het.	Exon 14	MUTYH-associated adenomatous polyposis	Autosomal recessive	Pathogenic
Genomic Position			**Variant Frequency**			
GRCh37 chr1: 45796891-45796891			4/16512 of South Asian chromosomes in ExAC			

VARIANT INTERPRETATION: The p.Glu477del variant in MUTYH (previously reported as p.Glu466del or c.1395_1397delGGA) has been reported in more than 15 individuals with MUTYH-associated adenomatous polyposis either in the homozygous or compound heterozygous state, and segregated with disease in at least 6 affected family members from 3 families (Halford 2003, Gismondi 2004, Di Gregorio 2006, Vogt 2009, Buisine 2013). This variant is a deletion of the glutamate residue (Glu) at position 477 and is not predicted to alter the protein reading-frame. In vitro functional studies provide some evidence that the p.Glu477del variant may impact protein function (Dagostino 2010, Goto 2010, Molatore 2010). This variant has also been identified in 10/66728 European and 4/16512 of South Asian chromosomes by the Exome Aggregation Consortium, including one homozygote (ExAC, http://exac.broadinstitute.org). Please note that variants associated with diseases that have reduced penetrance and late age-of-onset may be present at a low frequency in large population studies; therefore the frequency of this variant is consistent with the known prevalance and penetrance of this disease. In summary, this variant meets our criteria to be classified as pathogenic for MUTYH-associated adenomatous polyposis in an autosomal recessive manner (http://www.partners.org/personalizedmedicine/LMM) based upon its frequency in patients, segregation studies, and functional evidence.

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DISEASE INFORMATION: MUTYH-related adenomatous polyposis (or autosomal recessive familial adenomatous polyposis; OMIM# 608456) is caused by biallelic mutations in MUTYH and is characterized by multiple colorectal adenomas and a high risk of colorectal cancer (43% to almost 100% in the absence of timely surveillance). Although typically associated with tens to a few hundred colonic adenomatous polyps that are evident at a mean age of about 50 years, colon cancer develops in some individuals with biallelic MUTYH mutations in the absence of polyposis. Duodenal adenomas are found in 17%-25% of individuals; the lifetime risk of duodenal cancer is about 4%. Individuals may also have modestly increased risk for rather late-onset malignancies of the ovary, bladder, skin, breast and endometrial cancer. Although MUTYH-related familial adenomatous polyposis is a recessive disorder, studies suggest that heterozygous carriers of MUTYH variants may have higher risk for colorectal cancer compared to the general population (OR: 2-3) (Jenkins 2006, Jones 2009). (Adapted from GeneReviews http://www.ncbi.nlm.nih.gov/books/NBK107219/)

PREVALENCE/CARRIER FREQUENCY: MUTYH-related adenomatous polyposis is estimated to have a prevalence of ~1/20,000-40,000, with a carrier frequency of 1-2% in the European population.

FAMILIAL RISK: MUTYH-related adenomatous polyposis is inherited in an autosomal recessive pattern. Two carriers have a 25% (or 1 in 4) risk for having a child with the disease. Other biologically related family members may also be carriers of this variant.

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.

METHODOLOGY

Sequencing of this individual's genome was performed and covered a minimum of 95% of all positions at 8X coverage or higher. Reads are aligned to the human 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 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.

The initial sequencing component of this test was performed by the Illumina Clinical Services Laboratory (San Diego, CA CLIA#05D1092911) and the alignment, variant calling, data filtering, Sanger confirmation and interpretation were performed 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.

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FINAL REPORT by: Ozge Birsoy, PhD on November 13, 2015

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

DOB: **12/31/1999** MRN: **0123456789** Specimen: **Blood, Peripheral**
Sex: **Male** Referring facility: **Double Helix Hospital** Lab Control Number: **ABC123**
Race/Ethnicity: **White** Referring physician: **Dr. DNA** Received: **01/24/2014**
Family #: **F012345** Copies to: **CGC**

REPORT SUPPLEMENT

COVERAGE OF ANALYZED GENES

Analysis included 335 genes that have been previously implicated in cardiac diseases and myopathies including cardiomyopathies, myopathies, congenital heart diseases, arrhythmias, conduction disorders, and cardiac amyloid. The table below provides the list of these genes (and their coverage at ≥8X). Please note that the presence of pathogenic variation in genes not analyzed or with incomplete coverage cannot be fully excluded.

Gene	8x coverage (%)	Gene	8x coverage (%)	Gene	8x coverage (%)	Gene	8x coverage (%)	Gene	8x coverage (%)
AARS2	100	CTF1	100	HCN4	100	MYO6	100	SDHA	100
ABCA1	100	CTNNA3	100	HIF1A	100	MYOCD	100	SEMA3A	100
ABCC9	100	CXADR	100	HLA-DPB1	100	MYOM1	100	SEPN1	100
ACAD9	100	CYP11B1	100	HRAS	100	MYOT	100	SGCA	100
ACADVL	100	CYP11B2	100	HRC	100	MYOZ2	100	SGCB	100
ACE	100	CYP19A1	100	HSPA1L	100	MYPN	100	SGCD	100
ACE2	100	CYR61	100	HTR2A	100	NAA10	100	SGCE	100
ACTA1	100	DAG1	100	IFT172	100	NDUFA10	100	SGCG	100
ACTA2	100	DDX39B	100	ILK	100	NDUFA2	100	SHOC2	100
ACTC1	100	DES	100	IRX4	100	NDUFAF1	100	SHOX2	100
ACTN2	100	DMD	98.2	IRX5	100	NDUFS4	100	SLC25A20	100
ACVR1	100	DMPK	100	ISL1	100	NDUFS8	100	SLC25A3	100
ADAM10	100	DNAJB6	100	ISPD	100	NDUFV2	100	SLC25A4	100
ADAM15	100	DNAJC19	100	ITGB1BP2	100	NEB	100	SLC3A1	100
ADRA1B	100	DNM2	100	JAG1	100	NEBL	100	SLC6A4	100
ADRA2C	100	DOLK	100	JPH2	100	NEXN	100	SLN	100
ADRB1	100	DOT1L	100	JUP	100	NFKBIL1	100	SMYD1	100
ADRB2	100	DPP6	100	KALRN	100	NKX2-5	100	SNTA1	100
AGK	100	DSC2	100	KCNA3	99.7	NOS3	100	SOD2	100
AGT	100	DSG2	100	KCNA5	100	NOTCH1	100	SOS1	100
AGTR1	100	DSP	100	KCND3	100	NPHP3	100	SRI	100
AGTR2	100	DTNA	100	KCNE1	100	NPPA	100	STK11	100
AKAP10	100	DYSF	100	KCNE1L	100	NPPB	100	STK4	100
AKAP9	100	ECE1	100	KCNE2	100	NRAS	100	SYNE1	100
ALG10	100	ECE2	100	KCNE3	100	NUP155	100	SYNM	100
ALG10B	100	EDN2	100	KCNE4	100	OBSCN	100	TAB2	100
ANK2	100	ELAC2	100	KCNH2	100	PABPN1	100	TAZ	100
ANKRD1	100	ELN	100	KCNJ2	100	PDLIM3	100	TBX20	100
ANO5	100	EMD	100	KCNJ5	100	PEPD	100	TBX5	100
AP3B1	100	ESR1	100	KCNJ8	100	PIGL	100	TCAP	100
APOA1	100	ESR2	100	KCNK3	100	PIK3C2A	100	TCF21	100
AR	100	EYA4	100	KCNN2	100	PITX2	100	TDGF1	100
ARFGEF2	100	FBN1	100	KCNN3	100	PKP2	100	TFAM	100

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Gene	8x coverage (%)	Gene	8x coverage (%)	Gene	8x coverage (%)	Gene	8x coverage (%)	Gene	8x coverage (%)
ARHGAP24	100	FBN2	100	KCNQ1	99.4	PLA2G7	100	TFB1M	100
ARHGEF10	100	FBXL4	100	KLF10	100	PLEC	100	TGFB3	100
B3GAT3	100	FHL1	100	KLHL40	100	PLN	100	TGFBR1	100
BAG3	100	FHL2	100	KRAS	100	POLG	100	TGFBR2	100
BIN1	100	FHOD3	100	LAMA2	100	POMGNT1	100	TLL1	100
BRAF	100	FKRP	99.7	LAMA4	100	POMT1	100	TMEM43	100
CACNA1C	100	FKTN	100	LAMP2	99.9	POMT2	100	TMEM70	100
CACNA1D	100	FLNA	100	LDB3	99.9	PPARGC1A	100	TMPO	100
CACNB2	100	FLNC	100	LDLR	100	PPARGC1B	100	TNNC1	100
CALM1	100	FLT1	100	LMNA	100	PQBP1	100	TNNI1	100
CALM3	100	FOXD4	100	LRP6	100	PRDM16	100	TNNI3	100
CALR3	100	FOXH1	100	MAP2K1	100	PRKAG2	100	TNNT1	100
CAPN3	100	FOXRED1	100	MAP2K2	100	PRKAR1A	100	TNNT2	100
CASQ2	100	FXN	100	MED13L	100	PSEN1	100	TPM1	100
CAV1	100	G6PC3	100	MEF2A	100	PSEN2	100	TPM2	100
CAV3	100	GATA4	100	MEF2C	100	PTK2B	100	TPM3	100
CBL	100	GATA5	100	MICA	100	PTPN1	100	TRDN	100
CD36	100	GATA6	100	MICB	100	PTPN11	100	TRIM32	100
CEP85L	100	GATAD1	100	MLYCD	100	PTRF	100	TRIM63	100
CFC1	100	GDF1	100	MMP3	100	RAF1	100	TRPM4	100
CFL2	100	GJA1	100	MPO	100	RBM20	100	TRPM7	100
CHRM2	100	GJA5	100	MRPL3	100	RETN	100	TSFM	100
CHST3	100	GLA	100	MRPS22	100	RPP30	100	TSPO	100
CITED2	100	GLB1	100	MTM1	100	RYR1	100	TTN	100
CMA1	100	GNAI2	100	MTO1	100	RYR2	100	TTR	100
CNBP	100	GPD1L	100	MURC	100	SALL4	100	TXNRD2	100
COA5	100	GSN	100	MYBPC3	100	SCN10A	100	VCL	100
COL1A2	100	GYG1	100	MYH11	100	SCN1B	100	VEGFA	100
COL3A1	100	GYS1	100	MYH6	100	SCN2B	100	VPS13A	100
COX15	100	HADHA	100	MYH7	100	SCN3B	100	WISP3	100
CRELD1	100	HADHB	100	MYH8	100	SCN4B	100	YARS2	100
CRP	100	HAND1	100	MYL2	100	SCN5A	100	ZFHX3	100
CRYAB	100	HAND2	100	MYL3	100	SCO1	100	ZFPM2	100
CSRP3	100	HCN2	98.6	MYLK2	100	SCO2	100	ZIC3	100