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

LABORATORY FOR MOLECULAR MEDICINE
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Name: LAST, FIRST
DOB: MM/DD/XXXX
Sex: Female/Male
Family #: F00000
Test Performed: Genome Sequencing

MRN: XXXXX
Referring Facility: XXXX
Referring Physician: XXXX

LMM Accession ID: PM-19-X00000
Specimen: Blood, peripheral
Received: MM/DD/XXXX

Test Codes: lmWGS-pnlF_L, lmSeqConV2_L, lmPGX-pnlB_L, lmRISK-pnlB_L

GENOME SEQUENCING RESULTS SUMMARY

Sequencing of this individual's genome identified 1 risk allele and 1 carrier status variant. Pharmacogenomic associations are also included in this report. Result details are listed below.

VARIANT SUMMARY

REPORT SECTION	Disease, Inheritance	*Gene* Transcript	Variant	Allele State	Classification
A. MONOGENIC DISEASE FINDINGS	None identified.				
B. RISK ALLELES	Non-Alcoholic Fatty Liver Disease Type 1 (NAFLD1)	*PNPLA3* NM_025225.2	c.444C>G (p.Ile148Met)	Homozygous	Established Risk Allele
C. CARRIER STATUS VARIANTS	Congenital Adrenal Insufficiency, Autosomal Recessive	*CYP11A1* NM_000781.2	c.391C>T (p.Gln131X)	Heterozygous	Likely Pathogenic
D. PHARMACOGENOMIC ASSOCIATIONS	See below.				

DETAILED VARIANT INFORMATION

A. MONOGENIC DISEASE FINDINGS

This test did not identify any variants with the potential to cause monogenic disease in this individual.

B. RISK ALLELES

This test identified 1 risk allele variant. The *PNPLA3* variant is associated with an increased risk of developing non-alcoholic fatty liver disease when identified in the homozygous state.

Disease	*Gene* Transcript	Variant	Allele state	Classification
Non-Alcoholic Fatty Liver Disease Type 1 (NAFLD1)	*PNPLA3* NM_025225.2	c.444C>G (p.Ile148Met)	Homozygous	Established Risk Allele
Genomic variant nomenclature		**Location**	**Odds Ratio**	**Disease Prevalence (Estimated)**
g.44324727C>G (chr22, GRCh37)		Exon 3	3-5	1 in 4

VARIANT INTERPRETATION: The p.Ile148Met variant in *PNPLA3* has been associated with increased risk for non-alcoholic fatty liver disease type 1 (NAFLD1). A meta-analysis and an additional case-control study have reported an odds ratio of 3-5 for homozygotes developing NAFLD as compared to individuals who are homozygous for the reference allele (Ile) at this position (Sookoian 2011, Oniki 2015). In vivo and in vitro functional studies provide some evidence that the p.Ile148Met variant may impact protein function (Smagris 2015, Bruschi 2017); however, these types of assays may not accurately represent biological function. Of note, this variant has been identified in 55% (18897/34356) of Latino chromosomes (including 5447 homozygotes) by the Genome Aggregation Database (gnomAD, http://gnomad.broadinstitute.org; dbSNP rs738409). In summary, this variant is not expected to cause highly penetrant Mendelian disease, but this variant is an established risk factor for NAFLD1 in the homozygous state.

DISEASE INFORMATION: Non-alcoholic fatty liver disease (NAFLD) is a buildup of excessive fat in the liver that can lead to liver damage resembling the damage caused by alcohol abuse, but occurring in people who do not drink heavily. The fat deposits in the liver associated with NAFLD usually cause no symptoms, although they may cause increased levels of liver enzymes that are detected in routine blood tests. Some affected individuals have abdominal pain or fatigue. Between 7-30% of people with NAFLD develop inflammation of the liver (non-alcoholic steatohepatitis, also known as NASH), leading to liver damage. Severe or long-term damage can lead to liver fibrosis, resulting in irreversible cirrhosis. People with NAFLD, NASH, and cirrhosis are also at increased risk of developing hepatocellular cancer. NAFLD is most common in middle-aged or older people, although younger people, including children, can also be affected.

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C. CARRIER STATUS VARIANTS

This test identified 1 carrier status variant for autosomal recessive congenital adrenal insufficiency. Autosomal recessive disorders are caused by the presence of pathogenic variants in both copies of the same gene. Being a carrier of this variant does not put this individual at risk for disease but may impact disease risk in this individual's children. PLEASE NOTE: We cannot definitively rule out the presence of a second pathogenic variant in this gene due to the technical and analytical limitations of this assay.

FAMILIAL AND REPRODUCTIVE RISK: The risk to this individual's child or future child of developing the condition described below is dependent on the carrier status of the individual's reproductive partner(s). Two carriers have a 25% risk for having a child with the associated disease. First degree relatives have a 50% chance of being carriers of this variant other biologically related family members may also be carriers.

Disease, Inheritance	***Gene* Transcript**	**Variant**	**Allele State**	**Classification**
Congenital Adrenal Insufficiency, Autosomal Recessive	*CYP11A1* NM_000781.2	c.391C>T (p.Gln131X)	Heterozygous	Likely Pathogenic
Genomic Variant Nomenclature	**Location**	**Penetrance**	**Carrier Phenotype**	**Gene Coverage**
g.74640275G>A (chr15, GRCh37)	Exon 2	High	None Reported	100% at 15X
VARIANT INTERPRETATION: The p.Gln131X variant in *CYP11A1* has not been previously reported in individuals with adrenal insufficiency and was absent from large population studies. This nonsense variant leads to a premature termination codon at position 131, which is predicted to lead to a truncated or absent protein. Loss of function of the *CYP11A1* gene is an established disease mechanism in autosomal recessive congenital adrenal insufficiency. In summary, although additional studies are required to fully establish its clinical significance, this variant meets criteria to be classified as likely pathogenic for autosomal recessive congenital adrenal insufficiency. ACMG/AMP Criteria applied: PVS1, PM2.				
DISEASE INFORMATION: Congenital adrenal insufficiency is rare disorder that can present as severe, early-onset, salt-wasting adrenal insufficiency or acute adrenal insufficiency in infancy or childhood. Adrenal steroids are inappropriately low or absent. The 46,XY patients have female external genitalia, sometimes with clitoromegaly. The phenotypic spectrum ranges from prematurity, complete underandrogenization, and severe early-onset adrenal failure to term birth with clitoromegaly and later-onset adrenal failure. Patients with congenital adrenal insufficiency do not manifest the massive adrenal enlargement typical of congenital lipoid adrenal hyperplasia. (https://ghr.nlm.nih.gov/gene/CYP11A1#conditions), www.orpha.net				
FAMILIAL AND REPRODUCTIVE RISK				
Disease Prevalence (Estimated)	**Carrier Frequency (Estimated)**	**Reproductive Risk (Estimated)**		
<1/1,000,000	<1/500	<1/2000		

D. PHARMACOGENOMIC ASSOCIATIONS

Detailed dosing instructions are not provided in the brief interpretation notes below. Extrinsic factors (e.g. diet, smoking status, co-administered medications) and intrinsic factors (e.g. gender, age, weight, renal or hepatic function) may affect drug response. Patients should not use the test results to stop or change any medication unless directed by a qualified clinician. Clinicians should seek information in the FDA-approved drug label regarding whether genetic information should be used for determining therapeutic treatment. These labels are found at https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm and a table of current PGx biomarkers at https://www.fda.gov/Drugs/ScienceResearch/ucm572698.htm. The Clinical Pharmacogenetics Implementation Consortium (CPIC®) Guidelines and PharmGKB websites may be consulted for their most current recommendations, at https://cpicpgx.org/guidelines/ and https://www.pharmgkb.org/; however, these are informational and have NOT received FDA-approval. Always consult a clinician or clinical pharmacologist before changing drug dosage or for additional information.

Gene(s) Diplotype	Phenotype	Therapeutic Area	FDA - Drugs with PGx Labeling
TPMT *1/*1	TPMT Normal metabolizer	Oncology	Mercaptopurine, Thioguanine, Cisplatin
		Rheumatology	Azathioprine
NUDT15 c.415C/c.415C>T (Het)	NUDT15 Intermediate metabolizer	Oncology	Mercaptopurine, Thioguanine
		Rheumatology	Azathioprine
IFNL3 c.-3180G (Hom) (rs12979860: CC)	IFNL3 Increased activity level	Infectious diseases	Boceprevir, Daclatasvir, Dasabuvir, Elbasvir, Grazoprevir, Ledipasvir, Ombitasvir, Paritaprevir, Peginterferon Alfa-2b, Ritonavir, Simeprevir, Sofosbuvir, Telaprevir, Velpatasvir, Voxilaprevir
CYP2C9 *1/*1	CYP2C9 Normal metabolizer	Gastroenterology	Dronabinol
		Gynecology	Flibanserin, Ospemifene
		Neurology	Phenytoin
		Rheumatology	Celecoxib, Flurbiprofen, Lesinurad, Piroxicam

CYP2C19 *2/*3	CYP2C19 Poor metabolizer	Rheumatology	Carisoprodol
		Psychiatry	Citalopram, Escitalopram, Doxepin
		Neurology	Brivaracetam, Diazepam, Phenytoin, Clobazam
		Infectious Diseases	Voriconazole
		Gynecology	Flibanserin
		Gastroenterology	Dexlansoprazole, , Esomeprazole, Lansoprazole, Omeprazole, Pantoprazole, , Rabeprazole
		Cardiology	Clopidogrel
CYP2C9 *1/*1 VKORC1 -1639 A/A CYP4F2 *1/*3 (V433M CT)	CYP2C9 Normal metabolizer Low VKORC1 expression Decreased CYP4F2 function	Hematology	Warfarin
SLCO1B1 *1A/*1A	SLCO1B1 Normal function	Gynecology	Elagolix
		Endocrinology	Rosuvastatin
DPYD - No tested variants detected	DPYD Normal metabolizer – Activity Score 2	Oncology	Capecitabine, Fluorouracil
		Dermatology	Fluorouracil
CYP3A5 *3/*3	CYP3A5 Poor metabolizer	Transplantation	N/A

Gene(s) Diplotype	Phenotype	Therapeutic Area	FDA - Drugs with PGx Labeling
TPMT *1/*1	TPMT Normal metabolizer	Oncology	Mercaptopurine, Thioguanine, Cisplatin
		Rheumatology	Azathioprine
NUDT15 c.415C/c.415C>T (Het)	NUDT15 Intermediate metabolizer	Oncology	Mercaptopurine, Thioguanine
		Rheumatology	Azathioprine
IFNL3 c.-3180G (Hom) (rs12979860: CC)	IFNL3 Increased activity level	Infectious diseases	Boceprevir, Daclatasvir, Dasabuvir, Elbasvir, Grazoprevir, Ledipasvir, Ombitasvir, Paritaprevir, Peginterferon Alfa-2b, Ritonavir, Simeprevir, Sofosbuvir, Telaprevir, Velpatasvir, Voxilaprevir
CYP2C9 *1/*1	CYP2C9 Normal metabolizer	Gastroenterology	Dronabinol
		Gynecology	Flibanserin, Ospemifene
		Neurology	Phenytoin
		Rheumatology	Celecoxib, Flurbiprofen, Lesinurad, Piroxicam
CYP2C19 *2/*3	CYP2C19 Poor metabolizer	Rheumatology	Carisoprodol
		Psychiatry	Citalopram, Escitalopram, Doxepin
		Neurology	Brivaracetam, Diazepam, Phenytoin, Clobazam
		Infectious Diseases	Voriconazole
		Gynecology	Flibanserin
		Gastroenterology	Dexlansoprazole, , Esomeprazole, Lansoprazole, Omeprazole, Pantoprazole, , Rabeprazole
		Cardiology	Clopidogrel
CYP2C9 *1/*1 VKORC1 -1639 A/A CYP4F2 *1/*3 (V433M CT)	CYP2C9 Normal metabolizer Low VKORC1 expression Decreased CYP4F2 function	Hematology	Warfarin
SLCO1B1 *1A/*1A	SLCO1B1 Normal function	Gynecology	Elagolix
		Endocrinology	Rosuvastatin
DPYD - No tested variants detected	DPYD Normal metabolizer – Activity Score 2	Oncology	Capecitabine, Fluorouracil
		Dermatology	Fluorouracil
CYP3A5 *3/*3	CYP3A5 Poor metabolizer	Transplantation	N/A

RECOMMENDATIONS

These results should be interpreted in the context of this individual's personal medical history and family history. Genetic counseling is recommended for this individual and their relatives. Familial variant testing is available if desired.

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COVERAGE SUMMARY

Sequencing of this individual's genome covered 97.5% of all positions at 15X coverage or higher. Please note that the presence of pathogenic variants in genes not analyzed, genes with incomplete coverage, or regions not captured by filtering strategies cannot be fully excluded.

METHODOLOGY AND LIMITATIONS

Genome sequencing and variant interpretation: Genome sequence is generated from genomic DNA that is fragmented and barcoded followed by sequencing on the Illumina HiSeq X instrument with a minimum coverage of at least 20X for 95%. Technical sensitivity of this assay is 99.84% (95% CI: 99.83-99.85%) and positive predictive value is 99.18% (95% CI: 99.12-99.24%). 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 in 3,734 genes with some level of published evidence for a gene-disease association are subsequently filtered to identify: (1) variants classified as disease causing mutations in public databases that have a minor allele frequency <5.0% in the Genome Aggregation Database (gnomAD, http://gnomadexac.broadinstitute.org/); (2) nonsense, frameshift, and +/-1,2 splice-site variants in disease-associated genes with a minor allele frequency ≤1.0% in gnomAD; and (3) curated established and likely risk alleles with an odds-ratio of at least 2-4. The evidence for phenotype-causality is then evaluated for each variant identified from the filtering strategies listed above and variants are classified based on ACMG/AMP criteria (Richards et al. 2015) with ClinGen rule specifications (https://www.clinicalgenome.org/working-groups/sequence-variant-interpretation/). Variants are reported according to HGVS nomenclature (http://varnomen.hgvs.org/). Only those variants with evidence for causing or contributing to disease are reported. All disease-associated variants on this report are confirmed via Sanger sequencing or another orthogonal technology. Please contact the laboratory for additional information.

Risk Alleles: Genotype calls for specific genomic positions are identified using the Genomic Analysis Tool Kit (GATK) and a custom script. The following likely or established risk alleles are examined and reported if identified in the "reported genotype" listed below. Some variants in these genes are associated with additional diseases and therefore other variants identified in these genes may be included on different sections of this report. Additional risk variants, if identified, may also be included on this report at the discretion of the laboratory.

***Gene* (Transcript)**	**Associated Risk**	**Reportable Variants**	**Reportable Genotypes**
APC (NM_000038.4)	Colorectal Cancer	c.3920T>A (p.Ile1307Lys)	Heterozygous or homozygous
APOE (NM_000041.2)	Alzheimer's Disease	*e4 Allele*- c.388T>C (p.Cys130Arg)	Heterozygous with e2 or e3 or homozygous (e2/e4, e3/e4, e4/e4)
APOL1 (NM_003661.3)	Non-diabetic Nephropathy	*G1 Allele* – c.1164_1169delTTATAA (p.Asn388_Tyr389del)	Homozygous (G1/G1 or G2/G2) or compound heterozygous (G1/G2)
		G2 Allele - c.[1024A>G;1152T>G] (p.[Ser342Gly;Ile384Met])	
CHEK2 (NM_001005735)	Breast, Colorectal, and Papillary Thyroid Cancers	c.599T>C (p.Ile200Thr)	Heterozygous or homozygous
CTRC (NM_007272.2)	Pancreatitis	c.760C>T (p.Arg254Trp)	Heterozygous or homozygous
F2 (NM_000506.3)	Venous Thromboembolism	c.*97G>A	Heterozygous or homozygous
F5 (NM_000130.4)	Factor V Deficiency	c.1601G>A (p.Arg534Gln)	Heterozygous or homozygous
GBA (NM_001005741.2)	Parkinson's Disease	c.1226A>G (p.Asn409Ser)	Heterozygous or homozygous
HFE (NM_000410.3)	Hemochromatosis	c.845G>A (p.Cys282Tyr)	Homozygous
KCNE1 (NM_000219.3)	Long QT Syndrome	c.253G>A (p.Asp85Asn)	Heterozygous or homozygous
LRRK2 (NM_198578.3)	Parkinson's Disease	c.6055G>A (p.Gly2019Ser)	Heterozygous or homozygous
MC1R (NM_002386)	Melanoma	c.880G>C (p.Asp294His)	Heterozygous or homozygous
MITF (NM_000248.3)	Melanoma	c.952G>A (p.Glu318Lys)	Heterozygous or homozygous
MUC5B (NM_002458.2)	Pulmonary Fibrosis	c.-3133G>T	Heterozygous or homozygous
PNPLA3 (NM_025225.2)	Non-alcoholic Fatty Liver Disease Type 1	c.444C>G (p.Ile148Met)	Homozygous
PRNP (NM_000311.3)	Prion Disease	c.628G>A (p.Val210Ile)	Heterozygous or homozygous
SERPINA1 (NM_001127701.1)	Alpha-1 Antitrypsin Deficiency	*S Allele*- c.863A>T (p.Glu288Val)	Homozygous Z allele (Z/Z) or compound heterozygous Z and S allele (Z/S)
		Z Allele- c.1096G>A (p.Glu366Lys)	
SERPINC1 (NM_000488)	Venous Thromboembolism	c.1246G>T (p.Ala416Ser)	Heterozygous or homozygous
SPINK1 (NM_003122)	Pancreatitis	c.101A>G (p.Asn34Ser)	Heterozygous or homozygous

PGx: Genotype calls for specific genomic positions are identified using the Genomic Analysis Tool Kit (GATK) and a custom script. Diplotypes and phenotypes are generated using the Clinical Pharmacogenetics Implementation Consortium (CPIC®) allele tables (https://cpicpgx.org/guidelines/). The following pharmacogenomic variants are detected by this assay: *TPMT*: rs1800462, rs1800460, rs1142345, rs1800584; *CYP2C9*: rs1799853, rs1057910, rs28371686, rs9332131, rs7900194, rs28371685; *VKORC1*: rs9923231; *CYP4F2*: rs2108622; *IFNL3*: rs12979860; *DPYD*: rs3918290, rs55886062, rs67376798, rs72549309, rs115232898, rs1801266, rs78060119, rs56038477, rs72549303, rs1801268; *SLCO1B1*: rs4149056; CYP2C19: rs4244285, rs4986893, rs28399504, rs56337013, rs72552267, rs72558186, rs41291556, rs12248560; *NUDT15*: rs116855232; *CYP3A5*: rs776746, rs10264272, rs41303343. Additionally, variants in *G6PD*, *RYR1*, and *CACNA1S* associated with an altered metabolism status are reported, if identified. This test does not report all pharmacogenomic variants that might alter protein function. Therefore, a result does not exclude the possibility that an individual has a different phenotype that may alter drug response. This risk may vary among ethnic groups. This assay cannot determine if multiple variants in the same gene are present in cis or trans, leading to an inability to definitively assign a diplotype and phenotype. This test does not detect copy number variants. Clinicians should seek information in the FDA-approved drug label regarding whether genetic information should be used for determining therapeutic treatment. These labels are found at https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm and a table of current PGx biomarkers at https://www.fda.gov/Drugs/ScienceResearch/ucm572698.htm.

Limitations: Specific types of genetic variation, such as triplet repeat expansions, structural variation, and copy number events are currently not reliably detected by genome sequencing. Additionally, while genome sequencing covers ~95% of the genome; there are certain regions for which the assay may fail to adequately generate sequence information. Moreover, not all disease-associated genes have been identified and the clinical significance of variation in many genes is not well understood. Variant interpretation may change over time if more information becomes available.

This test was developed and its performance characteristics were 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.

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