LABORATORY FOR MOLECULAR MEDICINE
65 Landsdowne St, Cambridge, MA 02139
Phone: (617) 768-8500 / Fax: (617) 768-8513
http://pcpgm.partners.org/lmm

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

Name: Doe, Jeffrey
DOB: 12/34/5678 **MRN: 123456789**
Sex: Male **Specimen: Blood, Peripheral**
Race: Caucasian **Received: 12/34/5678**
Indication for testing: MedSeq
Test: WGS-pnlA, SeqConV2, WGS-GGR

Accession ID: PMXX-12345
Family #: F12345
Referring physician: MedSeq
Referring facility: MedSeq

GENOME REPORT

RESULT SUMMARY

Sequencing of this individual's genome was performed and covered 95.7% of all positions at 8X coverage or higher, resulting in over 5.4 million variants compared to a reference genome. These data were analyzed to identify previously reported variants of potential clinical relevance as well as novel variants that could reasonably be assumed to cause disease (see methodology below). All results are summarized on page 1 with further details on subsequent pages.

A. MONOGENIC DISEASE RISK: 1 VARIANT IDENTIFIED

Disease, Inheritance	Phenotype	Gene Transcript	Zygosity Variant	Classification
Factor V Leiden thrombophilia, Multi-factorial	Venous thromboembolism	F5 NM_000130.4	Heterozygous c.1601G>A p.Arg534Gln	Risk allele

B. CARRIER RISK: 2 VARIANTS IDENTIFIED

This test identified carrier status for 2 autosomal recessive disorders.

Disease, Inheritance	Phenotype	Gene Transcript	Zygosity Variant	Classification	Phenotype in carriers *
Achromatopsia, Autosomal recessive	Color blindness	CNGA3 NM_001298.2	Heterozygous c.101+1G>A	Likely pathogenic	None reported
Hereditary hemochromatosis, Autosomal recessive	Excessive iron storage	HFE NM_000410.3	Heterozygous c.187C>G p.His63Asp	Pathogenic	None reported

As a carrier for recessive genetic variants, this individual is at higher risk for having a child with one or more of these highly penetrant disorders. To determine the risk for this individual's future children to be affected, the partner of this individual would also need to be tested for variants in these genes. Other biologically related family members may also be carriers of these variants. *Carriers for some recessive disorders may be at risk for certain phenotypes. Please see variant descriptions for more information.

C. PHARMACOGENOMIC ASSOCIATIONS

This test identified the following pharmacogenomic associations. Additional pharmacogenomic results may be requested, but will require additional molecular confirmation prior to disclosure.

Drug	Risk and Dosing Information
Warfarin	Standard dose requirement
Clopidogrel	Typical response to clopidogrel
Digoxin	Intermediate metabolism and serum concentration of digoxin
Metformin	Typical glycemic response to metformin
Simvastatin	Typical risk of simvastatin-related myopathy

D. RED BLOOD CELL AND PLATELET ANTIGENS

This test identified the ABO Rh blood type as B Negative. Additional blood group information is available at the end of the report.

It should be noted that the disease risk section of this report is limited only to variants with strong evidence for causing highly penetrant disease, or contributing to highly penetrant disease in a recessive manner. Not all variants identified have been analyzed, and not all regions of the genome have been adequately sequenced. 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. For questions about this report, please contact the Genome Resource Center at GRC@partners.org

GENOME REPORT (CONTINUED)

DETAILED VARIANT INFORMATION

A. MONOGENIC DISEASE RISK

Disease, Inheritance	Gene Transcript	Zygosity Variant Classification	Variant Frequency	Disease Prevalence	References
Factor V Leiden Thrombophilia, Multi-factorial	F5 NM_000130.4	Heterozygous c.1601G>A p.Arg534Gln Risk allele	3-8% European American	Unknown	Kujovich 2011 Simone 2013
VARIANT INTERPRETATION: The Arg534Gln (legacy name Arg506Gln) in F5 is commonly referred to as "factor V Leiden" and has been associated with increased risk for venous thromboembolism (VTE) with an overall odds ratio (OR) of 4.3 (Simone 2013). The frequency of this variant varies by population, with the highest heterozygosity rate found in Europe. It has been identified in 3% (259/8600) of European American chromosomes and 0.4% (19/4406) of African American chromosomes by the NHLBI Exome Sequencing Project (http://evs.gs.washington.edu/EVS/; dbSNP rs6025). The factor V Leiden mutation is present in approximately 15-20% of individuals with a first deep vein thrombosis (DVT) and in up to 50% of individual with recurrent VTE or an estrogen-related thrombosis. Many individuals with the factor V Leiden allele never develop thrombosis, however, evidence suggests that the relative risk for VTE is increased 3- to 8-fold in factor V Leiden heterozygotes and 10- to 80-fold in homozygotes. Lastly, heterozygosity for factor V Leiden is associated with a 2- to 3-fold increase in relative risk for pregnancy loss, and possibly other pregnancy complications such as preeclampsia, fetal growth retardation, and placental abruption.					
DISEASE INFORMATION: Factor V Leiden thrombophilia is the most common inherited form of thrombophilia. It is characterized by a poor anticoagulant response to activated protein C (APC) and an increased risk for venous thromboembolism (VTE), which is a common complex (multifactorial) disease. Deep venous thrombosis (DVT) is the most common VTE, with the legs being the most common site. Thrombosis in unusual locations is less common. The clinical expression of factor V Leiden thrombophilia is influenced by the number of factor V Leiden alleles, coexisting genetic or acquired thrombophilic disorders and circumstantial risk factors (e.g., travel, pregnancy, oral contraceptives, central venous catheters, advancing age and surgery). Adapted from GeneReviews: http://www.ncbi.nlm.nih.gov/books/NBK1368/.					
FAMILIAL RISK: This Factor V Leiden risk allele increases the chance of developing thrombophilia, likely in conjunction with other genetic and/or environmental risk factors. For a heterozygous individual, there is a 50% chance of passing on the variant and its risk of thrombophilia to a first degree relative. For homozygous individuals, there is a 100% chance of passing on the variant and its risk of thrombophilia to a first degree relative.					

B. CARRIER RISK

Disease, Inheritance	Gene Transcript	Zygosity Variant Classification	Variant Frequency	Disease Prevalence (Carrier Freq.)	References	Phenotype in carriers
Achromatopsia, Autosomal recessive	CNGA3 NM_001298.2	Heterozygous c.101+1G>A Likely pathogenic	0.08% (7/8600) European American	<1/30,000 (Unknown)	Wissinger 2001	None reported
VARIANT INTERPRETATION: The c.101+1G>A variant in CNGA3 has not been previously reported in individuals with achromatopsia, but has been identified in 0.08% (7/8600) of European American chromosomes and 0.02% (1/4406) of African American chromosomes by the NHLBI Exome Sequencing Project (http://evs.gs.washington.edu/EVS/; dbSNP rs147118493). Although this variant has been seen in the general population, its frequency is low enough to be consistent with a recessive carrier frequency. This variant occurs in the invariant region (+/- 1,2) of the splice consensus sequence and is predicted to cause altered splicing leading to an abnormal or absent protein. Complete loss of CNGA3 function is an established disease mechanism in individuals with achromatopsia (Wissinger 2001). In summary, although additional studies are required to fully establish its clinical significance, the c.101+1G>A variant is likely pathogenic.						
DISEASE INFORMATION: Achromatopsia is characterized by reduced visual acuity, pendular nystagmus, increased sensitivity to light (photophobia), a small central scotoma, eccentric fixation, and reduced or complete loss of color discrimination. Individuals with achromatopsia have impaired color discrimination along all three axes of color vision (red, green, and blue). Adapted from GeneReviews abstract: http://www.ncbi.nlm.nih.gov/books/NBK1418/						
FAMILIAL RISK: Achromatopsia is inherited in an autosomal recessive manner. The risk of this patient's child having the disease is dependent on the carrier status of the patient's partner. Two carriers have a 25% risk for having a child with achromatopsia. Other biologically related family members may also be carriers of this variant.						

GENOME REPORT (CONTINUED)

Disease, Inheritance	Gene Transcript	Zygosity Variant Classification	Variant Frequency	Disease Prevalence (Carrier Freq.)	References	Phenotype in Carriers
Hereditary hemochromatosis, Autosomal recessive	HFE NM_000410.3	Heterozygous c.187C>G p.His63Asp Pathogenic	15% (1301/8600) European American	3-5/1000 (9%)	Gochee 2002 Beutler 2002 Gurrin 2009 Pederson 2009	None reported

VARIANT INTERPRETATION: The His63Asp variant in HFE is a well-studied variant for hereditary hemochromatosis (HH) (Gochee 2002). Although it is considered pathogenic, the penetrance is much reduced. Although 13% of His63Asp homozygous individuals and 17% of Cys282Tyr/His63Asp compound heterozygous individuals exhibit elevated transferrin saturation (Pederson 2009), the clinical penetrance is even lower with ≤5% in individuals who are homozygous or compound heterozygous for pathogenic HFE variants exhibiting symptoms (Beutler 2002, Gurrin 2009). In summary, this variant meets our criteria for pathogenicity but with much reduced penetrance.

DISEASE INFORMATION: Hereditary hemochromatosis (HH) is characterized by excessive storage of iron in the liver, skin, pancreas, heart, joints, and testes. In untreated individuals, symptoms may include abdominal pain, weakness, lethargy, weight loss, increased skin pigmentation, diabetes mellitus, congestive heart failure and/or arrhythmias, arthritis, and hypogonadism. The risk of cirrhosis is significantly increased when the serum ferritin is > 1,000 ng/mL. The biochemical and clinical penetrance of HH varies (Beutler 2002, Gurrin 2009, Pederson 2009) and HH is more common in men than women. Adapted from GeneReviews abstract: http://www.ncbi.nlm.nih.gov/books/NBK1440/

FAMILIAL RISK: Hereditary hemochromatosis is inherited in an autosomal recessive manner. The risk of this patient's child having the disease is dependent on the carrier status of the patient's partner. Two carriers have a 25% risk for having a child with Hereditary hemochromatosis. Other biologically related family members may also be carriers of this variant.

PHARMACOGENOMIC ASSOCIATIONS AND BLOOD GROUPS

C. PHARMACOGENOMIC ASSOCIATIONS

Drug (Indication)	Summary	Variants Evaluated and Genotypes Identified	Interpretation	References (PMID)
Warfarin (Anti-coagulation)	**Standard dose requirement**	*CYP2C9* rs1799853 rs1057910 Genotype: *1/*2 c.[430C;1075A]; c.[430C>T;1075A] *VKORC1* rs9923231 Genotype: AA	Patients with the CYP2C9*1/*2 genotype may require a lower dose of warfarin as compared to patients with theCYP2C9*1/*1 genotype. Patients with theVKORC1 AA genotype may require a lower dose of warfarin as compared to patients with the VKORC1 GG or GA genotypes. However, patients with the combination of the CYP2C9*1/*2 genotype and VKORC1 AA genotype are predicted to require standard doses of warfarin compared to other patients. Refer to warfarindosing.org for dosing based on genotype and other clinical factors.	Johnson 2011

VKORC1/CYP2C9 genotype combination frequencies

Dosing Group	VKORC1 rs9923231	CYP2C9 Genotypes	Approximate Frequency
Lower	AA	*1/*3, *2/*2, *2/*3, *3/*3	6%
	GA	*2/*3, *3/*3	3%
Standard	AA	*1/*1, *1/*2	37%
	GA	*1/*2, *1/*3, *2/*2	14%
	GG	*1/*3, *2/*2, *2/*3	<1%
Higher	GA	*1/*1	28%
	GG	*1/*1, *1/*2	13%

<table>
<tr><th>Drug (Indication)</th><th>Summary</th><th>Variants Evaluated and Genotypes Identified</th><th>Interpretation</th><th>References (PMID)</th></tr>
<tr><td>Clopidogrel (Anti-coagulation)</td><td rowspan="2">Typical response to clopidogrel</td><td>CYP2C19
rs4244285
rs4986893
rs12248560

Genotype: *1/*1
c.[806C(;)681G(;)636G];
[-806C(;)681G(;)636G]</td><td>Patients with the CYP2C19 *1/*1 genotype may have extensive (typical) metabolism of clopidogrel as well as well as typical response to clopidogrel as compared to ultrarapid or poor clopidogrel metabolizers. Additional information and dosing recommendations for this result can be found at: http://www.pharmgkb.org/drug/PA449053.</td><td>Scott 2013</td></tr>
<tr><td colspan="3">CYP2C19 genotype frequencies
<table>
<tr><th>Metabolism</th><th>Genotypes</th><th>Frequency</th></tr>
<tr><td>Ultrarapid</td><td>*1/*17, *17/*17</td><td>5-30%</td></tr>
<tr><td>Extensive (typical)</td><td>*1/*1</td><td>35-50%</td></tr>
<tr><td>Intermediate</td><td>*1/*2, *1/*3, *2/17, *3/*17</td><td>18-35%</td></tr>
<tr><td>Poor</td><td>*2/*2, *2/*3, *3/*3</td><td>2-15%</td></tr>
</table></td></tr>
<tr><td>Digoxin (Dysrhythmias, heart failure)</td><td>Intermediate metabolism and serum concentration of digoxin</td><td>ABCB1
rs1045642
Genotype: CT

Genotype frequencies:
CC: 22% CT: 51% TT:27%</td><td>Patients with the CT genotype who take oral digoxin may have intermediate metabolism and serum concentrations of digoxin as compared to patients with the CC and TT genotypes.</td><td>Aarnoudse 2008, Kurata 2002, Hoffmeyer 2000</td></tr>
<tr><td>Metformin (Type 2 diabetes mellitus)</td><td>Typical glycemic response to metformin</td><td>C11orf65
rs11212617
Genotype: TT

Genotype frequencies:
TT:37% TG:48% GG:15%</td><td>Patients with the TT genotype who have Type 2 Diabetes Mellitus and are treated with metformin may have a decreased glycemic response as compared to patients with the GG genotype. An association with increased or decreased glycemic response to metformin was not seen in people diagnosed with impaired glucose tolerance in the absence of Type 2Diabetes Mellitus.</td><td>Florez 2012, GoDARTS and UKPDS Diabetes Pharmacogenetics Study Group 2011</td></tr>
<tr><td>Simvastatin (Hyperlipidemia)</td><td>Typical risk of simvastatin-related myopathy</td><td>SLCO1B1
rs4149056
Genotype: TT

Genotype frequencies:
TT:68% TC:30% CC:2%</td><td>Patients with the TT genotype may have a lower risk of simvastatin-related myopathy as compared to patients with the CT or CC genotype.</td><td>Wilke 2012</td></tr>
</table>

D. RED BLOOD CELL AND PLATELET ANTIGENS

SUMMARY

ABO Rh Blood type: B Negative

Rare RBC Antigens

No rare presence or absence of RBC antigens was identified.

Rare Platelet Antigens

No rare presence or absence of platelet antigens was identified.

DISCUSSION

These red blood cell (RBC) and human platelet antigen (HPA) predictions are based on published genotype to phenotype correlations for the alleles present. Some antigens have also been serologically determined using traditional blood typing methods.
During pregnancy or transfusion alloantibodies to blood group antigens and platelet antigens can form against foreign RBCs that contain immunogenic blood group and platelet antigens that the recipient is missing. These alloantibodies can cause clinically important complications during future transfusions and pregnancy.

Blood Production Transfusion

This individual does NOT have an increased risk of forming unusual RBC or platelet alloantibodies, since this test revealed a normal presence of high frequency antigens and no antigen gene rearrangements.

Blood Production Donation

This individual does NOT pose an increased risk to blood product recipients since this test revealed a normal presence of high frequency antigens and no antigen gene rearrangements.

RED BLOOD CELL ANTIGENS

A	B	H	D	C	c	E	e	K	k	Jk(a)	Jk(b)	Fy(a)	Fy(b)
-	+	+	-	-	+	-	+	-	+	+	+	+	-

M	N	S	S	Lu(a)	Lu(b)	Au(a)	Au(b)	Kp(a)	Kp(b)	Kp(c)	Di(a)	Di(b)
+	-	+	-	[+]	[+]	[+]	[+]	[-]	[+]	[-]	[-]	[+]

Wr(a)	Wr(b)	Yt(a)	Yt(b)	Sc1	Sc2	Do(a)	Do(b)	Jo(a)	Hy	Co(a)	Co(b)	LW(a)	LW(b)
[-]	[+]	[+]	[-]	[+]	[-]	[+]	[-]	[+]	[+]	[+]	[-]	[+]	[-]

Cr(a)	Kn(a)	Kn(b)	Sl(a)	Vil	Yk(a)	KCAM	McC(a)	McC(b)	In(a)	In(b)
[+]	[+]	[-]	[+]	[-]	[+]	[+]	[+]	[-]	[-]	[+]

Ok(a)	MER2	JMHK	JMHL	FORS
[+]	[+]	[+]	[+]	[-]

PLATELET ANTIGENS

1a	1b	2a	2b	3a	3b	4a	4b	5a	5b	6bw	7bw	8bw	9bw
[+]	[+]	[+]	[-]	[+]	[-]	[+]	[-]	[+]	[-]	[-]	[-]	[-]	[-]

10bw	11bw	12bw	13bw	14bw	15a	15b	16bw	17bw	18bw	19bw	20bw	21bw	22bw
[-]	[-]	[-]	[-]	[-]	[+]	[+]	[-]	[-]	[-]	[-]	[-]	[-]	[-]

23bw	24bw	25bw	26bw	27bw
[-]	[-]	[-]	[-]	[-]

Key: [+] presence of antigen predicted by genotyping; + presence of antigen predicted by genotyping and confirmed by serology; +* presence of antigen detected by serology, genotype prediction not available; [+w] weak presence of antigen predicted by genotyping; +w weak presence of antigen predicted by genotyping and confirmed by serology; +w* weak presence of antigen detected by serology, genotype prediction not available; [−] absence of antigen predicted by genotyping; - absence of antigen predicted by genotyping and confirmed by serology, -* absence of antigen detected by serology, genotype prediction not available; NC indicates no sequencing coverage, Dis indicates discordant. Rare (less than 5% population frequency) presence or absence of antigen is indicated in **red**.

METHODOLOGY

Genomic sequencing is performed using next generation sequencing on the Illumina HiSeq platform. Genomes are sequenced to at least 30X mean coverage and a minimum of 95% of bases are sequenced to at least 8X coverage. Paired-end 100bp 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 subsequently filtered to identify: (1) variants classified as disease causing in public databases; (2) nonsense, frameshift, and +/-1,2 splice-site variants that are novel or have a minor allele frequency <1% in European American or African American chromosomes from the NHLBI Exome Sequencing Project (http://evs.gs.washington.edu/EVS/); and (3) rs11212617 (C11orf65; metformin), rs12248560 (CYP2C19; clopidogrel), rs4244285 (CYP2C19; clopidogrel), rs4986893 (CYP2C19; clopidogrel), rs28399504 (CYP2C19; clopidogrel), rs41291556 (CYP2C19; clopidogrel), rs72552267 (CYP2C19; clopidogrel), rs72558186 (CYP2C19; clopidogrel), rs56337013 (CYP2C19; clopidogrel), rs1057910 (CYP2C9; warfarin), rs1799853 (CYP2C9; warfarin), rs7900194 (CYP2C9; warfarin), rs9332131 (CYP2C9; warfarin), rs28371685 (CYP2C9; warfarin), rs28371686 (CYP2C9; warfarin), rs9923231 (VKORC1; warfarin), rs4149056 (SLCO1B1; simvastatin), and rs1045642 (ABCB1; digoxin). 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 highly penetrant disease or contributing to disease in a recessive manner are reported. Before reporting, all variants are 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 the Partners Healthcare Center for Personalized Genetic Medicine (Cambridge, MA

CLIA#22D1005307). This test has not been cleared or approved U.S. Food and Drug Administration (FDA). The FDA has determined that such clearance or approval is not necessary.

LIMITATIONS

It should be noted that this test does not sequence all bases in a human genome and not all variants have been identified or interpreted. 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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GENOME REPORT (CONTINUED)

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