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05/31/2018 This report was addended to include PGx variants

**Pharmacogenetics Finding: POSITIVE**

**Pharmacogenetics Finding: POSITIVE**

Individual carries two increased function alleles in CYP2C19.

**Recommendations**: Clopidogrel - label recommended dosage and administration



Details in Section 3

**Patient**: Danny Doe

Date of Birth: 01/01/1980

MRN: 123456

**Reason for Testing**: Arrhythmia

Ordered ByDr. John Smith

Report Date: 03/25/2018

The HeartCare Gene Panel tests 158 genes associated with Cardiovascular Disease. See [page 2](#Section1) for more details.

**158 Cardiac Gene Panel: POSITIVE**



**Positive Result:** A potentially pathogenic change was found in the FBN1 gene, consistent with a diagnosis of Marfan syndrome.

**Recommendations**: Aortic imaging with echocardiography in patient and referral to an Adult Genetics Clinic. Consider echo and site-specific genetic testing in all first-degree relatives.

Details in Section 1

**Polygenic Risk Score: HIGH**

Patient is in the **High** genetic risk group for coronary artery disease.

**Recommendations**: Studies show that a healthy lifestyle like the AHA’s Life’s Simple 7 is associated with a nearly 50% lower risk of coronary artery disease in the high genetic risk group.



Details in Section 2

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| xxx, MD, FACMG  ABMGG Certified Molecular Geneticist  Assistant Laboratory Director  06/15/2018 | xxx, M.D., FACMG  ABMGG Certified Molecular Geneticist  Medical Director  06/15/2018 |

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| **Ordering Physician:**  Dr. John Smith  1 Baylor Plaza,  Houston TX 77030  Ph: 713 798 0000 | **Patient Name**: Danny Doe  Date of Birth: 01/01/1980  Sex: Male  MRN: 8097987 | HGSC-CL Accession No.: 100008998  Specimen Type: Blood  Specimen Collected Date: 02/23/2018  Specimen Received Date: 02/25/2018  Report Date: 03/25/2018 |
| **Reason for Testing:** Arrhythmia | | |

The HeartCare Gene Panel interrogates the protein-coding and exon-splicing regions of 158 genes that may impact Cardiovascular diseases. Small genomic changes and large duplications and deletions are interpreted for their impact on the patient. See [Methodology](#Section4) for more details.

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| **Overall Interpretation** |
| A clinically-relevant genetic change was found. A pathogenic mutation in the ***FBN1*** gene was detected, consistent with a diagnosis of Marfan syndrome. Aortic imaging with echocardiography are recommended, as well as a referral to the Adult Genetics Clinic. Consider echo and site-specific genetic testing in all first-degree relatives. In addition, this individual is homozygous for the rs4149056 C/C allele in the SLCO1B1 gene. Based on the genotype result, this patient is predicted to have low SLCO1B1 function. This patient may be at a high risk for an adverse response to medications that are affected by SLCO1B1. To avoid an untoward drug response, dose adjustments or alternative therapeutic agents may be necessary for medications affected by SLCO1B1. If simvastatin is prescribed to a patient with low SLCO1B1 function, there is a high risk of developing simvastatin-associated myopathy; such patients may need an alternative statin agent, and creatine kinase levels may need to be monitored routinely. Lastly, this individual has an elevated risk for coronary artery disease. Lifestyle modifications are recommended, including not smoking, getting regular physical activity and eating a healthy diet.  Management Recommendations: Comprehensive management by a multidisciplinary team including a clinical geneticist, cardiologist, ophthalmologist, orthopedist, and cardiothoracic surgeon is strongly recommended. Annual imaging of ascending aorta with echocardiography and periodic surveillance of the entire aorta with CTA/MRA is standard of care. Surgical repair of the aorta is indicated when the maximal measurement of the aortic root approaches 5.0 cm in adults or there is rapid dilatation. Consider medications that reduce hemodynamic stress on aorta, including beta blockers and/or angiotensin receptor blockers. Avoid contact sports and isometric exercise.  Family Screening: Because Marfan syndrome is an autosomal dominant disorder, screening of first-degree relatives is recommended to identify affected individuals who can undergo routine surveillance for early detection of medically significant complications, particularly potentially life-threatening cardiac manifestations. |

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| **Section 1 :: 158 Cardiac Gene Panel: POSITIVE** |
| Pathogenic or Likely Pathogenic variants  This sequence change replaces cysteine with tyrosine at codon 1977 of the FBN1 protein (p.Cys1977Tyr). The cysteine residue is highly conserved and there is a large physicochemical difference between cysteine and tyrosine. This variant is not present in population databases (ExAC no frequency). This variant has been reported in individuals affected with Marfan syndrome (PMID: 9399842, 15241795), a multisystemic connective tissue disorder associated with aortic aneurysms and dissection. Experimental studies indicate that this missense change causes EGF-l intradomain misfolding (PMID: 15371449). This variant affects a cysteine residue located within an epidermal-growth-factor (EGF)-like domain of the FBN1 protein. Cysteine residues in these domains have been shown to be involved in the formation of disulfide bridges, which are critical for FBN1 protein structure and stability (PMID: 10486319, 3495735, 4750422, 16677079). In addition, missense substitutions within the FBN1 EGF-like domains affecting cysteine residues are significantly overrepresented among patients with Marfan syndrome (PMID: 16571647, 17701892). Two additional missense substitutions at this codon (p.Cys1977Arg, p.Cys1977Trp) have been reported in individuals affected with Marfan syndrome (PMID: 12161601, 18435798). For these reasons, this variant has been classified as Pathogenic.  Table 1: Details of Pathogenic and Likely Pathogenic Variants   |  |  |  |  |  |  |  | | --- | --- | --- | --- | --- | --- | --- | | **Disease** | **Inheritance** | **Gene** | **Variant** | **Zygosity** |  | **Interpretation** | | Marfan Syndrome | AD | FBN1 | c.5930G>A  (p.Cys1977Tyr) | Heterozygous |  | Pathogenic | |

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| **Section 2 :: Polygenic Risk Score: HIGH** |
| This patient is in the **High** risk category for coronary artery disease.  Across four studies involving 55,685 participants, genetic and lifestyle factors were independently associated with susceptibility to coronary artery disease. The relative risk of incident coronary events was 91% higher among participants at high genetic risk (top quintile of polygenic scores) than among those at low genetic risk (bottom quintile of polygenic scores) (hazard ratio, 1.91; 95% confidence interval [CI], 1.75 to 2.09). A favorable lifestyle (defined as at least three of the four healthy lifestyle factors) was associated with a substantially lower risk of coronary events than an unfavorable lifestyle (defined as no or only one healthy lifestyle factor), regardless of the genetic risk category. See reference 7 for more information. |

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| **Section 3 :: Pharmacogenetics Finding: POSITIVE** |
| Pharmacogenetic Variants  Pharmacogenetics variants are returned for the following genes: CYP2C19, SLCO1B1, CYP2C9/VKORC1. Star alleles are determined based on the variants detected by this assay. Star alleles may not be accurately defined due to the limitations of this assay which include: 1) The presence of additional variants defining functional and non functional alleles in a patient, not detected by this assay, and 2) the lack of ability to determine the phase of the variants when a star allele is defined by multiple variants. Additionally, undetected genetic and/or non genetic factors such as drug-drug interactions, may also impact the phenotype. Refer to the current recommendation for dosage guidelines. See Methodology for details.  Table 2: Details of pharmacogenetic variants   |  |  |  |  |  | | --- | --- | --- | --- | --- | | **Gene** | **Drug** | **Diplotype** | **Phenotype** | **Recommendation** | | CYP2C19 | clopidogrel | \*1/\*17 | Rapid metabolizer | https://cpicpgx.org/guidelines/guideline-for-clopidogrel-and-cyp2c19/ | | voriconazole | https://cpicpgx.org/guidelines/guideline-for-voriconazole-and-cyp2c19/ | | citalopram, escitalopram | https://cpicpgx.org/guidelines/guideline-for-selective-serotonin-reuptake-inhibitors-and-cyp2d6-and-cyp2c19/ | | amitriptyline | https://cpicpgx.org/guidelines/guideline-for-tricyclic-antidepressants-and-cyp2d6-and-cyp2c19/ | | SLCO1B1 | simvastatin | \*5/\*5 | Low function, High simvastatin induced myopathy risk | https://cpicpgx.org/guidelines/guideline-for-simvastatin-and-slco1b1/ | | CYP2C9 | warfarin | \*1/\*2 | Intermediate metabolizer | https://cpicpgx.org/guidelines/guideline-for-warfarin-and-cyp2c9-and-vkorc1/ | | VKORC1 | C/T |   Interpretation of pharmacogenetic variants:  This individual is heterozygous for the increased function allele of the CYP2C19 gene. Based on the genotype result, this patient is predicted to have a CYP2C19 rapid metabolizer phenotype. This genotype information can be used by patients and clinicians as part of the shared decision-making process for several drugs metabolized by CYP2C19 including clopidogrel, voriconazole, amitriptyline, citalopram and escitalopram. For clopidogrel, individuals with this diplotype are expected to have normal platelet inhibition and normal residual platelet aggregation in response to clopidogrel. Label recommended dosage and administration are recommended. Refer to current guidelines for dosage and recommendations at https://cpicpgx.org/guidelines/guideline-for-clopidogrel-and-cyp2c19/. For voriconazole, for adult patients, the probability of attainment of therapeutic voriconazole concentrations in individuals with this genotype is modest with standard dosing. An alternative agent that is not dependent on CYP2C19 metabolism as primary therapy in lieu of voriconazole such as isavuconazole, liposomal amphotericin B, and posaconazole, is recommended. For pediatric rapid metabolizer patients, therapy should be initiated at recommended standard of care dosing, then therapeutic dosing monitoring should be used to titrate dose to therapeutic trough concentrations. Refer to current guidelines for dosage and recommendations at https://cpicpgx.org/guidelines/guideline-for-voriconazole-and-cyp2c19/. For citalopram and escitalopram, an alternative drug not predominantly metabolized by CYP2D19 is recommended. Refer to current guidelines for dosage and recommendations at https://cpicpgx.org/guidelines/guideline-for-selective-serotonin-reuptake-inhibitors-and-cyp2d6-and-cyp2c19/. For amitriptyline, an alternative drug not predominantly metabolized by CYP2D19 is recommended. If a tricyclic is warranted, therapeutic drug monitoring to guide dose adjustment is recommended. Refer to current guidelines for dosage and recommendations at https://cpicpgx.org/guidelines/guideline-for-tricyclic-antidepressants-and-cyp2d6-and-cyp2c19/. For citalopram, escitalopram and amitriptyline, if CYP2D6 genotyping is available, refer to the current guidelines for dosing recommendations.  The \*5/\*5 diplotype was identified in this sample indicating two decreased function alleles and a high risk of myopathy with simvastatin. Current CPIC guidelines recommend prescribing a lower simvastatin dose or considering an alternative statin (e.g. pravastatin or rosuvastatin).  This individual is heterozygous for the low function allele in the CYP2C9 gene. Based on the genotype result, this patient is predicted to have intermediate CYP2C9 function. This individual is also heterozygous for the variant allele for the VKORC1 gene. Expression level of the VKORC1 gene is associated with warfarin sensitivity. Based on the genotype result, this patient is predicted to have medium sensitivity to warfarin. |

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| **Methodology and Test Limitations** |
| 1. HeartCare NGS Panel: for the paired-end pre-capture library procedure, genome DNA is fragmented by sonicating genome DNA and ligating to the Illumina multiplexing PE adapters (reference 1). The adapter-ligated DNA is then PCR amplified using primers with sequencing barcodes (indexes). For target enrichment capture procedure, the pre-capture library is enriched by hybridizing to biotin labeled in-solution probes (reference 2) at  56°C for 16 - 19 hours.  For massively parallel sequencing, the post-capture library DNA is subjected to sequence analysis on Illumina HiSeq platform for 100 bp paired-end reads. The following quality control metrics of the sequencing data are generally achieved: >70% of reads aligned to target, >99% target base covered at >20X, >98% target base covered at >40X, average coverage of target bases >200X. SNP concordance to SNPTrace genotype array: >99%. This test may not provide detection of certain genes or portions of certain genes due to local sequence characteristics or the presence of closely related pseudogenes. Gross deletions or duplications, changes from repetitive sequences may not be accurately identified by this methodology. Genomic rearrangements cannot be detected by this assay.  2. As a quality control measure, the individual's DNA is also analyzed by a SNP-array (Fluidigm SNPTrace panel (reference 3) ). The SNP data are compared with the NGS panel data to ensure correct sample identification and to assess sequencing quality.  3. Data are analyzed by the Mercury 3.4 (reference 4) pipeline. The output data from Illumina HiSeq are converted from bcl file to FastQ file by Illumina bcl2fastq 1.8.3 software, and mapped to the hg19 human genome reference by the BWA program (reference 5). The variant calls are performed using Atlas-SNP and Atlas-indel developed in-house by BCM HGSC. Copy number variants were detected using Atlas-pcnv v0, developed in-house by the BCM HGSC. Variant annotations are performed using the Cassandra tool, developed in-house. Neptune version v1.3 was used to match variants against curated variants in the VIP database version [2018-02-06-19-27-57.vip] and generate this report.\*\*  4. The variants were interpreted according to ACMG guidelines (reference 6) and patient phenotypes. Synonymous variants, intronic variants not affecting splicing site, and common benign variants are excluded from interpretation unless they were previously reported as pathogenic variants. Reviewed variants are added to the VIP database for inclusion on future reports. It should be noted that the interpretation of the data is based on our current understanding of genes and variants at the time of reporting.  Clinical interpretation and reporting are provided for pathogenic and likely pathogenic variants following genes: ABCA1, ABCC6, ABCC9, ABCG5, ABCG8, ACTA2, ACTC1, ACTN2, ACVRL1, ADRB1, AKAP9, ALMS1, ANGPTL3, ANK2, APOA1, APOA5, APOB, APOC2, APOE, ATP6V0A2, BAG3, BMPR2, CACNA1C, CACNA1D, CACNB2, CALM1, CALR3, CASQ2, CAV1, CAV3, CBS, CHST14, COL1A1, COL1A2, COL2A1, COL3A1, COL4A1, COL5A1, COL5A2, CRYAB, CSRP3, CTNNA3, DES, DMD, DPP6, DSC2, DSG2, DSP, DTNA, EFEMP2, ELN, EMD, ENG, EYA4, FBLN5, FBN1, FBN2, FKTN, FLNA, GATA4, GATAD1, GJA5, GLA, GNAI2, GPD1L, GPIHBP1, GSN, HADH, HCN4, JPH2, JUP, KCNA5, KCNE1, KCNE1L, KCNE2, KCNE3, KCNH2, KCNJ2, KCNJ5, KCNJ8, KCNQ1, LAMA4, LAMP2, LCAT, LDB3, LDLR, LDLRAP1, LIPC, LIPI, LMF1, LMNA, LPA, LPL, LTBP4, MAT2A, MIB1, MTTP, MYBPC3, MYF6, MYH11, MYH6, MYH7, MYL2, MYL3, MYLK, MYLK2, MYO6, MYOCD, MYOZ2, MYPN, NEXN, NOTCH1, NPPA, PCSK9, PKP2, PLN, PLOD1, PNPLA3, PPARG, PRDM16, PRKAG2, PRKAR1A, PRKG1, PSEN1, PSEN2, RBM20, RNF213, RPSA, RYR1, RYR2, SCN1B, SCN3B, SCN4B, SCN5A, SDHA, SGCD, SLC2A10, SLC6A2, SMAD3, SMAD4, SNTA1, SYNE2, TBX20, TCAP, TGFB2, TGFB3, TGFBR1, TGFBR2, TMEM43, TMPO, TNNC1, TNNI3, TNNT2, TPM1, TTN, TTR, USF1, and VCL. For autosomal recessive disorders, only homozygous or biallelic variants will be returned.  5. Variants related to patient phenotypes are confirmed by Sanger sequencing if the variant has been observed and confirmed fewer than 5 times by our laboratory. Sanger confirmation is noted in the 'Notes' section of the tables if performed.  6. The polygenic risk score is calculated following the process in reference 7. |

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| **Gene Coverage** |
| All genes have 100% of targeted bases sequenced to redundant coverage of 20x or greater with the following exceptions: COL1A1 (99.39%), ELN (97.47%), RYR1 (98.03%), SYNE2 (98.29%), TCAP (98.87%), TGFB2 (96.25%). Further information, including specific coverage for this patient's sample, is available in the ExCID report. |

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| **References** |
| 1. Illumina, Inc. (2011) Multiplexing Sample Preparation Guide (Part # 1005361 Rev. D). 2011. 2. Roche NimbleGen, Inc. (2010) NimbleGen SeqCap EZ Exome Library SR User's Guide (Version 2.2). 3. Liang-Chu MM, Yu M, Haverty PM, Koeman J, Ziegle J, Lee M, Bourgon R, Neve RM. Human biosample authentication using the high-throughput, cost-effective SNPtrace(TM) system. PLoS One. 2015 Feb 25;10(2):e0116218.  4. Reid JG, Carroll A, Veeraraghavan N, Dahdouli M, Sundquist A, English A, Bainbridge M, White S, Salerno W, Buhay C, Yu F, Muzny D, Daly R, Duyk G, Gibbs RA, Boerwinkle E. 2014. Launching genomics into the cloud: deployment of Mercury, a next generation sequence analysis pipeline. BMC bioinformatics, 15(1), p.1. PMID: 24475911. 5. Li H. and Durbin R. (2009) Fast and accurate short read alignment with Burrows-Wheeler Transform. Bioinformatics, 25:1754-60. PMID:19451168. 6. Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, Grody WW, Hegde M, Lyon E, Spector E, Voelkerding K, Rehm HL; ACMG Laboratory Quality Assurance Committee. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genetics in Medicine (2015) 17, 405-423. PMID: 25741868.  7. Khera AV, Emdin CA, Drake I, Natarajan P, Bick AG, Cook NR, Chasman DI, Baber U, Mehran R, Rader DJ, Fuster V, Boerwinkle E, Melander O, Orho-Melander M, Ridker PM, Kathiresan S. N Engl J Med. 2016 Dec 15;375(24):2349-2358. Epub 2016 Nov 13. PMID: 27959714 |

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