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Preliminary Report

goo.gl/cLdKB8

Patient Name:		Sample Collected Date:	
Patient ID:		Sample Received Date:	03/16/2016
Age:		Report Date:	
DOB:		Sample Type:	
Sex:		Indication for Testing:	
Patient Sample ID:		Ordering Physician Name:	
Accession #:			

emerge network
ELECTRONIC MEDICAL RECORDS AND GENOMICS

Preliminary eMERGE-Seq Panel Sequencing Report

HGSC-CL

This test interrogates the protein-coding and exon-splicing regions of 109 genes as well as 1551 single-nucleotide polymorphisms that may impact human health and disease. Clinical interpretation and reporting are provided for pathogenic and likely pathogenic variants for genes and single nucleotide polymorphisms as described in the methodology section.

PATHOGENIC AND/OR LIKELY PATHOGENIC VARIANTS DETECTED

A homozygous c.350G>A (p.R117H) pathogenic variant in the CFTR (NM_000492.3) gene was detected in this individual. Defects in CFTR are the cause of cystic fibrosis (CF) [MIM 219700], an autosomal recessive common generalized disorder of the exocrine glands which impairs clearance of secretions in a variety of organs. It is characterized by the triad of chronic bronchopulmonary disease (with recurrent respiratory infections), pancreatic insufficiency (which leads to malabsorption and growth retardation), and elevated sweat electrolytes. Defects in CFTR are also the cause of congenital bilateral absence of the vas deferens (CBAVD) [MIM 277180], an important cause of sterility in men and could represent an incomplete form of cystic fibrosis, as the majority of men suffering from cystic fibrosis lack the vas deferens.

Table 1: Details of Pathogenic and Likely Pathogenic Variants

Disease	Inh.	Gene	Position (NCBI 37)	Variant	Zyg.	Notes	Interpretation
Cystic fibrosis [MIM 219700]; Congenital bilateral absence of the vas deferens [MIM 277180]	AR	CFTR	chr7 g.117171029G>A	c.350G>A p.R117H	Homozygous	PMID 2344617, 23420618, 21228398, 21594800, 10103316, 24440181, 21507732, 22366207, 7506096, 22975760, 23951356, 12767731, 22658665, 20619026, 26324139, 23974870, 19880712, 23891399, 15246977, 26846474, 22332135, 20021716, 21520337, 23378603, 20797923, 20923678, 18778819, 19885835, 22572128, 23751316; rs78655421; [5T]	Pathogenic

Table 2: Details of Copy Number Variants:

No CNVs found for this sample.

Table 3: Details of Pharmacogenomic Variants

Pharmacogenomics variants are returned for the following genes: CYP2C19, DPYD, INFL3, SLCO1B1, TPMT, 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. This pharmacogenomic report is limited to CPIC level A alleles and drug recommendations. Additional (level B and lower) drugs may be metabolized by these

reported enzymes; and additional enzymes, not reported here, may affect the metabolism of a reported drug. Refer to the current recommendation for dosage guidelines. See Methodology for details.

Gene	Drug	Diplotype	Phenotype	Recommendation
CYP2C19	clopidogrel	*1/*1	Normal 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/
DPYD	capecitabine	*1/*1	Normal DPD activity and "normal" risk for fluoropyrimidine toxicity	https://cpicpgx.org/guidelines/guideline-for-fluoropyrimidines-and-dpyd/
	fluorouracil			
	tegafur			
IFNL3	peginterferon alfa-2a	rs12979860 C/C	Favorable response genotype	https://cpicpgx.org/guidelines/guideline-for-peg-interferon-alpha-based-regimens-and-ifnl3/
	peginterferon alfa-2b			
	ribavirin			
SLCO1B1	simvastatin	rs4149056 T/C	Intermediate function, Intermediate simvastatin induced myopathy risk	https://cpicpgx.org/guidelines/guideline-for-simvastatin-and-slco1b1/
TPMT	azathioprine	*1/*1	High activity	https://cpicpgx.org/guidelines/guideline-for-thiopurines-and-tpmt/
	mercaptopurine			
	thioguanine			
CYP2C9	warfarin	*1/*3	Intermediate metabolizer	https://cpicpgx.org/guidelines/guideline-for-warfarin-and-cyp2c9-and-vkorc1/
VKORC1		T/T		

Interpretation of Pharmacogenomic Variants:

This individual is homozygous for the wild type allele of the CYP2C19 gene. Based on the genotype result, this patient is predicted to have a CYP2C19 normal 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, normal voriconazole metabolism is expected in individuals with this genotype. Initiate therapy with recommended standard of care dosing. Refer to current guidelines for dosage and recommendations at https://cpicpgx.org/guidelines/guideline-for-voriconazole-and-cyp2c19/. For citalopram and escitalopram, initiate therapy with recommended starting dose. 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, initiate therapy with recommended starting dose. 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.

This individual is homozygous for the functional allele of the DPYD gene. This genotype information can be used by patients and clinicians as part of the shared decision-making process for fluoropyrimidines (capecitabine, fluorouracil, tegafur). Based on the genotype result, this patient is predicted to have a normal DPD activity phenotype. Individuals with this diplotype are expected to have "normal" risk for fluoropyrimidine toxicity. Recommendations include the use of label recommended dosage and administration. Refer to current guidelines for dosage and recommendations at https://cpicpgx.org/guidelines/guideline-for-fluoropyrimidines-and-dpyd/.

This individual is homozygous for the rs12979860 C/C allele in the IFNL3 gene. This variant is the strongest baseline predictor of response to peginterferon alfa and ribavirin therapy in previously untreated patients and can be used by patients and clinicians as part of the shared decision-making process for initiating treatment for hepatitis C virus infection. Based on the genotype result, this patient is predicted to have an increased likelihood of response (higher sustained virologic response rate) to peginterferon alfa and ribavirin therapy as compared with patients with unfavorable response genotype. Refer to current guidelines for dosage and recommendations at https://cpicpgx.org/guidelines/guideline-for-peg-interferon-alpha-based-regimens-and-ifnl3/.

This individual is heterozygous for the rs4149056 T/C allele in the SLCO1B1 gene. This genotype information can be used by patients and clinicians as part of the shared decision-making process for simvastatin and other drugs affected by SLCO1B1. Based on the genotype result, this patient is predicted to have intermediate SLCO1B1 function. This patient may be at risk for an adverse response to medications that are affected by SLCO1B1. To avoid an untoward drug response, dose adjustments may be necessary for medications affected by SLCO1B1. If simvastatin is prescribed to a patient with intermediate SLCO1B1 function, there is an increased risk for developing simvastatin-associated myopathy; such patients may need a lower starting dose of simvastatin or an alternate statin agent. Refer to current guidelines for dosage and recommendations at https://cpicpgx.org/guidelines/guideline-for-simvastatin-and-slco1b1/.

This individual is homozygous for the normal high activity allele of the TPMT gene. Decreased TPMT gene activity is associated with toxicity and myelosuppression in response to thiopurines, and this genotype information can be used by patients and clinicians as part of the shared decision-making process for initiating treatment. Based on the genotype result, this patient is predicted to have normal TPMT function. Individuals with this diplotype are expected to have a normal response to mercaptopurine, azathioprine and thioguanine. A normal dose of thiopurine and adjustment following the disease-specific guidelines is recommended. Refer to current guidelines for dosage and recommendations for each specific thiopurine drug at https://cpicpgx.org/guidelines/guideline-for-thiopurines-and-tpmt/.

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 homozygous 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 high sensitivity to warfarin.

Comments & Recommendations:

It is recommended that correlation of these findings with the clinical phenotype be performed. Genetic counseling for the patient and at-risk family members is recommended.

This is a preliminary report because the variant has not yet been confirmed by Sanger sequencing.

Gene Coverage:

All genes have 100% of targeted bases sequenced to redundant coverage of 20x or greater with the following exceptions: APOB (99.39%), CACNA1B (96.45%), COL5A1 (98.03%), GRM5 (99.92%), KCNQ1 (94.28%), PKP2 (98.76%), PRKAG2 (99.83%), RYR1 (98.69%), TGFBR1 (93.56%). Further information, including specific coverage for this patient's sample, is available in the ExCID report.

Methodology:

1. eMERGE-Seq Version 2 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 $VERSION was used to match variants against curated variants in the VIP database version [/hgsccl/next-gen/neptune/vip/vip.2016-11-07] 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 as requested by BMGL for the following 68 medically actionable genes: ACTA2, ACTC1, APC, APOB, BMPR1A, BRCA1, BRCA2, CACNA1A, CACNA1S, COL3A1, COL5A1, DSC2, DSG2, DSP, FBN1, GLA, HNF1A, HNF1B, KCNE1, KCNH2, KCNJ2, KCNQ1, LDLR, LMNA, MEN1, MLH1, MSH2, MSH6, MUTYH, MYBPC3, MYH11, MYH7, MYL2, MYL3, MYLK, NF2, OTC, PALB2, PCSK9, PKP2, PMS2, POLD1, POLE, PRKAG2, PTEN, RB1, RET, RYR1, RYR2, SCN5A, SDHAF2, SDHB, SDHC, SDHD, SMAD3, SMAD4, STK11, TGFBR1, TGFBR2, TMEM43, TNNI3, TNNT2, TP53, TPM1, TSC1, TSC2, VHL, WT1, the following non medically actionable genes: ANK2, ATM, ATP1A2, BMPR2, CACNA1C, CFH, CFTR, CHEK2, FLG, MC4R, MTHFR, NTRK1, SCN1A, SCN9A, SERPINA1, SLC2A10, TCF4, TCIRG1, TTR, TYK2, UMOD, VDR, the following medically actionable SNPs: rs77931234, rs387906225, rs79761867, rs386834233, rs113993962, rs397509431, rs6467, rs6025, rs80338898, rs1801175, rs1800562, rs28940579, rs61752717, rs193922376; and non medically actionable SNPs: rs151344623, rs76151636, rs111033258, rs786205104, rs786205103, rs147394623, rs121964990, rs121965064, rs121965063, rs104886456, rs201227603, rs74315447, rs61755320, rs724159981. For autosomal recessive disorders, only homozygous or biallelic variants will be returned. Variants in exon 3 of the FLG gene are not reported.

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 or the Baylor Genetics Laboratory. Sanger confirmation is noted in the 'Notes' section of the tables if performed.

6. For the pharmogenomic variants, the star alleles are determined based on the variants detected by this assay. Alleles reported for TPMT are limited to *1, *2, *3A, *3B, *3C and *4. Alleles reported for CYP2C19 are limited to *1, *2, *4A, *4B, *5, *6, *7, *8, *17. If reported, alleles for DPD are limited to *1, *2A , *13 and rs67376798. Alleles reported for CYP2C9 are limited to *1, *2 and *3; and rs9923231 for VKORC1. Additional rare star alleles have been reported with reduced or no function for TPMT, CYP2C19 and DPD; however, the variants defining these additional star alleles are not detected with this assay. For SLCO1B1, this assay only detects rs4149056. The minor C allele at rs4149056 defines the SLCO1B1*5 (rs4149056 alone) but also tags the *15 and *17 alleles. Thus a *5 allele may represent a *15 or *17 allele. However, the magnitude of the phenotypic effect is similar for *5, *15, and *17 alleles.

** The VIP variant database was developed in conjunction with Baylor Genetics and the Partners Healthcare Laboratory for Molecular Medicine.

References:

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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.
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