Genesis Healthcare

DRUG RESPONSE

PERFORMED AT YEBISU GARDEN PLACE TOWER 26F 4-20-3
EBISU, SHIBUYA-KU, TOKYO, JAPAN, 150-6026

ORDERING PRACTICE

Practice Code: 100
Sample Cardiology Clinic
374 Broadway
New York, NY 10001
Physician: Dr. Sample

JANE DOE

DOB: 1973-02-19
Gender: Female
Ethnicity: European
Procedure ID: 87000
Kit Barcode: 201612092248585
Specimen: Blood, #10000
Specimen Collected: 2016-01-12
Specimen Received: 2016-01-13
Specimen Analyzed: 2016-01-21
Report Generated: 2016-02-03

TEST INFORMATION

Panel: Drug Response Panel

SUMMARY OF RESULTS

Consider Alternatives/Use with Extreme Caution

The drugs below are expected to have serious adverse effects or are contraindicated based on the patient's genotype.

CARDIOVASCULAR

Drug	Drug Type	Gene	Variant / Haplotype	Interpretation	Reference Type	Reference (PMID)
Clopidogrel	Antiplatelets	CYP2C19	rs4244285 G/A (*1/*2)	1) May have poor metabolism of clopidogrel and decreased formation of active drug metabolite, resulting in decreased response 2) May have an increased risk for secondary cardiovascular events	CPIC Guideline	21716271;23698643
Simvastatin	Statins	SLOC1B	rs4149056 T/C	Increased risk of simvastatin-related myopathy, as compared to patients with the TT genotype.	CPIC Guideline	22617227;24918167

Use with Caution

The drugs below may be less effective or result in adverse effects based on the patient's genotype.

PSYCHIATRY

Drug	Drug Type	Gene	Variant / Haplotype	Interpretation	Reference Type	Reference (PMID)
Citalopram	SSRI	CYP2C19	rs4244285 G/A (*1/*2)	Decreased drug clearance/metabolism and decreased tolerance, especially in combination with another no function allele (*2, *3, *4, *6, *8) (poor metabolizer phenotype) as compared to patients with the CYP2C19 *1/*1 genotype	CPIC Guideline	25974703
Escitalopram	SSRI				CPIC Guideline	25974703
Sertraline	SSRI	CYP2C19	rs4244285 G/A (*1/*2)	Increased clearance as compared to patients with the *2/*2 or *2/*3 diplotype and a decreased clearance as compared to patients with the *1/*1 diplotype	CPIC Guideline	25974703
Amitriptyline	Tricyclic Antidepressant	CYP2C19	rs4244285 G/A (*1/*2)	Decreased metabolism, CYP2C19 alleles *17 rs12248560 and *3 rs4986893, along with clinical factors, may also influence a patient's required dose	CPIC Guideline	2323254; 26094938

CLIA #31D2123554

Use with Caution (continued)

The drugs below may be less effective or result in adverse effects based on the patient's genotype.

INFECTIOUS DISEASE						
Drug	**Drug Type**	**Gene**	**Variant / Haplotype**	**Interpretation**	**Reference Type**	**Reference (PMID)**
Voriconazole	Antifungal	CYP2C19	rs4244285 G/A (*1/*2)	Decreased metabolism of voriconazole as compared to patients with the CYP2C19 *1/*1 diplotype (normal metabolizers) or the CYP2C19 *1/*17 or *17/*17 diplotypes (rapid and ultrarapid metabolizers), or may have increased metabolism as compared to patients with the CYP2C19 *2/*2, *3/*3 or *2/*3 diplotypes (poor metabolizers).	CPIC Guideline	27981572

Normal Response Expected

The drugs below are expected to have a normal response based on the patient's genotype.

Drug Type	Drug	Reference (PMID)
CARDIOVASCULAR		
ACE Inhibitors	Captopril	22992668
Antiarrhythmic	Digoxin	22992668
	Flecainide	22992668
	Propafenone	*See drug label
	Quinidine	*See drug label
Anticoagulant	Acenocoumarol	22992668
	Phenprocoumon	22992668
	Warfarin	21900891;28198005
Beta Blockers	Carvedilol	*See drug label
	Timolol	22992668
	Metoprolol	*See drug label
Diuretics	Furosemide	22992668
	Spironolactone	22992668
Statins	Atorvastatin	22992668
	Cerivastatin	22992668
	Pravastatin	22992668
	Rosuvastatin	*See drug label
ENDOCRINOLOGY		
Antithyroid	Carbimazole	22992668
	Methimazole	22992668
	Propylthiouracil	22992668

Drug Type	Drug	Reference (PMID)
GASTROENTEROLOGY		
Proton Pump Inhibitors (PPIs)	Dexlansoprazole	*See drug label
	Esomeprazole	*See drug label
	Lansoprazole	*See drug label
	Omeprazole	*See drug label
	Pantoprazole	*See drug label
	Rabeprazole	*See drug label
Laxatives	Moviprep	*See drug label
PAIN MANAGEMENT		
Nonsteroidal Anti-Inflammatory Drugs (NSAIDS)	Aspirin	22992668
	Celecoxib	*See drug label
	Diclofenac	22992668
	Flurbiprofen	*See drug label
	Piroxicam	*See drug label
Opioids	Alfentanil	22992668
	Fentanyl	22992668
	Heroin	22992668
	Codeine	22205192;24458010
	Methadone	22992668
	Morphine	22992668
	Naloxone	22992668
	Naltrexone	22992668

Normal Response Expected (continued)

The drugs below are expected to have a normal response based on the patient's genotype.

Drug Type	Drug	Reference (PMID)
ENDOCRINOLOGY (CONT'D.)		
Sulfonylureas (cont'd.)	Chlorpropamide	*See drug label
	Glibenclamide	*See drug label
	Glipizide	*See drug label
Thiazolidnediones	Rosiglitazone	22992668
IMMUNOLOGY		
	Adalimumab	22992668
	Allopurinol	23232549;26094938
	Azathioprine	21270794;23422873
	Cyclosporine	22992668
	Etanercept	22992668
	Infliximab	22992668
	Lesinurad	*See drug label
	Pegloticase	*See drug label
	Probenecid	*See drug label
	Sirolimus	22992668
	Sulfasalazine	*See drug label
	Tacrolimus	25801146
PSYCHIATRY		
Antipsychotics	Amisulpride	22992668
	Aripiprazole	*See drug label
	Brexpiprazole	*See drug label
	Clozapine	*See drug label
	Haloperidol	22992668
	Iloperidone	*See drug label
	Olanzapine	22992668
	Paliperidone	22992668
	Perphenazine	*See drug label
	Pimozide	*See drug label
	Quetiapine	22992668
	Risperidone	22992668
	Thioridazine	*See drug label
	Ziprasidone	22992668
Benzodiazepines	Clobazam	*See drug label

Drug Type	Drug	Reference (PMID)
PAIN MANAGEMENT (CONT'D.)		
Opioids (cont'd.)	Oxycodone	22992668
	Tramadol	*See drug label
Others	Carisoprodol	*See drug label
	Lidocaine	*See drug label
	Prilocaine	*See drug label
NEUROLOGY		
Anticonvulsant	Brivaracetam	*See drug label
	Carbamazepine	23695185
	Lamotrigine	22992668
	Oxcarbazepine	*See drug label
	Phenytoin	25099164
Central ACH Inhibitors	Donepezil	*See drug label
Central Monoamine-Depleting Agents	Tetrabenazine	*See drug label
INFECTIOUS DISEASE		
Antibiotics	Dapsone	*See drug label
	Erythromycin Ethylsuccinate and Sulfisoxazole Acetyl	*See drug label
	Ethambutol	22992668
	Isoniazid	*See drug label
	Mafenide	*See drug label
	Nalidixic acid	*See drug label
	Nitrofurantoin	*See drug label
	Norfloxacin	*See drug label
	Pyrazinamide	22992668
	Rifampin	22992668
	Sulfadiazine	*See drug label
	Sulfamethoxazole	*See drug label
	Sulfisoxazole	*See drug label
	Trimethoprim	*See drug label
Antimalarials	Chloroquine	*See drug label
	Chlorproguanil	22992668
	Primaquine	*See drug label
	Quinine	*See drug label

Normal Response Expected (continued)

The drugs below are expected to have a normal response based on the patient's genotype.

Drug Type	Drug	Reference (PMID)
PSYCHIATRY (CONT'D.)		
Benzodiazepines	Diazepam	*See drug label
	Lorazepam	22992668
	Midazolam	22992668
	Oxazepam	22992668
Selective Serotonin Reuptake Inhibitors	Fluoxetine	*See drug label
	Fluvoxamine	25974703
	Paroxetine	25974703
Serotonin-Norepinephrine Reuptake Inhibitors	Atomoxetine	*See drug label
	Duloxetine	*See drug label
	Venlafaxine	22992668
Tricyclic Antidepressants	Amitriptyline	23486447;27997040
	Clomipramine	23486447;27997040
	Desipramine	23486447;27997040
	Doxepin	23486447;27997040
	Imipramine	23486447;27997040
	Nortriptyline	23486447;27997040
	Protriptyline	*See drug label
	Trimipramine	23486447;27997040
Others	Bupropion	22992668
	Flibanserin	*See drug label
	Mirtazapine	22992668
	Modafinil	*See drug label

Drug Type	Drug	Reference (PMID)
INFECTIOUS DISEASE (CONT'D.)		
Antivirals	Boceprevir	*See drug label
	Peginterferon Alfa-2A	24096968
	Peginterferon Alfa-2B	24096968
	Ribavirin	24096968
	Abacavir	22378157;24561393
	Atazanavir	26417955
	Dolutegravir	*See drug label
	Efavirenz	*See drug label
	Epclusa	*See drug label
	Ledipasvir/Sofosbuvir	*See drug label
	Nevirapine	22992668
	Simeprevir	*See drug label
	Sofosbuvir	*See drug label
	Technivie	*See drug label
	Telaprevir	*See drug label
	Zepatier	22992668

GENOTYPING RESULTS

Gene	Genotype	Phenotype	Variants/ Haplotypes Assayed
ABCB1	*1/*1	Wildtype	rs2032582, rs1045642, *1/*1, *1/*2, *2/*2
ABCG2	WT/WT	Wildtype	rs2231142
ACE	WT/WT	Wildtype	rs1799752
ADD1	WT/WT	Wildtype	rs4961
ADORA2A	WT/WT	Wildtype	rs2298383
ANKK1	WT/WT	Wildtype	rs1800497
APOE	WT/WT	Wildtype	rs7412

Gene	Genotype	Phenotype	Variants/ Haplotypes Assayed
HLA-C	WT/WT	Wildtype	*03:02, *01:02:01
HLA-DPB1	WT/WT	Wildtype	*03:01:01
HLA-DQA1	WT/WT	Wildtype	*02:01
HLA-DRB1	WT/WT	Wildtype	*01:01:01
HMGCR	WT/WT	Wildtype	rs17244841
HTR1A	WT/WT	Wildtype	rs6295
HTR2A	WT/WT	Wildtype	rs7997012

GENOTYPING RESULTS (CONT'D.)

Gene	Genotype	Phenotype	Variants/ Haplotypes Assayed
ATIC	WT/WT	Wildtype	rs4673993
CBR3	WT/WT	Wildtype	rs1056892
CCHCR1	WT/WT	Wildtype	rs746647
CES1	WT/WT	Wildtype	rs71647871
CETP	WT/WT	Wildtype	rs1532624
CFTR	WT/WT	Wildtype	rs78655421, rs80282562, rs121908757, rs121908755, rs121909005, rs121909013, rs75527207, rs267606723, rs74503330, rs121909041, rs193922525, rs113993960, rs113993959, rs75039782, rs77010898
COMT	WT/WT	Wildtype	rs4680, rs13306278
COQ2	WT/WT	Wildtype	rs4693075
CRHR1	WT/WT	Wildtype	rs1876828
CRHR2	WT/WT	Wildtype	rs7793837
CYP2B6	WT/WT	Wildtype	*1,*6, *18, rs4803419
CYP2C19	*1/*1	Wildtype	*1, *2, *3, *4, *5, *6, *7, *8, *12, *9, *10, *17
CYP2C8	WT/WT	Wildtype	rs10509681
CYP2C9	*1/*1	Normal Metabolizer	*1, *2, *3, *5, *6, *8, *11, *4, rs4917639
CYP2D6	*1/*1	Normal Metabolizer	*1, *2, *35, *9, *10, *5, *17, *36, *41, *29, *3, *4, *6, *14, *21, *31, *40, *1XN, *2XN
CYP3A4	*1/*1	Wildtype	*1, *1B, *1G
CYP3A5	*1/1*1	Normal Metabolizer	*1, *3, *3A, *1A, *6, *7
CYP4F2	*1/*1	Normal Metabolizer	*1, *3

Gene	Genotype	Phenotype	Variants/ Haplotypes Assayed
HTR2C	WT/WT	Wildtype	rs1414334, rs3813929
IFNL3	WT/WT	Favorable Response Genotype	rs12979860, rs8099917, rs11881222
ITPA	WT/WT	Wildtype	rs1127354, rs7270101
KCNIP4	WT/WT	Wildtype	rs145489027
KIF6	WT/WT	Wildtype	rs20455
LPA	WT/WT	Wildtype	rs10455872
LTC4S	WT/WT	Wildtype	rs730012
MC4R	WT/WT	Wildtype	rs17782313, rs489693
MTHFR	WT/WT	Wildtype	rs1801133
NAT2	WT/WT	Wildtype	rs1041983, rs1799930, *12, *13, *14, *4, *5, *6, *7
NQO1	WT/WT	Wildtype	rs1800566
NT5C2	WT/WT	Wildtype	rs11598702
NUDT15	WT/WT	Wildtype	rs116855232
OPRM1	WT/WT	Wildtype	rs1799971
PTGS1	WT/WT	Wildtype	rs10306114
PTPGFR	WT/WT	Wildtype	rs3753380
SCN1A	WT/WT	Wildtype	rs3812718
SEMA3C	WT/WT	Wildtype	rs7779029

GENOTYPING RESULTS (CONT'D.)

Gene	Genotype	Phenotype	Variants/ Haplotypes Assayed
DPYD	WT/WT	Wildtype	*1, *2A, *13, rs67376798
DRD2	WT/WT	Wildtype	rs1799978, rs1800497, rs1076560
DYNC2H1	WT/WT	Wildtype	rs716274
EPHX1	WT/WT	Wildtype	rs1051740, rs2234922
ERCC1	WT/WT	Wildtype	rs3212986, rs11615
F2	WT/WT	Wildtype	G20210A
F5	WT/WT	Wildtype	rs6025
FASTKD3,MTRR	WT/WT	Wildtype	rs1801394
FDPS	WT/WT	Wildtype	rs2297480
G6PD	WT/WT	Wildtype	Null alleles
GRIK4	WT/WT	Wildtype	rs1954787
GSTM1	WT/WT	Wildtype	Null alleles
GSTP1	WT/WT	Wildtype	rs1695
HAS3	WT/WT	Wildtype	rs2232228
HLA-A	WT/WT	Wildtype	*33:03, *31:01:02
HLA-B	WT/WT	Wildtype	*15:02:01, *57:01:01, *58:01, *13:01:01, *15:11:01, *40:01:01, *35:01:01:01, *38:02:01, *59:01:01:01

Gene	Genotype	Phenotype	Variants/ Haplotypes Assayed
SLC28A3	WT/WT	Wildtype	rs7853758, rs885004
SLC6A4	WT/WT	Wildtype	5-HTTLPR Long allele/long allele
SLCO1B1	RS4149056 T/C	Decreased activity	rs4149056, rs4149015, rs11045879, *1, *5, *15, *1A, *1B
TANC1	WT/WT	Wildtype	rs264651, rs264631, rs10497203, rs7582141, rs6432512, rs264588
TCF7L2	WT/WT	Wildtype	rs7903146
TNF	WT/WT	Wildtype	rs1800629
TP53	WT/WT	Wildtype	rs1042522
TPMT	*1/*1	Wildtype	*1, *2, *3A, *3B, *3C, *4
TYMS	WT/WT	Wildtype	rs151264360
UGT1A1	WT/WT	Wildtype	rs887829, rs8175347, rs4148323
UGT1A4	WT/WT	Wildtype	rs2011425
UGT2B15	WT/WT	Wildtype	rs1902023
UMPS	WT/WT	Wildtype	rs1801019
VDR	WT/WT	Wildtype	rs2228570
VKORC1	WT/WT	Wildtype	rs9923231, rs7294, rs9934438, rs9923231, rs7294, rs2359612, rs8050894, rs17708472, rs2884737, rs61742245, rs7196161
XPC	WT/WT	Wildtype	rs2228001
XRCC1	WT/WT	Wildtype	rs25487

WT = Wildtype, HT = Heterogeneous

METHODS

SEQUENCING

Genomic DNA obtained from the submitted sample is enriched for targeted regions using a hybridization-based protocol and sequenced using Illumina technology. Reads are aligned to the reference sequence (Grch37, standard genome build hg19), and sequence changes are identified and interpreted in the context of a single clinically relevant transcript. Exonic deletions and duplications are called using a copy number variation (CNV) algorithm. The CNV algorithm calculates a statistical likelihood of each copy number state by comparing the depth of sequencing coverage at targeted exons to a baseline depth measure in control samples. A confidence threshold is used for each assertion of copy number state for each exon where the sequence data met a minimum quality standard of >20x depth of unique properly paired reads. This algorithm detects most intragenic deletions and duplications, although rare single-exon events may be missed.

The analytical sensitivity and specificity of this assay is >99% and >99%, respectively. All reportable variants are confirmed by orthogonal technologies as part of our ongoing quality management process. Unless otherwise indicated, all targeted regions were sequenced with >20x depth of coverage. Regions with a read depth below this are supplemented with orthogonal testing, if they contain previously reported pathogenic variants. The assay targets all coding regions of the indicated transcript, 10 base pairs of flanking intronic sequence, and specific intronic and intragenic genomic regions demonstrated to be causative of disease. However, for some genes, only targeted loci are analyzed.

All data is processed and analyzed using Elements Software Version 1.

Phosphorus can be contacted via phone at 1-855-746-7423 or by email at support@phosphorus.com.

LIMITATIONS

Although this test is highly accurate, no genetic test is 100% sensitive. This analysis is designed to detect variants with pharmacogenomics association within the genes included in this assay. Hence this analysis will not detect novel sequence variants in the promoter region and other non-coding regions, as well as it does not assay untranslated exons. Also, the sensitivity to detect insertions and deletions larger than 15 base pairs but smaller than a full exon may be reduced. Some exons of a few individual genes have inherent sequence properties that yield suboptimal data, and pathogenic variants in those regions may not be reliably identified. The low-level mosaicism will not be detected. Moreover, this analysis does not detect every pathogenic variant associated with this disease because of genes not included in the current panel or unknown to be associated with the disease at this time. It also does not test for all known genetic diseases. Errors in testing (both false positives and false negatives) may also occur for reasons that include, but are not limited to specimen issues (e.g. inaccurately marked samples causing sample mix-up, DNA quality and quantity not meeting minimum requirements), rare genetic variants interfering with analysis, assay technical limitations, biological factors (e.g. recent blood transfusions, circulating hematolymphoid neoplasm, or history of bone marrow transplantation), and other technical issues. If a pathogenic variant is detected, the patient may be a carrier of, affected with, predisposed to, or at risk for certain disease(s) or condition(s) associated with that variant. If no pathogenic variant is found, the patient may be at reduced risk of being carrier of, affected with, predisposed to, or at risk for the disease(s) or condition(s) tested for in the current panel. However, further testing may be necessary, since negative test results may reduce, but do not eliminate, the chance that the patient is a carrier of, affected with, predisposed to, or at risk of having said disease(s) or condition(s). In addition, other pathogenic variant(s) or factors that are not included in our services may impact an individual's risk of, or predisposition to certain disease(s) or condition(s). Thus, this report does not provide definitive conclusions regarding risk of, predisposition to, or diagnosis of certain disease(s) or condition(s).

DISCLAIMER

This report reflects the analysis of an extracted DNA sample; and it does not constitute medical advice. Any questions or concerns regarding the contents of this report or any prevention, cure, mitigation, or treatment of a medical condition or disease should be directed to a qualified medical professional.

This test was developed and its performance characteristics determined by Phosphorus Diagnostics, LLC. It has not been cleared or approved by the FDA. The laboratory is regulated under CLIA as qualified to perform high-complexity testing. These test results are to be used for clinical purposes and should not be regarded as investigational or for research.

This assay only detects and reports variants with known pharmacogenomic associations, as listed in the Genotyping Results section, and does not report all variants in the genes assayed.

VARIANT CLASSIFICATION

This test includes analysis of variants with strong evidence of pharmacogenomic association. The variants included in this test are either classified as evidence level A and B by the Clinical Pharmocogenetics Implementation Consortium (CPIC), evidence level 1 and 2 by PharmGKB, or referenced in an FDA drug label.

SIGNED BY

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