Phosphorus Diagnostics

DRUG RESPONSE

PERFORMED AT PHOSPHORUS DIAGNOSTICS,
400 PLAZA DRIVE 4TH FLOOR, SUITE 401, SECAUCUS, NJ 07094

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	Poor Metabolizer (*2/*2)	Patients with this genotype may experience decreased drug efficacy and may have an increased risk for adverse cardiovascular events; use of an alternative drug is recommended.	CPIC Guideline	21716271;23698643
Simvastatin	Statins	SLOC1B	rs4149056 C/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	Poor Metabolizer (*2/*2)	Patients with this genotype may have significantly reduced metabolism of this drug which could increase the risk for side effects. A reduced starting dosage is recommended, or consideration of an alternative drug.	CPIC Guideline	25974703
Sertraline	SSRI	CYP2C19	Poor Metabolizer (*2/*2)	Patients with this genotype may have significantly reduced metabolism of this drug which could increase the risk for side effects. A reduced starting dosage is recommended, or consideration of an alternative drug.	CPIC Guideline	25974703
Escitalopram	SSRI	CYP2C19	Poor Metabolizer (*2/*2)	Patients with this genotype may have significantly reduced metabolism of this drug which could increase the risk for side effects. A reduced starting dosage is recommended, or consideration of an alternative drug.	CPIC Guideline	25974703

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)
Ribavirin	Antiviral	VDR	rs2228570 G/ rs2228570 G	Patients with this genotype may have a decreased likelihood of sustained virological response.	Other	24073221; 26911666

Normal Response Expected

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

Drug Type	Drug	Reference
CARDIOVASCULAR		
Antiarrhythmic	Digoxin	22992668
	Flecainide	22992668
	Propafenone	*See drug label
Anticoagulant	Warfarin	21900891;28198005
Beta Blockers	Carvedilol	*See drug label
	Metoprolol	*See drug label
Diuretics	Furosemide	22992668
	Spironolactone	22992668
Statins	Atorvastatin	22992668
	Pravastatin	22992668
	Simvasttatin	22992668
	Rosuvastatin	*See drug label
ENDOCRINOLOGY		
Antithyroid	Methimazole	22992668
	Propylthiouracil	22992668
Sulfonylureas	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

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Normal Response Expected (continued)

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

Drug Type	Drug	Reference
IMMUNOLOGY (CONT'D.)		
	Infliximab	22992668
	Lesinurad	*See drug label
	Pegloticase	*See drug label
	Probenecid	*See drug label
	Sirolimus	22992668
	Sulfasalazine	*See drug label
	Tacrolimus	25801146
PSYCHIATRY		
Antipsychotics		*See drug label
		*See drug label
		*See drug label
		22992668
		*See drug label
		*See drug label
Benzodiazepines	Clobazam	*See drug label
	Lorazepam	22992668
	Oxazepam	*See drug label
Selective Serotonin Reuptake Inhibitors	Fluvoxamine	25974703
	Paroxetine	25974703
Serotonin-Norepinephrine Reuptake Inhibitors	Atomoxetine	*See drug label
	Venlafaxine	*See drug label
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
	Mirtazapine	22992668
GASTROENTEROLOGY		
Proton Pump Inhibitors (PPIs)	Lansoprazole	*See drug label
	Dexlansoprazole	*See drug label

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Normal Response Expected (continued)

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

Drug Type	Drug	Reference
GASTROENTEROLOGY (CONT'D.)		
Proton Pump Inhibitors (PPIs)	Omeprazole	*See drug label
	Rabeprazole	*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
	Codeine	22205192;24458010
	Methadone	22992668
	Morphine	22992668
	Naloxone	22992668
	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

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Normal Response Expected (continued)

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

Drug Type	Drug	Reference
INFECTIOUS DISEASE (CONT'D.)		
Antibiotics	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
Antimalarials	Chloroquine	*See drug label
	Chlorproguanil	22992668
	Primaquine	*See drug label
	Quinine	*See drug label
	Peginterferon Alfa-2B	24096968
	Ribavirin	24096968
	Abacavir	22378157;24561393
	Atazanavir	26417955
	Efavirenz	*See drug label
	Nevirapine	22992668

GENOTYPING RESULTS

Gene	Genotype	Phenotype	Variants/Haplotypes Assayed
ABCB1	*1/*1	Wildtype	rs1045642, rs2032582
ABCG2	WT/WT	Wildtype	rs2231142
ADD1	WT/WT	Wildtype	rs4961
ANKK1	WT/WT	Wildtype	rs1800497
APOE	WT/WT	Wildtype	rs7412
CBR3	WT/WT	Wildtype	rs1056892
CES1	WT/WT	Wildtype	rs71647871
CFTR	WT/WT	Wildtype	rs74551128, rs80282562, rs74503330, rs397508537, rs121908755, rs113993958, rs141033578, rs397508288, rs121908752, rs77834169, rs397508442, rs397508759, rs77932196, rs121909013, rs202179988, rs75527207, rs121909020, rs78769542, rs121909005, rs78655421, rs186045772, rs113993960, rs267606723, rs397508256, rs75541969, rs397508513, rs121908757, rs368505753, rs193922525, rs121909041, rs121908753, rs11971167, rs150212784, rs113993960, rs113993959, rs77010898
COMT	WT/WT	Wildtype	rs4680, rs13306278
CYP2B6	WT/WT	Wildtype	rs28399499, rs3745274, rs2279343
CYP2C19	*2/*2	Poor Metabolizer	rs12248560, rs4244285, rs4986893 (*2, *3, *17)

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GENOTYPING RESULTS (CONT'D.)

Gene	Genotype	Phenotype	Variants/Haplotypes Assayed
CYP2C8	WT/WT	Wildtype	rs10509681
CYP2C9	*1/*1	Normal Metabolizer	rs1057910, rs1799853, rs28371686, rs9332131, rs7900194, rs28371685 (*2, *3, *5, *6, *8, *11)
CYP3A4	*1/*1	Wildtype	rs2740574, rs2242480 (*1B,*1G)
CYP3A5	*1/1*1	Normal Metabolizer	*rs10264272, rs776746, rs41303343 (*3, *6, *7)
CYP4F2	*1/*1	Normal Metabolizer	rs2108622 (*3)
DPYD	WT/WT	Wildtype	rs3918290, rs67376798, rs55886062 (*2A, *13)
DRD2	WT/WT	Wildtype	rs1799978
EPHX1	WT/WT	Wildtype	rs1051740, rs2234922
ERCC1	WT/WT	Wildtype	rs3212986, rs11615
F2	WT/WT	Wildtype	G20210A
F5	WT/WT	Wildtype	rs6025
MTRR	WT/WT	Wildtype	rs2297480
G6PD	WT/WT	Wildtype	Null alleles
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
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
ITPA	WT/WT	Wildtype	rs1127354, rs7270101
KIF6	WT/WT	Wildtype	rs20455
LPA	WT/WT	Wildtype	rs10455872
LTC4S	WT/WT	Wildtype	rs730012
MTHFR	WT/WT	Wildtype	rs1801133
NAT2	WT/WT	Wildtype	rs1801280, rs1799930, rs1799931, rs1208, rs1041983, rs1801279 (*4, *5, *6, *7, *12, *13, *14)
NQO1	WT/WT	Wildtype	rs1800566
NUDT15	WT/WT	Wildtype	rs116855232, rs147390019, rs186364861 (*3, *4, *5)
OPRM1	WT/WT	Wildtype	rs1799971
PTGS1	WT/WT	Wildtype	rs10306114
PTPGFR	WT/WT	Wildtype	rs3753380
CYP2D6	*1/*1	Normal Metabolizer	rs5030656, rs1065852, rs28371725, rs35742686, rs3892097, rs5030655, rs28371706, rs1058164, rs5030867, rs5030865, rs5030863, rs72549357, rs16947, rs1135840, rs16947, rs59421388, rs61736512 (*2, *3, *4, *5, *6, *7, *8, *9, *10, *11, *15, *17, *29, *41)
SLC28A3	WT/WT	Wildtype	rs7853758, rs885004
SLC6A4	WT/WT	Wildtype	5-HTTLPR Long allele/long allele
SLCO1B1	RS4149056 C/C	Decreased activity	rs4149056
TNF	WT/WT	Wildtype	rs1800629

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GENOTYPING RESULTS (CONT'D.)

Gene	Genotype	Phenotype	Variants/Haplotypes Assayed
TP53	WT/WT	Wildtype	rs1042522
TPMT	*1/*1	Wildtype	rs1142345, rs1800460, rs1800462, rs1800584 (*2, *3A, 3B*, 3C*, *4)
TYMS	WT/WT	Wildtype	rs151264360
UGT1A1	WT/WT	Wildtype	rs887829, rs8175347, rs4148323 (*6, *28, *80)
UGT1A4	WT/WT	Wildtype	rs2011425
UGT2B15	WT/WT	Wildtype	rs1902023
UMPS	WT/WT	Wildtype	rs1801019
VDR	rs2228570 G/ rs2228570 G	rs2228570 GG	rs2228570
VKORC1	WT/WT	Wildtype	rs9923231
XPC	WT/WT	Wildtype	rs2228001
XRCC1	WT/WT	Wildtype	rs25487

WT = Wildtype

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. Assignment of "normal response" is based only the variants assayed- variants not assayed may contribute to a patient's response to a drug. All treatment decisions are ultimately the responsibility of the treating provider. This assay does not interrogate drug/drug interactions or drug/environment interactions. Some of the drugs included may require careful therapeutic monitoring.

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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