

Name:  
 Patient ID:  
 DOB:  
 Sex:

Specimen Type:  
 Date Drawn:  
 Date Received:  
 Date Reported:

## PGx 25 Gene Panel Report

### INDICATION FOR TEST: SERIOUS ADVERSE DRUG REACTION (ICD-10 T50.995A)

**RESULTS: POSITIVE.** At Least One Gene in Table 1 and 2 is predicted to have significantly Altered Function. Significantly Altered Function includes but is not limited to, 'poor' or ultrarapid metabolizer status, altered transporter/receptor function, as well as altered response to treatment.

**GENES with Abnormal Results:**

**CYP2D6, G6PD, HLA-B\*57:01 have abnormal results.**

**Table 1: MEDICALLY ACTIONABLE RESULTS.** Clinically relevant test results are listed below in tables 1-2. Please note, genotypes listed as \*1/\*1 indicate the absence of detectable alterations or pathogenic alleles, it does not imply presence of wildtype sequence or normal reference allele(s).

Gene	Phenotype term <sup>#</sup>	Allele function	Patient Genotype (Known/Predicted call)
BCHE	Normal risk	See interpretation key	rs28933389G/rs28933389G
	FDA Guidance(s): Succinylcholine		
CACNA1S*	Normal risk for malignant hyperthermia	See interpretation key	WT/WT
	CPIC Guideline(s): Volatile anesthetics (i.e., desflurane, enflurane, halothane, isoflurane, methoxyflurane, sevoflurane), either alone or in conjunction with a depolarizing muscle relaxant (specifically, succinylcholine)		
RYR1*	Normal risk for malignant hyperthermia	See interpretation key	WT/WT
	CPIC Guideline(s): Volatile anesthetics (i.e., desflurane, enflurane, halothane, isoflurane, methoxyflurane, sevoflurane), either alone or in conjunction with a depolarizing muscle relaxant (specifically, succinylcholine)		
CFTR	Absence of G551D or F508del alleles	See interpretation key	WT/WT
	CPIC Guideline(s): Ivacaftor (favorable treatment response in CF when at least one G551D allele is present)		
CYP2B6	Normal metabolizer	normal/normal	*1/*1
	CPIC Guideline(s): Efavirenz		
CYP2C8	Normal metabolizer	normal/normal	*1A/*1B
	CPIC Guideline(s): no current dosing recommendations for Diclofenac, Ibuprofen (see also CYP2C9 for NSAIDs)		
CYP2C9	Normal metabolizer	normal/normal	*1/*1
	CPIC Guideline(s): NSAIDs, Warfarin (interpret results in context with CYP4F2 and VKORC1), Phenytoin		

**PATIENT INFORMATION**

Name:  
Patient ID:  
DOB:  
Sex:

**SPECIMEN DETAILS**

Specimen Type:  
Date Drawn:  
Date Received:  
Date Reported:

**ORDERED BY**

<b>CYP4F2</b>	<b>Normal metabolizer</b>	See interpretation key	<b>*1/*1</b>
	CPIC Guideline(s): Warfarin (interpret results in context with CYP2C9 and VKORC1)		
<b>VKORC1</b>	<b>Indeterminate</b>	<b>sensitive/resistant</b>	<b>H1/H7</b>
	CPIC Guideline(s): Warfarin (interpret results in context with CYP2C9 and CYP4F2)		
<b>CYP2C19</b>	<b>Normal metabolizer</b>	<b>normal/normal</b>	<b>*1/*1</b>
	CPIC Guideline(s): Amitriptyline, Citalopram, Clomipramine, Clopidogrel, Dexlansoprazole, Doxepin, Escitalopram, Esomeprazole, Imipramine, Lansoprazole, Omeprazole, Pantoprazole, Rabeprazole, Sertraline, Trimipramine, Voriconazole		
<b>CYP2D6<sup>s</sup></b>	<b>Poor metabolizer</b>	<b>no/no</b>	<b>*4/*4; CN = 2; AS = 0.0</b>
	CPIC Guideline(s): Amitriptyline, Atomoxetine, Clomipramine, Codeine, Desipramine, Doxepin, Fluvoxamine, Hydrocodone, Imipramine, Methadone, Nortriptyline, Ondansetron, Oxycodone, Paroxetine, Tamoxifen, Tramadol, Trimipramine, Tropicisetron.		
<b>CYP3A5</b>	<b>Intermediate metabolizer</b>	<b>normal/no</b>	<b>*1/*3</b>
	CPIC Guideline(s): Tacrolimus		
<b>DPYD</b>	<b>Normal metabolizer</b>	<b>normal/normal</b>	<b>c./c.=</b>
	CPIC Guideline(s): Capecitabine, Fluorouracil, Tegafur		
<b>G6PD</b>	<b>Deficient – High risk for hemolysis</b>	<b>III/null</b>	<b>A-(202A_376G)/null</b>
	CPIC Guideline(s): Rasburicase		
<b>IFNL3</b>	<b>Favorable response</b>	See interpretation key	<b>rs12979860C/rs12979860C</b>
	CPIC Guideline(s): Peginterferon alfa-2a, Peginterferon alfa-2b, Ribavirin		
<b>IFNL4</b>	<b>Favorable response</b>	See interpretation key	<b>rs12979860C/rs12979860C</b>
	CPIC Guideline(s): Peginterferon alfa-2a, Peginterferon alfa-2b, Ribavirin		
<b>NAT2</b>	<b>Rapid acetylator</b>	<b>rapid/rapid</b>	<b>*4/*4</b>
	FDA Guidance(s): Amifampridine, Sulfamethoxazole/trimethoprim, Sulfasalazine		
<b>NUDT15<sup>%</sup></b>	<b>Intermediate metabolizer</b>	<b>normal/no</b>	<b>*1/*3</b>

**PATIENT INFORMATION**

Name:  
 Patient ID:  
 DOB:  
 Sex:

**SPECIMEN DETAILS**

Specimen Type:  
 Date Drawn:  
 Date Received:  
 Date Reported:

**ORDERED BY**

	CPIC Guideline(s): Azathioprine, Mercaptopurine, Thioguanine		
TPMT <sup>#</sup>	Normal metabolizer	normal/normal	*1/*1
	CPIC Guideline(s): Azathioprine, Mercaptopurine, Thioguanine		
SLCO1B1	Normal metabolizer	normal/normal	*1A/*1B
	CPIC Guideline(s): Simvastatin		
UGT1A1	Normal metabolizer	normal/normal	*1/*1
	CPIC Guideline(s): Atazanavir		

<sup>§</sup>**CYP2D6** genotypes should be used in association with copy number. On the WPS assay the CYP2D6 copy number state is interrogated using three different regions, the 3' flank region, exon 9 and the 5' flanking region. Total CYP2D6 copy number state is determined using the exon 9 and 5' flanking copy number status. When the copy number state is three or greater it will be reported as CN 3. Genotype and phenotype assignment for more than 2 CN samples will be based on CN state of three or more from these genes. \***CACNA1S** and **RYR1** are included in the ACMG (American College of Medical Genetics and Genomics) recommendations for reporting of incidental findings in clinical exome and genome sequencing. This test only screens for specific DNA variants associated with pharmacogenomic function and a negative/normal test result does not rule out the presence of other possible pathogenic DNA variants in these genes. <sup>#</sup>**TPMT**, the \*3A haplotype is defined by two SNPs present on the same allele. However, each of these two SNPs have also been observed to exist on their own allele (\*3B or \*3C) in some populations. If both SNPs are detected heterozygous, the likelihood of them being on separate alleles (i.e. a \*3B/\*3C individual instead of a \*1/\*3A) is 1 in 515,861 (in Caucasians). Further phenotypic testing may be required. <sup>%</sup>**NUDT15**, this assay only tests for presence of the common \*3 no-function allele, other decreased function variants/alleles will not be detected; hence a negative test result does not rule out possible enzyme dysfunction. To better assess the risk for adverse drug reactions in patients treated with thiopurines please consider ordering the more comprehensive CNT genotyping panel.

**PATIENT INFORMATION**

Name:  
 Patient ID:  
 DOB:  
 Sex:

**SPECIMEN DETAILS**

Specimen Type:  
 Date Drawn:  
 Date Received:  
 Date Reported:

**ORDERED BY**

**Table 2: HLA genotyping results for pharmacogenetically relevant HLA alleles. The results are reported as Positive or Negative**

Gene	Patient Result
HLA-A*31:01	<b>Negative</b>
	CPIC Guideline(s): Carbamazepine
HLA-B*15:02	<b>Negative</b>
	CPIC Guideline(s): Carbamazepine
HLA-B*57:01	<b>Positive</b>
	CPIC Guideline(s): Abacavir
HLA-B*58:01	<b>Negative</b>
	CPIC Guideline(s): Allopurinol
HLA-DQA1, HLA-DRB1	<b>Negative</b>
	CPIC Guideline(s): Azathioprine, Mercaptopurine, Lapatinib

Name:  
Patient ID:  
DOB:  
Sex:

Specimen Type:  
Date Drawn:  
Date Received:  
Date Reported:

**Table 3: Variants and haplotypes tested.**

Gene	Variants/alleles
BCHE	rs28933389
CACNA1S	rs1800559; rs772226819
CFTR	WT, F508delCTT, G551D
CYP2B6	*1,*2,*3,*4,*5,*6,*7,*8,*11,*12,*13,*14,*15,*16,*17,*18,*19,*20,*21,*22,*24,*25,*26,*27,*28,*35,*36,*37,*38,R109Q,V183I,F213L,R253H
CYP2C19	*1,*2,*3,*4A,*4B,*5,*6,*7,*8,*9,*10,*12,*13,*14,*15,*16,*17,*18,*19,*22,*23,*24,*25,*26,*28,*34,*35,M74T,E92D,V113I,A161P,F168L,E241FS,T302R,V331I,D360N,V394M,G439FS
CYP2C8	*1A,*1B,*1C,*2,*3,*4+1C,*5,*7,*8,*10,*11,*12,*13,*14,P404A,L390S
CYP2C9	*1,*2,*3,*4,*5,*6,rs9332094C,*9,*10,*11,*12,*13,*15,*16,*17,*18,*19,*20,*21,*23,*24,*25,*26,*28,*29,*30,*31,*32,*34,*36,*37,*38,*39,*40,*42,*43,*44,*45,*46,*47,*48,*49,*50,*51,*52,*53,*54,*55,*56,*57,*58,Y358C,L413P,N474S
CYP2D6	*1,*2,*3A,*3B,*4,*6,*7,*8,*9,*10,*11,*12,*114,*14,*15,*17,*18,*19,*20,*22,*23,*25,*28,*29,*31,*33,*35,*37,*38,*40,*41,*42,*43,*44,*45,*46,*47,*48,*49,*51,*53,*54,*55,*56A,*56B,*59,*62,*70,*71,*72,*73,*75,*81,*82,*84,*85,*86,*88,*89,*95,*100,*101,*102,*103,*107,*109,L91M,H94R,R173C,G212E,K281Frameshift,S311L,P325L,R365H,G373S,L421P,S467L,T470A,H478Y,S486T,Y490C,E418K,*5
CYP3A5	*1,*2,*3,*3G,*4,*5,*6,*7,*8,*9,*2+3,H30Y,G31FS,Y53C,L82R,S100C,S100Y,F446S,I488T
CYP4F2	*1,*2,*3,*2+3,W12C,P13R,G185V,L278F,L519M
DPYD	c.61C>T,c.295_298delTCAT,c.557A>G,c.703C>T,c.1129-5923C>G, c.1156G>T, c.1679T>G, c.1898delC, c.1905+1G>A,c.2846A>T,c.2983G>T,R21Q,C29R,M166V,K259E,V335L,S534N,I543V,N635K,V732I,R886C,R886H
G6PD	Class I, II, III, IV
HLA-A*31:01	rs1061235; rs1633021
HLA-B*15:02	rs3909184; rs2844682
HLA-B*57:01	rs2395029
HLA-B*58:01	rs9263726
HLA-DQA1; HLA-DRB1	rs2647087
IFNL3	rs12979860
IFNL4	rs12979860
NAT2	*4,*5,*5E,*5I,*5L,*5M,*5N,*5O,*5P,*5S,*5X,*5Y,*6,*6G,*6H,*6I,*6J,*6K,*6M,*6O,*6P,*6V,*7,*7D,*10,*12D,*12E,*12F,*12G,*12H,*12J,*12K,*12O,*13D,*13F,*14,*14D,*14F,*14H,*14K,*17,*18,*19,*21,*23,*24,M205L,K268R,S287P
NUDT15	*1,*3
RYR1	WT,1571V+3933C
SLCO1B1	*1A,*1B,*2,*3,*4,*5,*6,*7,*8,*9,*11,*13,*14,*15,*16,*17,*18,*21,*22,*23,*24,*25,*26,*27,*28,*29,*30,*31,*32,*33,*35,P336R
TPMT	*1,*2,*3A,*3B,*3C,*3D,*4,*5,*6,*7,*8,*9,*10,*11,*12,*13,*14,*15,*16,*17,*18,*19,*20,*21,*23,*24,*25,*26,*27,*28,*29,*30,*31,*33,*34,*35,*36,*37
UGT1A1	*1,*6,*8,*12,*14,*15,*27,*28,*43,*45,*60,*62,*112,F83I
VKORC1	rs9923231

**PATIENT INFORMATION**

Name:  
 Patient ID:  
 DOB:  
 Sex:

**SPECIMEN DETAILS**

Specimen Type:  
 Date Drawn:  
 Date Received:  
 Date Reported:

**ORDERED BY**
**INTERPRETATION KEY (FOR TABLE 1 AND 2):**

Gene category (names)	Phenotype term	Functional definition	Genetic definition
BCHE	Normal risk	Normal enzyme function	Absence of rs28933389 G>A allele
	Increased risk	Cholinesterase deficiency can result in postanesthetic apnea	One or two rs28933389 G>A alleles detected
CFTR	Absence of G551D or F508del alleles	Normal transporter function	Absence of decreased function alleles, i.e. F508del
	Decreased function (DF)	Decreased transporter function (typically not associated with CF)	Combination of normal function allele and decreased function allele, i.e. F508del or G551D
	Favorable treatment response or Poor function (PF)	Decreased transporter function. Favorable treatment response in CF with Ivacaftor  Little to no transporter function	Combination of one G551D allele with another G551D allele or one F508del allele.  Combination of two F508del alleles
	Ultraprapid metabolizer	Increased enzyme activity compared to rapid metabolizers	Two increased function alleles or more than 2 normal function alleles
Drug-metabolizing enzymes (CYP2B6, CYP2C8; CYP2C9; CYP2C19; CYP2D6; CYP3A5; CYP4F2; DPYD; NUDT15; TPMT; UGT1A1)	Rapid metabolizer	Increased enzyme activity compared to normal metabolizers but less than ultrarapid metabolizers	Combinations of normal function and increased function alleles
	Normal metabolizer	Fully functional enzyme activity	Combinations of normal function and decreased function alleles
	Intermediate metabolizer	Decreased enzyme activity (activity between normal and poor metabolizers)	Combinations of normal function, decreased function, and/or no function alleles
	Poor metabolizer	Little to no enzyme activity	Combination of no function alleles and/or decreased function alleles
	Increased function	Increased transporter function compared to normal function	One or more increased function alleles
SLCO1B1	Normal function	Fully functional transporter function	Combinations of normal function and/or decreased function alleles
	Decreased function	Decreased transporter function (function between normal and poor function)	Combinations of normal function, decreased function, and/or no function alleles
	Poor function	Little to no transporter function	Combination of no function alleles and/or decreased function alleles
	Rapid acetylator	Rapid or fast acetylation	Combination of two rapid alleles
NAT2	Intermediate acetylator	Decreased acetylation (activity between rapid and slow acetylator)	Combination of one slow and one rapid alleles
	Slow acetylator	Slow acetylation	Combination of two slow alleles
	Off acetylator	Little to no acetylation	Combination of two no function/no activity alleles
	Deficient—High risk for hemolysis	Severe enzyme deficiency with chronic nonspherocytic hemolytic anemia (class I); or severe enzyme deficiency less than 10% (class II); or moderate to mild enzyme deficiency (10-60%, class III)	A male carrying a deficient (class I-III) allele. A female carrying two deficient (class I-III) alleles

**PATIENT INFORMATION**

Name:  
Patient ID:  
DOB:  
Sex:

**SPECIMEN DETAILS**

Specimen Type:  
Date Drawn:  
Date Received:  
Date Reported:

**ORDERED BY**

	<b>Indeterminate</b> -Decreased enzyme activity, moderate risk for hemolysis	Moderate-mild enzyme deficiency (10-100%, class III or IV).	A female carrying one deficient (class I-III) allele and one class IV allele
	<b>Low risk</b> for hemolysis	Very mild enzyme deficiency or increased enzyme activity (class IV or V)	A female carrying two class IV alleles or a male carrying a class IV or V allele
<b>IFNL3, IFNL4</b>	Favorable Response	Increased likelihood of response to PEG-IFN- $\alpha$ and RBV therapy	An individual carrying two favorable response alleles (CC for rs12979860)
	Unfavorable Response	Decreased likelihood of response to PEG-IFN- $\alpha$ and RBV therapy	An individual carrying at least one unfavorable response allele (CT or TT for rs12979860)
<b>CACNA1S, RYR1</b>	Normal risk for malignant hyperthermia	Absence of specific high risk (MH) alleles	An individual <u>does not</u> carry the 1571V+3933C allele in RYR1 and <u>does not</u> carry either rs1800559(T) or rs772226819(A) in CACNA1S
	Increased risk for malignant hyperthermia	Presence of at least one specific high risk (MH) allele	An individual carrying at least one 1571V+3933C allele in RYR1 or carrying either rs1800559(T) allele or rs772226819(A) in CACNA1S
<b>VKORC1</b>	Resistant++; Resistant+; Normal; Sensitive-; Sensitive--	Resistance to inhibition by vitamin K antagonists	Combination of resistant, normal and sensitive alleles, [may need example here]
<b>HLA</b>	HLA-A*31:01	Increased risk of Stevens-Johnson syndrome and toxic epidermal necrolysis after carbamazepine treatment.	<b>Positive:</b> Presence of one or more copies of the non-reference (high risk) allele.  <b>Negative:</b> Absence of any copy of the non-reference (high risk) allele.
	HLA-B*15:02	Increased risk of Stevens-Johnson syndrome and toxic epidermal necrolysis after carbamazepine treatment.	
	HLA-B*57:01	Increased risk of drug hypersensitivity when treated with abacavir in people with HIV.	
	HLA-B*58:01	Increased risk of drug hypersensitivity when treated with allopurinol in people with HIV.	
	HLA-DQA1 *02:01; HLA-DRB1 *07:01	Increased risk of developing pancreatitis after administration of a thiopurine. Increased risk for hepatotoxicity in individuals receiving Lapatinib (TYKERB) for breast cancer in which tumors overexpress HER2 (ERBB2).	

**METHODS:**

Analysis of purified genomic DNA samples for specific drug metabolizing enzyme and transporter gene variants in a limited number of genes within the human genome was performed using the PharmacoScan™ Assay (WPS) [1-6]. Data was analyzed using the Axiom™ Analysis Suite software v4.0.3.3 (Array type: PharmacoScan\_24F.r8). This assay genotypes 1,030 markers in the 25 specified genes. In addition, it reports the copy number state for CYP2D6. For CYP2D6 it can additionally detect greater than two copies. When the copy number state is three or greater it will be reported as CN 3. Genotype and phenotype assignment for more than 2 CN samples will be based on CN state of three or more. In some rare cases, greater than three copies of a gene may be present in an individual, which may alter the patient's genotype and phenotype. These additional duplications will not be captured or reported on this assay. For CYP2D6 multiple gene regions are interrogated for copy number analysis. This allows for the detection of "hybrid gene arrangements" and will be reported as either "Copy Number Hybrid Gain (CN\_HybridGain)" or "Indeterminate" if there is a Copy Number Hybrid Loss [7-8]. Samples that report a CN\_HybridGain may contain a duplication event on one allele that generates three or more full CYP2D6 copies but show a loss in either the 3' or 5' flanking regions. Samples that report a CN\_HybridLoss may contain two full copies of

**PATIENT INFORMATION**

Name:  
Patient ID:  
DOB:  
Sex:

**SPECIMEN DETAILS**

Specimen Type:  
Date Drawn:  
Date Received:  
Date Reported:

**ORDERED BY**

CYP2D6, a \*5 allele and duplication on the second allele in which either the 3' or 5' flanking region is loss. This result represents a difference in the copy number state of different regions within the gene.

**LIMITATIONS:**

The assay tests for genetic variants at the specific loci listed in the PharmacoScan™ annotation. Other variants that are not included in the assay may be present in the patient. The presence of additional variants may affect the accuracy of the detection of the variants reported. Analytical specificity and sensitivity for detection of the variants listed is >95%. Bone marrow transplants and liver transplants will interfere with this test. If this patient has had either a hematopoietic stem cell transplant or a liver transplant and this test was performed on a blood sample from the recipient after the transplant occurred, then the results will not be applicable to this patient. This assay cannot detect mosaicism. Metabolizer status of the genes has been determined following CPIC guidelines published on [PharmGKB](#). The clinical relevance of the metabolizer status requires an interpretation in the context of the relevant drug, drug interaction and additional clinical information such as gender, age, weight, ethnicity, disease state, diet, organ function and concomitant therapy. These test results are not meant to be the sole source to determine drug treatment and a consultation with a pharmacist or equivalent health care professional is recommended. This test was developed, and its performance characteristics determined by RPRD Diagnostics LLC to identify specific drug metabolizing enzyme and other pharmacogenetically relevant variants within the human genome. It has not been cleared or approved by the U.S. Food and Drug Administration (FDA). The FDA has determined that such clearance or approval is not necessary. This test is used for clinical purposes. It should not be regarded as investigational or for research. The laboratory has established accuracy and precision of the test which is expected to be highly accurate. The chance of a genotyping error cannot be completely excluded. This laboratory is certified under the Clinical Laboratory Amendments of 1988 (CLIA) as qualified to perform high complexity clinical laboratory testing.

**RECOMMENDATIONS:**

Consultation with a physician and pharmacist knowledgeable in pharmacogenomics is recommended. Interpretations of the genetic results need to be made in the context of each patient's unique genotype and risk profile. Only your medical provider can decide if the patient's treatment needs to be adjusted or changed. Even a moderate increase or decrease in function of one gene can be associated with serious adverse drug reactions, especially if the patient is treated with multiple medications.

**DISCLAIMER:**

PGx 25 Gene Panel is a comprehensive genotyping platform aimed at identifying medically actionable genetic variation in a defined number of genes associated with drug metabolism, transport and clearance. CACNA1S and RYR1 are included in the list recommended for reporting of secondary findings in clinical exome and genome sequencing samples (see the 2016 update, ACMG SF v2.0: A policy statement of the American College of Medical Genetics and Genomics). By our laboratory standard RPRD Diagnostics does not routinely report on genotypic variation in the genes listed by ACMG, but the data can be made available upon request. Please submit the request prior to ordering the test. Since the comprehensive scope of the genotyping platform does include more genes and genetic variants than required for selective/targeted testing of limited gene panels, we will not analyze or report variants in genes not included in a selective gene panel. The DNA testing as reported here will not detect all genetic variations in the genes examined. Absence of a detectable pathogenic sequence variant or polymorphism does not rule out the possibility that a patient has a different phenotype than reported. Rare, unreported gene variations may interfere with the testing and yield inaccurate results.

**REFERENCES:**

1. PharmacoScan™ Assay 24-Array Format. Manual Protocol UserGuide. P/N 703286 Rev. 2. 2016. Affymetrix Inc.;
2. PharmacoScan™ Protocol. RPRD Diagnostics 09-001. 2017;
3. Axiom™ Analysis 2.0 UserGuide. P/N 70337 Rev. 3. 2016;
4. PharmacoScan™ Analysis Protocol. RPRD Diagnostics 09-002. 2017;
5. Axiom™ HLA Analysis v1.1 UserGuide. P/N 703338 Rev. 2. 2015;
6. PharmacoScan™ HLA Analysis Protocol. RPRD Diagnostics 09-003. 2017;
7. Mendelian Inheritance in Man, OMIM (TM). Johns Hopkins University, Baltimore, MD., URL: <http://www.ncbi.nlm.nih.gov/omim/>;
8. Frequency of Undetected CYP2D6 Hybrid Genes in Clinical Samples: Impact on Phenotype Prediction. Black JL, Walker.

Signature

Gunter Scharer, M.D.

Medical Director, RPRD Diagnostics

Date