PRIMAHEALTH

PATIENT: Patient 1, Test1
GENDER: F DOB: 05/05/1955
ACCESSION: UTP170010
REPORTED: 05/06/2017
SPECIMEN: Buccal Swab

FACILITY:
PHYSICIAN: System Check
COLLECTED: 05/03/2017
RECEIVED: 05/05/2017
SIGNED: Scott Griffith, DPh.

CURRENT PATIENT MEDICATIONS

Drug summary for prescribed medications.

carvedilol (Coreg), clopidogrel (Plavix), duloxetine (Cymbalta), lisinopril (Prinivil), oxycodone (Oxycontin), warfarin (Coumadin)

REPORT LEGEND

(Low/No Genetic Impact) indicates that there were no genetic issues of clinical relevance that were found with the medication and the particular gene(s)tested. Standard precautions are recommended.

(Moderate Genetic Impact) indicates that extra caution should be observed because of genetic issues of clinical relevance that were found with the medication and the particular gene(s) tested.

(High Genetic Impact) indicates that extreme caution or avoidance should be considered because serious genetic issues of clinical relevance were found with the medication and the particular gene(s) tested.

GENETIC DRUG INTERACTIONS

Medications affected by the patient's genetic results that are currently prescribed.

clopidogrel (Plavix) - CYP2C19 [*2/*2]
This phenotype consists of two inactive CYP2C19 alleles. CYP2C19 poor metabolizers (PMs) have greatly decreased enzyme activity. For prodrugs requiring activation by CYP2C19, PMs do not readily convert the drug into its active metabolite. Thus, PMs may require alternative treatment or increased dosage of prodrug. For parent (active) drugs that do not require activation, consider empirical dosage reduction and careful monitoring to avoid possible adverse effects. Consider alternative medications in this therapeutic class, if available. In addition, please consult drug labeling for further dosing guidance.
Analysis: Clopidogrel (Plavix) is activated via CYP2C19 into its functional form and poor metabolizers have lower levels of this functional metabolite. This could potentially lead to reduced platelet inhibition, increased residual platelet aggregations and increased risk for adverse cardiovascular events. CPIC recommends an alternative antiplatelet therapy. The FDA label has a boxed warning that states "Consider alternative treatment or treatment strategies in patients identified as CYP2C19 poor metabolizers. "

warfarin (Coumadin) - VKORC1 [A/A]
This patient has high sensitivity for warfarin. A lower dose is recommended for these patients. The genotype for CYP2C9 should also be taken into consideration for warfarin dosing. In addition, please see package insert for further dosing guidance.

duloxetine (Cymbalta) - CYP1A2 [*1J/*1J]
The patient is susceptible to both decreased and increased inducibility.
Analysis: Duloxetine is metabolized by CYP2D6 and CYP1A2. This individual is expected to be a normal metabolizer of CYP1A2 unless induced or inhibited. The Decreased + Increased Inducibility phenotype could be clinically significant if co-administered with one the following drugs or substances known to increase (induce) CYP1A2 activity. These include broccoli, brussel sprouts, char-grilled meat, insulin, methylcholanthrene, modafinil, nafcillin, beta-naphthoflavone, omeprazole, and tobacco. It could also be clinically significant if co-administered with one of the following drugs or substances known to decrease (inhibit) CYP1A2 activity. These include amiodarone, cimetidine, fluoroquinolones, fluvoxamine, furafylline, interferon, methoxsalen, and oral contraceptives (ethinyloestradiol, norethisterone, desogestrel, norgestimate, and levonorgestrel). If CYP1A2 inhibitors or inducers are stopped or started, a change in phenotype is possible.

warfarin (Coumadin) - CYP2C9 [*1/*2]
Intermediate (lower than normal) CYP2C9 metabolism is anticipated. This phenotype consists of one inactive CYP2C9 allele and one active CYP2C9 allele. It is suggested that intermediate metabolizers be administered CYP2C9 metabolized drugs at a reduced dosage. In addition, please consult drug labeling for further dosing guidance.
Analysis: Warfarin levels may increase in CYP2C9 intermediate metabolizers. Patient may need lower doses of warfarin on average. These results should be taken into account with VKORC1 and lifestyle factors. Adjust based on patient's response and INR.

carvedilol (Coreg) - CYP2D6 [*2/*41]
The patient is an extensive (normal) metabolizer, and changes in metabolism are not generally expected.

duloxetine (Cymbalta) - CYP2D6 [*2/*41]
The patient is an extensive (normal) metabolizer, and changes in metabolism are not generally expected.
Analysis: Duloxetine is metabolized by CYP2D6 and CYP1A2. The patient is an extensive (normal) metabolizer of CYP2D6, and changes in metabolism are not generally expected. The phenotype of CYP1A2 should be taken into consideration for duloxetine.

oxycodone (Oxycontin) - CYP2D6 [*2/*41]
The patient is an extensive (normal) metabolizer, and changes in metabolism are not generally expected.
Analysis: Oxycodone is metabolized to its more potent metabolite, oxymorphone, by CYP2D6 and to its weaker metabolite, noroxycodone, by CYP3A4. The patient is a extensive (normal) metabolizer, and changes in metabolism are not generally expected due to CYP2D6. The phenotype of CYP3A4 should be taken into consideration for oxycodone.

oxycodone (Oxycontin) - CYP3A4 [*1/*1]
The patient is an extensive (normal) metabolizer, and changes in metabolism are not generally expected.
Analysis: Oxycodone is metabolized to its more potent metabolite, oxymorphone, by CYP2D6 and to its weaker metabolite, noroxycodone, by CYP3A4. The patient is an extensive (normal) metabolizer, and changes in metabolism are not generally expected due to metabolism of CYP3A4. The phenotype of CYP2D6 should be taken into consideration for oxycodone.

oxycodone (Oxycontin) - OPRM1 [A/A]
This patient is wildtype for OPRM1. Wildtype genotypes usually require standard dosing.

CASE NOTES

Based on the CYP450-2C9 and VKORC1 genotypes (*1/*2 and A/A), this patient's expected therapeutic dose of warfarin is 3 - 4 mg/day.

GENETIC DETAILS

The genetic makup of the patient.

GENES AFFECTING DRUG METABOLISM

ENZYME: CYP1A2 GENOTYPE: *1J/*1J PHENOTYPE: Decreased + Increased Inducibility
The patient is susceptible to both decreased and increased inducibility.

ENZYME: CYP2B6 GENOTYPE: *1/*1 PHENOTYPE: Extensive Metabolizer
The patient is an extensive (normal) metabolizer, and changes in metabolism are not generally expected.

ENZYME: CYP2C19 GENOTYPE: *2/*2 PHENOTYPE: Poor Metabolizer
This phenotype consists of two inactive CYP2C19 alleles. CYP2C19 poor metabolizers (PMs) have greatly decreased enzyme activity. For prodrugs requiring activation by CYP2C19, PMs do not readily convert the drug into its active metabolite. Thus, PMs may require alternative treatment or increased dosage of prodrug. For parent (active) drugs that do not require activation, consider empirical dosage reduction and careful monitoring to avoid possible adverse effects. Consider alternative medications in this therapeutic class, if available. In addition, please consult drug labeling for further dosing guidance.

ENZYME: CYP2C9 GENOTYPE: *1/*2 PHENOTYPE: Intermediate Metabolizer
Intermediate (lower than normal) CYP2C9 metabolism is anticipated. This phenotype consists of one inactive CYP2C9 allele and one active CYP2C9 allele. It is suggested that intermediate metabolizers be administered CYP2C9 metabolized drugs at a reduced dosage. In addition, please consult drug labeling for further dosing guidance.

ENZYME: CYP2D6 GENOTYPE: *2/*41 PHENOTYPE: Extensive Metabolizer
The patient is an extensive (normal) metabolizer, and changes in metabolism are not generally expected.

ENZYME: CYP3A4 GENOTYPE: *1/*1 PHENOTYPE: Extensive Metabolizer
The patient is an extensive (normal) metabolizer, and changes in metabolism are not generally expected.

ENZYME: CYP3A5 GENOTYPE: *3/*3 PHENOTYPE: Poor Metabolizer
The patient is a CYP3A5 poor metabolizer (PM). This phenotype consists of two inactive CYP3A5 alleles. CYP3A5 PMs have significantly lower levels of enzyme activity. For drugs metabolized by CYP3A5, PMs may require alternative treatments or less than standard dosage to avoid possible adverse effects. In addition, please consult drug labeling for further dosing guidance.

ENZYME: UGT2B15 GENOTYPE: *1/*2 PHENOTYPE: Intermediate Metabolizer
Patients with the *1/*2 genotype may have a decreased clearance for oxazepam and lorazepam. Other genetic and clinical factors may also influence the clearance of these drugs.

GENES AFFECTING RESPONSE OR FUNCTION

ENZYME: APOE GENOTYPE: E3/E3 PHENOTYPE: Normal Risk

Individuals with this genotype, E3/E3, are predicted to have normal levels of LDL-C (bad cholesterol) and triglyceride with no associated risk of developing cardiovascular disease. Patients with the E3/E3 genotype are normal responders to statins. Dietary and lifestyle choices should be considered as part of risk management for prevention of elevated lipid levels. The E3 variant is not associated with a higher risk of developing late-onset Alzheimer's disease. However, additional genetic and clinical factors not evaluated from this test may play a role in whether a person actually develops disease.

ENZYME: COMT GENOTYPE: G/G PHENOTYPE: High Activity

Patients with this genotype (G/G) are associated with higher COMT enzymatic activity and tend to have low dopamine levels. Individuals with this genotype are predicted to have an increased therapeutic response to amphetamine stimulants. Other genetic and clinical factors may also influence a patient's overall medication management.

ENZYME: DRD2 GENOTYPE: A2/A2 PHENOTYPE: Normal Response

The A2 homozygous wild-type haplotype is associated with average (normal) DRD2 gene expression. Patients with this haplotype may have a decreased, but not non-existant, risk of side effects including hyperprolactinemia and weight gain, and may have an increased risk of tardive dyskinesia, during treatment with antipsychotic drugs as compared to patients with the A1/A2 or A1/A1 haplotypes.

ENZYME: FactorII GENOTYPE: G/G PHENOTYPE: Normal Risk

The patient is wildtype for Factor II (Prothrombin). Patients with this genotype (G/G) are associated with a normal risk of developing an abnormal blood clot.

ENZYME: FactorV GENOTYPE: G/G PHENOTYPE: Normal Risk

The patient is wildtype for the Factor V gene. Patients with this genotype (G/G) are associated with a normal risk of developing an abnormal blood clot.

ENZYME: GRIK4 GENOTYPE: T/T PHENOTYPE: Poor Responder

Patients with the TT genotype may have a reduced response to citalopram. Other genetic and clinical factors may also influence a patient's response to citalopram.

ENZYME: MTHFR GENOTYPE: CC-677/AC-1298 PHENOTYPE: Low Risk

This genotype is associated with average (normal) enzymatic activity of MTHFR. This is associated with normal homocysteine levels, normal risk of developing abnormal blood clots, and normal risk of developing cardiovascular disease. Patient is expected to have normal folic acid metabolism. Patient is expected to have normal response to SSRI/SNRI therapy.

ENZYME: OPRM1 GENOTYPE: A/A PHENOTYPE: Normal Responder

This patient is wildtype for OPRM1. Wildtype genotypes usually require standard dosing.

ENZYME: SLCO1B1 GENOTYPE: *1/*5 PHENOTYPE: Intermediate Responder

This patient's genotype is associated with intermediate transporter function and the patient may be at risk for an adverse response to medications that are affected by SLCO1B1.

ENZYME: VKORC1 GENOTYPE: A/A PHENOTYPE: High Sensitivity

This patient has high sensitivity for warfarin. A lower dose is recommended for these patients. The genotype for CYP2C9 should also be taken into consideration for warfarin dosing. In addition, please see package insert for further dosing guidance.

PERSONALIZED MEDICATION GUIDE

Categorized medication interactions for the patient.

ADHD Medications

Low/No Genetic Impact

amphetamine/ dextroamphetamine (Adderall)	atomoxetine (Strattera)	dexmethylphenidate (Focalin)	dextroamphetamine (Dexedrine Spansule)	guanfacine (Intuniv)
lisdexamfetamine (Vyvanse)	methylphenidate (Concerta)			

Moderate Genetic Impact

High Genetic Impact

Cardiovascular

Low/No Genetic Impact

aliskiren (Tekturna)	amiodarone (Cordarone)	amlodipine (Norvasc)	apixaban (Eliquis)	carvedilol (Coreg)
diltiazem (Cardizem)	dofetilide (Tikosyn)	doxazosin (Cardura)	dronedarone (Multaq)	eplerenone (Inspra)
felodipine (Plendil)	flecainide (Tambocor)	metoprolol (Lopressor)	mexiletine (Mexitil)	nebivolol (Bystolic)
nicardipine (Cardene)	nifedipine (Adalat,Procardia)	nisoldipine (Sular)	pindolol (Visken)	prasugrel (Effient)
propafenone (Rhythmol)	quinidine (Quinidex)	ranolazine (Ranexa)	rivaroxaban (Xarelto)	ticagrelor (Brilinta)
timolol (Blocadren)	verapamil (Calan)			

Moderate Genetic Impact

atorvastatin (Lipitor)	azilsartan (Edarbi)	cilostazol (Pletal)	fluvastatin (Lescol)	irbesartan (Avapro)
losartan (Cozaar)	lovastatin (Advicor,Mevacor)	pitavastatin (Livalo)	pravastatin (Pravachol)	propranolol (Inderal)
rosuvastatin (Crestor)	simvastatin (Juvisync,Vytorin,Zocor)	torsemide (Demadex)	valsartan (Diovan)	

High Genetic Impact

clopidogrel (Plavix)	labetalol (Trandate)	warfarin (Coumadin)

Gastrointestinal

Low/No Genetic Impact

aprepitant (Emend)	ondansetron (Zofran)	promethazine (Phenergan)

Moderate Genetic Impact

dronabinol (Marinol)

High Genetic Impact

dexlansoprazole (Dexilant)	esomeprazole (Nexium)	lansoprazole (Prevacid)	omeprazole (Prilosec)	pantoprazole (Protonix)
rabeprazole (Aciphex)				

Pain

Low/No Genetic Impact

alfentanil (Alfenta)	bupivacaine (Sensorcaine)	codeine	dihydrocodeine	fentanyl
hydrocodone (Lortab)	hydromorphone (Dilaudid)	ketamine (Ketalar)	methadone	morphine (Roxanol)
oxycodone (Oxycontin)	oxymorphone (Opana)	tramadol (Ultram)		

Moderate Genetic Impact

celecoxib (Celebrex)	cyclobenzaprine (Flexeril)	diclofenac (Voltaren)	flurbiprofen (Ansaid)	ibuprofen (Advil,Motrin)
indomethacin (Indocin)	lidocaine (Lidoderm)	meloxicam (Mobic)	nabumetone (Relafen)	naproxen (Aleve,Anaprox,Naprosyn)
piroxicam (Feldene)	tapentadol (Nucynta)	tizanidine (Zanaflex)	zolmitriptan (Zomig)	

High Genetic Impact

carisoprodol (Soma)

Psychotropic

Low/No Genetic Impact

alprazolam (Xanax)	bupropion	buspirone (Buspar)	chlordiazepoxide (Librium)	chlorpromazine (Thorazine)
clonazepam (Klonopin)	desipramine (Norpramin)	estazolam (Prosom)	fluoxetine (Prozac)	fluphenazine (Prolixin)
flurazepam (Dalmane)	fluvoxamine (Luvox)	haloperidol (Haldol)	iloperidone (Fanapt)	lurasidone (Latuda)
maprotiline (Ludiomil)	midazolam (Versed)	mirtazapine (Remeron)	nefazodone (Serzone)	nortriptyline (Pamelor)
paroxetine (Paxil)	perphenazine (Trilafon)	pimozide (Orap)	quetiapine (Seroquel)	thioridazine (Mellaril)
trazodone (Desyrel)	triazolam (Halcion)	venlafaxine (Effexor)	ziprasidone (Geodon)	

Moderate Genetic Impact

aripiprazole (Abilify)	clozapine (Clozaril)	duloxetine (Cymbalta)	lorazepam (Ativan)	olanzapine (Zyprexa)
oxazepam	risperidone (Risperdal)			

High Genetic Impact

amitriptyline (Elavil)	citalopram (Celexa)	clomipramine (Anafranil)	diazepam (Valium)	doxepin (Silenor)
escitalopram (Lexapro)	imipramine (Tofranil)	sertraline (Zoloft)	trimipramine (Surmontil)	

Other

Low/No Genetic Impact

alfuzosin (Uroxatral)	carbamazepine (Tegretol)	chlorpheniramine (Chlor-Trimeton)	cinacalcet (Sensipar)	clarithromycin (Biaxin)
cyclosporine (Neoral)	delavirdine (Rescriptor)	dexamethasone (Decadron)	dextromethorphan	diphenhydramine (Benadryl)
donepezil (Aricept)	dutasteride (Avodart)	efavirenz (Sustiva)	erythromycin	finasteride (Proscar)
imatinib (Gleevec)	indinavir (Crixivan)	itraconazole (Sporanox)	ketoconazole (Nizoral)	linagliptin (Tradjenta)
loratadine (Claritin)	meclizine (Antivert)	methylprednisolone (Medrol)	nevirapine (Viramune)	oxybutynin (Ditropan)
pioglitazone (Actos)	prednisone (Deltasone)	repaglinide (Prandin)	ritonavir (Norvir)	saquinavir (Invirase)
saxagliptin (Onglyza)	selegiline (Eldepryl)	sildenafil (Viagra)	silodosin (Rapaflo)	sitagliptin (Januvia)
tadalafil (Cialis)	tamoxifen (Nolvadex)	tamsulosin (Flomax)	telithromycin (Ketek)	terbinafine (Lamisil)
tolterodine (Detrol)	Topiramate (Topamax)	vardenafil (Levitra)	zolpidem (Ambien)	

Moderate Genetic Impact

chlorpropamide (Diabinese)	glimepiride (Amaryl)	glipizide (Glucotrol)	glyburide (DiaBeta)	nateglinide (Starlix)
phenobarbital	rosiglitazone (Avandia)	tolbutamide (Orinase)	valproic acid	zafirlukast (Accolate)
zileuton (Zyflo)				

High Genetic Impact

nelfinavir (Viracept)	phenytoin (Dilantin)	voriconazole (Vfend)

LEGAL NOTICES

The interpretation of these results is meant to assist the ordering clinician with managing a patient's drug regimen and is not intended to be used as a treatment recommendation. Only qualified healthcare professionals should provide advice to patients regarding the use of prescribed or OTC medications. Patient treatment and diagnosis is the sole responsibility of the ordering clinician. It is strongly recommended that these results be communicated to the patient in a setting that includes appropriate counseling.

The individual response to medications is multifactorial. This test should not be used as the sole means of treatment decision making and should be regarded by the ordering physician as adjunctive to the overall patient management strategy. Besides genetic variants, further variables, for example, age, disease, comorbidity, concomitant medication, organ function and patient compliance may have an impact on pharmacotherapy and need to be addressed when medication is prescribed.

Drug-drug and drug-gene interactions that lead to enzymatic inhibition and induction may lead to altered metabolism. Results should always be interpreted in context with the clinical picture and all co-administered medication.

Results should be taken into the whole clinical picture and should not supersede the provider's clinical judgment. Therefore, Prima Health and employees of Prima Health shall have no liability to any person or entity with regard to claims, loss, or damage caused, or alleged to be caused, directly or indirectly, by the use of information contained herein.

This test was developed and its performance characteristics determined by Prima Health. It has not been cleared or approved by the US Food and Drug Administration. FDA does not require this test to go through premarket FDA review. This test is used for clinical purposes. It should not be regarded as investigational or for research. This laboratory is certified under the Clinical Laboratory Improvement Amendments (CLIA) as qualified to perform high complexity clinical laboratory testing.

Specimen Information: Type: Buccal swab, Test Method: Real-time PCR

Limitations

This technology detects the most common variations of the Cytochrome P450 gene family and other genes of known clinical significance. Only the targeted allelic variants specified in this report will be detected. Additional alleleic variants in these genes will not be detected, therefore, these results do not rule out the possibility that this individual could be a carrier of other mutations/variations not detected by this gene panel.

References

Prima Health may utilize one or more of the following references in connection with the preparation of this report:

- PharmGKB, located at www.pharmgkb.org
- Dosing Guidelines of the Clinical Pharmacogenetics Implementation Consortium (CPIC), located at www.pharmgkb.org/view/dosing-guidelines.do
- FDA labeling information, located at www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cf
- Epocrates, located at www.epocrates.com
- Lexicomp, located at www.lexicomp.com
- Langman L and Dasgupta A. Pharmacogenomics in Clinical Therapeutics. Hoboken:Wiley-Blackwell, 2011.

PHARMACOGENETIC ANALYSIS

PATIENT: Patient 1, Test1
DOB: 05/05/1955
FACILITY:
PHYSICIAN: System Check

GENES AFFECTING DRUG METABOLISM		
GENE	GENOTYPE	PHENOTYPE
CYP1A2	*1J/*1J	Decreased + Increased Inducibility
CYP2B6	*1/*1	Extensive Metabolizer
CYP2C19	*2/*2	Poor Metabolizer
CYP2C9	*1/*2	Intermediate Metabolizer
CYP2D6	*2/*41	Extensive Metabolizer
CYP3A4	*1/*1	Extensive Metabolizer
CYP3A5	*3/*3	Poor Metabolizer
UGT2B15	*1/*2	Intermediate Metabolizer
GENES AFFECTING RESPONSE OR FUNCTION		
GENE	GENOTYPE	PHENOTYPE
APOE	E3/E3	Normal Risk
COMT	G/G	High Activity
DRD2	A2/A2	Normal Response
FactorII	G/G	Normal Risk
FactorV	G/G	Normal Risk
GRIK4	T/T	Poor Responder
MTHFR	CC-677/AC-1298	Low Risk
OPRM1	A/A	Normal Responder
SLCO1B1	*1/*5	Intermediate Responder
VKORC1	A/A	High Sensitivity