MyGENETX
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Laboratory Director: Jack Pearson

Genetic Medication Report Created for: Jane Doe

Patient:	Jane Doe	DOB:	1/1/1970
Accession #:	99909	Gender:	Female
Collection Date:		Received Date:	
Ordered By:		Report Generated:	6/4/2015

Test Summary

Gene	Genotype	Phenotype
ANKK1/DRD2	DRD2:Taq1A GG	Unaltered DRD2 function
COMT	Val158Met GG	High/Normal COMT Activity
CYP1A2	*1A/*1A	Normal Metabolizer- Possible Inducibility
CYP2B6	*1/*1	Normal Metabolizer
CYP2C19	*2/*2	Poor Metabolizer
CYP2C9	*1/*8	Intermediate Metabolizer
CYP2D6	*1/*1 XN	Rapid Metabolizer
CYP3A4	*1B/*1B	Intermediate Metabolizer
CYP3A5	*1/*1	Normal Metabolizer
OPRM1	A118G AA	Normal OPRM1 Function
SLCO1B1	521T>C TT	Normal Transporter Function
VKORC1	-1639G>A G/G	Low Warfarin Sensitivity

Current Patient Medications

Current Medication List: Buprenorphine, Oxycodone, Cyclobenzaprine, Coumadin, Plavix, Brintellix, Wellbutrin, Aricept

Medications Affected by Patient Genetic Results

✓ **Buprenorphine (Butrans, Buprenex)**

Normal Response to Buprenorphine — Evidence Level: **Informative**

Pharmacogenetic guidance: no genetically guided drug selection or dosing recommendations are available. Buprenorphine is primarily metabolized by CYP3A4 to norbuprenorphine and by UGT enzymes (mainly UGT1A1 and 2B7). The effects of genetic variants in these enzymes on its response have not been studied. **Polypharmacy guidance:** The concomitant use of buprenorphine with all CYP3A4 inhibitors may result in an increase in the drug levels, which could increase or prolong adverse drug effects. Monitor patients receiving buprenorphine with a CYP3A4 inhibitor. CYP and UGT inducers may decrease buprenorphine levels.

✓ **Wellbutrin (Bupropion)**

Good Response to Bupropion (ANKK1 DRD2:Taq1A GG Unaltered DRD2 function) — Evidence Level: **Informative**

Smoking Cessation: The patient's genotype result is associated with a positive response with bupropion treatment.

⚑ **Plavix (Clopidogrel)**

Significantly Reduced Response to Clopidogrel (CYP2C19 *2/*2 Poor Metabolizer) — Evidence Level: **Actionable**

Consider alternative therapy. Examples of alternative drugs: prasugrel (contraindicated in TIA/Stroke patients), ticagrelor, aspirin, aspirin plus dipyridamole.

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✓ **Cyclobenzaprine (Flexeril, Amrix)**

Normal Response to Cyclobenzaprine — Evidence Level: **Informative**

Pharmacogenetic guidance: Cyclobenzaprine is excreted primarily as a glucuronide via the kidneys, and as an N-demethylated metabolite by CYP3A4, CYP1A2, and to a lesser extent CYP2D6. Due to the minor involvement of CYP2D6 in the metabolism of cyclobenzaprine, the polymorphism of this enzyme is not of concern in its the clinical use. no genetically guided drug selection or dosing recommendations are available.

⚠ **Aricept (Donepezil)**

Possible Altered Response to Donepezil (CYP2D6 *1/*1 XN Rapid Metabolizer) — Evidence Level: **Informative**

When compared to a normal metabolizer, a rapid metabolizers has a 24% increase in donepezil clearance. The clinical significance of this increase is not well documented. Consider using a standard dosing regimen and adjust dosage in response to clinical response and tolerability.

⚠ **Oxycodone (Percocet, Oxycontin)**

Possible Altered Response to Oxycodone (CYP2D6 *1/*1 XN Rapid Metabolizer) — Evidence Level: **Actionable**

Increased conversion of oxycodone to the more active metabolite oxymorphone is expected in CYP2D6 rapid metabolizers. Usually, adequate pain relief without an increase in adverse events can be achieved by using standard or lower oxycodone doses. Other opioids not metabolized by CYP2D6 (e.g., morphine, oxymorphone, buprenorphine, fentanyl, methadone, and hydromorphone) may also be considered if excessive side effects are reported.

✓ **Brintellix (Vortioxetine)**

Normal Sensitivity to Vortioxetine (CYP2D6 *1/*1 XN Rapid Metabolizer) — Evidence Level: **Actionable**

There is little evidence documenting the exposure of this drug in CYP2D6 rapid metabolizer. Vortioxetine plasma concentrations may decrease, but the clinical relevance of this change is not documented. Vortioxetine can be prescribed at standard label-recommended dosage and administration. The recommended starting dose is 10 mg/day, which can then be increased to 20 mg/day, as tolerated.

⚠ **Coumadin (Warfarin)**

Mild Sensitivity to Warfarin (CYP2C9 *1/*8 VKORC1 -1639G>A G/G) — Evidence Level: **Actionable**

Initiation Therapy: a dose decrease may be required. Consider using the warfarin dose range provided in the FDA-approved label: **5-7 mg/day.** OR consider using a personalized dose calculated by a pharmacogenetic algorithm. The estimated time to reach steady state is 8-10 days.

Guidance Levels

- Based upon the patient's genotype, a medication has potentially reduced efficacy or increased toxicity or the patient has an increased risk for the indicated condition.
- ⚠ Based upon the patient's genotype, guidelines exist for adjusting dosage or increased vigilance or the patient has a moderate risk for the indicated condition.
- ✓ Based on this patient's genotype, the medication can be prescribed according to standard regimens or the patient's risk for the indicated condition is not increased.

Evidence Levels

Actionable - Recommendations based upon publications by international pharmacogenetic expert groups, consortia or regulatory bodies (CPIC, DPWG, FDA. EMEA). Recommendations are suitable for implementation in a clinical setting. Guidelines may change as new knowledge arises.
Informative - There are insufficient or contradictory findings documenting the impact of a given genetic polymorphism or drug interaction. Recommendations are informative and implementation in a clinical setting is optional.

Potentially Impacted Medications

Category	Standard Precautions	Use With Caution	Consider Alternatives
5-Alpha Reductase Inhibitors for Benign Prostatic Hyperplasia	Dutasteride (Avodart) Finasteride (Proscar)		

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Potentially Impacted Medications

Category	Standard Precautions	Use With Caution	Consider Alternatives
Alpha-Blockers for Benign Prostatic Hyperplasia	Alfuzosin (UroXatral) Doxazosin (Cardura) Silodosin (Rapaflo) Tamsulosin (Flomax) Terazosin (Hytrin)		
Angiotensin II Receptor Antagonists	Irbesartan (Avapro)		
Antiaddictives	Bupropion (Wellbutrin, Zyban, Aplenzin, Contrave)	Naltrexone (Vivitrol)	
Anti-ADHD Agents	Amphetamine (Adderall) Dexmethylphenidate (Focalin) Dextroamphetamine (Dexedrine) Lisdexamfetamine (Vyvanse) Methylphenidate (Ritalin)		Atomoxetine (Strattera)
Antianginal Agents	Ranolazine (Ranexa)		
Antiarrhythmics		Mexiletine (Mexitil) Propafenone (Rythmol)	Flecainide (Tambocor)
Anticoagulants	Apixaban (Eliquis) Dabigatran Etexilate (Pradaxa) Fondaparinux (Arixtra) Rivaroxaban (Xarelto)	Warfarin (Coumadin)	
Anticonvulsants	Carbamazepine (Tegretol, Carbatrol) Eslicarbazepine Acetate (Aptiom) Ethosuximide (Zarontin) Ezogabine (Potiga) Felbamate (Felbatol) Gabapentin (Neurontin) Lacosamide (Vimpat) Lamotrigine (Lamictal) Levetiracetam (Keppra) Oxcarbazepine (Trileptal) Perampanel (Fycompa) Pregabalin (Lyrica) Rufinamide (Banzel) Tiagabine (Gabitril) Topiramate (Topamax) Valproic Acid (Depakote, Depakene) Vigabatrin (Sabril)	Fosphenytoin (Cerebyx) Phenobarbital (Luminal) Phenytoin (Dilantin) Primidone (Mysoline) Zonisamide (Zonegran)	
Antidementia Agents	Galantamine (Razadyne) Memantine (Namenda)	Donepezil (Aricept)	

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Potentially Impacted Medications

Category	Standard Precautions	Use With Caution	Consider Alternatives
Antidepressants	Desvenlafaxine (Pristiq) Duloxetine (Cymbalta) Fluoxetine (Prozac, Sarafem) Levomilnacipran (Fetzima) Mirtazapine (Remeron) Nefazodone (Serzone) Vilazodone (Viibryd) Vortioxetine (Brintellix)	Amoxapine (Amoxapine) Citalopram (Celexa) Escitalopram (Lexapro) Fluvoxamine (Luvox) Maprotiline (Ludiomil) Sertraline (Zoloft)	Amitriptyline (Elavil) Clomipramine (Anafranil) Desipramine (Norpramin) Doxepin (Silenor) Imipramine (Tofranil) Nortriptyline (Pamelor) Paroxetine (Paxil, Brisdelle) Protriptyline (Vivactil) Trimipramine (Surmontil) Venlafaxine (Effexor)
Antiemetics	Metoclopramide (Reglan)		Ondansetron (Zofran)
Antifungals		Voriconazole (Vfend)	
Antiplatelets	Prasugrel (Effient) Ticagrelor (Brilinta) Vorapaxar (Zontivity)		Clopidogrel (Plavix)
Antipsychotics	Aripiprazole (Abilify) Asenapine (Saphris) Clozapine (Clozaril) Iloperidone (Fanapt) Lurasidone (Latuda) Olanzapine (Zyprexa) Paliperidone (Invega) Quetiapine (Seroquel) Thioridazine (Mellaril) Thiothixene (Navane) Trazodone (Oleptro) Trifluoperazine (Stelazine) Ziprasidone (Geodon)	Chlorpromazine (Thorazine) Fluphenazine (Prolixin) Perphenazine (Trilafon) Pimozide (Orap) Tetrabenazine (Xenazine)	Haloperidol (Haldol) Risperidone (Risperdal)
Antispasmodics for Overactive Bladder	Darifenacin (Enablex) Fesoterodine (Toviaz) Mirabegron (Myrbetriq) Oxybutynin (Ditropan) Solifenacin (Vesicare) Tolterodine (Detrol) Trospium (Sanctura)		
Benzodiazepines	Clonazepam (Klonopin)	Clobazam (Onfi) Diazepam (Valium)	
Beta Blockers	Carvedilol (Coreg) Labetalol (Normodyne, Trandate) Nebivolol (Bystolic) Propranolol (Inderal) Timolol (Timoptic)		Metoprolol (Lopressor)
Fibromyalgia Agents	Milnacipran (Savella)		
Immunosupressants		Tacrolimus (Prograf)	
Muscle Relaxants	Cyclobenzaprine (Flexeril, Amrix) Metaxalone (Skelaxin) Methocarbamol (Robaxin) Tizanidine (Zanaflex)	Carisoprodol (Soma)	

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Potentially Impacted Medications			
Category	**Standard Precautions**	**Use With Caution**	**Consider Alternatives**
NSAIDs	Ibuprofen (Advil, Motrin) Ketoprofen (Orudis) Ketorolac (Toradol) Nabumetone (Relafen) Naproxen (Aleve) Sulindac (Clinoril)	Celecoxib (Celebrex) Diclofenac (Voltaren) Flurbiprofen (Ansaid) Indomethacin (Indocin) Meloxicam (Mobic) Piroxicam (Feldene)	
Opioids	Alfentanil (Alfenta) Buprenorphine (Butrans, Buprenex) Fentanyl (Actiq) Hydromorphone (Dilaudid, Exalgo) Levorphanol (Levo Dromoran) Meperidine (Demerol) Methadone (Dolophine) Oxymorphone (Opana, Numorphan) Sufentanil (Sufenta) Tapentadol (Nucynta)	Dihydrocodeine (Synalgos-DC) Hydrocodone (Vicodin) Morphine (MS Contin) Oxycodone (Percocet, Oxycontin)	Codeine (Codeine; Fioricet with Codeine) Tramadol (Ultram)
Phosphodiesterase Inhibitors for Erectile Dysfunction	Avanafil (Stendra) Sildenafil (Viagra) Tadalafil (Cialis) Vardenafil (Levitra)		
Proton Pump Inhibitors	Dexlansoprazole (Dexilant) Esomeprazole (Nexium) Lansoprazole (Prevacid) Omeprazole (Prilosec) Pantoprazole (Protonix) Rabeprazole (Aciphex)		
Statins	Atorvastatin (Lipitor) Lovastatin (Mevacor) Pitavastatin (Livalo) Pravastatin (Pravachol) Rosuvastatin (Crestor) Simvastatin (Zocor)	Fluvastatin (Lescol)	
Sulfonylureas	Glimepiride (Amaryl) Glipizide (Glucotrol) Glyburide (Micronase) Tolbutamide (Orinase)		

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Dosing Guidance

Amitriptyline (Elavil)

Non-Response to Amitriptyline (CYP2D6 *1/*1 XN Rapid Metabolizer) Evidence Level: **Actionable**

Consider an alternative drug, or prescribe amitriptyline at an increased dose and monitor the plasma concentration of amitriptyline and metabolites.

Amoxapine (Amoxapine)

Possible Non-Response to Amoxapine (CYP2D6 *1/*1 XN Rapid Metabolizer) Evidence Level: **Informative**

Like other tricyclic and tetracyclic antidepressants, amoxapine is metabolized by CYP2D6. However, the overall contribution of this enzyme in the metabolism of this drug is not well documented. Patients with increased CYP2D6 function may metabolize amoxapine more rapidly which can result in sub-therapeutic drug concentrations; these patients may require higher doses to achieve adequate plasma concentrations. There are no established dosing adjustments for patients with increased CYP2D6 function therefore, therapy must be initiated cautiously and adjusted according to the patient's response.

Atomoxetine (Strattera)

Non-Response to Atomoxetine (CYP2D6 *1/*1 XN Rapid Metabolizer) Evidence Level: **Informative**

Consider prescribing atomoxetine with careful titration and monitoring for reduced efficacy. There is insufficient data to calculate dose adjustment. OR consider an alternative drug such as methylphenidate.

Carisoprodol (Soma)

Altered Sensitivity to Carisoprodol (CYP2C19 *2/*2 Poor Metabolizer) Evidence Level: **Actionable**

CYP2C19 poor metabolizers have a lower capacity to metabolize carisoprodol to meprobamate, and may therefore have an increased risk of developing concentration-dependent side effects such as drowsiness and hypotension when receiving standard doses of carisoprodol. Carisoprodol should be used with caution in patients with reduced CYP2C19 activity. Because there is insufficient data to allow calculation of dose adjustment, consider reducing the dose or using an alternative medication.

Celecoxib (Celebrex)

Possible Sensitivity to Celecoxib (CYP2C9 *1/*8 Intermediate Metabolizer) Evidence Level: **Informative**

Celecoxib can be prescribed at standard label-recommended dosage and administration. Evaluate response the first week and be alert to gastrointestinal adverse events.

Chlorpromazine (Thorazine)

Possible Non-Response to Chlorpromazine (CYP2D6 *1/*1 XN Rapid Metabolizer) Evidence Level: **Informative**

Chlorpromazine is metabolized by CYP2D6, CYP3A4 and flavin-containing monooxygenases. Subjects with increased CYP2D6 function will metabolize chlorpromazine more rapidly which can result in sub-therapeutic drug concentrations. Consider a standard dose and adjust dosage according to the patient's tolerability and response. Higher doses may be necessary to achieve efficacy.

Citalopram (Celexa)

Increased Sensitivity to Citalopram (CYP2C19 *2/*2 Poor Metabolizer) Evidence Level: **Actionable**

Consider using citalopram at lower doses, and monitor the patient for side effects. Dose escalations over 20 mg/day for CYP2C19 poor metabolizers are not recommended.

Clobazam (Onfi)

Increased Sensitivity to Clobazam (CYP2C19 *2/*2 Poor Metabolizer) Evidence Level: **Actionable**

In CYP2C19 poor metabolizers, plasma levels of the active metabolite N-desmethylclobazam were 5-fold higher than those found in CYP2C19 normal metabolizers. Therefore, the starting dose should be 5 mg/day and dose titration should proceed slowly according to weight. Patients should be titrated initially to 10 mg /day (≤30 kg body weight) or 20 mg/day (>30 kg body weight). If necessary and based upon clinical response, an additional titration to the maximum doses 20 mg/day (≤30 kg body weight) or 40 mg/day (>30 kg body weight) may be started on day 21.

Clomipramine (Anafranil)

Non-Response to Clomipramine (CYP2D6 *1/*1 XN Rapid Metabolizer) Evidence Level: **Actionable**

Consider an alternative drug, or prescribe clomipramine at an increased dose and monitor the plasma concentration of clomipramine and desmethylclomipramine.

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Clopidogrel (Plavix)

Significantly Reduced Response to Clopidogrel (CYP2C19 *2/*2 Poor Metabolizer) Evidence Level: **Actionable**

Consider alternative therapy. Examples of alternative drugs: prasugrel (contraindicated in TIA/Stroke patients), ticagrelor, aspirin, aspirin plus dipyridamole.

Codeine (Codeine; Fioricet with Codeine)

Increased Response to Codeine (CYP2D6 *1/*1 XN Rapid Metabolizer) Evidence Level: **Actionable**

Codeine is converted into its active metabolite morphine by CYP2D6. Since this patient is a rapid metabolizer, greatly increased morphine levels are expected, and the patient is at high risk of toxicity when taking codeine. Avoid prescribing codeine, and consider an alternative opioid or a non-opioid analgesic such as a NSAID or a COX-2 inhibitor. Unless contraindicated, available alternative opioids not sensitive to CYP2D6 function include: fentanyl, morphine, hydromorphone, oxymorphone, and tapentadol.

Desipramine (Norpramin)

Non-Response to Desipramine (CYP2D6 *1/*1 XN Rapid Metabolizer) Evidence Level: **Actionable**

Consider an alternative drug, or prescribe desipramine at increased dosage and observe the patient for decreased efficacy. Adjust dosage in response to desipramine and metabolites plasma concentrations and clinical response.

Diazepam (Valium)

Increased Sensitivity to Diazepam (CYP2C19 *2/*2 Poor Metabolizer) Evidence Level: **Actionable**

CYP2C19 poor metabolizers have a lower capacity to metabolize diazepam and its active metabolite nordiazepam. Therefore, they may experience more concentration-dependent side effects, such as increased or prolonged sedation, if treated with standard doses of diazepam. Diazepam should be used with caution in these patients, and a reduced dose or longer dosing interval may be needed.

Diclofenac (Voltaren)

Possible Sensitivity to Diclofenac (CYP2C9 *1/*8 Intermediate Metabolizer) Evidence Level: **Informative**

Diclofenac is extensively metabolized by hydroxylation and direct glucuronidation. About 50% of diclofenac is eliminated as a 4-hydroxymetabolite, a reaction mediated by CYP2C9. Other CYP enzymes including CYP2C8, CYP2C19 and CYP3A4 are also involved in the formation of a 5-hydroxymetabolite. A substantial portion of the drug is also directly glucuronidated by UGT2B7 and UGT2B4. Individuals with decreased CYP2C9 activity (i.e intermediate metabolizers) should be closely monitored for increased gastrointestinal adverse events when prescribed diclofenac and lower doses may be more appropriate for these patients.

Dihydrocodeine (Synalgos-DC)

Possible Altered Response to Dihydrocodeine (CYP2D6 *1/*1 XN Rapid Metabolizer) Evidence Level: **Actionable**

Increased conversion of dihydrocodeine to the more active metabolite dihydromorphine is expected in CYP2D6 rapid metabolizers. This may result in an exaggerated response. Adequate pain relief can be achieved by decreasing the dose in response to pain symptoms. Other opioids not metabolized by CYP2D6 (i.e., morphine, oxymorphone, buprenorphine, fentanyl, methadone, and hydromorphone) may also be considered if signs of overdose (excessive sleepiness, confusion, or shallow breathing) are reported.

Donepezil (Aricept)

Possible Altered Response to Donepezil (CYP2D6 *1/*1 XN Rapid Metabolizer) Evidence Level: **Informative**

When compared to a normal metabolizer, a rapid metabolizers has a 24% increase in donepezil clearance. The clinical significance of this increase is not well documented. Consider using a standard dosing regimen and adjust dosage in response to clinical response and tolerability.

Doxepin (Silenor)

Non-Response to Doxepin (CYP2D6 *1/*1 XN Rapid Metabolizer) Evidence Level: **Actionable**

Consider an alternative drug or increase doxepin dose by 100%. Adjust maintenance dose according to nordoxepin plasma concentrations.

Escitalopram (Lexapro)

Increased Sensitivity to Escitalopram (CYP2C19 *2/*2 Poor Metabolizer) Evidence Level: **Informative**

Consider using escitalopram at lower than the recommended dose, and monitor the patient for side effects.

Flecainide (Tambocor)

Altered Response to Flecainide (CYP2D6 *1/*1 XN Rapid Metabolizer) Evidence Level: **Actionable**

Titrate carefully and consider adjusting the dose in response to plasma concentration and ECG monitoring, OR consider an alternative drug. Examples of alternatives drugs not affected by CYP2D6 include: sotalol, disopyramide, quinidine, and amiodarone.

Fluphenazine (Prolixin)

Possible Non-response to Fluphenazine (CYP2D6 *1/*1 XN Rapid Metabolizer) Evidence Level: **Informative**

Fluphenazine is metabolized by CYP2D6, CYP1A2 and other enzymes. **Patients with increased CYP2D6 function will metabolize fluphenazine more rapidly which can result in sub-therapeutic drug concentrations; these patients may require higher doses to achieve adequate plasma concentrations.** There are no established dosing adjustments for patients with increased CYP2D6 function therefore, therapy must be initiated cautiously with oral or parenteral fluphenazine hydrochloride. When the pharmacological effects and an appropriate dosage are apparent, an equivalent dose of fluphenazine decanoate (IM or SC) may be administered and subsequent dosage adjustments may be necessary.

Flurbiprofen (Ansaid)

Possible Sensitivity to Flurbiprofen (CYP2C9 *1/*8 Intermediate Metabolizer) Evidence Level: **Informative**

The patient may have high plasma levels of the drug. Flurbiprofen can be prescribed at standard label-recommended dosage and administration with closer monitoring for gastrointestinal side effects.

Fluvastatin (Lescol)

Possible Sensitivity to Fluvastatin (CYP2C9 *1/*8 Intermediate Metabolizer) Evidence Level: **Actionable**

Increased fluvastatin plasma concentrations due to reduced CYP2C9 activity may occur, resulting in myotoxicity/hepatotoxicity. Consider monitoring the patient for treatment-related adverse effects, and adjust dose as needed. Other adverse events and predisposing factors include advanced age (≥65), diabetes, hypothyroidism, renal or hepatic impairments, high statin dose, CYP2C9 inhibitors, ABCG2 inhibitors, and female gender.

Fluvoxamine (Luvox)

Possible Abnormal Response to Fluvoxamine (CYP2D6 *1/*1 XN Rapid Metabolizer) Evidence Level: **Informative**

There is a risk for decreased efficacy at standard dosage. If a standard dose is prescribed to a CYP2D6 rapid metabolizer, suboptimal plasma concentrations of the drug are likely. There is insufficient data to calculate dose adjustments and careful titration is recommended until a favorable response is achieved.

Fosphenytoin (Cerebyx)

Moderate Sensitivity to Fosphenytoin (CYP2C9 *1/*8 Intermediate Metabolizer) Evidence Level: **Actionable**

The genotype results indicate that the patient is a CYP2C9 substrate intermediate metabolizer. Plasma concentrations of phenytoin are likely to increase, resulting in an increased risk of mild to moderate neurological toxicity. Consider a standard loading dose, and reduce the maintenance dose by 25%. Evaluate response and serum concentrations after 7-10 days. Be alert to neurological concentration-related adverse events.

Haloperidol (Haldol)

Non-Response to Haloperidol (CYP2D6 *1/*1 XN Rapid Metabolizer) Evidence Level: **Actionable**

Consider an alternative drug, or prescribe haloperidol at the standard dose and adjust dosage to achieve a favorable clinical response. Be alert to decreased haloperidol plasma concentrations.

Hydrocodone (Vicodin)

Possible Altered Response to Hydrocodone (CYP2D6 *1/*1 XN Rapid Metabolizer) Evidence Level: **Informative**

Increased conversion of hydrocodone to the more active metabolite hydromorphone is expected in CYP2D6 rapid metabolizers. Usually, adequate pain relief without an increase in adverse events can be achieved by using standard or lower hydrocodone doses. Other opioids not metabolized by CYP2D6 (e.g., morphine, oxymorphone, buprenorphine, fentanyl, methadone, and hydromorphone) may also be considered if excessive side effects are reported.

Imipramine (Tofranil)

Non-Response to Imipramine (CYP2D6 *1/*1 XN Rapid Metabolizer) Evidence Level: **Actionable**

Consider an alternative drug or consider prescribing imipramine at an increased dose, then adjust dosage in response to imipramine and desipramine plasma concentrations.

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Indomethacin (Indocin)

Possible Sensitivity to Indomethacin (CYP2C9 *1/*8 Intermediate Metabolizer) Evidence Level: **Informative**

Indomethacin is metabolized mainly by O-demethylation to its inactive metabolite O-desmethylindomethacin, a reaction catalyzed by CYP2C9. At standard doses, indomethacin plasma concentrations may be higher in individuals with decreased CYP2C9 function. Although indomethacin can be prescribed at standard label recommended-dosage and administration, a closer monitoring for signs of gastrointestinal toxicity during long-term administration is recommended.

Maprotiline (Ludiomil)

Possible Non-response to Maprotiline (CYP2D6 *1/*1 XN Rapid Metabolizer) Evidence Level: **Informative**

Like other tricyclic and tetracyclic antidepressants, maprotiline is metabolized by CYP2D6 as well as CYP1A2. Patients with increased CYP2D6 function may metabolize maprotiline more rapidly which can result in sub-therapeutic drug concentrations; these patients may require higher doses to achieve adequate plasma concentrations. **There are no established dosing adjustments for patients with increased CYP2D6 function. Seizures have been associated with the use of maprotiline especially at high doses. Therefore, therapy must be initiated at a lower dose and gradually increased in small increments according to the patient's response.**

Meloxicam (Mobic)

Possible Sensitivity to Meloxicam (CYP2C9 *1/*8 Intermediate Metabolizer) Evidence Level: **Informative**

Meloxicam plasma concentrations may be higher in individual with decreased CYP2C9 function. A reduction in meloxicam dosage may be needed with a closer monitoring for signs of gastrointestinal toxicity during long-term administration.

Metoprolol (Lopressor)

Possible Non-Responder to Metoprolol (CYP2D6 *1/*1 XN Rapid Metabolizer) Evidence Level: **Actionable**

The patient may experience a decrease in the pharmacological effect when taking metoprolol at standard dosage. Heart Failure: Consider alternative beta-blockers such as bisoprolol or carvedilol, or prescribe metoprolol at a higher dose. Other indications: Consider alternative beta-blockers such as bisoprolol or atenolol, or prescribe metoprolol at a higher dose. If metoprolol is prescribed, titrate the dose to a maximum of 250% of the normal dose in response to efficacy and adverse events.

Mexiletine (Mexitil)

Altered Response to Mexiletine (CYP2D6 *1/*1 XN Rapid Metabolizer) Evidence Level: **Informative**

Because mexiletine plasma concentrations may be decreased, consider adjusting dose in response to mexiletine plasma concentration and ECG monitoring, until a favorable response in achieved.

Morphine (MS Contin)

Altered Response to Morphine (COMT Val158Met GG High/Normal COMT Activity) Evidence Level: **Informative**

The patient does not carry the COMT Val158Met mutation. The patient may require higher doses of morphine for adequate pain control. The dosing regimen needs to be individualized for each patient, taking into account the patient's prior analgesic treatment experience.

Naltrexone (Vivitrol)

Altered Response to Naltrexone (OPRM1 A118G AA Normal OPRM1 Function) Evidence Level: **Informative**

Treatment of alcohol dependence: the patient has the wild-type genotype for OPRM1 that is associated with a poorer outcome with naltrexone therapy. Naltrexone-treated patients not carrying the 118A> G mutation are less likely to respond to this drug, and may have higher relapse rates than those who are carriers of this mutation.

Nortriptyline (Pamelor)

Non-Response to Nortriptyline (CYP2D6 *1/*1 XN Rapid Metabolizer) Evidence Level: **Actionable**

Consider an alternative drug, or prescribe nortriptyline at an increased dose and monitor the plasma concentration of amitriptyline and hydroxynortriptyline.

Ondansetron (Zofran)

Non-Response to Ondansetron (CYP2D6 *1/*1 XN Rapid Metabolizer) Evidence Level: **Informative**

A substantially decreased antiemetic effect has been reported in CYP2D6 rapid metabolizers. Consider prescribing an alternative drug not metabolized by CYP2D6 such as granisetron.

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Oxycodone (Percocet, Oxycontin)

Possible Altered Response to Oxycodone (CYP2D6 *1/*1 XN Rapid Metabolizer) Evidence Level: **Actionable**

Increased conversion of oxycodone to the more active metabolite oxymorphone is expected in CYP2D6 rapid metabolizers. Usually, adequate pain relief without an increase in adverse events can be achieved by using standard or lower oxycodone doses. Other opioids not metabolized by CYP2D6 (e.g., morphine, oxymorphone, buprenorphine, fentanyl, methadone, and hydromorphone) may also be considered if excessive side effects are reported.

Paroxetine (Paxil, Brisdelle)

Abnormal Response to Paroxetine (CYP2D6 *1/*1 XN Rapid Metabolizer) Evidence Level: **Actionable**

There is a risk for decreased efficacy at standard dosage. If a standard dose is prescribed to a CYP2D6 rapid metabolizer, suboptimal plasma concentrations of the drug are likely. Consider an alternative drug, or increase the paroxetine dose and adjust dosage in response to efficacy. Because paroxetine half-life is shorter in rapid metabolizers, the SSRI discontinuation syndrome at treatment termination may be more pronounced in these patients.

Perphenazine (Trilafon)

Possible Non-Response to Perphenazine (CYP2D6 *1/*1 XN Rapid Metabolizer) Evidence Level: **Actionable**

Subjects with increased CYP2D6 function will metabolize perphenazine more rapidly, which can result in sub-therapeutic drug concentrations. Consider a dose increase with close monitoring until a favorable response is achieved.

Phenobarbital (Luminal)

Possible Sensitivity to Phenobarbital (CYP2C19 *2/*2 Poor Metabolizer) Evidence Level: **Informative**

CYP2C19 is partly involved in the metabolism of phenobarbital, and although CYP2C19 poor metabolizers have a 20% lower clearance of phenobarbital than normal metabolizers, no significant changes in clinical outcome has been reported with this antiepileptic drug. Therefore, phenobarbital can be prescribed at standard label-recommended dosage and administration with a closer monitoring for adverse events.

Phenytoin (Dilantin)

Moderate Sensitivity to Phenytoin (CYP2C9 *1/*8 Intermediate Metabolizer) Evidence Level: **Actionable**

The genotype results indicate that the patient is a CYP2C9 substrate intermediate metabolizer. Plasma concentrations of phenytoin are likely to increase, resulting in an increased risk of mild to moderate neurological toxicity. Consider a standard loading dose, and reduce the maintenance dose by 25%. Evaluate response and serum concentrations after 7-10 days. Be alert to neurological concentration-related adverse events.

Pimozide (Orap)

Possible Non-Response to Pimozide (CYP2D6 *1/*1 XN Rapid Metabolizer) Evidence Level: **Actionable**

There is insufficient data to calculate dose adjustment, and if pimozide is prescribed at standard dosing, monitor response and be alert to reduced efficacy. Standard starting dose: 1 to 2 mg/day (adult) or 0.05 mg/kg/day (children). Doses may be increased to a maximum of 10 mg/day or 0.2 mg/kg/day.

Piroxicam (Feldene)

Possible Sensitivity to Piroxicam (CYP2C9 *1/*8 Intermediate Metabolizer) Evidence Level: **Informative**

Piroxicam plasma concentrations may be higher in individual with decreased CYP2C9 function. Although piroxicam can be prescribed at standard label-recommended dosage and administration, a closer monitoring for signs of gastrointestinal toxicity during long-term administration is recommended.

Primidone (Mysoline)

Possible Sensitivity to Primidone (CYP2C19 *2/*2 Poor Metabolizer) Evidence Level: **Informative**

CYP2C19 is partly involved in the metabolism of primidone and although CYP2C19 poor metabolizers have a 20% lower clearance of phenobarbital (active metabolite) than normal metabolizers, no significant changes in clinical outcome has been reported with this antiepileptic drug. Therefore, primidone can be prescribed at standard label-recommended dosage and administration with a closer monitoring for adverse events.

Propafenone (Rythmol)

Altered Response to Propafenone (CYP2D6 *1/*1 XN Rapid Metabolizer) Evidence Level: **Actionable**

There is insufficient data to allow calculation of dose adjustment. Titrate carefully and adjust the dose in response to plasma concentration and ECG monitoring. OR consider alternative drug such as sotalol, disopyramide, quinidine, or amiodarone.

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Protriptyline (Vivactil)

Non-Response to Protriptyline (CYP2D6 *1/*1 XN Rapid Metabolizer) Evidence Level: **Actionable**

Consider alternative drugs or prescribe protriptyline at increased dosage and observe the patient for decreased efficacy. Adjust dosage in response to protriptyline and metabolites plasma concentrations and clinical response.

Risperidone (Risperdal)

Non-Response to Risperidone (CYP2D6 *1/*1 XN Rapid Metabolizer) Evidence Level: **Actionable**

Consider an alternative drug, OR prescribe risperidone , be extra alert to insufficient response, and adjust dosage in response to clinical response and adverse events.

Sertraline (Zoloft)

Increased Sensitivity to Sertraline (CYP2C19 *2/*2 Poor Metabolizer) Evidence Level: **Actionable**

Reduce sertraline dose by 50% and monitor patient for side effects.

Tacrolimus (Prograf)

Insufficient Response to Tacrolimus (CYP3A5 *1/*1 Normal Metabolizer) Evidence Level: **Actionable**

The genotype result predicts that the patient expresses the CYP3A5 protein. Therefore, the patient may metabolize tacrolimus more rapidly, resulting in low tacrolimus trough levels. Studies have shown patients with this genotype may be at increased risk for acute transplant rejection while taking a standard dose of tacrolimus. Therefore, tacrolimus dose increase with close monitoring are strongly recommended to achieve therapeutic effect.

Tetrabenazine (Xenazine)

Unknown Sensitivity to Tetrabenazine (CYP2D6 *1/*1 XN Rapid Metabolizer) Evidence Level: **Actionable**

There is insufficient data to calculate dose adjustment, and if tetrabenazine is prescribed, individualization of dose with careful weekly titration is required. The first week's starting dose is 12.5 mg daily; second week, 25 mg (12.5 mg twice daily); then slowly titrate at weekly intervals by 12.5 mg to a tolerated dose. **The maximum daily dose in CYP2D6 rapid metabolizers is not defined. The maximum daily dose in normal metabolizers is 100 mg with a maximum single dose of 37.5 mg.** If serious adverse events occur, titration should be stopped and the dose of tetrabenazine should be reduced. If the adverse event(s) do not resolve, consider withdrawal of tetrabenazine.

Tramadol (Ultram)

Increased Response to Tramadol (CYP2D6 *1/*1 XN Rapid Metabolizer) Evidence Level: **Actionable**

The patient is at high risk of toxicity when taking tramadol at standard dosing. Consider reducing tramadol dose by 30%. Careful monitoring for side effects and weekly titration are recommended. If toxicity, consider alternative opioids other than codeine, or a non-opioid analgesic such as a NSAID or a COX-2 inhibitor. Unless contraindicated, available alternative opioids not sensitive to CYP2D6 function include: fentanyl, morphine, hydromorphone, oxymorphone, and tapentadol.

Trimipramine (Surmontil)

Non-Response to Trimipramine (CYP2D6 *1/*1 XN Rapid Metabolizer) Evidence Level: **Actionable**

Consider an alternative drug, or consider prescribing trimipramine at an increased dose, then adjust dosage in response to trimipramine plasma concentrations.

Venlafaxine (Effexor)

Non-Response to Venlafaxine (CYP2D6 *1/*1 XN Rapid Metabolizer) Evidence Level: **Actionable**

The patient is unlikely to achieve adequate serum levels of venlafaxine and O-desmethylvenlafaxine when taking standard doses of venlafaxine. Consider an alternative drug, or increase the venlafaxine dose to a maximum of 150% of the normal dose and monitor venlafaxine and O-desmethylvenlafaxine plasma concentrations.

Voriconazole (Vfend)

Increased Sensitivity to Voriconazole (CYP2C19 *2/*2 Poor Metabolizer) Evidence Level: **Actionable**

Voriconazole plasma concentrations are expected to be high, which may increase the risk of dose-dependent adverse events. Voriconazole should be used with caution in patients with a reduced CYP2C19 activity, such as poor metabolizers. Monitor closely voriconazole plasma concentrations, and adjust the dose accordingly.

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Warfarin (Coumadin)

Mild Sensitivity to Warfarin (CYP2C9 *1/*8 VKORC1 -1639G>A G/G) Evidence Level: **Actionable**

Initiation Therapy: a dose decrease may be required. Consider using the warfarin dose range provided in the FDA-approved label: **5-7 mg/day.** OR consider using a personalized dose calculated by a pharmacogenetic algorithm. The estimated time to reach steady state is 8-10 days.

Zonisamide (Zonegran)

Possible Sensitivity to Zonisamide (CYP2C19 *2/*2 Poor Metabolizer) Evidence Level: **Informative**

CYP2C19 is partly involved in the metabolism of zonisamide, and although preliminary studies show that CYP2C19 poor metabolizers have a slightly lower (30%) zonisamide clearance than normal metabolizers, no significant change in the clinical outcome has been reported with this antiepileptic drug. Therefore, zonisamide can be prescribed at standard label-recommended dosage and administration with a closer monitoring for adverse events.

Test Details

Gene	Genotype	Phenotype	Alleles Tested
ANKK1/DRD2	DRD2:Taq1A GG	Unaltered DRD2 function	DRD2:Taq1A
COMT	Val158Met GG	High/Normal COMT Activity	Val158Met
CYP1A2	*1A/*1A	Normal Metabolizer- Possible Inducibility	*1C, *1D, *1F, *1K, *1L, *1V, *1W
CYP2B6	*1/*1	Normal Metabolizer	*6, *9
CYP2C19	*2/*2	Poor Metabolizer	*2, *3, *4, *4B, *5, *6, *7, *8, *9, *17
CYP2C9	*1/*8	Intermediate Metabolizer	*2, *3, *5, *6, *8, *11, *27
CYP2D6	*1/*1 XN	Rapid Metabolizer	*2, *3, *4, *4M, *6, *7, *8, *9, *10, *12, *14A, *14B, *17, *29, *35, *41, *5 (gene deletion), XN (gene duplication)
CYP3A4	*1B/*1B	Intermediate Metabolizer	*1B, *2, *3, *12, *17, *22
CYP3A5	*1/*1	Normal Metabolizer	*2, *3, *3C, *6, *7, *8, *9
OPRM1	A118G AA	Normal OPRM1 Function	A118G
SLCO1B1	521T>C TT	Normal Transporter Function	521T>C
VKORC1	-1639G>A G/G	Low Warfarin Sensitivity	-1639G>A

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All clinical decisions relative to test results should be directed by the patient's healthcare provider. Silverstaff Clinical laboratories makes no representations or recommendations in regards to results. Please consult your physician for all medical advice

Methodology: All SNP genotyping tests performed at SilverStaff Clinical Laboratories, Inc. use the Applied Biosystems (ABI) TaqMan technology and the LifeTechnology Quant Studio 12K Flex platform. All PCR based methods are subject to rare interference such as inhibitors or quality or quantity of DNA. If present, the interference typically yields a no result requiring a repeat rather than an inaccurate one.

Lab CLIA #: 44D-2031868

Lab Director: Dr. Jack Pearson

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ANKK1/DRD2 Monograph

Clinical Utility

Dopamine, a key neurotransmitter that controls cognition, emotion, locomotor activity, and other endocrine functions, exerts its action by binding to five different receptors, including the dopamine D2 receptor (DRD2). Dysregulation of dopaminergic signal transmission is found in many pathological conditions such as Parkinson's disease and schizophrenia, and compounds that act as DRD2 agonists or antagonists are used to treat these conditions. Therapeutic and adverse events of several antipsychotics both result from their high affinity to antagonize DRD2.

Assay Interpretation

Within the several genetic variants of DRD2 that are relevant to disease susceptibility and therapeutic response, the Taq1A (32806C>T; rs1800497) is one of the most studied. This variant is located downstream of the DRD2 gene within the ankyrin repeat of the ANKK1 gene. The presence of the Taq1A T variant defines the A1 allele that is associated with a reduced DRD2 gene expression and function. The A2 allele defines the reference allele. The frequency of the minor Taq1A T allele differs among ethnic populations. It occurs in 22% of Caucasians, and 42% of Asians and Africans.

The reference range for the Taq1A variant is 32806C>T CC (A2/A2) and is associated with a normal DRD2 expression.

Clinical Implications

The presence of the Taq1A A1 allele (32806C>T) seems to be associated with nicotine dependence and the efficacy of bupropion and nicotine replacement therapy. Smokers carrying the normal DRD2 phenotype (A2/A2 genotype) using bupropion for smoking cessation are three times more likely to be abstinent at the end of treatment than non-carriers of this genotype. Smokers with the Taq1A T variant allele (A1) seem to derive greater benefits from nicotine replacement therapies. Antipsychotic agents have been associated with hyperprolactinemia and tardive dyskinesia (TD). TD-positive patients taking antipsychotics have a higher A2 allele frequency, while A1 allele is overrepresented among those experiencing hyperprolactinemia.

References

1: Young et al. Prolactin levels in antipsychotic treatment of patients with schizophrenia carrying the DRD2*A1 allele. Br J Psychiatry. 2004 Aug;185:147-51. 2 : Zai et al. Meta-analysis of two dopamine D2 receptor gene polymorphisms with tardive dyskinesia in schizophrenia patients. Mol Psychiatry. 2007 Sep;12 (9):794-5. 3 : Bakker et al. Antipsychotic-induced tardive dyskinesia and polymorphic variations in COMT, DRD2, CYP1A2 and MnSOD genes: a meta-analysis of pharmacogenetic interactions. Mol Psychiatry. 2008 May;13(5):544-56. 4 : Johnstone et al. Pharmacogenetics. 2004 Feb;14(2):83-90. Genetic variation in dopaminergic pathways and short-term effectiveness of the nicotine patch. 5 : David et al. Bupropion efficacy for smoking cessation is influenced by the DRD2 Taq1A polymorphism: analysis of pooled data from two clinical trials. Nicotine Tob Res. 2007 Dec;9(12):1251-7.

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COMT Monograph

Clinical Utility

Catechol-O-Methyltransferase (COMT) is an enzyme responsible for the metabolism of catecholamines and catechol-estrogens in the central nervous system and other organs. Dopamine is cleared mainly by COMT in the frontal cortex, and a reduced activity of this enzyme results in higher synaptic levels of dopamine, which affects prefrontal cortex cognitive response to certain drugs. A single nucleotide polymorphism of the COMT gene produces an amino acid change from valine to methionine (Val158Met) and reduces the enzyme activity by 3- to 4-fold.

Assay Interpretation

The most well studied COMT genetic variant (rs4680; 472G>A) is the one resulting in a valine to methionine change at codon 158. The variant allele called the Met allele is found in 30-47% of Caucasians, 23% of Africans, and 27-32% of Asians. The phenotype is defined by the presence of the reduced activity Met allele (A variant). The wild-type genotype (Val/Val; GG) predicts a high/normal COMT activity, the heterozygous genotype (Val/Met; GA) predicts an intermediate COMT activity, and the homozygous (Met/Met; AA) results in a low COMT activity.

The reference range for COMT metabolic status is COMT Val158Met GG (Val/Val) (wild-type), which is consistent with a high/normal COMT activity.

Clinical Implications

Several complex associations with the Val158Met variant as a risk factor for numerous diseases have been found, but seem to have limited predictive value. The response to some psychotropic medications seems to be dependent to some extent upon the COMT status. In general, the wild-type genotype result predicts a good response to methylphenidate and amphetamines in the treatment of attention deficit hyperactivity disorder. In the treatment of pain, patients homozygous for the Met allele require lower doses of morphine to achieve analgesia.

References

1: De Gregori et al. Genetic variability at COMT but not at OPRM1 and UGT2B7 loci modulates morphine analgesic response in acute postoperative pain. Eur J Clin Pharmacol. 2013 May 19. 2 : Hamidovic et al. Catechol-O-methyltransferase val158met genotype modulates sustained attention in both the drug-free state and in response to amphetamine. Psychiatr Genet. 2010 Jun;20(3):85-92. 3 : Blasi et al. Effect of catechol-O-methyltransferase val158met genotype on attentional control. J Neurosci. 2005 May 18;25(20):5038-45. 4 : Mattay et al. Catechol O-methyltransferase val158-met genotype and individual variation in the brain response to amphetamine. Proc Natl Acad Sci U S A. 2003 May 13;100(10):6186-91.

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CYP1A2 Monograph

Clinical Utility

The cytochrome P450 1A2 (CYP1A2) accounts for 13% of total CYP in the human liver, and is responsible for metabolizing 8-10% of commonly used drugs as well as natural compounds such as caffeine. A large inter-individual variability in the elimination of drugs that are metabolized by CYP1A2 has been observed, which has been ascribed to genetic variations and environmental factors. CYP1A2 activity is highly inducible (increased) by environmental factors including smoking (tobacco), some drugs, and several dietary compounds (cruciferous vegetables).

Assay Interpretation

More than 20 different alleles have been characterized for the CYP1A2 gene, and some have been shown to affect enzyme activity and its sensitivity towards inducers (inducibility). The CYP1A2*1F is the most studied allele and results in a rapid metabolizer phenotype in the presence of inducers, while CYP1A2*1K and *1C alleles result in enzymes that are less active and less sensitive to induction. The CYP1A2*1F allele is found in 25-50% of Caucasians, 30% of Asians, and 50% of Ethiopians. The genotype-phenotype relationship for CYP1A2 is not well established, and can be expressed in terms of metabolic capacity as well as sensitivity towards induction (inducibility). Individuals are predicted to have CYP1A2 normal, intermediate, or poor metabolic capacity, with high, possible, or low inducibility depending on their genotype.

The reference range for CYP1A2 metabolic status is CYP1A2 *1A/ *1A, which is consistent with a normal metabolizer that is possibly inducible.

Clinical Implications

CYP1A2 genotype can help identify patients with high or low sensitivity to inducing agents, especially those released during smoking. **The clinical relevance of this sensitivity becomes important in patients who are smokers or who quit smoking.** Patients with the highly inducible genotype CYP1A2*1F/*1F can experience loss of response to drug substrates while they are exposed to dietary or environmental inducers, and therefore may require higher doses.

The following drugs used in the management of pain and various psychiatric conditions are metabolized extensively by CYP1A2 and are sensitive to its function: clozapine (Clozaril), duloxetine (Cymbalta), olazapine (Zyprexa), and tizanidine (Zanaflex). CYP1A2 also metabolizes other important drugs such as melatonin, ondansetron (Zofran), pomalidomide (Pomalyst), ramelteon (Rozerem), ropivacaine (Naropin), and tasimelteon (Hetlioz).

CYP1A2 metabolism is highly sensitive to inhibition and induction, and the occurrence of drug-drug interactions can have profound effects on the pharmacokinetics, response, and safety profiles of many CYP1A2 drug substrates.

Inhibitors

Some known **strong** CYP1A2 inhibitors include: ciprofloxacin (Cipro), enoxacin (Penetrex), fluvoxamine (Luvox), and zafirlukast (Accolate).

Some known **moderate to weak** CYP1A2 inhibitors include: oral contraceptives, mexiletine (Mexitil), allopurinol (Zyloprim), peginterferon alfa-2a (Pegasys), norfloxacin (Norflox), ticlopidine (Ticlide), vemurafenib (Zelboraf), and zileuton (Zyflo).

Inducers

Known CYP1A2 inducers include: carbamazepine (Tegretol), montelukast (Singulair), rifampin (Rifadin), phenytoin (Dilantin), moricizine (Ethmozine), omeprazole (Prilosec), phenobarbital, and primidone (Mysoline).

Some dietary and environmental compounds found in cigarette smoke, cruciferous vegetables, and charcoal-grilled food can also increase CYP1A2 activity.

References

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CYP2B6 Monograph

Clinical Utility

The cytochrome P450 2B6 (CYP2B6) is involved in the metabolism of 4% of clinically important medications. This enzyme is highly polymorphic: to date, 37 different variants have been identified. The CYP2B6 assay identifies some common variants that are associated with variability in enzyme activity.

Assay Interpretation

CYP2B6 enzyme activity defines a normal or an abnormal (intermediate or poor) metabolizer status for a given individual. Several variant alleles have been identified and result in different CYP2B6 isoforms that functionally are fully active, partially active, inactive, or have increased activity. The CYP2B6*1 allele is considered wild-type and encodes a functionally active enzyme (normal). The alleles *6, *7, *9, *11, *16, *18, and *36 encode a decreased activity enzyme. The *22 alleles represents a gain-of-function allele. The functional impact of variants that define the CYP2B6 *4 and *5 alleles is drug dependent.

The most common functionally deficient allele is CYP2B6*6. It is found in 7-18%, 10-17%, 23%, and 33% of Caucasians, Asians, Mexican-Americans, and African-Americans, respectively. CYP2B6 *18 is found only in individuals of African descent, with a frequency of 4-7%.

The genotype-phenotype relationship is not well established, and there is a lack of consistency regarding the clinical impact of certain allelic variants. The following provisional genotype-to-phenotype assignment can be used: individuals with two fully active alleles are considered normal (extensive) metabolizers. Individuals with one fully active allele with either a partially active or an inactive allele are considered intermediate metabolizers. Individuals with two partially active alleles or two inactive alleles are considered poor metabolizers. Individuals carrying two increased function alleles or one active allele with a gain-of-function allele are classified as normal/rapid metabolizers.

The reference range for CYP2B6 metabolic status is CYP2B6 *1/ *1, which is consistent with a normal metabolizer.

Clinical Implications

CYP2B6 plays a role in the metabolism of the following drugs: artemisinin, bupropion (Wellbutrin), cyclophosphamide (Cytoxan), efavirenz (Sustiva), ketamine (Ketalar), meperidine (Demerol), methadone (Dolophine), nevirapine (Viramune), propofol (Diprivan), and selegiline (Eldepryl).

The impact of CYP2B*6 polymorphism on the pharmacokinetics and the clinical response have been studied in patients taking methadone, bupropion, and efavirenz. Limited evidence exists regarding the clinical impact of other polymorphisms.

Inhibitors or inducers othe CYP2B6 enzyme may modify its activity and change the patient’s metabolizer status. This can result in drug-drug interactions when a drug substrate is prescribed with known CYP2B6 inhibitors or inducers.

Inhibitors

Some known CYP2B6 inhibitors include: clopidogrel, darunavir, prasugrel, ticlopidine, voriconazole, ritonavir, and thiotepa.

Inducers

Some CYP2B6 inducers include: artemether, carbamazepine, dabrafenib, efavirenz, metamizole, nevirapine, phenobarbital, phenytoin, rifampin, ritonavir, and St. John’s wort.

References

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CYP2C19 Monograph

Clinical Utility

The cytochrome P450 2C19 (CYP2C19) is involved in the metabolism of 10% of clinically important medications. This enzyme is highly polymorphic: more than 30 different variant alleles have been identified. The CYP2C19 assay identifies some common variants that are associated with variability in CYP2C19 enzyme activity, which has important pharmacological and toxicological implications for antidepressants, benzodiazepines, antiplatelets, and proton-pump inhibitors.

Assay Interpretation

CYP2C19 enzyme activity defines a normal or abnormal (intermediate, poor, or rapid) metabolizer status for a given individual. Several variant alleles have been identified and result in different isoforms of the CYP2C19 enzyme that functionally are fully active, partially active, inactive, or with increased activity. The CYP2C19*1 allele is considered wild-type and encodes a functionally active enzyme (normal). The alleles *2, *3 *4, *5, *6, and *8 encode an inactive enzyme and are referred to as loss-of-function alleles. Individuals with a *17 allele have an increased CYP2C19 activity.

The genotype-phenotype relationship is established based on the allele's activity. Individuals with two fully functional alleles are considered normal (extensive) metabolizers. Individuals with one or two loss-of-function alleles are considered intermediate or poor metabolizers, respectively. Individuals with one or two increased function alleles are considered rapid or ultra-rapid metabolizers, respectively. Because of limited evidence, an individual with one increased function allele and one loss-of-function allele is provisionally classified as an intermediate metabolizer.

The reference range for CYP2C19 metabolic status is CYP2C19 *1/ *1, which is consistent with a normal metabolizer.

Clinical Implications

There is substantial evidence linking the CYP2C19 polymorphisms to variability in the pharmacological and safety profiles of the following therapies used in psychiatric conditions and pain management: amitriptyline (Elavil), sertraline (Zoloft), clobazam (Onfi), citalopram (Celexa), escitalopram (Lexapro), diazepam (Valium), imipramine (Tofranil), and carisoprodol (Soma). CYP2C19 plays a minor role in the elimination of methadone (Dolophine).

Cardiovascular medications that are metabolized by CYP2C19 include the prodrug clopidogrel (Plavix), propranolol (Inderal), and cilostazol (Pletal). Proton-pump inhibitors such as omeprazole (Prilosec), esomeprazole (Nexium), lansoprazole (Prevacid), dexlansoprazole (Dexilant), and pantoprazole (Protonix) are major substrates of CYP2C19.

Inhibitors or inducers of CYP2C19 enzyme may modify its activity and change the patient’s metabolizer status. This can result in drug-drug interactions when a drug substrate is prescribed with known CYP2C19 inhibitors or inducers.

Inhibitors

Some known CYP2C19 inhibitors include: fluconazole (Diflucan), fluvoxamine (Luvox), fluoxetine (Prozac), felbamate (Felbatol), ticlopidine (Ticlid), omeprazole (Prilosec), esomeprazole (Nexium), voriconazole (Vfend), armodafinil (Nuvigil), delavirdine (Rescriptor), modafinil (Provigil), oxcarbazepine (Trileptal), etravirine (Intelence), topiramate (Topamax), and moclobemide (Manerix).

Inducers

Some known CYP2C19 inducers include: artemether (Coartem), carbamazepine (Tegretol), efavirenz (Sustiva), enzalutamide (Xtandi), fosphenytoin (cerebyx), primidone (Mysoline), phenobarbital, phenytoin (Dilantin), rifampin (Rifadin), and St. John’s wort.

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CYP2C9 Monograph

Clinical Utility

The cytochrome P450 2C9 (CYP2C9) is involved in the metabolism of 15% of clinically important medications. This enzyme is highly polymorphic: to date, 30 variants have been identified. The CYP2C9 assay identifies some common variants that are associated with variability in CYP2C9 enzyme activity, which has important pharmacological and toxicological implications for anticonvulsants, anticoagulants, and certain antidiabetics.

Assay Interpretation

CYP2C9 enzyme activity defines a normal or abnormal (intermediate and poor) metabolizer status for a given individual. Several variant alleles have been identified and result in different CYP2C9 isoforms that functionally are fully active, partially active, or inactive. The CYP2C9*1 allele is considered wild-type and encodes a functionally active enzyme (normal). The alleles *2, *3, *4, *5, and *11 encode a partially active enzyme. The allele *6 is a null (inactive) allele corresponding to a whole gene deletion.

The genotype-phenotype relationship is established based on the allele's activity. Individuals with two fully active alleles are considered normal (extensive) metabolizers. Individuals with one fully active allele with either a partially active or an inactive allele are considered intermediate metabolizers. Individuals with two partially active alleles or with two inactive alleles are considered poor metabolizers.

The reference range for CYP2C9 metabolic status is CYP2C9 *1/*1, which is consistent with a normal metabolizer.

Clinical Implications

CYP2C9 plays a role in the metabolism of the following psychotropic drugs: fluoxetine (Prozac), phenytoin (Dilantin), and primidone (Mysoline). Several NSAIDs and Cox-2 inhibitors are substrates of CYP2C9, and patients with reduced CYP2C9 activity may have higher plasma levels of celecoxib (Celebrex), flurbiprofen (Ocufen), piroxicam (Feldene), or meloxicam (Mobic). CYP2C9 plays a minor role in the elimination of diclofenac (Voltaren), sulindac (Clinoril), and naproxen (Aleve).

Cardiovascular medications that are metabolized by CYP2C9 include warfarin (Coumadin), fluvastatin (Lescol), losartan (Cozaar), and irbesartan (Avapro).

Other important drugs metabolized by CYP2C9 include antidiabetics such as tolbutamide, glibeclamide (Micronase), glipizide (Glucotrol), and nateglinide (Starlix).

Inhibitors or inducers of the CYP2C9 enzyme may modify its activity and change the patient’s metabolizer status. This can result in drug-drug interactions when a drug substrate is prescribed with known CYP2C9 inhibitors or inducers.

Inhibitors

Some known CYP2C9 inhibitors include: amiodarone (Cordarone), 5-fluorouracil (Adrucil), chloramphenicol, cimetidine (Tagamet), danazol (Danocrine), disulfiram (Antabuse), fluconazole (Diflucan), fluoxetine (Prozac), fluvoxamine (Luvox), miconazole (Oravig), oxandrolone (Oxandrin), capecitabine (Xeloda), co -trimoxazole (Septra), delavirdine (Rescriptor), etravirine (Intelence), fluvastatin (Lescol), efavirenz (Sustiva), gemfibrozil (Lopid), lomitapide (Juxtapid), metronidazole (Flagyl), phenytoin (Dilantin), sulfamethoxazole (Bactrim), sulfinpyrazone (Anturane), tamoxifen (Nolvadex), toremifene (Fareston), tigecycline (Tygacil), voriconazole (Vfend), and zafirlukast (Accolate).

Inducers

Some known CYP2C9 inducers include: carbamazepine (Tegretol), rifampin (Rifadin, Rimactane), rifapentine (Priftin), St. John’s wort, enzalutamide (Xtandi), aprepitant (Emend), bosentan (Tracleer), dabrafenib (Tafinlar), phenobarbital, primidone (Mysoline), phenytoin (Dilantin), and ritonavir (Norvir).

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CYP2D6 Monograph

Clinical Utility

The cytochrome P450 2D6 (CYP2D6) is involved in the metabolism of 25% of clinically important medications. This enzyme is highly polymorphic: more than 100 different variants have been identified. The CYP2D6 assay identifies common variants that are associated with variability in CYP2D6 enzyme activity, which has important pharmacological and toxicological implications for antidepressants, antipsychotics, opioids, beta-blockers, and antiarrhythmics.

Assay Interpretation

CYP2D6 enzyme activity defines a normal or abnormal (intermediate, poor, or rapid) metabolizer status for a given individual. Commonly tested CYP2D6 variant alleles are classified into functional groups: Full or normal function (e.g., CYP2D6 *1 and *2), reduced function (e.g., CYP2D6*9, *10, *17, *29, and *41) and no function (e.g., CYP2D6 *3, *4, *5, *6, *7, *8, *12, and *14). Increased CYP2D6 activity is found in individuals carrying multiple copies of functional alleles. CYP2D6 is subject to gene duplications, and these are denoted “XN”, where N represents the number of CYP2D6 gene copies when available.

The genotype-phenotype relationship is established using a scoring system that assigns an activity value to every CYP2D6 allele, in order to assign a predicted phenotype. For a given genotype, the activity values of the constituent alleles are added together to calculate the CYP2D6 activity score. This activity score (AS) is then used to assign a predicted phenotype as follows: AS of 0 predicts a poor metabolizer, AS ranging between 1 and 2 predicts a normal (extensive) metabolizer, AS=0.5 predicts an intermediate metabolizer, and AS greater than 2 predicts a rapid (ultra-rapid) metabolizer. Fully functional alleles are assigned an activity value of 1, reduced function alleles have an activity value of 0.5, while non-functional alleles are assigned an activity value of 0.

The reference range for CYP2D6 metabolic status is a CYP2D6 *1/ *1 genotype, which is consistent with a normal metabolizer.

Clinical Implications

There is substantial evidence linking the CYP2D6 polymorphisms to variability in the pharmacological and safety profiles of the following psychotropics: desipramine (Norpramin), imipramine (Tofranil), amitriptyline (Elavil), nortriptyline (Pamelor), haloperidol (Haldol), trimipramine (Surmontil), venlafaxine (Effexor), doxepin (Silenor), aripiprazole (Abilify), atomoxetine (Strattera), duloxetine (Cymbalta), risperidone (Risperdal), clomipramine (Anafranil), and pimozide (Orap).

CYP2D6 polymorphisms have been shown to affect the pharmacological and safety profiles of the following analgesics: codeine, tramadol (Ultram), and hydrocodone (Vicodin). Codeine and tramadol are prodrugs that need to be activated by CYP2D6. Poor metabolizers are at high risk of therapy failure when given codeine or tramadol. On the other hand, rapid metabolizers may experience increased toxicity when given standard dosage of codeine or tramadol. Because CYP3A4 is also involved in the metabolism of oxycodone, patients with abnormal CYP2D6 activity may still experience adequate analgesia when taking this drug. CYP2D6 polymorphism has been shown to affect dihydrocodeine (Synalgos-DC) pharmacokinetics and can potentially alter the response to this drug.

Morphine, oxymorphone (Opana), hydromorphone (Dilaudid), butorphanol (Stadol), fentanyl (Duragesic), buprenorphine (Butrans), methadone (Dolophine), morphine (Avinza), and tapentadol (Nucynta) are not substrates of CYP2D6, and the patient’s response to these drugs is not expected to be affected by polymorphisms in this enzyme.

Several important cardiovascular medications are metabolized by CYP2D6, and include: metoprolol (Lopressor), carvedilol (Coreg), flecainide (Tambocor), and propafenone (Rythmol).

Inhibitors of the CYP2D6 enzyme may modify its activity and change the patient’s metabolizer status. This can result in drug-drug interactions when a drug substrate is prescribed with known CYP2D6 inhibitors. Although there are no known clinical inducers of CYP2D6, the pharmacokinetics of a drug substrate can be affected by inducers of other enzymes (such as CYP3A) that are involved in the metabolism of that drug.

Inhibitors

Some known **strong and moderate** CYP2D6 inhibitors include: abiraterone (Zytiga), bupropion (wellbutrin), cobicistat (Stribild), fluoxetine (Prozac), quinidine (Quinidex), paroxetine (Paxil), cinacalcet (Sensipar), duloxetine (Cymbalta), terbinafine (Lamisil), tipranavir/ritonavir (Aptivus), mirabegron (Myrbetriq), peginterferon alfa-2b (Sylatron) and ecstasy.

Some known **weak** CYP2D6 inhibitors include: amiodarone (Cordarone), celecoxib (Celebrex), clobazam (Onfi), desvenlafaxine (Pristiq), diltiazem (Cardiazem), diphenhydramine (Benadryl), escitalopram (Lexapro), febuxostat (Uloric), gefitinib (Iressa), hydralazine (Apresoline), hydroxychloroquine (Plaquenil), imatinib (Gleevec), methadone (Dolophine), perphenazine (Trilafon), propafenone (Rythmol), ranitidine (Zantac), ritonavir (Norvir), sertraline (Zoloft), telithromycin (Ketek), verapamil (Isoptin, Covera-HS), venlafaxine (Effexor), and Echinacea.

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CYP3A Monograph

Clinical Utility

The cytochrome P450 3A4 and 3A5 (CYP3A4 and CYP3A5) account for 40-80% of total CYP in human liver and intestine, respectively. Most importantly, CYP3A enzymes metabolize 50% of commonly used drugs. CYP3A4 and CYP3A5 enzymes have overlapping substrate specificity, and the contribution of CYP3A5 in the overall metabolism is smaller than the one for CYP3A4. The overall CYP3A metabolism status is expected to affect drugs that have a narrow therapeutic index.

Assay Interpretation

A limited number of variants identified within the CYP3A4 and CYP3A5 genes have been associated with significant alterations in enzyme activity and subsequent variability in therapeutic response. For CYP3A5, individuals with the less prevalent “normal metabolizer phenotype” may metabolize drugs faster than those with the more common “poor metabolizer phenotype”. This may result in increased toxicity or loss of efficacy.

The CYP3A4*1B variant is the most studied, and results in an enzyme with a moderately decreased activity. It occurs in 50% of African-Americans, 3-5% of Caucasians, and <1% of Asians. The CYP3A4*2, *3, *12, and *17 are also considered decreased activity alleles. Recently, the CYP3A4 *22 allele has been characterized as a decreased function allele that can be clinically relevant (associated with a decreased clearance of certain substrates). The genotype-phenotype relationship for CYP3A4 is not well established, and individuals are predicted to have a CYP3A4 normal or intermediate metabolic capacity.

The reference range for CYP3A4 metabolic status is CYP3A4 *1/ *1, which is consistent with a normal metabolizer.

The CYP3A5*3 variant results in an enzyme with no activity, and is the most common variant in the general population. The CYP3A5*3B and *6 are also null alleles resulting in no enzyme activity. The functional effects of the CYP3A5 alleles *2, *8, and *9 are not well established. The CYP3A5 *1 allele produces an active enzyme, and is found in 5% of Caucasians, 20% of Asians, and 15-50% of Africans. Individuals with two CYP3A5 inactive alleles are classified as poor metabolizers. Individuals carrying at least one copy of a CYP3A5 active allele are normal or intermediate metabolizers. **CYP3A5 poor metabolizers represent 50% of Asians and 90% of Caucasians**.

The reference range for CYP3A5 metabolic status is CYP3A5 *1/ *1, which is consistent with a normal metabolizer. This genotype is the least prevalent in Caucasians and Asians.

Clinical Implications

CYP3A4 and CYP3A5 genotypes can help identify patients with high or low overall CYP3A activity. Although these two enzymes metabolize many drugs, the response of only a few (such as narrow therapeutic index drugs) is expected to change significantly by genetic polymorphisms. Fentanyl (Duragesic) is a narrow therapeutic drug that is mainly metabolized by CYP3A. There is limited evidence suggesting that the response to this drug is altered in individuals with abnormal CYP3A activity.

The following drugs used in pain management and various psychiatric conditions are metabolized extensively by CYP3A: fentanyl (Duragesic), oxycodone (Oxycontin), buprenorphine (Suboxone), carbamazepine (Tegretol), quetiapine (Seroquel), ziprasidone (Geodon), alprazolam (Xanax), midazolam (Versed), triazolam (Halcion), nefazodone (Serzone), trazodone (Oleptro), vilazodone (Vibryd), zaleplon (Sonata), and zolpidem (Ambien). CYP3A contributes to a small extent in the elimination of methadone (Dolophine).

Within the major therapeutic classes used in cardiovascular conditions, the following drugs are substantially metabolized by CYP3A: atorvastatin (Lipitor), simvastatin (Zocor), lovastatin (Mevacor), nifedipine (Procardia), verapamil (Verelan), nicardipine (Cardene), felodipine (Plendil), nisoldipine (Sular), clopidogrel (Plavix), prasugrel (Effient), ticagrelor (Brilinta), cilostazol (Pletal), amiodarone (Cordarone), quinidine (Qualaquin), disopyramide (Norpace), losartan (Cozaar), rivaroxaban (Xarelto), and apixaban (Eliquis).

CYP3A metabolism is highly sensitive to inhibition and induction when a patient is taking multiple drugs. In this case, occurrence of drug-drug interactions can have profound effects on the pharmacokinetics, as well as the responses and safety profiles of many CYP3A drug substrates.

Inhibitors

Some known **strong** CYP3A inhibitors include: ketoconazole (Nizoral), itraconazole (Sporanox), posaconazole (Noxafil), voriconazole (Vfend), clarithromycin (Biaxin), telithromycin (Ketek), troleandomycin (TAO), conivaptan (Vaprisol), nefazodone (Serzone), ritonavir (Norvir), saquinavir (Invirase), lopinavir, (Kaletra), nelfinavir (viracept), tipranavir (aptivus), boceprevir (Victrelis), telaprevir (Incivek), and grapefruit juice (high dose), idelalisib (Zydelig).

Some known **moderate** CYP3A inhibitors include: amprenavir (agenerase), aprepitant (Emend), atazanavir (Reyataz), darunavir (Prezista), fosamprenavir (Lexiva), erythromycin (Eryc), ciprofloxacin (Cipro), diltiazem (cardiazem), verapamil (Isoptine, Covera-HS), fluconazole (Diflucan), imatinib (Gleevec), quinupristin/dalfopristin (Synercid), and grapefruit juice (low dose).

Some known **weak** CYP3A inhibitors include: amiodarone (Cordarone), amlodipine (Norvasc), atorvastatin (Lipitor), bicalutamide (Casodex), cilostazol (Pletal), fluvoxamine (Luvox), fluoxetine (Prozac), sertraline, cimetidine, ranitinide (Zantac), ranolazine (Ranexa), and ticagrelor (Brilinta).

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Inducers

Some known **strong** CYP3A inducers include: carbamazepine (Tegretol), enzalutamide (Xtandi), fosphenytoin (Cerebyx), phenytoin (Dilantin), phenobarbital, primidone (Mysoline), rifampin (Rifadin), rifapentine (Priftin), and St. John's wort.

Some known **moderate** CYP3A inducers include: artemether (Coartem), bosentan (Tracleer), dabrafenib (Tafinlar), efavirenz (Sustiva), etravirine (Intelence), modafinil (Provigil), nafcillin (Unipen), rifabutin (Mycobutin), and nevirapine (Viramune).

Some known **weak** CYP3A inducers include: fosamprenavir (Lexiva), aprepitant (Emend), clobazam (Onfi), Echinacea, pioglitazone (Actos), dexamethasone (Decadron), oxcarbazepine (Trileptal), methylprednisolone (Medrol), and rufinamide (Banzel).

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OPRM1 Monograph

Clinical Utility

"Mu" opioid receptors are the most important site of action of opioid drugs. Single polymorphisms in the human mu-opioid receptor (OPRM1) have been investigated for their role in human nociception, opiate efficacy, and addiction.

Assay Interpretation

The variant mostly studied is a single substitution at position 118, from an adenine to a guanine (A118G). This variant reduces the OPRM1 receptor signaling efficiency induced by exogenous opioids. Reduced OPRM1 mRNA expression levels were observed in carriers of the G variant. The variant allele (G) is present in 7-15% of Caucasians, 1.5% of African-Americans, and up to 48.5% of Asians. The major interest of this particular SNP is due to its pharmacological and physiological consequences; however the exact mechanism by which the altered receptor influences opioid analgesia is still unresolved. The presence of the G allele seems to reduce the effect of exogenous agonists but increase the effects of exogenous antagonists.

The reference range for the A118G SNP is A118G AA, and is associated with a normal OPRM1 receptor signaling efficiency.

Clinical Implications

The presence of the G allele (A118G) seems to be associated with pain sensitivity as well as opioid dosage requirements. But only weak evidence of these associations is available to date. It is suggested that patients carrying the G allele report higher intensity pain. In terms of drug response, patients with the G allele have a favorable response to the anti-addictive drug naltrexone. Several studies conducted in post-surgical settings or in cancer analgesia showed that G allele carriers require slightly higher doses of morphine or fentanyl. This association still needs to be confirmed in larger studies and does not hold in other situations such as labor pain.

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SLCO1B1 Monograph

Clinical Utility

The SLCO1B1 gene encodes a liver-specific transporter involved in the removal of endogenous compounds (bile acids, bilirubin) and drugs such as statins from the blood to the liver. Some variants of the SLCO1B1 gene result in a low-functioning protein, which impairs statin clearance, and may lead to an increased risk of muscle pain, tenderness, or weakness, called myopathy. Certain medications can potently inhibit SLCO1B1, causing clinically significant drug interactions.

Assay Interpretation

There are several variants of the SLCO1B1 that define over 15 alleles. One relatively common variant 521T>C results in a decreased SLCO1B1 function, which affects the transport of drug substrates such as statins. This variant is present alone on the *5 allele and in presence with another variant (388A>G) on the *15 allele. Both alleles are low-activity alleles (reduced hepatic uptake), and have a combined frequency of 15-20% in Caucasians, 10-15% in Asians, and 2% in sub-Saharan Africans and African-Americans.

The reference range for the 521T>C mutation of SLCO1B1 is 521 TT. This is consistent with a normal SLCO1B1 transport function.

Clinical Implications

All statins are substrates of SLCO1B1, but the effects of SLCO1B1 genetic polymorphism differ between individual statins. The effect is the largest on simvastatin, and individuals with the 521T>C variant have increased levels of the active simvastatin form. The variant is strongly associated with simvastatin-induced myopathy (with or without CK elevation), especially with high-dose simvastatin therapy. More than 60% of the myopathy cases could be attributed to its presence. The clinical spectrum of statin-induced myopathy ranges from a mild and common myalgia to a life-threatening and rare rhabdomyolysis. Other known risk factors for statin-induced myopathy include a high-statin dose, interacting drugs that raise statin levels, age, hypothyroidism, and certain inherited muscle disorders.

At therapeutic doses, the apparent sensitivity levels of the five statins to the presence of the 521T>C variant are simvastatin>pitavastatin>atorvastatin>pravastatin>rosuvastatin. Carriers of the 521 T>C variant should avoid high-dose simvastatin therapy. These patients can take other statins, such as atorvastatin, pitavastatin, rosuvastatin, or pravastatin, but at reduced doses. Fluvastatin is not affected by the 521 T>C variant and could therefore be considered a suitable alternative.

Other drugs that are substrates of SLCO1B1 transporter include enalapril, olmesartan, valsartan, atrasentan, repaglinide, nateglinide, methotrexate, and bosentan. However, there is insufficient evidence documenting the impact of the 521 T>C variant on the systemic exposure and safety profile of these drugs.

Inhibitors

Inhibitors of SLCO1B1 transporter may alter its activity and result in increased levels of drug substrates. These include gemfibrozil, cyclosporine, clarithromycin, protease inhibitors, simeprevir, teriflunomide, boceprevir, telaprevir, and eltrombopag.

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VKORC1 Monograph

Clinical Utility

The Vitamin K epoxide reductase complex, subunit 1 (VKORC1) is the target of anticoagulants. This enzyme is the rate-limiting step in the vitamin K cycle. Mutations in the VKORC1 gene results in variable expression levels of the VKORC1 enzyme and altered sensitivities towards anticoagulants. VKORC1 genotype defines three levels of clinical phenotype: high, moderate, and low sensitivity phenotypes towards warfarin (a widely used anticoagulant). Therefore, VKORC1 variant testing is usually used in conjunction with CYP2C9 variant testing to optimize warfarin dosing and minimize the risks of bleeding or thrombotic complications.

Assay Interpretation

The clinically relevant variants in the VKORC1 gene are in strong linkage disequilibrium, meaning that some allele combinations occur more frequently than others. These combinations are referred to as haplotypes. The eight variants analyzed by the VKORC1 assay are used to define three haplotypes that are associated with different warfarin sensitivities, as shown in the following table.

Clinical Implications

The -1639G>A is the common variant seen in the Caucasian populations, and is believed to be the causative agent for the low-dose warfarin requirement phenotype. The G>A mutation results in a decreased expression of VKORC1. The 358C>T (found in 21% of African-Americans) and 3730G>A variants are associated with high warfarin dose requirements.

When CYP2C9 and VKORC1 genotypes are combined with other demographic (age, weight, height), clinical (disease, co-medications), and environmental (smoking) factors, they account for 50% of warfarin dose variation between individuals.

The FDA changed the warfarin label to help clinicians offer genotype-guided warfarin therapy for their patients.

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