RESOLVE MDx

PATIENT INFORMATION		SPECIMEN DETAILS		PROVIDER INFORMATION
NAME:	**Test Patient**	**SPECIMEN TYPE:**		Vanilla Life Tech Test Provider
ACC #:	NA02016	**COLLECTION DATE:**	1/1/1900	
DOB:	1/1/1900	**RECEIVED DATE:**	1/1/1900	
SEX:		**REPORT DATE:**	4/11/2018	

Clinical Health Panel

Current Patient Medications

Prandin, Effexor, Codeine, Zocor, Clopidogrel, Citalopram

Clopidogrel | PLAVIX

Reduced Response to Clopidogrel (CYP2C19: Intermediate Metabolizer)

ACTIONABLE

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

Codeine | CODEINE; FIORICET WITH CODEINE

Non-Response to Codeine (CYP2D6: Poor Metabolizer)

ACTIONABLE

Greatly reduced morphine levels are expected, and the patient may not experience adequate pain relief when taking codeine. Avoid prescribing codeine, and consider alternative opioids other than tramadol, 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.

Effexor | VENLAFAXINE

Significantly Increased Sensitivity to Venlafaxine (CYP2D6: Poor Metabolizer)

ACTIONABLE

The patient has an increased risk of side effects when taking standard doses of venlafaxine. Consider an alternative drug, OR prescribe venlafaxine, be extra alert of adverse events, and adjust dosage in response to clinical response and tolerability. Monitor O-desmethylvenlafaxine plasma concentrations.

Zocor | SIMVASTATIN

High Myopathy Risk (SLCO1B1: Poor Function)

ACTIONABLE

Simvastatin plasma concentrations are expected to be elevated. **Consider avoiding simvastatin** and prescribe an alternative statin or another hypolipidemic drug, or consider prescribing simvastatin at a lower starting dose (20 mg/day). Routine creatine kinase (CK) monitoring is also advised. **The FDA recommends against the 80 mg daily dose.** Although the association between the SLCO1B1 521C>T variant and myopathy risk is not clearly established for other statins such as atorvastatin, pitavastatin, rosuvastatin, and pravastatin, caution is advised if high doses of these statins are used in this patient. Fluvastatin plasma levels are not affected by the SLCO1B1 521C>T variant.

Citalopram | CELEXA

Reduced Response to Citalopram (HTR2A: Homozygous for G allele (rs7997012))

INFORMATIVE

The patient is homozygous for G allele in HTR2A variant rs7997012. Preliminary studies report that this genotype may be associated with an unfavorable response to citalopram.

Prandin | REPAGLINIDE

Possible Sensitivity to Repaglinide (SLCO1B1: Poor Function)

INFORMATIVE

The patient carries two copies of the SLCO1B1 rs4149056 C allele, which is associated with reduced transporter function. Patients homozygous for the SLCO1B1 rs4149056 C allele are probably more susceptible to the blood glucose-lowering effect of repaglinide than those with other genotypes. Based on preliminary findings, the optimal starting dose of repaglinide may be lower in these patients. Selecting a lower starting dose may reduce the time needed to reach the correct maintenance dose, potentially with a smaller risk of hypoglycaemia. Repaglinide dose should be adjusted according to the actual blood glucose-lowering response.

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A medication has potentially reduced efficacy, increased toxicity or the patient has an increased risk for the indicated condition.	**ACTIONABLE**	Recommendations based upon publications by international pharmacogenetic expert groups, consortia or regulatory bodies (CPIC, DPWG, FDA, EMA). Recommendations are suitable for implementation in a clinical setting. Guidelines may change as knowledge arises.
Guidelines exist for adjusting dosage, increased vigilance or the patient has a moderate risk for the indicated condition.		
The medication can be prescribed according to standard regimens or the patient's risk for the indicated condition is not increased.	**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.

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Risk Management

⚠ Antipsychotic-Induced Tardive Dyskinesia

Increased Risk of Antipsychotic-Induced Tardive Dyskinesia

The patient does not carry the Taq1A variant (homozygous for the A2 allele).

The genotype results predict that the patient has normal dopamine receptor DRD2 density and hypodopaminergic functioning. The patient has increased risk for tardive dyskinesia when treated with antipsychotics.

Closely monitor the patient for signs of tardive dyskinesia.

✓ Antipsychotic-Induced Hyperprolactinemia

Normal Risk of Antipsychotic-Induced Hyperprolactinemia

The patient does not carry the Taq1A variant (homozygous for the A2 allele).

The genotype results predict that the patient has normal dopamine receptor DRD2 density and hypodopaminergic functioning. The patient has normal risk of hyperprolactinemia when treated with antipsychotics.

Monitor the patients closely for any signs of hyperprolactinemia.

✓ Antipsychotic-Induced Weight Gain

Low Risk of Antipsychotic-Induced Weight Gain

The patient does not carry the Taq1A variant (homozygous for the A2 allele).

The genotype results predict that the patient has normal dopamine receptor DRD2 density and hypodopaminergic functioning. The patient has a normal risk for weight gain when treated with antipsychotics.

Monitor the patient closely for signs weight gain.

✓ Type III Hyperlipoproteinemia

Not Associated with Type III Hyperlipoproteinemia

The patient is positive for the APOE c.388 T>C (Cys130Arg) mutation and negative for the APOE c.526 C>T (Arg176Cys) mutation. The patient's genotype is ε3/ε4 (frequency: 15-28%).

The APOE E3 is the normal APOE. The APOE E4 confers a limitation of HDL binding to its receptor, and is associated with increased plasma cholesterol, LDL, and triglycerides. Individuals that are heterozygous for this allele may have higher total cholesterol levels and elevated LDL cholesterol levels. The APOE ε3/ε4 genotype is associated with an increased risk for developing atherosclerosis and cardiovascular disease.

Consider dietary adjustments (very low fat diet) and lipid-lowering therapy based on lipid profiles and other risk factors.

✓ Hyperhomocysteinemia - Depression

No Increased Risk of Hyperhomocysteinemia

The patient does not carry the MTHFR C677T variant. MTHFR enzyme activity is normal.

Patients diagnosed with depression often have low folate levels and homocysteine is a highly sensitive marker of folate status. Functional folate deficiency is indicated by elevated homocysteine. With a normal MTHFR activity, this patient can process folate normally and is unlikely to have elevated plasma levels of homocysteine.

Patients diagnosed with depression: as lower folate levels are associated with poorer antidepressant response, and baseline levels of folate within the normal range predict antidepressant response, testing for homocysteine levels and serum folate levels may be informative for this patient before prescribing methylfolate as an antidepressant-augmenting agent.

✓ Thrombophilia

No Increased Risk of Thrombosis

The patient does not carry the Factor V Leiden G1691A mutation or Factor II G20210A mutation (wild-type).

The patient's risk of thrombosis is not increased (average risk of clotting is about 1 in 1000 for anyone in a year). However, because this test cannot find all of the inherited reasons for abnormal clotting, other factors may affect this risk assessment.

Unless other genetic and/or circumstantial risk factors are present (e.g., smoking or obesity...), estrogen-containing contraceptive and hormone replacement therapy can be used by the patient.

✓ Hyperhomocysteinemia - Thrombosis

No Increased Risk of Hyperhomocysteinemia

The patient carries one MTHFR A1298C mutation (heterozygous). MTHFR enzyme activity is reduced (80% of normal activity).

The patient's slightly reduced MTHFR activity is not a risk factor for hyperhomocysteinemia. Unless other risk factors are present, the patient is not expected to have an increased risk for venous thromboembolism (VTE).

The patient's MTHFR activity is slightly reduced.

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Potentially Impacted Medications

CATEGORY	DRUG CLASS	STANDARD PRECAUTIONS	USE WITH CAUTION	CONSIDER ALTERNATIVES
Anticancer Agents	**Antifolates**	Methotrexate (Trexall)		
Cardiovascular	**Angiotensin II Receptor Antagonists**	Azilsartan (Edarbi, Edarbyclor) Candesartan (Atacand) Eprosartan (Teveten) Irbesartan (Avapro) Losartan (Cozaar, Hyzaar) Olmesartan (Benicar) Telmisartan (Micardis) Valsartan (Diovan, Entresto)		
	Antianginal Agents		Ranolazine (Ranexa)	
	Antiarrhythmics		Flecainide (Tambocor) Mexiletine (Mexitil) Propafenone (Rythmol)	
	Anticoagulants	Apixaban (Eliquis) Betrixaban (Bevyxxa) Dabigatran Etexilate (Pradaxa) Edoxaban (Savaysa) Fondaparinux (Arixtra) Rivaroxaban (Xarelto)	Warfarin (Coumadin)	
	Antiplatelets	Prasugrel (Effient) Ticagrelor (Brilinta) Vorapaxar (Zontivity)		Clopidogrel (Plavix)
	Beta Blockers	Atenolol (Tenormin) Bisoprolol (Zebeta) Labetalol (Normodyne, Trandate) Nebivolol (Bystolic) Propranolol (Inderal)	Carvedilol (Coreg) Timolol (Timoptic)	Metoprolol (Lopressor)
	Diuretics	Torsemide (Demadex)		
	Statins	Fluvastatin (Lescol)	Atorvastatin (Lipitor) Lovastatin (Mevacor, Altoprev, Advicor) Pitavastatin (Livalo) Pravastatin (Pravachol) Rosuvastatin (Crestor)	Simvastatin (Zocor)
Diabetes	**Meglitinides**	Nateglinide (Starlix)	Repaglinide (Prandin, Prandimet)	
	Sulfonylureas	Chlorpropamide (Diabenese) Glimepiride (Amaryl) Glipizide (Glucotrol) Glyburide (Micronase) Tolbutamide (Orinase)		

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Gastrointestinal	**Antiemetics**	Aprepitant (Emend-oral) Dolasetron (Anzemet) Dronabinol (Marinol) Fosaprepitant (Emend-i.v) Granisetron (Sancuso, Sustol) Netupitant-Palonosetron (Akynzeo) Ondansetron (Zofran, Zuplenz) Palonosetron (Aloxi) Rolapitant (Varubi)	Metoclopramide (Reglan)	
	Proton Pump Inhibitors	Dexlansoprazole (Dexilant, Kapidex) Esomeprazole (Nexium) Lansoprazole (Prevacid) Omeprazole (Prilosec) Pantoprazole (Protonix) Rabeprazole (Aciphex)		
Infections	**Antifungals**	Amphotericin B (AmBisome, Abelcet) Anidulafungin (Eraxis) Caspofungin (Cancidas) Fluconazole (Diflucan) Isavuconazonium (Cresemba) Itraconazole (Sporanox) Micafungin (Mycamine) Posaconazole (Noxafil) Voriconazole (Vfend)		
	Anti-HIV Agents	Dolutegravir (Tivicay, Triumeq) Raltegravir (Isentress, Dutrebis)		
	Antimalarials	Proguanil (Malarone)		

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Pain	Fibromyalgia Agents	Milnacipran (Savella)		
	Muscle Relaxants	Carisoprodol (Soma) Cyclobenzaprine (Flexeril, Amrix) Metaxalone (Skelaxin) Methocarbamol (Robaxin)	Tizanidine (Zanaflex)	
	NSAIDs	Celecoxib (Celebrex) Diclofenac (Voltaren) Flurbiprofen (Ansaid) Ibuprofen (Advil, Motrin) Indomethacin (Indocin) Ketoprofen (Orudis) Ketorolac (Toradol) Meloxicam (Mobic) Nabumetone (Relafen) Naproxen (Aleve) Piroxicam (Feldene) Sulindac (Clinoril)		
	Opioids	Alfentanil (Alfenta) Buprenorphine (Butrans, Buprenex) Dihydrocodeine (Synalgos-DC) Fentanyl (Actiq) Hydromorphone (Dilaudid, Exalgo) Levorphanol (Levo Dromoran) Meperidine (Demerol) Methadone (Dolophine) Morphine (MS Contin) Oxymorphone (Opana, Numorphan) Sufentanil (Sufenta) Tapentadol (Nucynta)	Hydrocodone (Vicodin) Oxycodone (Percocet, Oxycontin)	Codeine (Codeine; Fioricet with Codeine) Tramadol (Ultram)
	Antiaddictives	Bupropion (Wellbutrin, Zyban, Aplenzin, Contrave)	Naltrexone (Vivitrol, Contrave)	
	Anti-ADHD Agents	Clonidine (Kapvay) Guanfacine (Intuniv)	Amphetamine (Adderall, Evekeo) Atomoxetine (Strattera) Dexmethylphenidate (Focalin) Dextroamphetamine (Dexedrine) Lisdexamfetamine (Vyvanse) Methylphenidate (Ritalin, Aptensio XR, Concerta, Metadate ER, Quillivant ER)	

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Psychotropic	Anticonvulsants	Brivaracetam (Briviact) Carbamazepine (Tegretol, Carbatrol, Epitol) Eslicarbazepine (Aptiom) Ethosuximide (Zarontin) Ezogabine (Potiga) Felbamate (Felbatol) Fosphenytoin (Cerebyx) Gabapentin (Neurontin) Lacosamide (Vimpat) Lamotrigine (Lamictal) Levetiracetam (Keppra) Oxcarbazepine (Trileptal, Oxtellar XR) Perampanel (Fycompa) Phenytoin (Dilantin) Pregabalin (Lyrica) Rufinamide (Banzel) Tiagabine (Gabitril) Topiramate (Topamax) Valproic Acid (Depakote, Depakene) Vigabatrin (Sabril)	Phenobarbital (Luminal) Primidone (Mysoline) Zonisamide (Zonegran)	
	Antidementia Agents	Memantine (Namenda)	Donepezil (Aricept) Galantamine (Razadyne)	
	Antidepressants	Desvenlafaxine (Pristiq) Escitalopram (Lexapro) Fluoxetine (Prozac, Sarafem) Levomilnacipran (Fetzima) Mirtazapine (Remeron) Sertraline (Zoloft) Trazodone (Oleptro) Vilazodone (Viibryd)	Amoxapine (Amoxapine) Citalopram (Celexa) Duloxetine (Cymbalta) Fluvoxamine (Luvox) Maprotiline (Ludiomil) Nefazodone (Serzone) Vortioxetine (Trintellix)	Amitriptyline (Elavil) Clomipramine (Anafranil) Desipramine (Norpramin) Doxepin (Silenor) Imipramine (Tofranil) Nortriptyline (Pamelor) Paroxetine (Paxil, Brisdelle) Protriptyline (Vivactil) Trimipramine (Surmontil) Venlafaxine (Effexor)
	Antipsychotics	Asenapine (Saphris) Cariprazine (Vraylar) Loxapine (Loxitane, Adasuve) Lurasidone (Latuda) Paliperidone (Invega) Pimavanserin (Nuplazid) Quetiapine (Seroquel) Thiothixene (Navane) Trifluoperazine (Stelazine) Ziprasidone (Geodon)	Aripiprazole (Abilify, Aristada) Brexpiprazole (Rexulti) Chlorpromazine (Thorazine) Clozapine (Clozaril) Fluphenazine (Prolixin) Iloperidone (Fanapt) Olanzapine (Zyprexa) Perphenazine (Trilafon) Pimozide (Orap)	Haloperidol (Haldol) Risperidone (Risperdal) Thioridazine (Mellaril)
	Benzodiazepines	Alprazolam (Xanax) Clonazepam (Klonopin) Diazepam (Valium)	Clobazam (Onfi)	
	Other Neurological Agents	Flibanserin (Addyi)	Deutetrabenazine (Austedo) Dextromethorphan / Quinidine (Nuedexta) Tetrabenazine (Xenazine) Valbenazine (Ingrezza)	

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CATEGORY	DRUG CLASS	STANDARD PRECAUTIONS	USE WITH CAUTION	CONSIDER ALTERNATIVES
Rheumatology	**Anti-Hyperuricemics and Anti-Gout Agents**	Colchicine (Mitigare) Febuxostat (Uloric) Lesinurad (Zurampic)		
	Immunomodulators	Apremilast (Otezla) Tofacitinib (Xeljanz)	Leflunomide (Arava)	
Transplantation	**Immunosuppressants**		Tacrolimus (Prograf)	
Urologicals	**5-Alpha Reductase Inhibitors for Benign Prostatic Hyperplasia**	Dutasteride (Avodart) Finasteride (Proscar)		
	Alpha-Blockers for Benign Prostatic Hyperplasia	Alfuzosin (UroXatral) Doxazosin (Cardura) Silodosin (Rapaflo) Terazosin (Hytrin)	Tamsulosin (Flomax)	
	Antispasmodics for Overactive Bladder	Fesoterodine (Toviaz) Mirabegron (Myrbetriq) Oxybutynin (Ditropan) Solifenacin (Vesicare) Trospium (Sanctura)	Darifenacin (Enablex) Tolterodine (Detrol)	
	Phosphodiesterase Inhibitors for Erectile Dysfunction	Avanafil (Stendra) Sildenafil (Viagra) Tadalafil (Cialis) Vardenafil (Levitra)		

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Dosing Guidance

Amitriptyline
Elavil

Increased Sensitivity to Amitriptyline (CYP2D6: Poor Metabolizer) — **ACTIONABLE**

Select an alternative drug, or consider prescribing amitriptyline at a reduced dose (50% reduction) with monitoring of plasma concentrations of amitriptyline and nortriptyline.

Clomipramine
Anafranil

Increased Sensitivity to Clomipramine (CYP2D6: Poor Metabolizer) — **ACTIONABLE**

Consider an alternative drug, or prescribe clomipramine at 50% of the recommended standard starting dose. Monitor plasma concentrations of clomipramine and desmethylclomipramine, and titrate accordingly until a favorable response is achieved.

Clopidogrel
Plavix

Reduced Response to Clopidogrel (CYP2C19: Intermediate Metabolizer) — **ACTIONABLE**

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

Codeine
Codeine; Fioricet with Codeine

Non-Response to Codeine (CYP2D6: Poor Metabolizer) — **ACTIONABLE**

Greatly reduced morphine levels are expected, and the patient may not experience adequate pain relief when taking codeine. Avoid prescribing codeine, and consider alternative opioids other than tramadol, 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

Increased Sensitivity to Desipramine (CYP2D6: Poor Metabolizer) — **ACTIONABLE**

Consider an alternative drug, or prescribe desipramine at 50% of recommended standard starting dose. Monitor plasma concentrations of desipramine and metabolites and titrate accordingly until a favorable response is achieved.

Doxepin
Silenor

Increased Sensitivity to Doxepin (CYP2D6: Poor Metabolizer) — **ACTIONABLE**

Consider an alternative drug or reduce doxepin starting dose by 50%. Adjust maintenance dose according to nordoxepin plasma concentrations.

Haloperidol
Haldol

Increased Sensitivity to Haloperidol (CYP2D6: Poor Metabolizer) — **ACTIONABLE**

Haloperidol is metabolized by CYP2D6, CYP3A4, and other enzymes. **Decreased CYP2D6 activity results in higher haloperidol concentrations, potentially leading to more adverse events.** Consider an alternative drug, or prescribe haloperidol at 50% of the usual starting dose, then adjust dosage to achieve a favorable clinical response.

Imipramine
Tofranil

Increased Sensitivity to Imipramine (CYP2D6: Poor Metabolizer) — **ACTIONABLE**

Consider an alternative drug, or consider a 50% reduction of the imipramine recommended starting dose, then titrate in response to imipramine and desipramine plasma concentrations.

Metoprolol
Lopressor

Significantly Increased Sensitivity to Metoprolol (CYP2D6: Poor Metabolizer) — **ACTIONABLE**

Based on the genotype result, this patient is at risk of excessive beta-blockade when taking metoprolol at standard dosage. Heart Failure: Consider alternative beta-blockers such as bisoprolol or carvedilol, or prescribe metoprolol at a lower dose. When compared to a normal metabolizer, a poor metabolizer may require a 75% dose reduction. Other indications: Consider alternative beta-blockers such as bisoprolol or atenolol, or prescribe metoprolol at a lower dose. When compared to a normal metabolizer, a poor metabolizer may require a 75% dose reduction. If metoprolol is prescribed, be alert to adverse events (e.g., bradycardia or cold extremities).

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Nortriptyline
Pamelor

Increased Sensitivity to Nortriptyline (CYP2D6: Poor Metabolizer) — **ACTIONABLE**

Select an alternative drug, or consider prescribing nortriptyline at a reduced dose (50% reduction) with monitoring of plasma concentrations of nortriptyline and metabolites.

Paroxetine
Paxil, Brisdelle

Increased Sensitivity to Paroxetine (CYP2D6: Poor Metabolizer) — **INFORMATIVE**

At standard label-recommended dosage, paroxetine levels are expected to be high, and adverse events may occur. Consider an alternative medication. If paroxetine is warranted, consider a 50% decrease of the initial dose and titrate based on the clinical response and tolerability. Some studies show that compared to normal metabolizers, poor metabolizers may experience more sexual dysfunction.

Protriptyline
Vivactil

Increased Sensitivity to Protriptyline (CYP2D6: Poor Metabolizer) — **INFORMATIVE**

Consider alternative or prescribe protriptyline at 50% of recommended standard starting dose. Monitor plasma concentrations of protriptyline and metabolites and titrate accordingly until a favorable response is achieved.

Risperidone
Risperdal

Significantly Increased Sensitivity to Risperidone (CYP2D6: Poor Metabolizer) — **ACTIONABLE**

Consider an alternative drug, OR prescribe risperidone at a reduced dose, be extra alert of adverse events, and adjust dosage in response to clinical response and tolerability.

Simvastatin
Zocor

High Myopathy Risk (SLCO1B1: Poor Function) — **ACTIONABLE**

Simvastatin plasma concentrations are expected to be elevated. **Consider avoiding simvastatin** and prescribe an alternative statin or another hypolipidemic drug, or consider prescribing simvastatin at a lower starting dose (20 mg/day). Routine creatine kinase (CK) monitoring is also advised. **The FDA recommends against the 80 mg daily dose.** Although the association between the SLCO1B1 521C>T variant and myopathy risk is not clearly established for other statins such as atorvastatin, pitavastatin, rosuvastatin, and pravastatin, caution is advised if high doses of these statins are used in this patient. Fluvastatin plasma levels are not affected by the SLCO1B1 521C>T variant.

Thioridazine
Mellaril

Increased Sensitivity to Thioridazine (CYP2D6: Poor Metabolizer) — **ACTIONABLE**

Reduced cytochrome CYP2D6 activity results in elevated plasma levels of thioridazine, would be expected to augment the prolongation of the QTc interval associated with thioridazine, and may increase the risk of serious, potentially fatal, cardiac arrhythmias, such as Torsades de pointes-type arrhythmias. Such an increased risk may result also from the additive effect of coadministering thioridazine with other agents that prolong the QTc interval. Therefore, thioridazine is contraindicated in patients with reduced levels of CYP2D6 activity.

Tramadol
Ultram

Non-Response to Tramadol (CYP2D6: Poor Metabolizer) — **ACTIONABLE**

The patient will not experience adequate pain relief when taking tramadol. Avoid prescribing tramadol, and 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

Increased Sensitivity to Trimipramine (CYP2D6: Poor Metabolizer) — **ACTIONABLE**

Consider an alternative drug, or consider a 50% reduction of the trimipramine recommended starting dose, then titrate in response to trimipramine plasma concentrations.

Venlafaxine
Effexor

Significantly Increased Sensitivity to Venlafaxine (CYP2D6: Poor Metabolizer) — **ACTIONABLE**

The patient has an increased risk of side effects when taking standard doses of venlafaxine. Consider an alternative drug, OR prescribe venlafaxine, be extra alert of adverse events, and adjust dosage in response to clinical response and tolerability. Monitor O-desmethylvenlafaxine plasma concentrations.

Amoxapine
Amoxapine

Possible Sensitivity to Amoxapine (CYP2D6: Poor Metabolizer) — **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. Decreased CYP2D6 activity may result in higher amoxapine concentrations potentially leading to higher adverse events. There are no established dosing adjustments for patients with decreased CYP2D6 function; therapy must be initiated cautiously and adjusted according to the patient's response.

Amphetamine
Adderall, Evekeo

Possible Increased Exposure to Amphetamine (CYP2D6: Poor Metabolizer) — **INFORMATIVE**

There is little evidence documenting the exposure of amphetamine in subjects with reduced CYP2D6 activity such as CYP2D6 poor metabolizers. Although the drug's plasma concentrations may be elevated in these subjects, the clinical relevance of this change is not well documented. Consider initiating therapy with lower doses and monitor the patient more frequently during drug titration. Consider adjusting the dose based on clinical response and tolerability. An alternative therapy may also be considered in patients with decreased tolerability.

Aripiprazole
Abilify, Aristada

Increased Sensitivity to Aripiprazole (CYP2D6: Poor Metabolizer) — **ACTIONABLE**

CYP2D6 poor metabolizers have a significantly reduced capacity to metabolize aripiprazole and its active metabolite, and should receive lower doses. Careful titration is recommended until a favorable response is achieved.

Daily dosing (oral or intramuscular): aripiprazole dose should initially be reduced to one-half (**50%**) of the usual dose, then adjusted to achieve a favorable clinical response. Reduce the **maximum dose to 10 mg/day** (67% of the maximum recommended daily dose). The dose of aripiprazole for CYP2D6 poor metabolizers who are administered a strong CYP3A4 inhibitor should be reduced to one-quarter (25%) of the usual dose.

Monthly dosing (intramuscular): for *Abilify Maintena*, the starting and maintenance monthly recommended dose is lower than the usually recommended dose, and should be **300 mg**. Some patients may benefit from a reduction to 200 mg. For *Aristada*, reduce the dose to the next lower strength (662 mg instead of 882 mg and 441 mg instead of 662 mg); no dosage adjustment is necessary in patients taking 441 mg *Aristada*, if tolerated. For *Abilify Maintena*, reduce the monthly dose to 200 mg if a CYP3A4 inhibitor is prescribed to CYP2D6 poor metabolizers receiving 300 mg of aripiprazole. For *Aristada*, reduce dose to 441 mg and avoid use at 662 mg or 882 mg dose if a CYP3A4 inhibitor is prescribed to CYP2D6 poor metabolizers for more than 14 days. No dosage adjustment is necessary in patients taking 441 mg *Aristada*, if tolerated.

Every 6 weeks or two months dosing with *Aristada* (intramuscular): reduce the dose to a lower strength of 441 mg every 4 weeks. If a strong CYP3A4 inhibitor is coadministered for more than 14 days, avoid using the 662 mg, 882 mg or 1064 mg doses and consider the lower dose strenght of 441 mg every 4 weeks.

Atomoxetine
Strattera

Increased Sensitivity to Atomoxetine (CYP2D6: Poor Metabolizer) — **ACTIONABLE**

When given a standard atomoxetine dose, CYP2D6 poor metabolizers are likely to have higher plasma levels of the drug, which may lead to a higher rate of adverse events. **Careful titration and dosing adjustment are recommended with monitoring for toxicity until a favorable response is achieved**. In children and adolescents up to 70 kg body weight, atomoxetine should be initiated at standard dosing of 0.5 mg/kg/day, and only increased to the usual target dose of 1.2 mg/kg/day if symptoms fail to improve after 4 weeks and the initial dose is well tolerated. In children and adolescents over 70 kg body weight and adults, atomoxetine should be initiated at standard dosing of 40 mg/day, and only increased to the usual target dose of 80 mg/day if symptoms fail to improve after 4 weeks and the initial dose is well tolerated.

Atorvastatin
Lipitor

Increased Myopathy Risk (SLCO1B1: Poor Function) — **INFORMATIVE**

The reduced SLCO1B1 function may result in elevated atorvastatin plasma levels. Because the risk of myopathy increases in patients with high statin plasma levels, the use of high atorvastatin doses in this patient should be avoided. If atorvastatin is used in this patient, a closer monitoring of serum creatine kinase and liver function is recommended. Other myopathy predisposing factors include advanced age (≥65), uncontrolled hypothyroidism, renal impairment, comedications, and female gender.

RESOLVE MDx

PATIENT INFORMATION

NAME: **Test Patient**
ACC #: NA02016
DOB: 1/1/1900
SEX:

Brexpiprazole
Rexulti

Increased Sensitivity to Brexpiprazole (CYP2D6: Poor Metabolizer) — **ACTIONABLE**

The exposure to brexpiprazole in CYP2D6 poor metabolizers is 120% higher than the exposure in CYP2D6 normal metabolizers. Because the incidence of akathisia is dose-related in patients suffering from schizophrenia or major depressive disorders, **it is recommended to prescribe half of the usual doses of brexpiprazole to CYP2D6 poor metabolizers.** Careful titration is recommended until a favorable response is achieved.

Adjunctive Treatment of Major Depression Disorder: the recommended starting doses should be reduced by half (0.25 mg or 0.5 mg once daily). The daily maintenance doses and maximum recommended dose are 0.5-1 mg and 1.5 mg, respectively. Schizophrenia: the recommended starting dose is 0.5 mg once daily. The daily maintenance doses and maximum recommended dose are 1-2 mg and 2 mg, respectively.

Dose adjustments with comedications: Administer **a quarter of the usual dose** if a strong/moderate CYP3A4 inhibitor is coadministered. Double usual dose over 1 to 2 weeks if a strong CYP3A4 inducer is coadministered.

Carvedilol
Coreg

Moderate Sensitivity to Carvedilol (CYP2D6: Poor Metabolizer) — **ACTIONABLE**

Carvedilol can be prescribed at standard label-recommended dosage and administration. CYP2D6 poor metabolizers may experience dizziness during up-titration. Careful titration is recommended with monitoring until a favorable response is achieved.

Chlorpromazine
Thorazine

Increased Sensitivity to Chlorpromazine (CYP2D6: Poor Metabolizer) — **INFORMATIVE**

Chlorpromazine is metabolized by CYP2D6, CYP3A4 and flavin-containing monooxygenases. Decreased CYP2D6 activity results in higher chlorpromazine concentrations potentially leading to higher adverse events. Consider prescribing chlorpromazine at a lower starting dose and then adjust dosage to achieve a favorable clinical response.

Citalopram
Celexa

Reduced Response to Citalopram (HTR2A: Homozygous for G allele (rs7997012)) — **INFORMATIVE**

The patient is homozygous for G allele in HTR2A variant rs7997012. Preliminary studies report that this genotype may be associated with an unfavorable response to citalopram.

Clobazam
Onfi

Possible Sensitivity to Clobazam (CYP2C19: Intermediate Metabolizer) — **ACTIONABLE**

In CYP2C19 intermediate metabolizers, plasma levels of the active metabolite N-desmethylclobazam were 2-fold higher than those found in CYP2C19 normal metabolizers. The dose adjustment for intermediate metabolizers is not well established, and therefore the recommendation for poor metabolizers is proposed. 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.

Clozapine
Clozaril

Non-Response to Clozapine (CYP1A2: Normal Metabolizer - Higher Inducibility) — **INFORMATIVE**

Smokers have a high risk for non-response at standard doses and may require higher doses. There is an association between high clozapine doses and the risk of seizures, and therefore careful monitoring is recommended during dosing adjustment. Smoking cessation will increase plasma drug levels, leading to adverse events. Therefore, therapeutic drug monitoring accompanied by dose reduction is recommended in patients who have quit smoking.

Darifenacin
Enablex

Possible Sensitivity to Darifenacin (CYP2D6: Poor Metabolizer) — **ACTIONABLE**

Darifenacin exposure is increased 30% in CYP2D6 poor metabolizers. Although dose adjustment may not be needed in these patients, monitor patients for increased side effects when darifenacin is prescribed at standard label-recommended dosage and administration.

RESOLVE MDx

PATIENT INFORMATION

NAME: **Test Patient**
ACC #: NA02016
DOB: 1/1/1900
SEX:

Deutetrabenazine
Austedo

Increased Sensitivity to Deutetrabenazine (CYP2D6: Poor Metabolizer) — **ACTIONABLE**

For treating chorea associated with Huntington's disease: The exposure to deutetrabenazine active metabolites alpha - and and beta-dihydrotetrabenazine is expected to be increased in CYP2D6 poor metabolizers (approximately 3-fold compared to CYP2D6 normal metabolizers) and clinically relevant QT prolongation might be expected in some patients at highest therapeutic doses. Therefore, the maximum recommended dosage of deutetrabenazine in CYP2D6 poor metabolizers is 36 mg per day. Individualization of dose with careful weekly titration is required. The first week's starting dose is 6 mg once daily then this dose should be slowly titrated at weekly intervals by 6 mg per day based on tolerability and up to a maximum recommended daily dosage of 36 mg (18 mg twice daily).

Dexmethylphenidate
Focalin

Decreased Response to Dexmethylphenidate (COMT: Intermediate COMT Activity) — **INFORMATIVE**

The patient's genotype result predicts a less optimal response to dexmethylphenidate. Dosage should be individualized according to the needs and response of the patient. Therapy should be initiated in small doses, with gradual weekly increments.

Dextroamphetamine
Dexedrine

Possible Increased Exposure to Dextroamphetamine (CYP2D6: Poor Metabolizer) — **INFORMATIVE**

There is little evidence documenting the exposure of dextroamphetamine in subjects with reduced CYP2D6 activity such as CYP2D6 poor metabolizers. Although the drug's plasma concentrations may be elevated in these subjects, the clinical relevance of this change is not well documented. Consider initiating therapy with lower doses and monitor the patient more frequently during drug titration. Consider adjusting the dose based on clinical response and tolerability. An alternative therapy may also be considered in patients with decreased tolerability.

Dextromethorphan / Quinidine
Nuedexta

Altered Sensitivity to Dextromethorphan-Quinidine (CYP2D6: Poor Metabolizer) — **ACTIONABLE**

Patients with Pseudobulbar Affect: the quinidine component of dextromethorphan-quinidine is intended to inhibit CYP2D6 so that higher exposure to dextromethorphan can be achieved compared to when dextromethorphan is given alone. Quinidine does not further inhibit CYP2D6 metabolism in poor metabolizers (PMs) and this component may expose PMs to an unnecessary risk since quinidine is not adding any benefit. Prescribers should consider the potential risk for quinidine-related adverse events relative to the benefit of administering the dextromethorphan-quinidine combination product (vs. dextromethorphan alone) in known CYP2D6 poor metabolizers.

Donepezil
Aricept

Possible Altered Response to Donepezil (CYP2D6: Poor Metabolizer) — **INFORMATIVE**

When compared to a normal metabolizer, a poor metabolizer has a 30% decrease in donepezil clearance. The clinical significance of this decrease is not well documented. Consider using a standard dosing regimen, be alert for adverse events, and adjust dosage in response to clinical response and tolerability.

Duloxetine
Cymbalta

Possible Sensitivity to Duloxetine (CYP2D6: Poor Metabolizer) — **INFORMATIVE**

Limited data suggest that duloxetine plasma concentrations might be increased in CYP2D6 poor metabolizers. Therefore, duloxetine can be prescribed at standard label-recommended dosage, and careful titration is recommended until a favorable response is achieved.

Flecainide
Tambocor

Significantly Increased Sensitivity to Flecainide (CYP2D6: Poor Metabolizer) — **ACTIONABLE**

Consider prescribing a lower flecainide dose. When compared to a CYP2D6 normal metabolizer, a poor metabolizer may require a 50% dose reduction. Careful titration with ECG recording and monitoring of flecainide plasma concentrations are recommended until a favorable clinical response is achieved.

Fluphenazine
Prolixin

Increased Sensitivity to Fluphenazine (CYP2D6: Poor Metabolizer) — **INFORMATIVE**

Fluphenazine is metabolized by CYP2D6, CYP1A2 and other enzymes. **Decreased CYP2D6 activity may result in higher fluphenazine concentrations potentially leading to higher adverse events such as extrapyramidal symptoms**. There are no established dosing adjustments for patients lacking 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.

Fluvoxamine
Luvox

Increased Sensitivity to Fluvoxamine (CYP2D6: Poor Metabolizer) — **INFORMATIVE**

At standard label-recommended dosage, fluvoxamine levels are expected to be high and adverse events may occur. Consider a 25-50% reduction of recommended starting dose to help prevent concentration-dependent adverse events and titrate based on the clinical response and tolerability. An alternative medication may also be considered.

Galantamine
Razadyne

Possible Sensitivity to Galantamine (CYP2D6: Poor Metabolizer) — **INFORMATIVE**

A CYP2D6 poor metabolizer has a drug exposure that is approximately 50% higher than the exposure in a normal metabolizer. Although dosage adjustment is not necessary in a patient identified as a CYP2D6 poor metabolizer as the dose of drug is individually titrated to tolerability, a slower titration can be considered as it may improve tolerability.

Hydrocodone
Vicodin

Possible Altered Response to Hydrocodone (CYP2D6: Poor Metabolizer) — **INFORMATIVE**

Decreased conversion of hydrocodone to the more active metabolite hydromorphone is expected in CYP2D6 poor metabolizers. However, there is insufficient evidence whether poor metabolizers have decreased analgesia when taking hydrocodone. Adequate pain relief can be achieved by increasing the dose in response to pain symptoms. Other opioids not metabolized by CYP2D6 may also be considered (i.e., morphine, oxymorphone, buprenorphine, fentanyl, methadone, and hydromorphone).

Iloperidone
Fanapt

Increased Sensitivity to Iloperidone (CYP2D6: Poor Metabolizer) — **ACTIONABLE**

Iloperidone **dose should be reduced by one-half and titrated slowly to avoid orthostatic hypotension**. Because iloperidone is associated with QTc prolongation, caution is warranted when prescribing the drug in patients with reduced CYP2D6 activity. If patients taking iloperidone experience symptoms that could indicate the occurrence of cardiac arrhythmias (e.g., dizziness, palpitations, or syncope), the prescriber should initiate further evaluation, including cardiac monitoring.

Leflunomide
Arava

Increased Sensitivity to Leflunomide (CYP2C19: Intermediate Metabolizer) — **INFORMATIVE**

Leflunomide is metabolized by CYP2C19 and CYP1A2 to its active metabolite teriflunomide. Preliminary studies indicate that patients with decreased CYP2C19 activity have a higher risk of developing gastrointestinal side effects and hepatotoxicity. There is insufficient data to calculate dose adjustment. If leflunomide is prescribed at standard dosing, monitor closely the patient's response and be alert to increased side effects. Full blood cell count (CBC) and liver function parameters should be checked no more than 6 months before beginning treatment, and every month for the initial 6 months of therapy. Blood pressure should be checked before beginning treatment and periodically thereafter.

Lisdexamfetamine
Vyvanse

Possible Increased Exposure to Lisdexamfetamine Active Metabolite (CYP2D6: Poor Metabolizer) — **INFORMATIVE**

There is little evidence documenting the exposure of lisdexamfetamine and its active metabolite dextroamphetamine in subjects with reduced CYP2D6 activity such as CYP2D6 poor metabolizers. Although dextroamphetamine plasma concentrations may be elevated in these subjects, the clinical relevance of this change is not well documented. Consider initiating therapy with lower doses and monitor the patient more frequently during drug titration. Consider adjusting the dose based on clinical response and tolerability. An alternative therapy may also be considered in patients with decreased tolerability.

Lovastatin
Mevacor, Altoprev, Advicor

Increased Myopathy Risk (SLCO1B1: Poor Function) — **INFORMATIVE**

The reduced SLCO1B1 function may result in elevated lovastatin acid plasma levels. Because the risk of myopathy increases in patients with high statin plasma levels, the use of high lovastatin doses in this patient should be avoided. If lovastatin is used in this patient, a closer monitoring of serum creatine kinase and liver function is recommended. Other myopathy predisposing factors include advanced age (≥65), uncontrolled hypothyroidism, renal impairment, comedications, and female gender.

Maprotiline
Ludiomil

Increased Sensitivity to Maprotiline (CYP2D6: Poor Metabolizer) — **INFORMATIVE**

Like other tricyclic and tetracyclic antidepressants, maprotiline is metabolized by CYP2D6 as well as CYP1A2. Compared to CYP2D6 normal metabolizers, CYP2D6 poor metabolizers have higher exposure to maprotiline at therapeutic doses which may increase the risk of concentration-dependent toxicities. There are no established dosing adjustments for patients with decreased CYP2D6 function however, it is recommended to initiate maprotiline therapy at a low dosage and gradually adjust the dosing according to the patient's response. The lowest effective dosage should always be considered during maintenance therapy.

Methylphenidate
Ritalin, Aptensio XR, Concerta, Metadate ER, Quillivant ER

Decreased Response to Methylphenidate (COMT: Intermediate COMT Activity) — **INFORMATIVE**

The patient's genotype result predicts a less optimal response to methylphenidate. Dosage should be individualized according to the needs and response of the patient. Therapy should be initiated in small doses, with gradual weekly increments.

Metoclopramide
Reglan

Increased Sensitivity to Metoclopramide (CYP2D6: Poor Metabolizer) — **INFORMATIVE**

Metoclopramide is metabolized at a slower rate in CYP2D6 poor metabolizers which results in significantly higher serum concentrations of the drug. Considering the CNS and extrapyramidal adverse effects of metoclopramide, close monitoring for toxicity and eventually a dose decrease is recommended. Patients with renal disease are at increased risk of CNS adverse events.

Mexiletine
Mexitil

Significantly Increased Sensitivity to Mexiletine (CYP2D6: Poor Metabolizer) — **ACTIONABLE**

Consider prescribing a lower mexiletine dose. A slow titration with ECG recording and monitoring of mexiletine plasma concentrations are recommended until a favorable clinical response is achieved.

Naltrexone
Vivitrol, Contrave

Altered Response to Naltrexone (OPRM1: Normal OPRM1 Function) — **INFORMATIVE**

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

Nefazodone
Serzone

Possible Sensitivity to Nefazodone (CYP2D6: Poor Metabolizer) — **INFORMATIVE**

Nefazodone is metabolized by CYP3A4 to its active metabolite m-chlorophenylpiperazine and other metabolites. The m-chlorophenylpiperazine metabolite which may contribute to adverse events, is further metabolized by CYP2D6. Individuals lacking CYP2D6 activity have higher levels of m-chlorophenylpiperazine metabolite and may experience more moderate and transient side effects when starting therapy. Consider prescribing nefazodone at a lower dose and adjust dose according to the patient's tolerability and clinical response.

Olanzapine
Zyprexa

Non-Response to Olanzapine (CYP1A2: Normal Metabolizer - Higher Inducibility) — **INFORMATIVE**

There is little evidence regarding the impact of CYP1A2 genetic variants on olanzapine response. Smokers may be at risk for non-response at standard doses. Careful monitoring is recommended during dosing adjustment. Smoking cessation may increase plasma drug levels, leading to adverse events. Therefore, therapeutic drug monitoring accompanied by dose reduction may be needed in patients who have quit smoking.

Oxycodone
Percocet, Oxycontin

Possible Altered Response to Oxycodone (CYP2D6: Poor Metabolizer) — **ACTIONABLE**

Decreased conversion of oxycodone to the more active metabolite oxymorphone is expected in CYP2D6 poor metabolizers. However, there is insufficient evidence whether poor metabolizers have decreased analgesia when taking oxycodone. Adequate pain relief can be achieved by increasing the dose in response to pain symptoms. Other opioids not metabolized by CYP2D6 may also be considered (i.e., morphine, oxymorphone, buprenorphine, fentanyl, methadone, and hydromorphone).

Perphenazine
Trilafon

Increased Sensitivity to Perphenazine (CYP2D6: Poor Metabolizer) — **ACTIONABLE**

Patients with a decreased CYP2D6 function will eliminate perphenazine more slowly, which can result in higher drug concentrations and possibly more adverse events (extrapyramidal symptoms). Consider close monitoring and dose reduction to avoid toxicity.

Phenobarbital
Luminal

Possible Sensitivity to Phenobarbital (CYP2C19: Intermediate Metabolizer) — **INFORMATIVE**

CYP2C19 is partly involved in the metabolism of phenobarbital, and although CYP2C19 intermediate metabolizers have a 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.

Pimozide
Orap

Increased Sensitivity to Pimozide (CYP2D6: Poor Metabolizer) — **ACTIONABLE**

The pimozide concentrations observed in poor CYP2D6 metabolizers are expected to be high, and the time to achieve steady-state pimozide concentrations is expected to be long (approximately 2 weeks). Consequently, CYP2D6 poor metabolizers are at an increased risk of QT prolongation at standard doses of pimozide. In CYP2D6 poor metabolizers, pimozide doses should not exceed 4 mg/day in adults or 0.05 mg/kg/day in children, and doses should not be increased earlier than 14 days.

Pitavastatin
Livalo

Increased Myopathy Risk (SLCO1B1: Poor Function) — **INFORMATIVE**

The reduced SLCO1B1 function may result in elevated pitavastatin plasma levels. Because the risk of myopathy increases in patients with high statin plasma levels, the use of high pitavastatin doses in this patient should be avoided. If pitavastatin is used in this patient, a closer monitoring of serum creatine kinase and liver function is recommended. Other myopathy predisposing factors include advanced age (≥65), uncontrolled hypothyroidism, renal impairment, comedications, and female gender.

Pravastatin
Pravachol

Increased Myopathy Risk (SLCO1B1: Poor Function) — **INFORMATIVE**

The reduced SLCO1B1 function may result in elevated pravastatin plasma levels. Because the risk of myopathy increases in patients with high statin plasma levels, the use of high pravastatin doses in this patient should be avoided. If pravastatin is used in this patient, a closer monitoring of serum creatine kinase and liver function is recommended. Other myopathy predisposing factors include advanced age (≥65), uncontrolled hypothyroidism, renal impairment, comedications, and female gender.

Primidone
Mysoline

Possible Sensitivity to Primidone (CYP2C19: Intermediate Metabolizer) — **INFORMATIVE**

CYP2C19 is partly involved in the metabolism of primidone, and although CYP2C19 intermediate metabolizers have a 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

Increased Sensitivity to Propafenone (CYP2D6: Poor Metabolizer) — ACTIONABLE

Consider reducing propafenone initial dose, and monitor ECG and plasma concentrations. Compared to normal metabolizers, poor metabolizers may require a 70% dose reduction of the initial dose.

Dose adjustments with comedications: increased exposure to propafenone may lead to cardiac arrhythmias and exaggerated beta-adrenergic blocking activity. Concurrent use of propafenone along with CYP3A4 inhibitors and CYP2D6 inhibitors may significantly increase the plasma concentration of propafenone and thereby increase the risk of proarrhythmia and other adverse events. Therefore, avoid simultaneous use of propafenone with a CYP3A4 inhibitor.

Ranolazine
Ranexa

Increased Sensitivity to Ranolazine (CYP2D6: Poor Metabolizer) — ACTIONABLE

Ranolazine is metabolized mainly by CYP3A4, and to a lesser extent by CYP2D6. At 500 mg twice daily, subjects lacking CYP2D6 activity (poor metabolizers) had 62% higher ranolazine exposure than subjects with normal CYP2D6 activity. The corresponding difference at 1000 mg twice daily dose was 25%.

The risk for increased exposure leading to adverse events is higher in patients lacking CYP2D6 activity (i.e., poor metabolizers). The recommended initial oral dose is 375 mg twice daily. **A slower up titration and additional monitoring is recommended in these patients.** Exposure related side effects might include nausea, vomiting, syncope, and dizziness. If a patient experiences treatment-related adverse events, down titration of the dose to 500 mg or 375 mg twice daily may be required. If symptoms do not resolve after dose reduction, treatment should be discontinued.

Ranolazine is a QTc prolonging drug. Caution should be observed when treating: 1- patients with a history of congenital or a family history of long QT syndrome, 2- patients with known acquired QT interval prolongation, and 3- patients treated with drugs affecting the QTc interval. Administration of CYP3A4 inhibitors increases the exposure of ranolazine significantly. As a consequence, the QTc prolongation by ranolazine in the presence of potent CYP3A inhibitors is significantly elevated relative to when the drug is administered alone.

Repaglinide
Prandin, Prandimet

Possible Sensitivity to Repaglinide (SLCO1B1: Poor Function) — INFORMATIVE

The patient carries two copies of the SLCO1B1 rs4149056 C allele, which is associated with reduced transporter function. Patients homozygous for the SLCO1B1 rs4149056 C allele are probably more susceptible to the blood glucose-lowering effect of repaglinide than those with other genotypes. Based on preliminary findings, the optimal starting dose of repaglinide may be lower in these patients. Selecting a lower starting dose may reduce the time needed to reach the correct maintenance dose, potentially with a smaller risk of hypoglycaemia. Repaglinide dose should be adjusted according to the actual blood glucose-lowering response.

Rosuvastatin
Crestor

Increased Myopathy Risk (SLCO1B1 521T>C C/C) — INFORMATIVE

The reduced SLCO1B1 function may result in elevated rosuvastatin plasma levels. Because the risk of myopathy increases in patients with high statin plasma levels, the use of high rosuvastatin doses in this patient should be avoided. If rosuvastatin is used in this patient, a closer monitoring of serum creatine kinase and liver function is recommended. Other myopathy predisposing factors include advanced age (≥65), uncontrolled hypothyroidism, renal impairment, comedications, and female gender.

Tacrolimus
Prograf

Insufficient Response to Tacrolimus (CYP3A5: Intermediate Metabolizer) — 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, increasing starting dose 1.5 to 2 times recommended starting dose with close monitoring is strongly recommended to achieve therapeutic effect. Total starting dose should not exceed 0.3mg/kg/day.

Tamsulosin
Flomax

Increased Sensitivity to Tamsulosin (CYP2D6: Poor Metabolizer) — ACTIONABLE

Tamsulosin is metabolized at a slower rate in CYP2D6 poor metabolizers, which results in significantly higher serum concentrations of tamsulosin. Therefore, this drug should be used with caution in patients known to be CYP2D6 poor metabolizers, particularly at a daily dose higher than 0.4 mg.

Tetrabenazine
Xenazine

Increased Sensitivity to Tetrabenazine (CYP2D6: Poor Metabolizer) — **ACTIONABLE**

For treating chorea associated with Huntington's disease: 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 poor metabolizers is 50 mg with a maximum single dose of 25 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.

Timolol
Timoptic

Increased Sensitivity to Timolol (CYP2D6: Poor Metabolizer) — **ACTIONABLE**

Potentiated systemic beta-blockade (e.g., bradycardia) has been reported during timolol treatment by patients with decreased CYP2D6 activity. Monitor patient for treatment-related adverse effects.

Tizanidine
Zanaflex

Possible Non-Response to Tizanidine (CYP1A2: Normal Metabolizer - Higher Inducibility) — **INFORMATIVE**

There is little evidence regarding the impact of CYP1A2 genetic variants on tizanidine response. Smokers may be at risk for non-response and may require higher doses. There is an association between high tizanidine plasma concentrations and the risk of hypotension and excessive sedation. Therefore, careful monitoring is recommended during dosing adjustment. Smoking cessation may increase plasma drug levels, leading to excessive hypotension and sedation. Careful monitoring accompanied by dose reduction may be needed in patients who have quit smoking.

Tolterodine
Detrol

Possible Sensitivity to Tolterodine (CYP2D6: Poor Metabolizer) — **INFORMATIVE**

Tolterodine is metabolized at a slower rate in CYP2D6 poor metabolizers, which results in significantly higher serum concentrations of tolterodine and negligible concentrations of its active metabolite (5-hydroxymethytolterodine). Considering the antimuscarinic potency of tolterodine and its active metabolite, and the protein binding of these compounds, tolterodine accounts for the major part of the clinical effect in poor metabolizers, and the same dosage can be applied irrespective of phenotype status.

Patients with congenital or acquired QT prolongation: the effect of tolterodine on the QT interval prolongation is greater for 8 mg/day (two times the therapeutic dose) compared to 4 mg/day, and is more pronounced in CYP2D6 poor metabolizers than normal metabolizers. This should be considered when tolterodine is prescribed to patients with a known history of QT prolongation, or patients who are taking Class IA or Class III antiarrhythmics.

Valbenazine
Ingrezza

Increased Sensitivity to Valbenazine (CYP2D6: Poor Metabolizer) — **ACTIONABLE**

The initial dose is 40 mg once daily. Based on tolerability, this dose may be maintained in CYP2D6 poor metabolizers to reduce the risk of exposure-related adverse events. Valbenazine may prolong the QT interval. The exposure to valbenazine and its major active metabolite in CYP2D6 poor metabolizers is significantly higher than the exposure in CYP2D6 normal metabolizers. Because the drug's QTc prolongation effect is concentration-dependent, it is appropriate to consider a reduced recommended dose based on the patient's tolerability. Other exposure-related adverse events include somnolence. Careful titration is recommended until a favorable response is achieved.

Dose adjustments with comedications: reduce the daily recommended dose to 40 mg if a strong CYP3A4 inhibitor is coadministered. Concomitant use with CYP3A4 inducers should be avoided.

Vortioxetine
Trintellix

Increased Sensitivity to Vortioxetine (CYP2D6: Poor Metabolizer) — **ACTIONABLE**

CYP2D6 is the primary enzyme catalyzing the metabolism of vortioxetine to its major, pharmacologically inactive carboxylic acid metabolite. CYP2D6 poor metabolizers have approximately twice the vortioxetine plasma concentrations of normal metabolizers. **Vortioxetine starting dose should be reduced by one-half. The maximum recommended dose is 10 mg/day in known CYP2D6 poor metabolizers.** Consider 5 mg/day for patients who do not tolerate higher doses.

RESOLVE MDx

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NAME: **Test Patient**
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⚠ Warfarin
Coumadin

Normal Sensitivity to Warfarin (CYP2C9 *1/*1 VKORC1 -1639G>A G/A) **ACTIONABLE**

Initiation Therapy: consider using the following standard warfarin dose range as 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 4-5 days.

⚠ Zonisamide
Zonegran

Possible Sensitivity to Zonisamide (CYP2C19: Intermediate Metabolizer) **INFORMATIVE**

CYP2C19 is partly involved in the metabolism of zonisamide, and although preliminary studies show that CYP2C19 intermediate metabolizers have a slightly lower (15%) 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.

RESOLVE MDx

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Test Details

Gene	Genotype	Phenotype	Clinical Consequences
ANKK1/DRD2	DRD2:Taq1A G/G	**Unaltered DRD2 function**	Consistent with a normal dopamine receptor D2 function.
Apolipoprotein E	ε3/ε4	**Altered APOE function**	Not associated with type III hyperlipoproteinemia - Increased risk of cardiovascular disease
COMT	Val158Met A/G	**Intermediate COMT Activity**	Consistent with a reduced catechol O-methyltransferase (COMT) function.
CYP1A2	*1A/*1F	**Normal Metabolizer - Higher Inducibility**	Consistent with a typical CYP1A2 activity in absence of inducing substances. Rapid Metabolism occurs in presence of inducers such as barbiturates, cruciferous vegetables, carbamazepine, rifampin and smoking.
CYP2B6	*1/*1	**Normal Metabolizer**	Consistent with a typical CYP2B6 activity. This test did not identify risks for side effects or loss of efficacy with drug substrates.
CYP2C19	*1/*2	**Intermediate Metabolizer**	Consistent with a moderate deficiency in CYP2C19 activity. Potential risk for side effects or loss of efficacy with drug substrates.
CYP2C9	*1/*1	**Normal Metabolizer**	Consistent with a typical CYP2C9 activity. This test did not identify risks for side effects or loss of efficacy with drug substrates.
CYP2D6	*3/*3	**Poor Metabolizer**	Consistent with a significant deficiency in CYP2D6 activity. Increased risk for side effects or loss of efficacy with drug substrates.
CYP3A4	*1/*1	**Normal Metabolizer**	Consistent with a typical CYP3A4 activity. Caution is advised when prescribing narrow therapeutic index drugs. Alternative drugs or dose adjustment may be required if CYP3A inhibitors or inducers are co-prescribed.
CYP3A5	*1/*3	**Intermediate Metabolizer**	Consistent with an intermediate CYP3A5 activity. Caution is advised when prescribing narrow therapeutic index drugs. Alternative drugs or dose adjustment may be required if CYP3A inhibitors or inducers are co-prescribed.
Factor II **Factor V Leiden**	20210G>A GG 1691G>A GG	**No Increased Risk of Thrombosis**	The patient's risk of thrombosis is not increased (average risk of clotting is about 1 in 1000 for anyone in a year). However, because this test cannot find all of the inherited reasons for abnormal clotting, other factors may affect this risk assessment.
FKBP5	rs4713916 A/G	**Heterozygous for rs4713916 A allele**	Consistent with a favorable response to citalopram.
GRIK4	83-10039T>C C/C	**Good Response to Citalopram**	Consistent with a favorable response to citalopram.
HTR2A	-1438G>A C/T	**Heterozygous for the T Allele (rs6311)**	The patient carries one copy of the variant allele at rs6311 which may be associated with greater serotonin 2A receptor gene expression.
HTR2A	rs7997012 G/G	**Homozygous for G allele (rs7997012)**	Reduced response to citalopram and escitalopram
MTHFR	677C>T CC	**Normal MTHFR Activity**	The patient does not carry the MTHFR C677T mutation (wild-type) and the patient's MTHFR activity is normal. This is not associated with an increased risk of hyperhomocysteinemia.
MTHFR	1298A>C AC 677C>T CC	**No Increased Risk of Hyperhomocysteinemia**	The patient's slightly reduced MTHFR activity is not a risk factor for hyperhomocysteinemia. Unless other risk factors are present, the patient is not expected to have an increased risk for venous thromboembolism (VTE).
OPRM1	A118G A/A	**Normal OPRM1 Function**	Consistent with a normal OPRM1 receptor signaling efficiency induced by exogenous opioids. This is associated with a good analgesia following standard opioid doses and a poor response to naltrexone.
SLCO1B1	521T>C C/C	**Poor Function**	Consistent with a severely decreased SLCO1B1 transporter function. The patient's risk for statin-induced myopathy is increased.
VKORC1 and CYP2C9	-1639G>A G/A, *1/*1	**Normal Sensitivity to Warfarin**	The CYP2C9 and VKORC1 genotype results predict a normal sensitivity to warfarin. The estimated time to reach steady state is 4-5 days.

RESOLVE MDx

PATIENT INFORMATION

NAME: **Test Patient**
ACC #: NA02016
DOB: 1/1/1900
SEX:

Alleles Tested: **ANKK1/DRD2** DRD2:Taq1A; **Apolipoprotein E** ε2, ε4, (ε3 is reference); **COMT** Val158Met; **CYP1A2** *1C, *1D, *1F, *1K, *1L, *1V, *1W; **CYP2B6** *6, *9; **CYP2C19** *2, *3, *4, *4B, *5, *6, *7, *8, *9, *17; **CYP2C9** *2, *3, *4, *5, *6, *11; **CYP2D6** *2, *3, *4, *4M, *6, *7, *8, *9, *10, *12, *14A, *14B, *17, *29, *35, *41, *5 (gene deletion), XN (gene duplication); **CYP3A4** *22; **CYP3A5** *1D, *2, *3, *3C, *6, *7, *8, *9; **Factor II** 20210G>A; **Factor V Leiden** 1691G>A; **FKBP5** rs4713916; **GRIK4** 83-10039T>C; **HTR2A** -1438G>A, 102C>T, rs7997012; **MTHFR** 1298A>C, 677C>T; **OPRM1** A118G; **SLCO1B1** 521T>C; **VKORC1** -1639G>A

Disclaimer: Resolve Molecular Diagnostics developed the genotyping-based test. The performance characteristics of this test were determined by Resolve Molecular Diagnostics. It has not been cleared or approved by the U.S. Food and Drug Administration (FDA).

Only a qualified healthcare professional should advise a patient on how to interpret the results and information found in this report. Resolve Molecular Diagnostics will not make any recommendations based on the results of the test performed, therefore, please seek advice from your healthcare provider.

Methodology: All single nucleic polymorphism (SNP) genotyping was performed using Applied BiosystemsTM TaqMan® chemistry on the QuantStudioTM 12K Flex Real-Time PCR System from ThermoFisher Scientific. Array based assays detects listed alleles, including all common and most rare variants with known clinical significance at analytical sensitivity and specificity >99%.

Limitations: This test will not detect all the known alleles that result in altered or inactive tested genes. This test does not account for all individual variations in the individual tested. Absence of a detectable gene mutation does not rule out the possibility that a patient has different phenotypes due to the presence of an undetected polymorphism or due to other factors such as drug-drug interactions, comorbidities and lifestyle habits.

Translational Software Disclaimer: The information presented on this report is provided as general educational health information. The content is not intended to be a substitute for professional medical advice, diagnosis, or treatment. Only a physician, pharmacist or other healthcare professional should advise a patient on the use of the medications prescribed.

The pharmacogenetic assay involves use of reporting software and genotype-phenotype associations performed by Translational Software (www.translationalsoftware.com). The software has not been evaluated by the Food and Drug Administration. The software, and the report generated by the software, is not intended to diagnose, treat, cure, or prevent any disease. A qualified designee within the lab uses Translational Software to generate and subsequently review the report. The pharmacogenetic report is one of multiple pieces of information that clinicians should consider in guiding their therapeutic choice for each patient. It remains the responsibility of the health-care provider to determine the best course of treatment for a patient. Adherence to dose guidelines does not necessarily assure a successful medical outcome.

Patient Information Card

This is a summary genetic report for your patient to share with other healthcare providers. The card can be cut out along the dashed line and carried with the patient.

REPORT DETAILS

Patient: Test Patient
DOB: 1/1/1900
ACC #: NA02016

Pharmacogenetic Test Summary

CYP2C19	*1/*2	Intermediate Metabolizer
CYP2C9	*1/*1	Normal Metabolizer
CYP2D6	*3/*3	Poor Metabolizer
CYP3A4	*1/*1	Normal Metabolizer
CYP3A5	*1/*3	Intermediate Metabolizer

Factor II Factor V Leiden	20210G>A GG 1691G>A GG	No Increased Risk of Thrombosis
MTHFR	677C>T CC	Normal MTHFR Activity
MTHFR	1298A>C AC 677C>T CC	No Increased Risk of Hyperhomocysteinemia
VKORC1 and CYP2C9	-1639G>A G/A, *1/*1	Normal Sensitivity to Warfarin

For a complete report contact Resolve Molecular Diagnostics