4U Health

PATIENT INFORMATION		SPECIMEN DETAILS		PROVIDER INFORMATION
NAME:	**Demo Patient**	**SPECIMEN TYPE:**	Buccal Swab	DEMO PHYSICIAN
ACC #:	DEMO	**COLLECTION DATE:**	8/20/2020	
DOB:	1/1/1900	**RECEIVED DATE:**	8/15/2020	
SEX:		**REPORT DATE:**	8/20/2020	

Cardiovascular Pharmacogenetic Report

Report Comment: VL BATCH 08202020-1 CO

Risk Management

Type III Hyperlipoproteinemia

Not Associated with Type III Hyperlipoproteinemia

The patient is negative for both the APOE c.388 T>C (Cys130Arg) and c.526 C>T (Arg176Cys) mutations. The patient's genotype is wild-type, which is the most common genotype in the general population (frequency: >60%).
A patient with wild-type genotype does not have a defect in the apolipoprotein E (APOE), which is an integral structure of lipoprotein particles that have critical roles in blood lipid metabolism and transport. The APOE ε3/ε3 genotype is not associated with increased risk of cardiovascular disease.
No action is needed when a patient is normolipidemic.

Platelet Hyperactivity

Normal Response to Aspirin

The patient is negative for the ITGB3 176T>C (Leu59Pro) mutation. The genotype for the integrin β3 gene is wild-type, which is the most common genotype in the general population.
The wild-type genotype results confers a "normal" platelet reactivity, and is not associated with a resistance to the antithrombotic effects of aspirin. However, because the variability in response to antiplatelet drugs is multifactorial and not caused by single gene mutations, testing for the ITGB3 mutation alone should not be used as a diagnostic tool.

Hyperlipidemia/Atherosclerotic Cardiovascular Disease

No increased risk of cardiovascular disease

The patient is a non carrier of the risk alleles in LPA gene for both the variants (rs3798220 and rs10455872).
The patient's genotype is associated with normal lipoprotein levels. The patient has no increased risk of atherosclerosis and cardiovascular disease as compared to the general population unless other risk factors are present.
No action is needed for this patient unless other genetic and non genetic risk factors (e.g. high blood pressure, smoking, diabetes, obesity, high blood cholesterol and excessive alcohol use) are present.

Thrombophilia

Normal Risk of Thrombosis

The patient does not carry the F5 c.1601G>A variant (also known as Factor V Leiden) or the F2 c.*97G>A variant (also known as Factor II 20210G>A).
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.
Assess thrombotic risk based on other genetic and/or circumstantial risk factors such as smoking, obesity, malignancy, prolonged immobilization or surgery.

Estrogen-containing contraceptive and hormone replacement therapy: unless other genetic and/or circumstantial risk factors are present, consider standard prescribing and monitoring practices.

Hyperhomocysteinemia - Thrombosis

No Increased Risk of Hyperhomocysteinemia

The patient carries one copy of MTHFR c.1286A>C variant (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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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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Potentially Impacted Medications

CATEGORY	DRUG CLASS	STANDARD PRECAUTIONS	USE WITH CAUTION	CONSIDER ALTERNATIVES
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	Amiodarone (Nexterone®, Pacerone®) Disopyramide (Norpace®) Quinidine (Quinidine®) Sotalol (Betapace®, Sorine®, Sotylize®)	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®) Carvedilol (Coreg®) Labetalol (Normodyne®, Trandate®) Nebivolol (Bystolic®) Propranolol (Inderal®)	Metoprolol (Lopressor®) Timolol (Timoptic®)	
	Diuretics	Torsemide (Demadex®)		
	Statins	Atorvastatin (Lipitor®) Fluvastatin (Lescol®) Lovastatin (Mevacor®, Altoprev®, Advicor®) Pitavastatin (Livalo®) Pravastatin (Pravachol®) Rosuvastatin (Crestor®) Simvastatin (Zocor®)		

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Dosing Guidance

Clopidogrel
Plavix®

Increased Response to Clopidogrel (CYP2C19: Ultra-Rapid Metabolizer) — ACTIONABLE

Clopidogrel can be prescribed at standard label-recommended dosage. Individuals with the *17 allele may have an increased risk of bleeding while taking clopidogrel.

Flecainide
Tambocor®

Increased Exposure to Flecainide (CYP2D6: Intermediate Metabolizer) — ACTIONABLE

The patient's genotype may be associated with an increased flecainide exposure following standard dosing. Consider prescribing a lower flecainide dose for therapeutic indications. When compared to a CYP2D6 normal metabolizer, an intermediate metabolizer may require a 25% dose reduction. Careful titration with ECG recording and monitoring of flecainide plasma concentrations are recommended until a favorable clinical response is achieved.

Dose adjustments are not required when flecainide is utilized for diagnostic uses.

Metoprolol
Lopressor®

Increased Exposure to Metoprolol (CYP2D6: Intermediate Metabolizer) — ACTIONABLE

The patient's genotype may be associated with an increased metoprolol exposure following standard dosing. When compared to a normal metabolizer, an intermediate metabolizer may require a 50% dose reduction. If metoprolol is prescribed, be alert to adverse events (e.g., bradycardia or cold extremities).

Mexiletine
Mexitil®

Increased Sensitivity to Mexiletine (CYP2D6: Intermediate 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.

Propafenone
Rythmol®

Increased Exposure to Propafenone (CYP2D6: Intermediate Metabolizer) — ACTIONABLE

The patient's genotype may be associated with an increased propafenone exposure following standard dosing. There is insufficient data to allow calculation of dose adjustment. Titrate carefully and adjust the dose in response to plasma concentration and ECG monitoring. An alternative medication such as sotalol, disopyramide, quinidine or amiodarone may also be considered.

Dose adjustments with co-medications: concurrent use of propafenone along with CYP3A4 inhibitors and CYP2D6 inhibitors may significantly increase the plasma concentration of propafenone increasing the risk of proarrhythmia and other adverse events. Therefore, avoid simultaneous use of propafenone with both a CYP2D6 inhibitor and a CYP3A4 inhibitor.

Timolol
Timoptic®

Possible Sensitivity to Timolol (CYP2D6: Intermediate Metabolizer) — INFORMATIVE

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.

Amiodarone
Nexterone®, Pacerone®

Normal Exposure to Amiodarone — INFORMATIVE

Pharmacogenetic guidance: Amiodarone is metabolized to N-desethylamiodarone. This process is mediated primarily by CYP3A. No genetically guided drug selection or dosing adjustments are recommended. **Polypharmacy guidance**: Co-administration of amiodarone with drugs that are, a strong inducer or inhibitor of CYP3A may affect drug plasma levels. In addition, co-administration of amiodarone with drugs known to prolong QT interval can precipitate drug induced long QT syndrome.

Apixaban
Eliquis®

Normal Response to Apixaban — INFORMATIVE

Pharmacogenetic guidance: Apixaban is not extensively metabolized and only ~20% of the dose is metabolized primarily by CYP3A4 and CYP3A5, with minor contributions from CYP1A2 and CYP2J2. This drug is a substrate for the efflux transport proteins P-gp (ABCB1) and BCRP (ABCG2). While these enzymes and transporters are polymorphic, genetic variations are unlikely to have a clinically significant impact on apixaban exposure, and no genotype-based dosing adjustments are recommended. **Polypharmacy guidance:** Exposure to apixaban increases by 100% when co-administered with ketoconazole, a strong CYP3A/P-gp inhibitor. This translates into an increased bleeding risk (70% increase). Hence, for patients receiving 5 mg twice daily, apixaban dose should be decreased to 2.5 mg twice daily when it is coadministered with drugs that are strong dual inhibitors of CYP3A4 and P-gp (e.g., ketoconazole, itraconazole, ritonavir, and clarithromycin). In patients already taking 2.5 mg twice daily, coadministration of apixaban with strong dual inhibitors of CYP3A4 and P-gp should be avoided. No dose adjustment is recommended when co-administered with moderate inhibitors. Co-administration with rifampin, a strong CYP3A/P-gp inducer, results in halving of exposure to apixaban. There is no clinical experience at these reduced exposures. Hence, concomitant administration of strong CYP3A/P-gp inducers should be avoided.

Atenolol
Tenormin®

Normal Response to Atenolol
INFORMATIVE

Pharmacogenetic guidance: The bioavailability of atenolol is approximately 40–50% and renal excretion eliminates approximately 90% of the absorbed drug in its unchanged form. A negligible amount of the drug is metabolized. Atenolol is a substrate of several organic anion and cation transporters including SLC22A1, SLC22A2, SLC47A1, and SLC47A2. No genetically-guided drug selection or dosing recommendations are available.

Atorvastatin
Lipitor®

Normal Myopathy Risk (SLCO1B1: Normal Function)
ACTIONABLE

The patient's genotype is associated with normal SLCO1B1 function which results in normal atorvastatin plasma concentrations. Consider prescribing atorvastatin at standard FDA-recommended starting doses and adjust based on disease-specific guidelines.

Atorvastatin
Lipitor®

Normal Response to Atorvastatin (CYP3A4: Normal Metabolizer)
INFORMATIVE

The genotype result indicates that the patient does not carry the CYP3A4*22 allele (this allele is associated with a decreased CYP3A4 enzyme activity). The patient is expected to achieve an optimal lipid control goal with standard atorvastatin dose requirements.

Azilsartan
Edarbi®, Edarbyclor®

Normal Azilsartan Exposure (CYP2C9: Normal Metabolizer)
INFORMATIVE

Azilsartan medoxomil is hydrolyzed to azilsartan, its active metabolite, in the gastrointestinal tract during absorption. Azilsartan is further metabolized to inactive metabolites by CYP2C9. Consider standard label-recommended dosage and administration.

Betrixaban
Bevyxxa®

Normal Response to Betrixaban
ACTIONABLE

Pharmacogenetic guidance: The predominant metabolic pathway of betrixaban is amide hydrolysis with minor cytochrome P450 enzymes-based metabolism (less than 1% of the drug is metabolized by CYP1A1, CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6 and CYP3A4). The main elimination pathway of the drugs is biliary excretion followed by urinary excretion. Betrixaban is a substrate for the efflux transport protein P-gp (ABCB1) and while this transporter is polymorphic, genetic variations are unlikely to have a clinically significant impact on betrixaban exposure, and no genotype-based dosing adjustments are available. **Polypharmacy guidance:** Concomitant use with P-gp inhibitors such as amiodarone, azithromycin, verapamil, ketoconazole, clarithromycin results in increased plasma levels of betrixaban and increased risk of bleeding. Dosing reduction and close monitoring are recommended in presence of P-gp inhibitors.

Bisoprolol
Zebeta®

Normal Response to Bisoprolol
INFORMATIVE

Pharmacogenetic guidance: Bisoprolol is eliminated by renal and non-renal pathways with 50% of the total dose being metabolized in the liver and 50% being excreted via the kidneys unchanged. Bisoprolol is predominantly metabolized by CYP3A4 with smaller contribution from CYP2D6. Limited studies suggest that bisoprolol plasma concentrations and its beta-adrenergic inhibition are not affected by CYP2D6 genetic variability. No genetically-guided drug selection or dosing recommendations are available.

Candesartan

Normal Sensitivity to Candesartan Cilexetil
ACTIONABLE

Atacand®

Pharmacogenetic guidance: Candesartan cilexetil is hydrolyzed to candesartan its active metabolite in the gastrointestinal tract during absorption. Candesartan undergoes minor hepatic metabolism by O-deethylation to an inactive metabolite. Genetic variability of the cytochrome P450 genes is not expected to affect the patient's response to candesartan cilexetil. No genotype-based dosing adjustments are available.

Carvedilol
Coreg®

Normal Exposure to Carvedilol — ACTIONABLE

Pharmacogenetic guidance: Carvedilol is metabolized to active metabolites primarily by CYP2D6 and CYP2C9 with lesser contribution from other CYP enzymes (including CYP3A4, CYP2C19, CYP1A2, and CYP2E1). Studies have shown that CYP2D6 poor metabolizers may experience dizziness during up-titration. No genetically guided drug selection or dosing recommendations are recommended. **Polypharmacy guidance**: Carvedilol is a racemic mixture of R(+) and S(-)-carvedilol. Strong CYP2D6 inhibitors may result in increased plasma concentrations of R(+)-carvedilol. It is postulated that this increase in R(+)-carvedilol could be responsible for the dizziness seen during up-titration in these patients.

Dabigatran Etexilate
Pradaxa®

Normal Response to Dabigatran — INFORMATIVE

Pharmacogenetic guidance: Dabigatran is eliminated primarily unchanged by the kidneys. After oral administration, dabigatran etexilate is converted to its active form dabigatran by esterases. A small portion (20%) of dabigatran dose is also conjugated to form pharmacologically active acyl glucuronides. Dabigatran is not a substrate, inhibitor, or inducer of CYP450 enzymes. Dabigatran etexilate is a substrate of the efflux transporter P-gp (ABCB1). Common genetic polymorphism of the ABCB1 gene (2677G>T/A and 3435 C>T) do not appear to affect dabigatran exposure.
Polypharmacy guidance: *1-Reduction in Risk of Stroke and Systemic Embolism in Non-valvular AF*: In patients with moderate renal impairment (CrCl 30-50 mL/min), concomitant use of the P-gp inhibitor dronedarone or systemic ketoconazole can be expected to produce dabigatran exposure similar to that observed in severe renal impairment. Consider reducing the dose of dabigatran to 75 mg twice daily. Dose adjustment is not necessary when coadministered with other P-gp inhibitors. In patients with CrCl<30 mL/min, avoid use of concomitant P-gp inhibitors with dabigatran. *2-Treatment of DVT and PE Reduction in the Risk of Recurrence of DVT and PE*: Avoid use of concomitant P-gp inhibitors with dabigatran in patients with CrCl <50 mL/min.

Disopyramide
Norpace®

Normal Exposure to Disopyramide — INFORMATIVE

Pharmacogenetic guidance: Disopyramide is metabolized mainly by CYP3A4 and to a lesser extent by CYP2D6. About 50% of the dose is excreted in urine as unchanged disopyramide and 30% as metabolites. Genetic polymorphisms of CYP2D6 have not been found to affect patient response to disopyramide. No genetically guided drug selection or dosing adjustments are recommended. No genetically guided drug selection or dosing adjustments are recommended.
Polypharmacy guidance: Co-administration of disopyramide with inhibitors of CYP3A4 may cause an increase in disopyramide plasma concentrations, which could result in a fatal interaction. Co-administration with CYP3A4 inducers may cause a decrease in disopyramide plasma concentrations. Caution should be used when co-administering drugs that can affect renal function.

Edoxaban
Savaysa®

Normal Response to Edoxaban — INFORMATIVE

Pharmacogenetic guidance: Edoxaban is eliminated primarily as unchanged drug in urine. There is minimal metabolism via hydrolysis (mediated by carboxylesterase 1; CES1), conjugation, and oxidation by CYP3A4. Edoxaban is a substrate of the efflux transporter P-gp and its active metabolite (formed by CES1) is a substrate of the uptake transporter SLCO1B1. Studies indicate that the two common variants SLCO1B1 rs4149056 and ABCB1 rs1045642 do not affect the exposure to edoxaban or its active metabolite. There are no genotype-based dosing recommendations. **Polypharmacy guidance**: Avoid the concomitant use of edoxaban with rifampin. No dose reduction is recommended for concomitant P-gp inhibitor use.

Eprosartan
Teveten®

Normal Sensitivity to Eprosartan — ACTIONABLE

Pharmacogenetic guidance: Eprosartan is eliminated by biliary and renal excretion, primarily as unchanged compound. Eprosartan is not metabolized by the cytochrome P450 enzymes. Genetic variability of the cytochrome P450 genes is not expected to affect the patient's response to eprosartan. No genotype-based dosing adjustments are available.

Fluvastatin
Lescol®

Normal Fluvastatin Exposure (CYP2C9: Normal Metabolizer) — INFORMATIVE

Fluvastatin plasma concentrations are not expected to increase, and unless other genetic or circumstantial risk factors are present, fluvastatin can be prescribed at standard FDA-recommended starting doses and adjusted based on disease-specific guidelines. 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.

Fondaparinux
Arixtra®

Normal Response to Fondaparinux — INFORMATIVE

Pharmacogenetic guidance: Fondaparinux is eliminated unchanged through renal excretion and is not metabolized by CYPs, and therefore genetic variations in these metabolizing enzymes are not expected to affect its efficacy or toxicity profiles. No genetically guided drug selection or dosing recommendations are available. **Polypharmacy guidance:** The concomitant use of fondaparinux with aspirin or NSAIDS may enhance the risk of hemorrhage. Discontinue agents that may enhance the risk of hemorrhage prior to initiation of therapy with fondaparinux unless essential. If co-administration is necessary, monitor patients closely for hemorrhage.

Irbesartan
Avapro®

Normal Irbesartan Exposure (CYP2C9: Normal Metabolizer) — INFORMATIVE

Irbesartan can be prescribed at standard label-recommended dosage and administration.

Labetalol
Normodyne®, Trandate®

Normal Response to Labetalol — INFORMATIVE

Pharmacogenetic guidance: Labetalol is extensively metabolized by UGT2B7, UGT1A1, and CYP2C19 to inactive metabolites. Preliminary studies indicate that following a single 200-mg oral dose, labetalol plasma concentrations are 2.9 -fold higher in Chinese individuals with the CYP2C19 *2/*2 genotype than those with the CYP2C19 *1/*1 genotype. The clinical impact of this change is unknown. **Polypharmacy guidance:** Cimetidine increases the bioavailability of labetalol, and clinical monitoring is advised when both drugs are coadministered.

Losartan
Cozaar®, Hyzaar®

Normal Response to Losartan (CYP2C9: Normal Metabolizer) — INFORMATIVE

Losartan is metabolized to its active metabolite by CYP2C9 and CYP3A4. The patient's genotype predicts a normal exposure to losartan and its active metabolite. Losartan can be prescribed at label-recommended dosage and administration.

Lovastatin
Mevacor®, Altoprev®, Advicor®

Normal Myopathy Risk (SLCO1B1: Normal Function) — INFORMATIVE

Lovastatin acid plasma concentration is not expected to be elevated. Unless other genetic or circumstantial risk factors are present, lovastatin can be prescribed at standard FDA-recommended starting doses and adjusted based on disease-specific guidelines. Other myopathy predisposing factors include advanced age (≥65), uncontrolled hypothyroidism, renal impairment, high statin dose, comedications, and female gender.

Lovastatin
Mevacor®, Altoprev®, Advicor®

Normal Response to Lovastatin (CYP3A4: Normal Metabolizer) — INFORMATIVE

The genotype result indicates that the patient does not carry the CYP3A4*22 allele (this allele is associated with a decreased CYP3A4 enzyme activity). The patient is expected to achieve an optimal lipid control goal with standard lovastatin dose requirements.

Nebivolol
Bystolic®

Normal Sensitivity to Nebivolol (CYP2D6: Intermediate Metabolizer) — ACTIONABLE

Nebivolol can be prescribed at standard label-recommended dosage and administration. Caution is recommended during up-titration until a favorable response is achieved.

Olmesartan
Benicar®

Normal Sensitivity to Olmesartan Medoxomil — ACTIONABLE

Pharmacogenetic guidance: Olmesartan medoxomil is hydrolyzed to olmesartan its active metabolite in the gastrointestinal tract during absorption. There is virtually no further metabolism of olmesartan. Genetic variability of the cytochrome P450 genes is not expected to affect the patient's response to olmesartan medoxomil. No genotype-based dosing adjustments are available.

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Pitavastatin
Livalo®

Normal Myopathy Risk (SLCO1B1: Normal Function) — **INFORMATIVE**

Pitavastatin plasma concentrations are not expected to increase, and unless other genetic or circumstantial risk factors are present, pitavastatin can be prescribed at standard FDA-recommended starting doses and adjusted based on disease-specific guidelines. The myopathy risk increases with use of the 4 mg daily dose. (Other myopathy predisposing factors include advanced age (≥65), uncontrolled hypothyroidism, renal impairment, high statin dose, comedications, and female gender.)

Prasugrel
Effient®

Normal Response to Prasugrel — **ACTIONABLE**

Pharmacogenetic guidance: Prasugrel is a prodrug that is hydrolyzed in the intestine to a thiolactone, which is then converted to the active metabolite primarily by CYP3A4 and CYP2B6, and to a lesser extent by CYP2C9 and CYP2C19. Prasugrel active metabolite exposure and platelet reactivity are not affected by CYP2C19 genetic variants. Prasugrel efficacy or safety profile are also unaffected by CYP2B6, CYP3A5, and CYP2C9 genetic variants. No genetically-guided drug selection or dosing recommendations are available. **Polypharmacy guidance**: Prasugrel can be administered with drugs that are inducers or inhibitors of cytochrome P450 enzymes.

Pravastatin
Pravachol®

Normal Myopathy Risk (SLCO1B1: Normal Function) — **INFORMATIVE**

Pravastatin plasma concentrations are not expected to increase, and unless other genetic or circumstantial risk factors are present, pravastatin can be prescribed at standard FDA-recommended starting doses and adjusted based on disease-specific guidelines. (Other myopathy predisposing factors include advanced age (≥65), uncontrolled hypothyroidism, renal impairment, high statin dose, comedications, and female gender.)

Propranolol
Inderal®

Normal Sensitivity to Propranolol (CYP2D6: Intermediate Metabolizer) — **ACTIONABLE**

Propranolol can be prescribed at standard label-recommended dosage and administration with careful titration and monitoring until a favorable response is achieved.

Quinidine
Quinidine®

Normal Exposure to Quinidine — **INFORMATIVE**

Pharmacogenetic guidance: In vitro studies using human liver microsomes have shown CYP3A as the primary metabolizing enzyme for quinidine. No genetically guided drug selection or dosing adjustments are recommended. **Polypharmacy guidance**: Co-administration of drugs/herbs that are known to induce or inhibit CYP3A can change plasma concentrations of quinidine. This may result in adverse events or sub-or supra-therapeutic drug concentration modulating the risk of QT prolongation.

Ranolazine
Ranexa®

Normal Sensitivity to Ranolazine (CYP2D6: Intermediate Metabolizer) — **ACTIONABLE**

Ranolazine is metabolized mainly by CYP3A4, and to a lesser extent by CYP2D6. This drug can be prescribed at standard label-recommended dosage and administration. The recommended initial dose is 375 mg twice daily. After 2–4 weeks, the dose should be titrated to 500 mg twice daily, and according to the patient's response, further titrated to a recommended maximum dose of 1000 mg twice daily.

If patient experiences treatment-related adverse events (e.g. dizziness, nausea, vomiting, or syncope), Down titration of ranolazine 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.

Rivaroxaban
Xarelto®

Normal Response to Rivaroxaban — **INFORMATIVE**

Pharmacogenetic guidance: Rivaroxaban is metabolized by CYP3A4, CYP3A5, and CYP2J2. It is also a substrate for P-gp (ABCB1) and BCRP (ABCG2) transporters. Genetic polymorphisms of these genes are not expected to affect the efficacy or safety profiles of rivaroxaban. **Polypharmacy guidance:** Avoid concomitant use of rivaroxaban with combined P-gp and strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, lopinavir/ritonavir, ritonavir, indinavir, and conivaptan). Avoid concomitant use of rivaroxaban with drugs that are combined P-gp and strong CYP3A4 inducers (e.g., carbamazepine, phenytoin, rifampin, and St. John's wort). Patients with renal impairment coadministered rivaroxaban with drugs classified as combined P-gp and moderate CYP3A4 inhibitors (e.g., diltiazem, verapamil, dronedarone, and erythromycin) have increased exposure compared with patients with normal renal function and no inhibitor use. Significant increases in rivaroxaban exposure may increase bleeding risk.

Rosuvastatin
Crestor®

Normal Myopathy Risk (SLCO1B1 521T>C T/T)
INFORMATIVE

Rosuvastatin plasma concentrations are not expected to increase, and unless other genetic or circumstantial risk factors are present, rosuvastatin can be prescribed at standard FDA-recommended starting doses and adjusted based on disease -specific guidelines. The myopathy risk increases with use of the 40 mg dose. (Other myopathy predisposing factors include advanced age (≥65), uncontrolled hypothyroidism, renal impairment, high statin dose, comedications, and female gender.)

Simvastatin
Zocor®

Normal Myopathy Risk (SLCO1B1: Normal Function)
ACTIONABLE

Simvastatin plasma concentrations are not expected to be elevated, and unless other genetic or circumstantial risk factors are present, simvastatin can be prescribed at standard FDA-recommended starting doses and adjusted based on disease-specific guidelines. **The FDA recommends against the use of the 80 mg daily dose unless the patient had already tolerated this dose for 12 months without evidence of myopathy.** Other myopathy predisposing factors include advanced age (≥65), uncontrolled hypothyroidism, renal impairment, high statin dose, comedications, and female gender.

Simvastatin
Zocor®

Normal Response to Simvastatin (CYP3A4: Normal Metabolizer)
INFORMATIVE

The genotype result indicates that the patient does not carry the CYP3A4*22 allele (this allele is associated with a decreased CYP3A4 enzyme activity). The patient is expected to achieve an optimal lipid control goal with standard simvastatin dose requirements.

Sotalol
Betapace®, Sorine®, Sotylize®

Normal Exposure to Sotalol
INFORMATIVE

Pharmacogenetic guidance: Excretion of sotalol is predominantly via the kidney in the unchanged form, and therefore lower doses are necessary in conditions of renal impairment. No genetically guided drug selection or dosing adjustments are recommended. **Polypharmacy guidance**: Co-administration of sotalol with drugs that can prolong the QT interval can increase the patient's risk for developing drug induced long QT syndrome.

Telmisartan
Micardis®

Normal Sensitivity to Telmisartan
ACTIONABLE

Pharmacogenetic guidance: Telmisartan is metabolized by conjugation to form a pharmacologically inactive acyl glucuronide. Telmisartan is not metabolized by the cytochrome P450 isoenzymes. Genetic variability of the cytochrome P450 genes is not expected to affect the patient's response to telmisartan. No genotype-based dosing adjustments are available.

Ticagrelor
Brilinta®

Normal Response to Ticagrelor
INFORMATIVE

Pharmacogenetic guidance: Ticagrelor is extensively metabolized by CYP3A4 and CYP3A5 to both active and inactive metabolites, and this drug does not require bioactivation to achieve its antiplatelet effect. The drug is also a substrate of P-glycoprotein, encoded by the ABCB1 gene. Studies have shown that the efficacy and safety profile of ticagrelor do not depend on CYP2C19 or CYP3A5 metabolizer statuses. Moreover, preliminary studies indicate that relevant genetic variants within the ABCB1, SLCO1B1, CYP3A4 and UGT2B7 genes do not affect ticagrelor exposure, efficacy or safety profiles. No genetically-guided drug selection or dosing recommendations are available. **Polypharmacy guidance:** In presence of strong CYP3A4 inhibitors, significantly increased exposure to ticagrelor is expected which may lead to adverse reactions such as dyspnea or bleeding. These drugs should be avoided with ticagrelor. Strong CYP3A4 inducers can significantly decrease ticagrelor exposure (resulting in a loss of efficacy) and these drugs should also be avoided. Ticagrelor is a weak inhibitor of CYP3A4 and P-glycoprotein and some substrates of these proteins should be closely monitored and their dosing adjusted when coadministered with this medication.

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Torsemide
Demadex®

Normal Torsemide Exposure (CYP2C9: Normal Metabolizer) — **INFORMATIVE**

The patient's genotype predicts a normal exposure to torsemide and this drug can be prescribed at label-recommended dosage and administration.

Valsartan
Diovan®, Entresto®

Normal Sensitivity to Valsartan — **ACTIONABLE**

Pharmacogenetic guidance: Valsartan is excreted largely as unchanged compound. CYP2C9 is responsible for the formation of a minor metabolite, valeryl 4-hydroxy valsartan, which accounts for about 9% of a dose. Given the limited contribution of CYP2C9 in the overall disposition of valsartan, genetic variability of the CYP2C9 gene is not expected to affect the patient's response to valsartan. No genotype-based dosing adjustments are available.

Vorapaxar
Zontivity®

Normal Response to Vorapaxar — **ACTIONABLE**

Pharmacogenetic guidance: vorapaxar is metabolized primarily by CYP3A4, with contribution from CYP2J2. Genetic polymorphisms of these genes are not expected to affect the efficacy or safety profiles of this drug. Vorapaxar is contraindicated in people who have had a stroke, transient ischemic attack (TIA), or intracranial hemorrhage, (ICH) because of the increased bleeding risk. **Polypharmacy guidance:** Avoid concomitant use of vorapaxar with strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, lopinavir/ritonavir, ritonavir, indinavir, and conivaptan). Significant increases in vorapaxar exposure may increase bleeding risk. Avoid concomitant use with drugs that are strong CYP3A4 inducers (e.g., carbamazepine, phenytoin, rifampin, and St. John's wort).

Warfarin
Coumadin®

Average Dosing Requirements are Expected (CYP2C9 *1/*1; VKORC1 -1639G>A G/G) — **ACTIONABLE**

When initiating warfarin treatment for indications with a target INR of 2-3, consider one of the following methods to estimate dosing requirements:

FDA Label: CYP2C9 and VKORC1 genotype results indicate an expected therapeutic dose of 5-7 mg/day.

Pharmacogenomics algorithms/calculators available at www.warfarindosing.org:

Caucasians and Asians: Use the patient's demographics and other clinical factors along with CYP2C9 and VKORC1 genotypes to calculate the expected therapeutic dose.

Africans and African Americans: Use the patient's demographics and other clinical factors along with CYP2C9 and VKORC1 genotypes to calculate the expected therapeutic dose.

The provided recommendations in Africans and African Americans apply only when all the following CYP2C9 alleles are tested: *5, *6, *8, *11.

4U Health

PATIENT INFORMATION

NAME: **Demo Patient**
ACC #: DEMO
DOB: 1/1/1900
SEX:

Test Details

Gene	Genotype	Phenotype	Alleles Tested
Apolipoprotein E	ε3/ε3	Normal APOE function	ε2, ε4, (ε3 is reference)
CYP2C19	*17/*17	Ultra-Rapid Metabolizer	*2, *3, *4A, *4B, *6, *7, *8, *9, *10, *17
CYP2C9	*1/*1	Normal Metabolizer	*2, *3, *4, *5, *6, *8, *11, *27
CYP2D6	*10/*17	Intermediate Metabolizer	*2, *3, *4, *4M, *6, *7, *8, *9, *10, *12, *114, *14, *17, *29, *35, *41, *5 (gene deletion), XN (gene duplication)
CYP3A4	*1/*1B	Normal Metabolizer	*1B, *22
CYP3A5	*3/*6	Poor Metabolizer	*2, *3, *6, *7
F2 F5	rs1799963 GG rs6025 CC	Normal Risk of Thrombosis	rs1799963, rs6025
ITGB3	176T>C T/T	Normal Platelet Reactivity	176T>C
LPA	rs10455872 A/A rs3798220 T/T	No increased risk of cardiovascular disease	rs3798220, rs10455872
MTHFR	c.1286A>C GT c.665C>T GG	No Increased Risk of Hyperhomocysteinemia	c.1286A>C, c.665C>T
SLCO1B1	521T>C T/T	Normal Function	521T>C
VKORC1	-1639G>A G/G	Low Warfarin Sensitivity	-1639G>A

Methodology: *Array based assays detect listed alleles, including all common and most rare variants with known clinical significance at analytical sensitivity and specificity >99%.*

Limitation: *This test will not detect all the known mutations that result in altered or inactive tested genes. Absence of a detectable gene mutation or polymorphism does not rule out the possibility that a patient has intermediate or high sensitivity phenotypes due to the presence of an undetected polymorphism or due to drug-drug interactions. There may be other genetic factors impacting individual patient dosing that are not included in this test.*

Disclaimer: *This test was developed and its performance characteristics determined by Vision Laboratories. It has not been cleared or approved by the US Food and Drug Administration (FDA). The FDA does not require this test to go through premarket FDA review. This test is used for clinical purposes. It should not be regarded as investigational or for research. This laboratory is certified under the Clinical Laboratory Improvement Amendments (CLIA) as qualified to perform high complexity clinical laboratory testing. Only a physician, pharmacist or other healthcare professional should advise a patient on the use of information in this report.*

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.

4U Health

PATIENT INFORMATION

NAME: **Demo Patient**
ACC #: DEMO
DOB: 1/1/1900
SEX:

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.

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Vision Laboratories

REPORT DETAILS
Name: Demo Patient
DOB: 1/1/1900
ACC #: DEMO

Pharmacogenetic Test Summary

Apolipoprotein E	ε3/ε3	Normal APOE function
CYP2C19	*17/*17	Ultra-Rapid Metabolizer
CYP2C9	*1/*1	Normal Metabolizer
CYP2D6	*10/*17	Intermediate Metabolizer
CYP3A4	*1/*1B	Normal Metabolizer
CYP3A5	*3/*6	Poor Metabolizer
Factor II	rs1799963 GG	Normal Thrombosis Risk
Factor V Leiden	rs6025 CC	Normal Thrombosis Risk
ITGB3	176T>C T/T	Normal Platelet Reactivity
LPA	rs10455872 A/A	Wild-type for rs10455872
LPA	rs3798220 T/T	Wild-type for rs3798220
MTHFR	c.665C>T GG	Normal MTHFR Activity
MTHFR	c.1286A>C GT	Reduced MTHFR Activity
SLCO1B1	521T>C T/T	Normal Function
VKORC1	-1639G>A G/G	Low Warfarin Sensitivity

For a complete report contact Vision Laboratories, LLC
visionlaboratories.com

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