VeritasGenetics
myGenome

Patient	Lisa Waddell	Sample Type	Saliva
DOB	May 17 1967	Sample Collected	Nov 07 2016
Sex	Female	Sample Received	Nov 14 2016
Provider	John Butcher	Batch ID	VGX1878R2RR,VGX1878R2R,
Date of Report	Dec 08 2017	Patient ID	55001604176800

SUMMARY OF FINDINGS

The following pathogenic/likely pathogenic variants have been identified and are summarized below. Please view the full Veritas myGenome Consumer or Web Report for detailed information.

CLINICALLY SIGNIFICANT FINDINGS

Pathogenic variant(s) identified may indicate that your patient is affected with or predisposed to develop a genetic disorder(s). The finding of a pathogenic variant does not guarantee your patient will develop the disease associated with that gene(s). All positive findings (pathogenic or likely pathogenic variants) should be interpreted in the context of the patient's clinical and family history. Genetic counseling is recommended for these patients as additional evaluation may be indicated.

GENE	TRANSCRIPT	VARIANT	ZYGOSITY[1]	DISEASE ASSOCIATION(S)	CLASSIFICATION	ACMG[2]	ClinVar[3]
APOE	NM_000041	[c.388T>C];[c.526C=]	homozygous	Alzheimer Disease	pathogenic/likely pathogenic	No	Yes

[1]When a genetic variant is found on the X chromosome in a male, it is hemizygous. This is because males have one X chromosome as compared to females who have 2 X chromosomes.
[2]The American College of Medical Genetics (ACMG) recommends that pathogenic/likely pathogenic variants in 59 specific genes should always be reported because they may be of clinical significance and impact medical management (Kalia SS, Adelman K, Bale SJ, et al. Recommendations for reporting of secondary findings in clinical exome and genome sequencing, 2016 update (ACMG SF v2.0): a policy statement of the American College of Medical Genetics and Genomics. Genet Med. 2016. PMID 27854360).
[3]Classified as pathogenic/likely pathogenic by at least one submitter.

REPRODUCTIVE HEALTH - CARRIER STATUS

Pathogenic variant(s) in autosomal recessive or x-linked genes may indicate that your patient is a carrier of a genetic disorder(s). In most cases these variants will not affect your patient's health, but can identify potential risk of passing a genetic disorder on to their children. When family planning is being considered, screening of the patient's partner is recommended. Genetic counseling is recommended to discuss testing options and implications.

GENE	TRANSCRIPT	VARIANT	ZYGOSITY[1]	DISEASE ASSOCIATION(S)	CLASSIFICATION	ACMG[2]	ClinVar[3]
AGL	NM_000642	c.3965delT (p.Val1322Alafs*27)	heterozygous	Glycogen Storage Disease Type III	pathogenic/likely pathogenic	No	Yes

[1]When a genetic variant is found on the X chromosome in a male, it is hemizygous. This is because males have one X chromosome as compared to females who have 2 X chromosomes.
[2]The American College of Medical Genetics (ACMG) recommends that pathogenic/likely pathogenic variants in 59 specific genes should always be reported because they may be of clinical significance and impact medical management (Kalia SS, Adelman K, Bale SJ, et al. Recommendations for reporting of secondary findings in clinical exome and genome sequencing, 2016 update (ACMG SF v2.0): a policy statement of the American College of Medical Genetics and Genomics. Genet Med. 2016. PMID 27854360).
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PHARMACOGENOMICS

Genetic variations can influence individual response to drugs. Knowing whether a patient carries any of these genetic variations can help prescribers individualize drug therapy, decrease the chance for adverse drug events, and increase the effectiveness of drugs.

Drug Category: Cardiovascular

DRUG	TRADE NAME(S)		GENE	VARIANT	IMPLICATIONS
Ace Inhibitors	benazepril (Lotensin®, Lotrel®), captopril, cilazapril, enalapril (Epaned®, Vasotec®), fosinopril, lisinopril (Prinivil®, Qbrelis®, Zestril®), moexipril, perindopril (Aceon®), quinapril (Accupril®), ramipril (Altace®), spirapril, trandolapril (Mavik®, Tarka®)	PharmGKB 2A	*KCNIP4*	rs145489027, GG	Patients with the GG genotype may be less likely to experience ACE inhibitor induced cough when taking ACE inhibitors as compared to patients with the AG and AA genotype. Other clinical and genetic factors may also influence likelihood of ACE inhibitor induced cough in patients who are taking ACE inhibitors.
atorvastatin	Lipitor®	PharmGKB 2A	*APOE*	rs7412, CC	Patients with the CC genotype who are treated with atorvastatin may have a reduced response (less reduction in LDL-cholesterol) as compared to patients with the CT or TT genotype. Other genetic and clinical factors may also influence a patient's response to atorvastatin treatment.
clopidogrel	Plavix®	CPIC	*CYP2C19*	*1/*17	**Implications:** Increased platelet inhibition; decreased residual platelet aggregation The CYP2C19*17 allele may be associated with increased risk of bleeding [Article 20083681]. **Metabolizer Status:** Ultrarapid metabolizer (UM) (~5-30% of patients) **Recommendations:** Clopidogrel - label recommended dosage and administration **Classification of Recommendation:** Strong
digoxin	Lanoxin®	PharmGKB 2A	*ABCB1*	rs1045642, AA	Patients with AA genotype may have decreased metabolism and increased serum concentration of digoxin as compared to patients with the GG genotype. Other genetic and clinical factors may also impact the metabolism of digoxin.
hmg coa reductase inhibitors (statins)	atorvastatin (Lipitor®), fluvastatin (Lescol®), lovastatin (Altoprev®), pitavastatin (Livalo®), pravastatin (Pravachol®), rosuvastatin (Crestor®), simvastatin (Zocor®)	PharmGKB 2A	*HMGCR*	rs17244841, AA	Patients with the AA genotype who are treated with statins may be more likely to respond as compared to patients with the AT or TT genotype. Other genetic and clinical factors may also influence a patient's response when treated with statins.
hmg coa reductase inhibitors (statins)	atorvastatin (Lipitor®), fluvastatin (Lescol®), lovastatin (Altoprev®), pitavastatin (Livalo®), pravastatin (Pravachol®), rosuvastatin (Crestor®), simvastatin (Zocor®)	PharmGKB 2A	*SLCO1B1*	rs4149056, TT	Patients with the TT genotype may have decreased plasma drug concentrations of particular statins as compared to patients with the CC or CT genotype. For some statins this is associated with decreased risk of adverse events - see individual drug annotations particularly for simvastatin. Other genetic and clinical factors may also influence a patient's metabolism and response to statins.
pravastatin	Pravachol®	PharmGKB 2A	*SLCO1B1*	rs4149056, TT	Patients with the TT genotype may have decreased plasma concentrations of pravastatin as compared to patients with the CC or CT genotype. Other genetic and clinical factors may also influence a patient's metabolism of pravastatin.
pravastatin	Pravachol®	PharmGKB 2A	*SLCO1B1*	rs4149015, GG	Patients carrying the GG genotype may have increased chance of response to pravastatin compared to patients carrying the AA or AG genotype. Other genetic and clinical factors may also influence a patient's response.
propafenone	Rythmol®	PharmGKB 2A	*CYP2D6*	*1/*4	No specific recommendations are available for this genotype.
rosuvastatin	Crestor®	PharmGKB 2A	*SLCO1B1*	rs4149056, TT	Patients with the TT genotype may have lower plasma concentrations of rosuvastatin as compared to patients with the CC genotype. No association is seen between genotypes of this variant and change in LDL-cholesterol levels in response to rosuvastatin treatment. Other genetic and clinical factors may also influence a patient's metabolism and response to rosuvastatin.
simvastatin	Zocor®	PharmGKB 2A	*ABCB1*	rs2032582, AC	Patients with the AC genotype who are treated with simvastatin may have a better response (as measured by higher reductions in total cholesterol) as compared to patients with the CC genotype. Other genetic and clinical factors may also influence a patient's response to simvastatin treatment.
simvastatin	Zocor®	PharmGKB 1A	*SLCO1B1*	rs4149056, TT	Patients with the TT genotype may have a lower risk of simvastatin-related myopathy as compared to patients with the CT or CC genotype. Other genetic and clinical factors may also influence a patient's risk for toxicity.

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Drug Category: Endocrinology

DRUG	TRADE NAME(S)		GENE	VARIANT	IMPLICATIONS
rosiglitazone	Avandia®	PharmGKB 2A	*CYP2C8*	rs10509681, TT	Patients with the TT (CYP2C8*1/*1) genotype may have decreased metabolism of rosiglitazone, a larger change in HbA1c, and an increased risk of edema as compared to patients with the CC (CYP2C8*3/*3) or CT (CYP2C8*3/*1) genotype. One study found no association with blood glucose levels. Other genetic and clinical factors may also influence metabolism of rosiglitazone, risk of edema and blood glucose levels.

Drug Category: Gastroenterology

DRUG	TRADE NAME(S)		GENE	VARIANT	IMPLICATIONS
azathioprine	Azasan®, Imuran®	PharmGKB 1B	*NUDT15*	rs116855232, CC	Patients with the CC genotype who are treated with thiopurines for inflammatory bowel diseases (IBD) or acute lymphoblastic leukemia (ALL) may have a reduced, but not absent risk of developing leukopenia or alopecia as compared to patients with the CT or TT genotype. Patients may also tolerate higher doses of thiopurines and be less likely to discontinue thiopurine treatment as compared to patients with the CT or TT genotype, possibly due to the reduced risk for adverse effects. Other genetic and clinical factors may also influence a patient's risk for leukopenia, alopecia or treatment discontinuation.
azathioprine	Azasan®, Imuran®	CPIC	*TPMT*	*1/*1S	**Implications:** Lower concentrations of TGN metabolites, higher methylTIMP, this is the "normal" pattern **Metabolizer Status:** Normal Metabolizer **Recommendations:** Start with normal starting dose (e. g. , 2-3 mg/kg/d) and adjust doses of azathioprine based on disease-specific guidelines. Allow 2 weeks to reach steady state after each dose adjustment. **Classification of Recommendation:** Strong
lansoprazole	Prevacid®	PharmGKB 2A	*CYP2C19*	*1/*17	No specific recommendations are available for this genotype.
omeprazole	Prilosec®, Zegerid®	PharmGKB 2A	*CYP2C19*	*1/*17	No specific recommendations are available for this genotype.
ondansetron	Zofran®, Zuplenz®	PharmGKB 2A	*ABCB1*	rs2032582, AC	Patients with genotype AC may have increased likelihood of nausea and vomiting shortly after being treated with ondansetron as compared to patients with the AA genotype. Other genetic and clinical factors may also influence a patient's response to ondansetron.
ondansetron	Zofran®, Zuplenz®	PharmGKB 2A	*ABCB1*	rs1045642, AA	Patients with genotype AA may have decreased likelihood of nausea and vomiting shortly after being treated with ondansetron as compared to patients with genotype AG or GG. Other genetic and clinical factors may also influence a patient's response to ondansetron.
ondansetron	Zofran®, Zuplenz®	CPIC	*CYP2D6*	*1/*4	**Implications:** Normal metabolism **Metabolizer Status:** Normal metabolizer **Recommendations:** Initiate therapy with recommended starting dose. **Classification of Recommendation:** Strong
rabeprazole	Aciphex®	PharmGKB 2A	*CYP2C19*	*1/*17	No specific recommendations are available for this genotype.
tropisetron	Navoban	CPIC	*CYP2D6*	*1/*4	**Implications:** Normal metabolism **Metabolizer Status:** Normal metabolizer **Recommendations:** Initiate therapy with recommended starting dose. **Classification of Recommendation:** Strong

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Drug Category: Hematology

DRUG	TRADE NAME(S)		GENE	VARIANT	IMPLICATIONS
acenocoumarol		PharmGKB 2A	*CYP2C9*	*1/*1	Patients with the *1/*1 genotype may require a higher dose of acenocoumarol as compared to patients with the *1/*2, *1/*3, *2/*2, *2/*3, or *3/*3 genotypes, although this is contradicted by some studies. Other genetic and clinical factors may also influence a patient's required acenocoumarol dosage.
acenocoumarol		PharmGKB 1B	*VKORC1*	rs9923231, CT	Patients with the CT genotype who are treated with acenocoumarol or phenprocoumon may require a lower dose as compared to patients with the CC genotype or may require a higher dose as compared to patients with the TT genotype. Other genetic and clinical factors may also influence a patient's acenocoumarol or phenprocoumon maintenance dose requirement.
clopidogrel	Plavix®	CPIC	*CYP2C19*	*1/*17	**Implications:** Increased platelet inhibition; decreased residual platelet aggregation The CYP2C19*17 allele may be associated with increased risk of bleeding [Article 20083681]. **Metabolizer Status:** Ultrarapid metabolizer (UM) (~5-30% of patients) **Recommendations:** Clopidogrel - label recommended dosage and administration **Classification of Recommendation:** Strong
phenprocoumon		PharmGKB 2A	*CYP4F2*	rs2108622, CC	Patients with the CC genotype who are treated with phenprocoumon may require a lower dose as compared to patients with the TT genotype. Other genetic and clinical factors may also influence a patient's required phenprocoumon dose.
phenprocoumon		PharmGKB 1B	*VKORC1*	rs9923231, CT	Patients with the CT genotype who are treated with acenocoumarol or phenprocoumon may require a lower dose as compared to patients with the CC genotype or may require a higher dose as compared to patients with the TT genotype. Other genetic and clinical factors may also influence a patient's acenocoumarol or phenprocoumon maintenance dose requirement.
rasburicase	Elitek®	CPIC	*G6PD*	*B/*B	**Implications:** Low or reduced risk of hemolytic anemia. **Phenotype (Genotype):** Normal. **Recommendations:** No reason to withhold rasburicase based on G6PD status. **Classification of Recommendation:** Strong
warfarin	Coumadin®, Jantoven®	N/A	*CYP2C9*	*1/*1	The best way to estimate the anticipated stable dose of warfarin is to use the algorithms available on http: //www. warfarindosing. org
warfarin	Coumadin®, Jantoven®	PharmGKB 1B	*CYP4F2*	rs2108622, CC	Patients with the CC genotype who are treated with warfarin may require a lower dose as compared to patients with the CT or TT genotype. Some studies have not found an association between genotypes of this variant and warfarin dose, or report finding a trend that was not statistically significant. PharmGKB. org lists this variant as not currently associated with time to international normalized ratio (INR), risk of hemorrhage, or risk of over-coagulation. Other genetic and clinical factors may also influence a patient's required warfarin dose. The best way to estimate the anticipated stable dose of warfarin is to use the algorithms available on http: //www. warfarindosing. org. Enter this genotype as CYP4F2 V433M CC (wildtype).
warfarin	Coumadin®, Jantoven®	PharmGKB 2A	*VKORC1*	rs9923231, CT	Patients with genotype CT may require shorter time to therapeutic international normalized ratio (INR) when treated with warfarin as compared with patients with genotype CC. Other genetic and clinical factors may also influence the response to warfarin. Patients with the CT genotype may have increased risk of over-anticoagulation when treated with warfarin as compared with patients with genotype CC. Other genetic and clinical factors may also influence the toxicity to warfarin. The best way to estimate the anticipated stable dose of warfarin is to use the algorithms available on http: //www. warfarindosing. org. Enter this genotype as VKORC1-1639/3673 AG.

Drug Category: Infectious Diseases

DRUG	TRADE NAME(S)		GENE	VARIANT	IMPLICATIONS
atazanavir	Reyataz®	PharmGKB 1A	*UGT1A1*	rs8175347, [6]/[7]	Patients with the (TA)6/(TA)7 genotype and HIV may have increased levels of bilirubin leading to an increased likelihood for hyperbilirubinemia when treated with atazanavir (in most studies boosted with low dose of ritonavir) as compared to patients with the (TA)6/(TA)6. However, contradictory findings exist. Other genetic and clinical factors may also influence a patient's response to atazanavir.

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atazanavir	Reyataz®	CPIC	*UGT1A1*	rs8175347, rs887829, rs4148323, [6]/[7], CT,GG	The UTG1A1 genotype could not be resolved. This is either due to the presence of a novel genotype or because there are multiple possible genotypes that cannot be resolved with the methodology used for this test.
chlorproguanil		PharmGKB 1B	*G6PD*	rs1050828, CC	Patients with the CC genotype with Malaria who are treated with chlorproguanil/dapsone/artesunate may have 1) a decreased, but not absent, risk of hemolysis and severe/ unsafe hemoglobin decreases 2) decreased, but not absent, risk of requiring a blood transfusion as compared to patients with the TT genotype. Other genetic and clinical factors may also influence a patient's response to chlorproguanil/dapsone/artesunate.
efavirenz	Sustiva®	PharmGKB 1B, 2A	*CYP2B6*	rs3745274, TT	Patients with the TT genotype and HIV infection may have increased plasma concentrations and decreased clearance of efavirenz as compared to patients with the GT or GG genotype. In addition, patients with the TT genotype may have an increased risk for efavirenz-induced side effects, including sleep- and central nervous system-related side effects, as compared to patients with the GG or GT genotype. However, patients with the TT genotype may also have a decreased risk for immunological failure, as compared to patients with the GG genotype. Other genetic and clinical factors may also influence a patient's exposure to efavirenz and risk for toxicity.
efavirenz	Sustiva®	PharmGKB 2A	*CYP2B6*	rs2279343, GG	Patients with the GG genotype and HIV may have decreased clearance and increased plasma concentration of efavirenz as compared to patients with the AG or AA genotype. Other genetic and clinical factors may also influence a patient's exposure to efavirenz.
efavirenz	Sustiva®	PharmGKB 2A	*CYP2B6*	rs2279345, CC	Patients with the CC genotype and HIV may have increased metabolism of efavirenz resulting in lower efavirenz plasma levels as compared to patients with the TT genotype. Other genetic and clinical factors may also influence metabolism and plasma concentrations of efavirenz.
efavirenz	Sustiva®	PharmGKB 2A	*CYP2B6*	rs28399499, TT	Patients with the TT genotype and HIV may have decreased plasma drug exposure when treated with efavirenz as compared to patients with the CT or CC genotype. Other genetic and clinical factors may also influence a patient's drug metabolism.
ethambutol	Myambutol	PharmGKB 2A	*NAT2*	rs1041983, TT	Patients with the TT genotype and tuberculosis (TB) may have an increased risk for hepatotoxicity when treated with anti-TB drugs as compared to patients with the CC genotype. Other genetic and clinical factors may also influence risk for hepatotoxicity.
ethambutol	Myambutol	PharmGkb 2A	*NAT2*	rs1799930, AA	Patients with the AA genotype and tuberculosis (TB) may have an increased risk of hepatotoxicity when treated with anti-TB drugs as compared to patients with the GG genotype. Other genetic and clinical factors may also influence risk for hepatotoxicity.
isoniazid	Laniazid	PharmGKB 2A	*NAT2*	*6/*6	Patients with the *6 allele and Tuberculosis who have another slow acetylator NAT2 allele (e. g. *5, *6, *7, *14) may have an increased risk of developing hepatotoxicity induced by isoniazid-containing anti-TB drug regimens, as compared to those with one or two NAT2 alleles conferring a rapid acetylator phenotype. Other genetic and clinical factors may also influence a patient's risk of drug-induced liver injury.
isoniazid	Laniazid	PharmGKB 2A	*NAT2*	rs1041983, TT	Patients with the TT genotype and tuberculosis (TB) may have an increased risk for hepatotoxicity when treated with anti-TB drugs as compared to patients with the CC genotype. Other genetic and clinical factors may also influence risk for hepatotoxicity.
isoniazid	Laniazid	PharmGKB 2A	*NAT2*	rs1799930, AA	Patients with the AA genotype and tuberculosis (TB) may have an increased risk of hepatotoxicity when treated with anti-TB drugs as compared to patients with the GG genotype. They also may have decreased clearance of isoniazid as compared to those with the AG or GG genotype. Other genetic and clinical factors may also influence risk for hepatotoxicity and clearance of isoniazid.
nevirapine	Viramune®	PharmGKB 2A	*ABCB1*	rs1045642, AA	Patients with the AA genotype and HIV-1 infection who are treated with nevirapine may have a decreased, but not absent, risk for nevirapine hepatotoxicity as compared to patients with the GG genotype. Other genetic and clinical factors may also influence a patient's risk for hepatotoxicity with nevirapine treatment.
nevirapine	Viramune®	PharmGKB 2A	*CYP2B6*	rs3745274, TT	Patients with the TT genotype and HIV infection may have decreased clearance of and increased exposure to nevirapine as compared to patients with the GG genotype. Other genetic and clinical factors may also influence clearance of nevirapine and exposure to drug.
nevirapine	Viramune®	PharmGKB 2A	*CYP2B6*	rs28399499, TT	Patients with the TT genotype and HIV may have decreased plasma drug exposure when treated with nevirapine as compared to patients with the CT or CC genotype. Other genetic and clinical factors may also influence a patient's drug metabolism.
Peginterferon-containing regimens	Pegasys®, Pegintron®, Sylatron®	PharmGKB 2A	*IFNL3*	rs11881222, AG	Patients with the AG genotype and hepatitis C or HIV may have a poorer response to treatment with peginterferon-alpha and ribavirin as compared to patients with the AA genotype. Other genetic and clinical factors may also influence response to peginterferon-alpha and ribavirin treatment.
Peginterferon-containing	Pegasys®, Pegintron®, Sylatron®	PharmGKB 1B	*IFNL3*	rs8099917, TT	Patients with the TT genotype may have increased response (higher sustained virologic response, SVR) to peginterferon alfa and ribavirin

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regimens	Pegasys®, Pegintron®, Sylatron®	PharmGKB 1B	*IFNL3*	rs8099917, TT	therapy in people with HCV genotype 1 as compared to patients with the GG or GT genotype. This association is significant in HCV genotype 1 patients, but may not be significant in HCV genotype 2, genotype 3 or genotype 5 patients. In addition, patients with the TT genotype may have higher response rates (SVR) to triple therapy (telaprevir, peginterferon alfa-2a/b and ribavirin) in people with Hepatitis C genotype 1 as compared to patients with the GG or GT genotype. Other genetic and clinical factors may also influence a patient's response to HCV peginterferon+ribavirin or triple therapy.
Peginterferon-containing regimens	Pegasys®, Pegintron®, Sylatron®	PharmGKB 1A	*IFNL4*	rs12979860, CT	Patients with the CT genotype and Hepatitis C genotype 1 may have decreased response (sustained virological response, SVR) when administered peg interferon alpha (2a, 2b) and ribavirin as compared to patients with the CC genotype. Patients with the CT genotype may also have lower spontaneous clearance in acute HCV infections than patients with the CC genotype. In addition, patients with the CT genotype and Hepatitis C genotype 1 may have lower response rates (SVR) to triple therapy (telaprevir or boceprevir in combination with peginterferon alfa-2a/b and ribavirin) as compared to patients with the CC genotype. The impact of IL28B genotype may be dampened in patients with prior PegIFN/RBV treatment failure. Other genetic and clinical factors may also influence a patient's response to peg interferon+ribavirin or triple therapy.
pyrazinamide		PharmGKB 2A	*NAT2*	rs1041983, TT	Patients with the TT genotype and tuberculosis (TB) may have an increased risk for hepatotoxicity when treated with anti-TB drugs as compared to patients with the CC genotype. Other genetic and clinical factors may also influence risk for hepatotoxicity.
pyrazinamide		PharmGKB 2A	*NAT2*	rs1799930, AA	Patients with the AA genotype and tuberculosis (TB) may have an increased risk of hepatotoxicity when treated with anti-TB drugs as compared to patients with the GG genotype. Other genetic and clinical factors may also influence risk for hepatotoxicity.
rifampin	Rifadin®, Rimactane	PharmGKB 2A	*NAT2*	rs1041983, TT	Patients with the TT genotype and tuberculosis (TB) may have an increased risk for hepatotoxicity when treated with anti-TB drugs as compared to patients with the CC genotype. Other genetic and clinical factors may also influence risk for hepatotoxicity.
rifampin	Rifadin®, Rimactane	PharmGKB 2A	*NAT2*	rs1799930, AA	Patients with the AA genotype and tuberculosis (TB) may have an increased risk of hepatotoxicity when treated with anti-TB drugs as compared to patients with the GG genotype. Other genetic and clinical factors may also influence risk for hepatotoxicity.

Drug Category: Neurology

DRUG	TRADE NAME(S)		GENE	VARIANT	IMPLICATIONS
clobazam	Onfi®	PharmGKB 2A	*CYP2C19*	*1/*17	No specific recommendations are available for this genotype.
phenytoin	Dilantin®, Phenytek®	PharmGKB 1A	*CYP2C9*	*1/*1	Patients with *1/*1 genotypes may have increased metabolism, decreased plasma concentration, decreased toxicity and decreased adverse drug reactions when treated with phenytoin in epilepsy when compared to patients with *1/*3, *2/*3 *2/*2 or *3/*3 genotypes. Other genetic and clinical factors may also influence a patient's response to therapy. **Note that this test does not include HLA genotyping.** This is important since there is a known strong association between the risk of developing Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN) and the presence of HLA-B*1502, an inherited allelic variant of the HLA B gene, in patients using carbamazepine. Limited evidence suggests that HLAB*1502 may also be a risk factor for the development of SJS/TEN in patients of Asian ancestry taking other antiepileptic drugs associated with SJS/TEN, including phenytoin. Consideration should be given to avoiding phenytoin as an alternative for carbamazepine in patients positive for HLA-B*1502.

Drug Category: OB/GYN

DRUG	TRADE NAME(S)		GENE	VARIANT	IMPLICATIONS
hormonal contraceptives for systemic use		PharmGKB 2A	*F5*	rs6025, CC	Patients with the CC genotype (normal Factor V) may have a decreased risk of experiencing thrombosis when receiving oral contraceptives as compared to patients with the CT or TT genotype (carriers of Factor V Leiden). Both Factor V Leiden and oral contraceptives have been found to independently increase the risk for thrombosis, but together they may have a cumulative effect on thrombosis risk. Other genetic and clinical factors may also influence risk of thrombosis.

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Drug Category: Oncology

DRUG	TRADE NAME(S)		GENE	VARIANT	IMPLICATIONS
Alkylating Agents	busulfan (Busulfex®, Myleran®), carmustine (Bicnu®, Gliadel®), chlorambucil (Leukeran®), cyclophosphamide, dacarbazine, ifosfamide (Ifex®), lomustine (Gleostine®), mechlorethamine (Mustargen®, Valchlor®), melphalan (Alkeran®, Evomela®), pipobroman, streptozocin (Zanosar®), temozolomide (Temodar®), thiotepa (Tepadina®)	PharmGKB 2A	*NQO1*	rs1800566, GG	Patients with the GG genotype and Breast Neoplasms and cancer who are treated with chemotherapy regimes that include platinum compounds, anthracyclines and related substances, and nucleoside inhibitors may have a better outcome (overall survival and progression-free survival) as compared to patients with the AA genotype. However, this has been contradicted in some studies. Other genetic and clinical factors may also influence a patient's treatment outcome.
anthracyclines and related substances	cyclophosphamide, daunorubicin (Cerubidine), doxorubicin (Doxil®), epirubicin (Ellence®), idarubicin (Idamycin PFS®), mitoxantrone, valrubicin (Valstar®)	PharmGKB 2A	*NQO1*	rs1800566, GG	Patients with the GG genotype and Breast Neoplasms and cancer who are treated with chemotherapy regimes that include platinum compounds, anthracyclines and related substances, and nucleoside inhibitors may have a better outcome (overall survival and progression-free survival) as compared to patients with the AA genotype. However, this has been contradicted in some studies. Other genetic and clinical factors may also influence a patient's treatment outcome.
azathioprine	Azasan®, Imuran®	PharmGKB 1B	*NUDT15*	rs116855232, CC	Patients with the CC genotype who are treated with thiopurines for inflammatory bowel diseases (IBD) or acute lymphoblastic leukemia (ALL) may have a reduced, but not absent risk of developing leukopenia or alopecia as compared to patients with the CT or TT genotype. Patients may also tolerate higher doses of thiopurines and be less likely to discontinue thiopurine treatment as compared to patients with the CT or TT genotype, possibly due to the reduced risk for adverse effects. Other genetic and clinical factors may also influence a patient's risk for leukopenia, alopecia or treatment discontinuation.
azathioprine	Azasan®, Imuran®	CPIC	*TPMT*	*1/*1S	**Implications:** Lower concentrations of TGN metabolites, higher methylTIMP, this is the "normal" pattern **Metabolizer Status:** Normal Metabolizer **Recommendations:** Start with normal starting dose (e. g. , 2-3 mg/kg/d) and adjust doses of azathioprine based on disease-specific guidelines. Allow 2 weeks to reach steady state after each dose adjustment. **Classification of Recommendation:** Strong
capecitabine	Xeloda®	CPIC	*DPYD*	*1/*5	**Implications:** Normal DPD activity and normal risk for fluoropyrimidine toxicity. **Recommendations:** Use label-recommended dosage and administration. **Classification of Recommendation:** Moderate
capecitabine	Xeloda®	PharmGKB 1A	*DPYD*	rs67376798, TT	Patients with the TT genotype and cancer who are treated with fluoropyrimidine-based chemotherapy may have 1) increased clearance of the drug and 2) decreased, but not absent, risk and reduced severity of drug toxicity as compared to patients with the AT genotype. Fluoropyrimidines are often used in combination chemotherapy such as FOLFOX (fluorouracil, leucovorin and oxaliplatin), FOLFIRI (fluorouracil, leucovorin and irinotecan) or FEC (fluorouracil, epirubicin and cyclophosphamide) or with other drugs such as bevacizumab, cetuximab, raltitrexed. The combination and delivery of the drug may influence risk for toxicity. Other genetic and clinical factors may also influence response to fluoropyrimidine-based chemotherapy.
capecitabine	Xeloda®	PharmGKB 2A	*TYMS*	rs151264360, delTTAAAG/TTAAAG	Patients with the TTAAAG/del genotype and cancer who are treated with fluoropyrimidine-based chemotherapy may have increased survival time as compared to those with the TTAAAG/TTAAAG genotype, and decreased risk of toxicity as compared to those with the del/del genotype. Fluoropyrimidines are often used in combination chemotherapy such as FOLFOX (fluorouracil, leucovorin and oxaliplatin) or FOLFIRI (fluorouracil, leucovorin and irinotecan) or with other drugs such as paclitaxel. Other genetic and clinical factors may also influence a patient's response to treatment.
carboplatin		PharmGKB 2A	*MTHFR*	rs1801133, AG	This genotype could not be determined due to low read count and/or sequencing quality at the position of interest.
cisplatin		PharmGKB 1B	*XPC*	rs2228001, GT	Patients with the GT genotype may have an increased risk for toxicity with cisplatin treatment, including hearing loss and neutropenia, as compared to patients with the TT genotype. Other genetic and clinical factors may also influence a patient's risk for toxicity.
cyclophosphamide	ASTA	PharmGKB 2A	*GSTP1*	rs1695, GG	Patients with the GG genotype and Breast Neoplasms who are treated with cyclophosphamide and epirubicin may have 1) decreased drug response 2) increased severity of toxicity as compared to patients with AG and AA genotype. Some patients were additionally treated with fluorouracil. Other genetic and clinical factors may influence a patient's response to cyclophosphamide, epirubicin and fluorouracil.

*See Technical Note

VeritasGenetics
myGenome

Patient	Lisa Waddell	Sample Type	Saliva
DOB	May 17 1967	Sample Collected	Nov 07 2016
Sex	Female	Sample Received	Nov 14 2016
Provider	John Butcher	Batch ID	VGX1878R2RR,VGX1878R2R,
Date of Report	Dec 08 2017	Patient ID	55001604176800

cyclophosphamide	ASTA	PharmGKB 2A	*MTHFR*	rs1801133, AG	This genotype could not be determined due to low read count and/or sequencing quality at the position of interest.
epirubicin	Ellence®	PharmGKB 2A	*GSTP1*	rs1695, GG	Patients with the GG genotype and Breast Neoplasms who are treated with cyclophosphamide and epirubicin may have 1) decreased drug response 2) increased severity of toxicity as compared to patients with AG and AA genotype. Some patients were additionally treated with fluorouracil. Other genetic and clinical factors may influence a patient's response to cyclophosphamide, epirubicin and fluorouracil.
fluorouracil	Carac®, Efudex®, Fluoroplex®, Tolak®	CPIC	*DPYD*	*1/*5	**Implications:** Normal DPD activity and normal risk for fluoropyrimidine toxicity. **Recommendations:** Use label-recommended dosage and administration. **Classification of Recommendation:** Moderate
fluorouracil	Carac®, Efudex®, Fluoroplex®, Tolak®	PharmGKB 1A	*DPYD*	rs67376798, TT	Patients with the TT genotype and cancer who are treated with fluoropyrimidine-based chemotherapy may have 1) increased clearance of the drug and 2) decreased, but not absent, risk and reduced severity of drug toxicity as compared to patients with the AT genotype. Fluoropyrimidines are often used in combination chemotherapy such as FOLFOX (fluorouracil, leucovorin and oxaliplatin), FOLFIRI (fluorouracil, leucovorin and irinotecan) or FEC (fluorouracil, epirubicin and cyclophosphamide) or with other drugs such as bevacizumab, cetuximab, raltitrexed. The combination and delivery of the drug may influence risk for toxicity. Other genetic and clinical factors may also influence response to fluoropyrimidine-based chemotherapy.
fluorouracil	Carac®, Efudex®, Fluoroplex®, Tolak®	PharmGKB 2A	*GSTP1*	rs1695, GG	Patients with the GG genotype and colorectal cancer who are treated with fluorouracil and oxaliplatin may have a better treatment outcome (increased response, increased overall survival time, reduced risk of death) as compared to patients with the AA genotype. Other genetic and clinical factors may also influence a patient's response to fluorouracil and oxaliplatin treatment.
fluorouracil	Carac®, Efudex®, Fluoroplex®, Tolak®	PharmGKB 2A	*NQO1*	rs1800566, GG	Patients with the GG genotype and Breast Neoplasms and cancer who are treated with chemotherapy regimes that include platinum compounds, anthracyclines and related substances, and nucleoside inhibitors may have a better outcome (overall survival and progression-free survival) as compared to patients with the AA genotype. However, this has been contradicted in some studies. Other genetic and clinical factors may also influence a patient's treatment outcome.
fluorouracil	Carac®, Efudex®, Fluoroplex®, Tolak®	PharmGKB 2A	*TYMS*	rs151264360, delTTAAAG/TTAAAG	Patients with the TTAAAG/del genotype and cancer who are treated with fluoropyrimidine-based chemotherapy may have increased survival time as compared to those with the TTAAAG/TTAAAG genotype, and decreased risk of toxicity as compared to those with the del/del genotype. Fluoropyrimidines are often used in combination chemotherapy such as FOLFOX (fluorouracil, leucovorin and oxaliplatin) or FOLFIRI (fluorouracil, leucovorin and irinotecan) or with other drugs such as paclitaxel. Other genetic and clinical factors may also influence a patient's response to treatment.
irinotecan	Camptosar®, Onivyde®	PharmGKB 2A	*UGT1A1*	rs4148323, GG	Patients with the GG genotype and cancer may have increased metabolism of SN-38 when treated with irinotecan as compared to patients with the AA genotype. SN-38 is the active metabolite of irinotecan, and is glucuronidated by UGT1A1. Patients with the GG genotype with cancer who are treated with irinotecan-based regimens may have a decreased risk of neutropenia as compared to patients with the AA genotype. Other genetic and clinical factors may also influence metabolism of SN-38 and risk of neutropenia.
irinotecan	Camptosar®, Onivyde®	PharmGKB 2A	*UGT1A1*	rs8175347, [6]/[7]	Patients with the (TA)6/(TA)7 genotype and cancer may have decreased metabolism of SN-38 when treated with irinotecan as compared to patients with the (TA)6/(TA)6 genotype, or increased metabolism compared to patients with the (TA)7/(TA)7 genotype. SN-38 is the active metabolite of irinotecan, and is glucuronidated by UGT1A1. Other genetic and clinical factors may also influence metabolism of SN-38. Patients with the (TA)6/(TA)7 genotype with cancer who are treated with irinotecan-based regimens may have an increased risk of neutropenia, diarrhea, or asthenia, as compared to patients with the (TA)6/(TA)6 genotype, and a decreased risk compared to those with the (TA)7/(TA)7 genotype. Evidence for an association between this genotype and neutropenia is stronger than that for diarrhea or asthenia, and some studies only show significant associations with neutropenia at medium and high doses of the drug. No significant associations have been seen for nausea, mucositis, infection, or tumor response. One study found a decreased overall survival time for carriers of the (TA)7 allele. One study found an increased risk of vomiting for this genotype, and another found an increased risk of treatment-related death, both compared to the (TA)6/(TA)6 genotype. Other genetic and clinical factors may also influence a patient's survival time and risk of neutropenia, diarrhea, asthenia, vomiting, or treatment-related death.
irinotecan	Camptosar®, Onivyde®	PharmGKB 2A	*UGT1A1*	rs8175347, rs887829, rs4148323, [6]/[7], CT,GG	The UTG1A1 genotype could not be resolved. This is either due to the presence of a novel genotype or because there are multiple possible genotypes that cannot be resolved with the methodology used for this test.
mercaptopurine	Purinethol®, Purixan®	PharmGKB 1B	*NUDT15*	rs116855232, CC	Patients with the CC genotype who are treated with thiopurines for inflammatory bowel diseases (IBD) or acute lymphoblastic leukemia (ALL) may have a reduced, but not absent risk of developing leukopenia or

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Date of Report	Dec 08 2017	Patient ID	55001604176800

mercaptopurine	Purinethol®, Purixan®	PharmGKB 1B	*NUDT15*	rs116855232, CC	alopecia as compared to patients with the CT or TT genotype. Patients may also tolerate higher doses of thiopurines and be less likely to discontinue thiopurine treatment as compared to patients with the CT or TT genotype, possibly due to the reduced risk for adverse effects. Other genetic and clinical factors may also influence a patient's risk for leukopenia, alopecia or treatment discontinuation.
mercaptopurine	Purinethol®, Purixan®	CPIC	*TPMT*	*1/*1S	**Implications:** Lower concentrations of TGN metabolites, higher methylTIMP, this is the "normal" pattern **Metabolizer Status:** Normal Metabolizer **Recommendations:** Start with normal starting dose (e. g. , 75 mg/m2/d or 1. 5 mg/kg/d) and adjust doses of mercaptopurine (and of any other myelosuppressive therapy) without any special emphasis on mercaptopurine compared to other agents. Allow 2 weeks to reach steady state after each dose adjustment. **Classification of Recommendation:** Strong
methotrexate	Otrexup®, Rasuvo®, Trexall®, Xatmep®	PharmGKB 2A	*ABCB1*	rs1045642, AA	Patients with the AA genotype and lymphoma or leukemia who are treated with methotrexate may have increased concentrations of the drug and may have an increased risk of toxicity as compared to patients with the GG genotype. Other genetic and clinical factors may also influence a patient's risk of methotrexate-induced toxicities.
methotrexate	Otrexup®, Rasuvo®, Trexall®, Xatmep®	PharmGKB 2A	*MTHFR*	rs1801133, AG	This genotype could not be determined due to low read count and/or sequencing quality at the position of interest.
methotrexate	Otrexup®, Rasuvo®, Trexall®, Xatmep®	PharmGKB 2A	*SLCO1B1*	rs11045879, TT	Patients with the TT genotype and precursor cell lymphoblastic leukemia-lymphoma who are treated with methotrexate: 1) may have increased clearance of methotrexate as compared to patients with the CC or CT genotype 2) may have an increased risk for GI toxicity when treated with methotrexate as compared to patients with the CC or CT genotype.
Platinum compounds	carboplatin, cisplatin, oxaliplatin (Eloxatin®)	PharmGKB 2A	*GSTP1*	rs1695, GG	Patients with the GG genotype and cancer who are treated with platinum-based drugs may have a decreased, but not absent, risk of toxicity as compared to patients with the AG and AA genotype. Other genetic and clinical factors may also influence a patient's risk for toxicity.
Platinum compounds	carboplatin, cisplatin, oxaliplatin (Eloxatin®)	PharmGKB 2A	*NQO1*	rs1800566, GG	Patients with the GG genotype and Breast Neoplasms and cancer who are treated with chemotherapy regimes that include platinum compounds, anthracyclines and related substances, and nucleoside inhibitors may have a better outcome (overall survival and progression-free survival) as compared to patients with the AA genotype. However, this has been contradicted in some studies. Other genetic and clinical factors may also influence a patient's treatment outcome.
radiotherapy		PharmGKB 2A	*TANC1*	rs264651, AA	Patients with the AA genotype and prostate cancer who are treated with radiotherapy may have a reduced risk of late stage toxicity as compared to patients with the GG genotype. Other genetic and clinical factors may also influence a patient's risk of radiotherapy-induced toxicity.
radiotherapy		PharmGKB 2A	*TANC1*	rs264631, CC	Patients with the CC genotype and prostate cancer who are treated with radiotherapy may have a reduced risk of late stage toxicity as compared to patients with the GG genotype. Other genetic and clinical factors may also influence a patient's risk of radiotherapy-induced toxicity.
rasburicase	Elitek®	CPIC	*G6PD*	*B/*B	**Implications:** Low or reduced risk of hemolytic anemia. **Phenotype (Genotype):** Normal. **Recommendations:** No reason to withhold rasburicase based on G6PD status. **Classification of Recommendation:** Strong
tamoxifen	Soltamox®	PharmGKB 2A	*CYP2D6*	rs3892097, CT	This genotype could not be determined due to low read count and/or sequencing quality at the position of interest.
tegafur		CPIC	*DPYD*	*1/*5	**Implications:** Normal DPD activity and normal risk for fluoropyrimidine toxicity. **Recommendations:** Use label-recommended dosage and administration. **Classification of Recommendation:** Moderate
thioguanine		CPIC	*TPMT*	*1/*1S	**Implications:** Lower concentrations of TGN metabolites, but note that TGN after thioguanine are 5-10x higher than TGN after mercaptopurine or azathioprine **Metabolizer Status:** Normal Metabolizer **Recommendations:** Start with normal starting dose. Adjust doses of thioguanine and of other myelosuppressive therapy without any special emphasis on thioguanine. Allow 2 weeks to reach steady state after each dose adjustment.

*See Technical Note

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thioguanine		CPIC	*TPMT*	*1/*1S	**Classification of Recommendation:** Strong
tropisetron	Navoban	CPIC	*CYP2D6*	*1/*4	**Implications:** Normal metabolism **Metabolizer Status:** Normal metabolizer **Recommendations:** Initiate therapy with recommended starting dose. **Classification of Recommendation:** Strong

Drug Category: Pain Medicine

DRUG	TRADE NAME(S)		GENE	VARIANT	IMPLICATIONS
Antiinflammatory agents, non-steroids	Aspirin, ibuprofen, naproxen, celecoxib, diclofenac, indomethacin, oxaprozin , piroxicam, etc.	PharmGKB 2A	*CYP2C9*	*1/*1	Patients with the *1/*1 genotype who are treated with non-steroid antiinflammatory agents, celecoxib or diclofenac may have a decreased, but not absent, risk of gastrointestinal bleeding as compared to patients with the *1/*3 and *3/*3 genotypes. Other genetic and clinical factors may also influence a patient's response to Antiinflammatory agents, non-steroids, celecoxib or diclofenac.
celecoxib	Celebrex®	PharmGKB 2A	*CYP2C9*	*1/*1	Patients with the *1/*1 genotype may have increased metabolism of celecoxib as compared to patients with the *1/*3 or *3/*3 genotypes. Other genetic and clinical factors may also influence a metabolism of celecoxib.
codeine		CPIC	*CYP2D6*	*1/*4	**Implications:** Normal morphine formation **Metabolizer Status:** Extensive metabolizer **Recommendations:** Use label recommended age- or weight-specific dosing. **Classification of Recommendation:** Strong

Drug Category: Psychiatry

DRUG	TRADE NAME(S)		GENE	VARIANT	IMPLICATIONS
amitriptyline		CPIC	*CYP2D6*	CYP2C19,CYP2D6, *1/*17,*1/*4	**Implications:** For CYP2D6: Normal metabolism of tricyclics. For CYP2C19: Increased metabolism of tertiary amines compared to normal metabolizers. Greater conversion of tertiary amines to secondary amines may affect response or side effects. **Recommendations:** Consider alternative drug not metabolized by CYP2C19. TCAs without major CYP2C19 metabolism include the secondary amines nortriptyline and desipramine. If amitriptyline is warranted, utilize therapeutic drug monitoring to guide dose adjustment. Utilizing therapeutic drug monitoring if a tricyclic is prescribed to a patient with CYP2D6 ultrarapid, intermediate or poor metabolism in combination with CYP2C19 ultrarapid, intermediate or poor metabolism is strongly recommended. Dosing recommendations only apply to higher initial doses of TCAs for treatment of conditions such as depression. **Classification of Recommendation:** Optional
bupropion	Aplenzin®, Forfivo XL®, Wellbutrin®, Zyban®	PharmGKB 1B	*ANKK1*	rs1800497, AG	Patients with the AG genotype who are treated with bupropion may be less likely to quit smoking as compared to patients with the GG genotype, although this has been contradicted in one study. Other genetic and clinical factors may also influence a patient's chance for quitting smoking.
citalopram	Celexa®	CPIC	*CYP2C19*	*1/*17	**Implications:** Increased metabolism when compared to extensive metabolizers. Lower plasma concentrations will increase probability of pharmacotherapy failure. **Metabolizer Status:** Ultrarapid metabolizer (~5-30% of patients) **Recommendations:** Consider an alternative drug not predominantly metabolized by CYP2C19. Drug-drug interactions and other patient characteristics (e. g. , age, renal function, liver function) should be considered when selecting an alternative therapy. **Classification of Recommendation:** Moderate
clomipramine	Anafranil®	CPIC	*CYP2D6*	CYP2C19,CYP2D6, *1/*17,*1/*4	**Implications:** For CYP2D6: Normal metabolism of tricyclics. For CYP2C19: Increased metabolism of tertiary amines compared to normal metabolizers. Greater conversion of tertiary amines to secondary amines may affect response or side effects.

*See Technical Note

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clomipramine	Anafranil®	CPIC	*CYP2D6*	CYP2C19,CYP2D6, *1/*17,*1/*4	**Recommendations:** The dosing recommendations are based on studies focusing on amitriptyline. Because tricyclic antidepressants have comparable pharmacokinetic properties, it may be reasonable to apply these guidelines to other tertiary amines including clomipramine, doxepin, imipramine and trimipramine. Consider alternative drug not metabolized by CYP2C19. TCAs without major CYP2C19 metabolism include the secondary amines nortriptyline and desipramine. If TCAs are warranted, utilize therapeutic drug monitoring to guide dose adjustment. Utilizing therapeutic drug monitoring if a tricyclic is prescribed to a patient with CYP2D6 ultrarapid, intermediate or poor metabolism in combination with CYP2C19 ultrarapid, intermediate or poor metabolism is strongly recommended. Dosing recommendations only apply to higher initial doses of TCAs for treatment of conditions such as depression. **Classification of Recommendation:** Optional
desipramine	Norpramin®	CPIC	*CYP2D6*	*1/*4	**Implications:** Normal metabolism of TCAs. **Metabolizer Status:** Normal metabolizer **Recommendations:** Initiate therapy with recommended starting dose. Patients may receive an initial low dose of a tricyclic, which is then increased over several days to the recommended steady-state dose. The starting dose in this guideline refers to the recommended steady-state dose. Dosing recommendations only apply to higher initial doses of TCAs for treatment of conditions such as depression. **Classification of Recommendation:** Strong
doxepin	Silenor®	CPIC	*CYP2D6*	CYP2C19,CYP2D6, *1/*17,*1/*4	**Implications:** For CYP2D6: Normal metabolism of tricyclics. For CYP2C19: Increased metabolism of tertiary amines compared to normal metabolizers. Greater conversion of tertiary amines to secondary amines may affect response or side effects. **Recommendations:** The dosing recommendations are based on studies focusing on amitriptyline. Because tricyclic antidepressants have comparable pharmacokinetic properties, it may be reasonable to apply these guidelines to other tertiary amines including clomipramine, doxepin, imipramine and trimipramine. Consider alternative drug not metabolized by CYP2C19. TCAs without major CYP2C19 metabolism include the secondary amines nortriptyline and desipramine. If TCAs are warranted, utilize therapeutic drug monitoring to guide dose adjustment. Utilizing therapeutic drug monitoring if a tricyclic is prescribed to a patient with CYP2D6 ultrarapid, intermediate or poor metabolism in combination with CYP2C19 ultrarapid, intermediate or poor metabolism is strongly recommended. Dosing recommendations only apply to higher initial doses of TCAs for treatment of conditions such as depression. **Classification of Recommendation:** Optional
escitalopram	Lexapro®, Zonalon®	CPIC	*CYP2C19*	*1/*17	**Implications:** Increased metabolism when compared to extensive metabolizers. Lower plasma concentrations will increase probability of pharmacotherapy failure. **Metabolizer Status:** Ultrarapid metabolizer (~5-30% of patients) **Recommendations:** Consider an alternative drug not predominantly metabolized by CYP2C19. Drug-drug interactions and other patient characteristics (e. g. , age, renal function, liver function) should be considered when selecting an alternative therapy. **Classification of Recommendation:** Moderate
fluvoxamine	Luvox®	CPIC	*CYP2D6*	*1/*4	**Implications:** Normal metabolism **Metabolizer Status:** Extensive metabolizer **Recommendations:** Initiate therapy with recommended starting dose. **Classification of Recommendation:** Strong
imipramine	Tofranil	CPIC	*CYP2D6*	CYP2C19,CYP2D6, *1/*17,*1/*4	**Implications:** For CYP2D6: Normal metabolism of tricyclics. For CYP2C19: Increased metabolism of tertiary amines compared to normal metabolizers. Greater conversion of tertiary amines to secondary amines may affect response or side effects. **Recommendations:** The dosing recommendations are based on studies focusing on amitriptyline. Because tricyclic antidepressants have comparable pharmacokinetic properties, it may be reasonable to apply these guidelines to other tertiary amines including clomipramine, doxepin, imipramine and trimipramine. Consider alternative drug not metabolized by CYP2C19. TCAs without major CYP2C19 metabolism include the secondary amines nortriptyline and desipramine. If TCAs are warranted, utilize

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imipramine	Tofranil	CPIC	*CYP2D6*	CYP2C19,CYP2D6, *1/*17,*1/*4	therapeutic drug monitoring to guide dose adjustment. Utilizing therapeutic drug monitoring if a tricyclic is prescribed to a patient with CYP2D6 ultrarapid, intermediate or poor metabolism in combination with CYP2C19 ultrarapid, intermediate or poor metabolism is strongly recommended. Dosing recommendations only apply to higher initial doses of TCAs for treatment of conditions such as depression. **Classification of Recommendation:** Optional
methadone	Methadose®	PharmGKB 2A	*CYP2B6*	rs3745274, TT	Patients with the TT genotype who are being treated with methadone for heroin addiction may require a decreased dose of the drug as compared to patients with the GG or GT genotype. Other genetic and clinical factors may also influence dose of methadone.
nicotine	Commit, Habitrol®, Nicoderm®, Nicorette®, Nicotrol®, Thrive	PharmGKB 2A	*COMT*	rs4680, GG	Patients with the GG genotype who are treated with nicotine replacement therapy may have a decreased likelihood of smoking cessation and increased risk of relapse as compared to patients with the AA genotype. However, some contradictory evidence exists. Other genetic and clinical factors may also influence a patient's response to nicotine replacement therapy.
nortriptyline	Pamelor®	CPIC	*CYP2D6*	*1/*4	**Implications:** Normal metabolism of tricyclics. **Metabolizer Status:** Extensive metabolizer **Recommendations:** Initiate therapy with recommended starting dose. Patients may receive an initial low dose of tricyclics, which is then increased over several days to the recommended steady-state dose. The starting dose in this guideline refers to the recommended steady-state dose. Dosing recommendations only apply to higher initial doses of nortriptyline for treatment of conditions such as depression. **Classification of Recommendation:** Strong
paroxetine	Brisdelle®, Paxil®, Pexeva®	CPIC	*CYP2D6*	*1/*4	**Implications:** Normal metabolism **Metabolizer Status:** Extensive metabolizer **Recommendations:** Initiate therapy with recommended starting dose. **Classification of Recommendation:** Strong
risperidone	Risperdal®	PharmGKB 2A	*DRD2*	rs1799978, TT	Patients with the TT genotype and schizophrenia who are treated with risperidone may be more likely to have improvement in symptoms as compared to patients with the CC genotype. Other genetic and clinical factors may also influence a patient's response to risperidone.
sertraline	Zoloft®	CPIC	*CYP2C19*	*1/*17	**Implications:** Increased metabolism when compared to extensive metabolizers. Lower plasma concentrations will increase probability of pharmacotherapy failure. **Metabolizer Status:** Ultrarapid metabolizer (~5-30% of patients) **Recommendations:** Initiate therapy with recommended starting dose. If patient does not respond to recommended maintenance dosing, consider alternative drug not predominantly metabolized by CYP2C19. Drug-drug interactions and other patient characteristics (e. g. , age, renal function, liver function) should be considered when selecting an alternative therapy. **Classification of Recommendation:** Optional
trimipramine	Surmontil®	CPIC	*CYP2D6*	CYP2C19,CYP2D6, *1/*17,*1/*4	**Implications:** For CYP2D6: Normal metabolism of tricyclics. For CYP2C19: Increased metabolism of tertiary amines compared to normal metabolizers. Greater conversion of tertiary amines to secondary amines may affect response or side effects. **Recommendations:** The dosing recommendations are based on studies focusing on amitriptyline. Because tricyclic antidepressants have comparable pharmacokinetic properties, it may be reasonable to apply these guidelines to other tertiary amines including clomipramine, doxepin, imipramine and trimipramine. Consider alternative drug not metabolized by CYP2C19. TCAs without major CYP2C19 metabolism include the secondary amines nortriptyline and desipramine. If TCAs are warranted, utilize therapeutic drug monitoring to guide dose adjustment. Utilizing therapeutic drug monitoring if a tricyclic is prescribed to a patient with CYP2D6 ultrarapid, intermediate or poor metabolism in combination with CYP2C19 ultrarapid, intermediate or poor metabolism is strongly recommended. Dosing recommendations only apply to higher initial doses of TCAs for treatment of conditions such as depression. **Classification of Recommendation:** Optional

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Drug Category: Pulmonology

DRUG	TRADE NAME(S)		GENE	VARIANT	IMPLICATIONS
albuterol (salbutamol)	AccuNeb®, ProAir®, Proventil®, Ventolin®, Vospire®, Xopenex®	PharmGKB 2A	*ADRB2*	rs1042713, AA	Children with the AA genotype with asthma who are treated with salmeterol or salbutamol may have a decreased response to treatment (as measured by increased risk of asthma excerbations and lower quality of life scores) as compared to children with the GG genotype. This association does not seem to apply to lung function measurements such as peak expiratory flow rate or FEV1. Other genetic and clinical factors may also influence a patient's response to treatment.
ataluren	Translarna®	PharmGKB 2A	*CFTR*	rs113993959, GG	Patients with the GG genotype and cystic fibrosis may not respond to treatment with ataluren. Randomized clinical trials did not find improvement in chloride transport or improved pulmonary function after 2 rounds of 2 weeks of treatment. Other genetic and clinical factors may also influence changes in chloride transport and improvement of pulmonary symptoms in patients with cystic fibrosis.
ataluren	Translarna®	PharmGKB 2A	*CFTR*	rs75039782, CC	Patients with the CC genotype and cystic fibrosis may not respond to treatment with ataluren. Randomized clinical trials did not find improvement in chloride transport or improved pulmonary function after 2 rounds of 2 weeks of treatment. Other genetic and clinical factors may also influence changes in chloride transport and improvement of pulmonary symptoms in patients with cystic fibrosis.
ataluren	Translarna®	PharmGKB 2A	*CFTR*	rs77010898, GG	Patients with the GG genotype and cystic fibrosis may not respond to treatment with ataluren. Randomized clinical trials did not find improvement in chloride transport or improved pulmonary function after 2 rounds of 2 weeks of treatment. Other genetic and clinical factors may also influence changes in chloride transport and improvement of pulmonary symptoms in patients with cystic fibrosis.
ivacaftor	Kalydeco®	PharmGKB 1A	*CFTR*	rs113993960 , CTT/CTT	Indication of ivacaftor in cystic fibrosis patients with the CTT/CTT genotype (no copies of the CFTR F508del variant) is dependent on the presence of other variants within the CFTR gene. FDA-approved drug labeling information and CPIC guidelines indicate use of ivacaftor in cystic fibrosis patients with at least one copy of a list of 10 CFTR genetic variants. Other genetic and clinical factors may also influence a patient's response to ivacaftor.
ivacaftor	Kalydeco®	PharmGKB 1A	*CFTR*	rs75527207, rs267606723, rs193922525, rs80282562, rs121909013, rs74503330, rs121909041, rs121908755, rs121908757, rs121909005, rs78655421	Patients with cystic fibrosis and this genotype (i. e. , do not have any of the variants listed below) have an unknown response to ivacaftor treatment, as response may depend on the presence of other CFTR variants. Ivacaftor is indicated in cystic fibrosis patients who have at least one of the following variants in the CFTR gene: G551D (rs75527207), G1244E (rs267606723), G1349D (rs193922525), G178R (rs80282562), G551S (rs121909013), S1251N (rs74503330), S1255P (rs121909041), S549N (rs121908755), S549R (rs121908757 or rs121909005) or R117H (rs78655421).
ivacaftor / lumacaftor	Orkambi®	PharmGKB 1B	*CFTR*	rs113993960 , CTT/CTT	The CTT/CTT genotype (no copies of the CFTR F508del variant) is not an indication for ivacaftor/lumacaftor in patients with cystic fibrosis.
salmeterol	Serevent®	PharmGKB 2A	*ADRB2*	rs1042713, AA	Children with the AA genotype with asthma who are treated with salmeterol or salbutamol may have a decreased response to treatment (as measured by increased risk of asthma excerbations and lower quality of life scores) as compared to children with the GG genotype. This association does not seem to apply to lung function measurements such as peak expiratory flow rate or FEV1. Other genetic and clinical factors may also influence a patient's response to treatment.

Drug Category: Transplantation Medicine

DRUG	TRADE NAME(S)		GENE	VARIANT	IMPLICATIONS
sirolimus (rapamycin)	Rapamune®	PharmGKB 2A	*CYP3A5*	rs776746, CC	Patients with the CC genotype and who are recipients of transplants may have decreased metabolism of sirolimus and require a lower dose as compared to patients with the CT and TT genotype. Other genetic and clinical factors may also influence a patient's sirolimus dose requirements.
tacrolimus	Astagraf®, Envarsus®, Prograf®, Protopic®	PharmGKB 2A	*CYP3A4*	rs2740574, TT	Transplant recipients with the TT (*1/*1) genotype may require a decreased dose of tacrolimus as compared to patients with the CT (*1B/*1) or CC (*1B/*1B) genotype. Other genetic and clinical factors, such as CYP3A5 *3 (rs776746), may also influence a patient's dose requirements.
tacrolimus	Astagraf®, Envarsus®, Prograf®, Protopic®	PharmGKB 1A	*CYP3A5*	rs776746, CC	Patients with the CC genotype who are recipients of a kidney, heart, lung or hematopoeitic stem cell transplant, or have other diseases, who are treated with tacrolimus may have decreased metabolism of tacrolimus resulting in increased exposure, and may require a lower dose as compared to patients with the CT or TT genotype. Patients with the CC genotype and recipients of kidney or hematopoietic stem cell transplant who are treated with tacrolimus may have a decreased, but not absent, risk of transplant rejection as compared to patients with the CT or TT genotype. Other genetic

*See Technical Note

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tacrolimus	Astagraf®, Envarsus®, Prograf®, Protopic®	PharmGKB 1A	*CYP3A5*	rs776746, CC	and clinical factors may also influence a patient's tacrolimus dose requirement and risk of transplant rejection.

*See Technical Note

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CPIC Guidelines

CPIC guideline articles are listed below. Please refer to guideline pages on cpicpgx.org for the most up-to-date information. For additional references, visit pharmgkb.org.

Hicks JK, Swen JJ, Thorn CF, et al. Clinical Pharmacogenetics Implementation Consortium guideline for CYP2D6 and CYP2C19 genotypes and dosing of tricyclic antidepressants. Clin Pharmacol Ther. 2013;93(5):402-8. PMID: 23486447

Hicks JK, Sangkuhl K, Swen JJ et al. Clinical pharmacogenetics implementation consortium guideline (CPIC) for CYP2D6 and CYP2C19 genotypes and dosing of tricyclic antidepressants: 2016 update. Clin Pharmacol Ther. 2016 Dec 20. PMID 27997040

Gammal RS, Court MH, Haidar CE, et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for UGT1A1 and Atazanavir Prescribing. Clin Pharmacol Ther. 2016;99(4):363-9. PMID: 26417955

Relling MV, Gardner EE, Sandborn WJ, et al. Clinical pharmacogenetics implementation consortium guidelines for thiopurine methyltransferase genotype and thiopurine dosing: 2013 update. Clin Pharmacol Ther. 2013;93(4):324-5. PMID: 23422873

Relling MV, Gardner EE, Sandborn WJ, et al. Clinical Pharmacogenetics Implementation Consortium guidelines for thiopurine methyltransferase genotype and thiopurine dosing. Clin Pharmacol Ther. 2011;89(3):387-91. PMID: 21270794

Caudle KE, Thorn CF, Klein TE, et al. Clinical Pharmacogenetics Implementation Consortium guidelines for dihydropyrimidine dehydrogenase genotype and fluoropyrimidine dosing. Clin Pharmacol Ther. 2013;94(6):640-5. PMID: 23988873

Hicks JK, Bishop JR, Sangkuhl K, et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for CYP2D6 and CYP2C19 Genotypes and Dosing of Selective Serotonin Reuptake Inhibitors. Clin Pharmacol Ther. 2015;98(2):127-34. PMID: 25974703

Scott SA, Sangkuhl K, Stein CM, et al. Clinical Pharmacogenetics Implementation Consortium guidelines for CYP2C19 genotype and clopidogrel therapy: 2013 update. Clin Pharmacol Ther. 2013;94(3):317-23. PMID: 23698643

Scott SA, Sangkuhl K, Gardner EE, et al. Clinical Pharmacogenetics Implementation Consortium guidelines for cytochrome P450-2C19 (CYP2C19) genotype and clopidogrel therapy. Clin Pharmacol Ther. 2011;90(2):328-32. PMID: 21716271

Crews KR, Gaedigk A, Dunnenberger HM, et al. Clinical Pharmacogenetics Implementation Consortium guidelines for cytochrome P450 2D6 genotype and codeine therapy: 2014 update. Clin Pharmacol Ther. 2014;95(4):376-82. PMID: 24458010

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Clancy JP, Johnson SG, Yee SW, et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines for ivacaftor therapy in the context of CFTR genotype. Clin Pharmacol Ther. 2014;95(6):592-7. PMID: 24598717

Muir AJ, Gong L, Johnson SG, et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines for IFNL3 (IL28B) genotype and PEG interferon--based regimens. Clin Pharmacol Ther. 2014;95(2):141-6. PMID: 24096968

Bell GC, Caudle KE, Whirl-Carrillo M et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline for CYP2D6 genotype and use of ondansetron and tropisetron. Clin Pharmacol Ther. 2016. PMID: 28002639

Caudle KE, Rettie AE, Whirl-Carrillo M, et al. Clinical pharmacogenetics implementation consortium guidelines for CYP2C9 and HLA-B genotypes and phenytoin dosing. Clin Pharmacol Ther. 2014;96(5):542-8. PMID: 25099164

Relling MV, Mcdonagh EM, Chang T, et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines for rasburicase therapy in the context of G6PD deficiency genotype. Clin Pharmacol Ther. 2014;96(2):169-74. PMID: 24787449

Ramsey LB, Johnson SG, Caudle KE, et al. The clinical pharmacogenetics implementation consortium guideline for SLCO1B1 and simvastatin-induced myopathy: 2014 update. Clin Pharmacol Ther. 2014;96(4):423-8. PMID: 24918167

Wilke RA, Ramsey LB, Johnson SG, et al. The clinical pharmacogenomics implementation consortium: CPIC guideline for SLCO1B1 and simvastatin-induced myopathy. Clin Pharmacol Ther. 2012;92(1):112-7. PMID: 22617227

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Birdwell KA, Decker B, Barbarino JM, et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) Guidelines for CYP3A5 Genotype and Tacrolimus Dosing. Clin Pharmacol Ther. 2015;98(1):19-24. PMID: 25801146

Johnson JA, Gong L, Whirl-carrillo M, et al. Clinical Pharmacogenetics Implementation Consortium Guidelines for CYP2C9 and VKORC1 genotypes and warfarin dosing. Clin Pharmacol Ther. 2011;90(4):625-9. PMID: 21900891

Johnson JA, Caudle KE, Gong L, et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for Pharmacogenetics-Guided Warfarin Dosing: 2017 Update. 2017. PMID 28198005

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TEST SUMMARY & DISCLAIMER

Veritas' myGenome test is a whole genome sequencing screening test for detecting variants related to disease risk, carrier status, pharmacogenetics markers, lifestyle traits, and ancestry. The test is performed on saliva or whole blood. Extracted genomic DNA is processed with the TruSeq DNA PCR-free sample preparation kit and sequenced at approximately 30X average coverage on a HiSeq X Ten or NovaSeq 6000 System next-generation sequencer (Illumina). For optimized sample tracking and quality assurance, each sample is also assessed with the Infinium QC Array-24 microarray (Illumina). Sequencing is performed in Veritas Genetics' CLIA laboratory.

Sequencing data are aligned to the human reference genome. The reportable region is approximately 4.4 billion base pairs and comprises the coordinates described as highly confident by Zook et al. (2016) as well as selected lifestyle traits and ancestry markers. At least 95% of the region has >=10X read coverage. Positions with less than 10X coverage are excluded from reporting. Analytic accuracy for SNPs and small insertions/deletions (less than 8 bases) is >99%. Only inherited (germline) variants are detected. The test is not configured to detect variants that are not present in every cell (somatic mosaicism, mitochondrial heteroplasmy).

Data analysis is performed with the Veritas Genetics pipeline, which uses Bayesian and statistical variant callers. Variant annotations are derived from snpEff and Ensembl's Variant Effect Predictor (VEP). Initial variant filtering is based on read coverage >=10, population frequency, and variant classifications in ClinVar (https://www.ncbi.nlm.nih.gov/clinvar/; Landrum et al., 2015). Veritas will assess all variants having at least one entry with a classification of pathogenic or likely pathogenic, using ACMG criteria (Richards et al. 2015). It is possible that some variants are incorrectly classified in ClinVar. For disease risk and carrier status, only variants with publicly available evidence for pathogenicity (pathogenic or likely pathogenic) found using the above methodology are reported. Benign variants, likely benign variants and variants of uncertain significance (VUS) are not reported.

A supplementary file is available upon request, free of charge, and provides chromosome, position, variant called, and certain functional information describing molecular consequences of having this variant. This is provided with no warranty or guarantee of the validity of the information provided. The supplementary file includes variants that are covered at a depth >=10X and only within the myGenome product region. All variants regardless of classification are included. An adjunct vcf file is also available upon request, for a fee. The adjunct vcf file reports all called variants, with no filtering for quality or read depth, and no warranty that the vcf file will work with third party tools. Please contact Veritas Support at support@veritasgenetics to request these additional files.

Pharmacogenetic data analysis and interpretation is based on a subset of guidelines from the Clinical Pharmacogenetics Implementation Consortium (CPIC, https://cpicpgx.org/) and the PharmGKB resource (https://www.pharmgkb.org; level 1A, 1B and 2A clinical annotations only). CPIC guidelines are highly vetted and preferred over PharmGKB results where both exist. The CPIC and PharmGKB guidelines and websites are updated frequently, and should always be consulted for the latest interpretations. PharmGKB levels of evidence are defined as follows: Level 1A: Annotation for a variant-drug combination in a CPIC or medical society-endorsed PGx guideline, or implemented at a PGRN (Pharmacogenomics Research Network) site or in another major health system. Level 1B: Annotation for a variant-drug combination where the preponderance of evidence shows an association. The association must be replicated in more than one cohort with significant p-values, and preferably will have a strong effect size. Level 2A: Annotation for a variant-drug combination that qualifies for level 2B (variant-drug combination with moderate evidence of an association. The association must be replicated but there may be some studies that do not show statistical significance, and/or the effect size may be small), where the variant is within a VIP (Very Important Pharmacogene) as defined by PharmGKB. The variants in level 2A are in known pharmacogenes, so functional significance is more likely. Clinical annotations are provided here for brief consultation only; they are either directly sourced from PharmGKB or modified by Veritas Genetics based on recent literature and available guidelines. ***Never change your drug regimen except under the guidance of a clinical pharmacologist or other authorized healthcare provider.***

Veritas' myGenome test covers germline variants (see table below) that impact drug efficacy, dosage adjustment, and adverse events for certain drugs. An important limitation to note is that gene fusions and copy number variations are not determined by this methodology, which means that certain haplotypes cannot be resolved (i.e., CYP2D6*1xN cannot be resolved from CYP2D6*1; CYP2D6*17x2 cannot be resolved from CYP2D6*17 etc.). These haplotypes have important effects and may be enriched in certain populations. CYP2D6*5 (full gene deletion) is inferred based on observed homozygosity across the entire gene; due to linkage disequilibrium, this may in some cases lead to an inaccurate result (i.e., the correct result being homozygosity for the non-*5 haplotype). Another known limitation is that this methodology does not allow for reliable determination of allelic phase for variants unless they are close together. In certain instances, this leads to ambiguity in diplotype calling (e.g., NAT2*6B/*13A cannot

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be resolved from NAT2*6A/*4, and NAT2*5D/*12C cannot be resolved from NAT2*5B/*4), leading to a no-call. In most cases where an individual is found to be heterozygous for more than one variant in a gene, for example CYP2C19 *2/*3, the pharmacogenetic haplotypes are reported as if the variant alleles were in trans (different chromosomes). The rare, but real, possibility exists that the variant alleles are in cis (same chromosome), which would result in a new, as-yet-unnamed haplotype, and possibly result in a different phenotype. It should also be noted that some individuals carry novel haplotypes, which can neither be resolved nor detected, leading to either a no-call, or, if the novel variant is not assessed by the algorithm, assignment of a known haplotype that may or may not have the same properties as the novel haplotype depending on the nature of the variant. For example, for genes using the star (*) allele nomenclature, a *1 haplotype is usually the default assignment if none of the tested variants are found. The predicted metabolizer phenotype for CYP2C19 *2-*8/*17 genotypes are provisional classifications. The currently available evidence indicates that the *17 gain-of-function allele is unable to completely compensate for the *2 loss-of-function allele; however, this data has not been consistently replicated and is therefore a provisional classification. For X-linked haplotypes (G6PD gene) in males, the given diplotype consisting of two identical haplotypes should be interpreted as a single haplotype. Individual positions within haplotypes with less than 10X coverage are manually assessed. If a call cannot be accurately made, the haplotype determination is inconclusive and reported as unresolved (note that for G6PD, positions with less than 10X coverage are not assessed and left out of the haplotype call. In rare cases, this could lead to an inaccurate result). This test does not cover HLA genes, which may carry important pharmacogenetics information; in particular, some HLA-B haplotypes are linked to significant adverse effects to certain drugs, including carbamazepine and abacavir. Finally, not all variants relevant to all known haplotypes are assessed, either because they are not deemed functionally useful (often due to lack of information for rare types) or because there is not a clear consensus on the location of the relevant variants.

The following SNPs and haplotypes are included in the analysis.

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ABCB1	rs2032582, rs1045642
ADRB2	rs1042713
ANKK1	rs1800497
APOE	rs7412
CFTR	rs113993959, rs121908757, rs121908755, rs121909005, rs75527207, rs78655421, rs75039782, rs267606723, rs74503330, rs121909041, rs77010898, rs193922525, rs80282562, rs113993960, rs121909013
COMT	rs4680
CYP2B6	rs3745274, rs2279343, rs2279345, rs28399499
CYP2C19	*1, *2, *3, *4, *5, *6, *7, *8, *9, *10, *11, *13, *15, *16, *17, *18, *19, *22, *24, *25, *26, *28
CYP2C8	rs10509681
CYP2C9	*1, *2, *3, *4, *5, *6, *7, *8, *9, *11, *12, *13, *15, *25, *31
CYP2D6	*1, *2, *3, *4, *5, *6, *7, *8, *9, *10, *11, *12, *14, *15, *17, *19, *20, *21, *29, *35, *38, *40, *44, rs3892097
CYP3A4	rs2740574
CYP3A5	rs776746
CYP4F2	rs2108622
DPYD	*1, *2, *3, *4, *5, *6, *7, *8, *9, *10, *11, *12, *13, rs67376798
DRD2	rs1799978
F5	rs6025

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G6PD	B, Mira_d'Aire, Sao_Borja, Insuli, Chinese-5, Rignano, Orissa, G6PDNice, Kamiube/Keelung, Neapolis, Aures, Split, Kambos, Palestrina, Metaponto, Musashino, Asahi, A-_202A_376G/Ferrara_I, Murcia_Oristano, Ube/Konan, Lagosanto, Guangzhou, Hammersmith, Sinnai, G6PD_A-_680T_376G, G6PD_A-_968C_376G/Betica/Selma/Guantanamo, Salerno/Pyrgos, Quing_Yan/Chinese-4, Lages, Ilesha, Mahidol, Malaga, Sibari, Mexico_City, Nanning, Seattle/Lodi/Modena/Ferrara_II/Athens-like, Bajo_Maumere, Montalbano, Kalyan-Kerala/Jamnaga/Rohini, Gaohe, Kamogawa, Costanzo, Amazonia, Songklanagarind, Hechi, Namouru, Bao_Loc, Crispim, Acrokorinthos, Santamaria, Ananindeua, Vanua_Lava, Valladolid, Belem, Liuzhou, Shenzen, Taipei/Chinese-3, Toledo, Naone, Nankang, Miaoli, Mediterranean/Dallas/Panama/Sassari/Cagliari/Birmingham, Coimbra/Shunde, Nilgiri, Radlowo, Roubaix, Haikou, Chinese-1, Mizushima, Osaka, Viangchan/Jammu, Seoul, Ludhiana, Chatham, Fushan, Partenope, Ierapetra, Anadia, Abeno, Surabaya, Pawnee, S._Antioco, Cassano, Hermoupolis, Union/Maewo/Chinese-2/Kalo, Andalus, Cosenza, Canton/Taiwan-Hakka/Gifu-like/Agrigento-like, Flores, Kaiping/Anant/Dhon/Sapporo-like/Wosera, Villeurbanne, Torun, Sunderland, Iwatsuki, Serres, Tondela, Loma_Linda, Aachen, Tenri, Montpellier, Calvo_Mackenna, Riley, Olomouc, Tomah, Lynwood, Madrid, Iowa/Walter_Reed/Springfield, Guadalajara, Beverly_Hills/Genova/Iwate/Niigata/Yamaguchi, Hartford, Praha, Krakow, Wisconsin, Nashville/Anaheim/Portici, Alhambra, Bari, Puerto_Limon, Covao_do_Lobo, Clinic, Utrecht, Suwalki, Riverside, Japan/Shinagawa, Kawasaki, Munich, Georgia, Sumare, Telti/Kobe, Santiago_de_Cuba/Morioka, Harima, Figuera_da_Foz, Amiens, Bangkok_Noi, Fukaya, Campinas, Buenos_Aires, Arakawa, Brighton, Kozukata, Amsterdam, 202G>A_376A>G_1264C>G, Swansea, Urayasu, Vancouver, Mt_Sinai, Plymouth, Volendam, Shinshu, Chikugo, Tsukui, Pedoplis-Ckaro, Santiago, Minnesota/Marion/Gastonia/LeJeune, Cincinnati, Harilaou, North_Dallas, Asahikawa, Durham, Stonybrook, Wayne, Aveiro, Cleveland_Corum, Lille, Bangkok, Sugao, La_Jolla, Wexham, Piotrkow, West_Virginia, Omiya, Nara, Manhattan, Rehevot, Honiara, A, Tokyo/Fukushima, Farroupilha, rs1050828
GSTP1	rs1695
HMGCR	rs17244841
IFNL3/4	rs11881222, rs12979860, rs8099917
KCNIP4	rs145489027
MTHFR	rs1801133
NAT2	*4, *5, *6, *7, *12, *13, rs1041983, rs1799930
NQO1	rs1800566
NUDT15	rs116855232
SLCO1B1	rs11045879, rs4149056, rs4149015
TANC1	rs264651, rs264631
TPMT	*1, *1S, *2, *3, *4, *5, *6, *8, *9, *10, *11, *12, *13, *16, *17, *18
TYMS	rs151264360
UGT1A1	*1, *6, *28, *36, *37, *80, rs4148323, rs8175347, rs887829
VKORC1	rs9923231
XPC	rs2228001

This whole genome test was developed, and its performance determined, by Veritas Genetics. It is a screening test intended for generally healthy adults and is not a diagnostic test. It has not been cleared or approved by the U.S. Food and Drug Administration (FDA). Veritas Genetics has conducted analytical validation of accuracy and precision. Limited genomic regions are analyzed (4,513,704,952 bases). Variant interpretation is based on professional guidelines including ACMG, NCCN, and CPIC. Certain types of variations in the genome are not analyzed, including, but not limited to, certain repeat expansions, inversions, deletions, duplications, translocations, and large structural rearrangements. Therefore, for genetic diseases known to be associated with such variant types, a disease specific test providing coverage of all necessary variant types should be

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considered. Negative results do not exclude the possibility of an undetected pathogenic variant. False negatives or positives can occur for a variety of reasons including technical issues, human error, and limited available scientific and clinical knowledge on data interpretation. Therefore, variants should be confirmed before taking any clinical action. If you have questions about this report or wish to speak with a Veritas genetic counselor, please call 888-507-6619.

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Clinical Findings

Summary of your results

Please note: Some variants may result in risks for multiple diseases. Therefore, you may see the same variant listed more than once in the table below. For these variants, please note disease association. It is important to understand that identifying a genetic variant in one or more of these genes does not mean that you will necessarily develop the disease associated."

CATEGORY	DISEASE ASSOCIATION(S)	GENE(S) & VARIANT(S), ZYGOSITY
Neurological Disorders	Alzheimer Disease	APOE [c.388T>C];[c.526C=] , homozygous
Reproductive and Carrier	Glycogen Storage Disease Type III	AGL c.3965delT (p.Val1322Alafs*27) , heterozygous
Cardiovascular Disease	N/A	No findings*
Endocrine and Metabolic Disorders	N/A	No findings*
Immune Disorders	N/A	No findings*
Inherited Cancers	N/A	No findings*
Mental and Mood Disorders	N/A	No findings*
Mitochondrial Diseases	N/A	No findings*
Organ Health	N/A	No findings*

**No known pathogenic or likely pathogenic variants were identified in this category.*

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Provider	John Butcher	Batch ID	VGX1878R2RR,VGX1878R2R,
Date of Report	Dec 08 2017	Patient ID	55001604176800

Alzheimer Disease

Disease Category: Neurological Disorders

GENE(S) & VARIANT(S), ZYGOSITY

APOE [c.388T>C];[c.526C=] , homozygous

VARIANT INTERPRETATION

You have the e4/e4 genotype in the APOE gene. You carry two e4 variants. People of most ethnicities who carry one copy of APOE e4 typically have an approximately 2 to 3-fold increased risk of later-life cognitive decline, while people who carry two copies typically have a greater than 10-fold risk. People of recent African descent have the highest e4 frequency, but they appear to be largely resistant to the pathogenic effects.

GENE OVERVIEW

The APOE gene is located on chromosome 19q13.2. APOE provides instructions for making a protein called apolipoprotein E. This protein combines with fats (lipids) in the body to form molecules called lipoproteins. Lipoproteins are responsible for packaging cholesterol and other fats and carrying them through the bloodstream. APOE is also involved in the transport of iron into the cerebrospinal fluid and brain. There are at least three main variants of the APOE gene: e2, e3, and e4. The most common variant is e3, the frequency of which typically exceeds 60% in most populations. The next most common variant in most populations is e4, and the frequency of this variant typically exceeds 10%.

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OTHER DISEASE NAMES
Alzheimer's Disease

DISEASE DESCRIPTION
Alzheimer disease is a degenerative disease of the brain. It is the most common form of dementia, which is a gradual loss of memory, judgment, and ability to function. This disorder usually appears in people older than age 65, but less common forms of the disease appear earlier in adulthood. Memory loss is the most common sign of Alzheimer disease. Forgetfulness may be subtle at first, but the loss of memory worsens over time until it interferes with most aspects of daily living. Even in familiar settings, a person with Alzheimer disease may get lost or become confused. Routine tasks such as preparing meals, doing laundry, and performing other household chores can be challenging. Additionally, it may become difficult to recognize people and name objects. Affected people increasingly require help with dressing, eating, and personal care. As the disorder progresses, some people with Alzheimer disease experience personality and behavioral changes and have trouble interacting in a socially appropriate manner. Other common symptoms include agitation, restlessness, withdrawal, and loss of language skills. People with this disease usually require total care during the advanced stages of the disease. Affected individuals usually survive an average of about 8 years after the appearance of symptoms, but the course of the disease can range from 1 to 25 years. Death usually results from pneumonia, malnutrition, or general body wasting (inanition). Alzheimer disease can be classified as early-onset or late-onset. The signs and symptoms of the early-onset form appear before age 65, while the late-onset form appears after age 65. The early-onset form is much less common than the late-onset form, accounting for less than 5 percent of all cases of Alzheimer disease.

EPIDEMIOLOGY
The most common variant of APOE is e3. The average worldwide frequency of e3 is about 75% to 80%. The average worldwide frequency of the e4 variant ranges from 6% to over 20%, with an average of about 13%, which is about the frequency in the United States. The average frequency of e2 is about 8%. Frequencies of other risk variants in genes other than APOE are typically rare. Because the risk of developing Alzheimer disease increases with age and more people are living longer, the number of people with this disease is expected to increase significantly in coming decades.

GENETIC CONTRIBUTION
Genetics are very important in the development of Alzheimer disease. The APOE gene is the most important genetic contributor, and the e4 variant in this gene is the most common high risk variant for the late-onset form of the disease. Not all people with Alzheimer disease have the e4 variant, and not all people who have the e4 variant will develop the disease. The early-onset form of Alzheimer disease is inherited in an autosomal dominant pattern, which means one copy of the altered gene in each cell is sufficient to cause the disorder. In most cases, an affected person inherits the altered gene from one affected parent. In addition to pathogenic effects of certain variants, other genetic variants are known to protect against Alzheimer disease.

RISK FACTORS
Multiple factors contribute to Alzheimer disease including variants in multiple genes. Increasing age and family history of Alzheimer disease have been shown to also contribute to an individual's lifetime risk. One important and controllable risk factor is excess dietary iron. Certain genetic variants that increase absorption of iron from food are synergistic with certain APOE variants, and increase risk above the risk posed by APOE variants. The HFE gene is an important regulator

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of iron absorption from the diet, and a particular variant in HFE (C282Y) can increase body iron stores, and also increase the risk of Alzheimer's disease. These HFE variants may also be synergistic with the APOE e4 variant, and may further increase risk. The affect of these risk factors varies among populations.

LIFESTYLE ACTION & PREVENTION

Individuals with this disease are recommended to inform their healthcare providers of their condition and may consider consulting with a neurologist to discuss medical management options. If you carry pathogenic variants of APOE or other genes involved in causation of Alzheimer disease, it is recommended that you limit dietary iron to allow sufficient but low body iron stores. While e4 is commonly considered the pathogenic variant of APOE, the protective effect of e2 underscores the mild pathogenicity of the e3 variant. Similarly, the protective effect of the rare A673T variant of APP underscores the pathogenic nature of the common "wild-type" variant. Consultation with your healthcare professional and/or genetic counseling is recommended as additional evaluation may be indicated. For more information, see The Mindspan Diet by Preston Estep. In English, Ballantine Books/Random House, ISBN: 978-1-101-88612-0. In simplified Chinese, Cheers Publishing, Beijing, ISBN: 978-7-213-07661-9

ICD10 CODE OF DISEASE

G30.9; Alzheimer's disease, unspecified G30.8; Other Alzheimer's disease Z15.89; Genetic susceptibility to other disease

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- Bettens K, Sleegers K, Van Broeckhoven C, Genetic insights in Alzheimer's disease., Lancet Neurol. 2013 Jan;12(1):92-104. doi: 10.1016/S1474-4422(12)70259-4.
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Glycogen Storage Disease Type III

Disease Category: Reproductive and Carrier

GENE(S) & VARIANT(S), ZYGOSITY

AGL c.3965delT (p.Val1322Alafs*27) , heterozygous

VARIANT INTERPRETATION

AGL c.3965delT (p.Val1322Alafs*27; also referred to as c.3964delT) is a pathogenic variant associated with autosomal recessive glycogen storage disease type 3 (GSD III). This variant causes a frameshift at amino acid 1322 and premature termination 27 amino acids downstream. At this position, this is expected to result in absent protein (loss of function), which is an established mechanism of disease for AGL. This variant has been reported in 2 unrelated affected homozygous individuals and segregated with the disease in one homozygous sibling (Shaiu 2000). This variant has been identified in 1/65402 European (non-Finnish) chromosomes by the Exome Aggregation Consortium (ExAC, http://exac.broadinstitute.org; dbSNP rs113994132), and is present in ClinVar (ID: 1103, accessed 8/31/17). In summary, the p.Val1322Alafs*27 variant meets criteria (ACMG, Richards 2015) to be classified as pathogenic for autosomal recessive GSD III.

GENE OVERVIEW

AGL, located on chromosome 1p21.2, codes for an enzyme that is involved in glycogen debranching. Variants in this gene that result in a missing or malfunctioning protein are associated with glycogen storage disease type III. AGL is also known as GDE.

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OTHER DISEASE NAMES
Cori Disease, Debrancher Deficiency, Forbes Disease, GSD III

DISEASE DESCRIPTION
Glycogen Storage Disease Type III (types IIIa-85% of all cases, IIIb, IIIc, and IIId account for the rest) is a metabolic condition due to an inability to break down glycogen, a component of sugar. This condition is characterized by variable liver disease, cardiomyopathy (cardiac muscle abnormality), and skeletal muscle myopathy. Symptoms range from asymptomatic (the majority) to severe cardiac dysfunction, congestive heart failure, and (rarely) sudden death. In addition, symptoms such as ketotic hypoglycemia, hepatomegaly (enlarged liver), hyperlipidemia, and elevated hepatic transaminases may be seen in infancy. Skeletal myopathy (muscle weakness) may be seen in the third to fourth decade of life. Other symptoms such as osteoporosis, osteopenia (low bone mineral density), and polycystic ovaries have also been reported. Onset and severity of the disease may vary depending upon the gene involved. Carriers of this condition typically do not display symptoms.

EPIDEMIOLOGY
The estimated prevalence of GSDIII is 1 in 100,000. The disease is more common in certain populations such as people of North African Jewish ancestry with an estimated frequency of 1 in 5,400 affected individuals.

GENETIC CONTRIBUTION
GSDIII is inherited in an autosomal recessive manner.

RISK FACTORS
Excessive sugar consumption may lead to a build up of glycogen and worsen symptoms. Additionally, steroid-based drugs and growth hormone replacement may worsen symptoms. Individuals with GSDIII may also consider discussing usage of hormonal contraception with a specialist, as it may be associated with increased risk of hepatic adenoma, and statin drugs due to risk of worsening of myopathy. Beta blockers may also increase risk of hypoglycemia.

LIFESTYLE ACTION & PREVENTION
Individuals with this disease are recommended to inform their healthcare providers of their condition. Individuals with GSDIII may consider consulting with a metabolic specialist, medical geneticist, nutritionist, and genetic counselor to discuss medical management options. Clinical treatment may involve pharmacotherapy and liver transplantation. Changing lifestyle habits may alleviate some symptoms of the condition. Carriers may consider having genetic testing performed for their partner, particularly if planning a family. Consultation with your healthcare professional and/or genetic counseling is recommended as additional evaluation may be indicated.

ICD10 CODE OF DISEASE
E74.03 Type III glycogen storage disease Z14.8; Genetic carrier of other disease

REFERENCES

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Notable Findings

Summary of your results

FINDING	GENE(S) & VARIANT(S), ZYGOSITY
Most common HFE variant not detected	HFE c.845G= (p.Cys282)

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Most common HFE variant not detected

DESCRIPTION

HFE is involved in the absorption of dietary iron and some variants in this gene are known to cause iron overload and related disorders. A well-studied variant in this gene, Cys282Tyr (c.845G>A), predisposes to the iron overload disease hemochromatosis. This variant is relatively common and causes the highest degree of iron overload. Individuals carrying only one copy of this variant will typically have higher than normal body iron stores, whereas having two copies (one from each parent) greatly increases iron above the one copy level, elevating the long-term risk for developing hemochromatosis. The absence of this variant in your genome does not guarantee that you do not carry other genetic variants that predispose you to increased risk of hemochromatosis.

Your Genotype	rsID	Gene & Variant	Genotype Description
GG	rs1800562	HFE c.845G= (p.Cys282)	Your whole genome screening test did not show the most common and serious variant in the HFE gene (p.Cys282Tyr).

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