GeneDose Genetic Response Report

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This report combines (i) an analysis of the patient's DNA by TruDiagnostic, Inc., identifying relevant genetic variants that are informative for medication efficacy, safety, and dosing, with (ii) an interpretation of the identified DNA variants by Coriell Life Sciences to bring you immediately actionable clinical guidance regarding safer, more effective medications and dosages for the patient. The Medication Report section lists the type of PGx guidance present on FDA-approved drug labels. Medications with no established FDA PGx guidance are provided solely for educational purposes.

Patient: Doe, Jane
Date of Birth: Jan 01, 1990
Sex: Female

Physician: Dr. Example
Practice: Example Health Associates

Specimen type: Buccal swab
Sample ID: example

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Genetic Summary Information

† When multiple activities are listed, check information in Medication Report Details (Pg. 8) for specific medication of interest.
Uncertain = No known diplotype/result (name) or activity for this combination of genetic variants; Uninterpretable Genotype.

Genetic Summary

Gene	Result	Activity †
ApoE	ε3|ε3	See ApoE Genotype Info
CYP2C19	*8|*8	Poor metabolizer
CYP2C9	*1|*1	Normal metabolizer
CYP2D6	*1|*1x2	Ultrarapid metabolizer
CYP3A4	*1B|*1B	Ultrarapid metabolizer
CYP3A5	*1A|*1A; or *1A|*1D; or *1D|*1D	Normal metabolizer
CYP4F2	*1|*1	Normal function
Factor V Leiden	Variant	See Thrombosis Profile
HLA-B*1502	WT|WT	Negative
MTHFR (A1298C)	Variant	See Thrombosis Profile
MTHFR (C677T)	Variant	See Thrombosis Profile
Prothrombin (F2)	Normal	See Thrombosis Profile
SLCO1B1	*1|*1	Normal liver uptake activity
TPMT	*1|*1	Normal metabolizer
VKORC1	*1|*1	Low sensitivity to warfarin

SAMPLE

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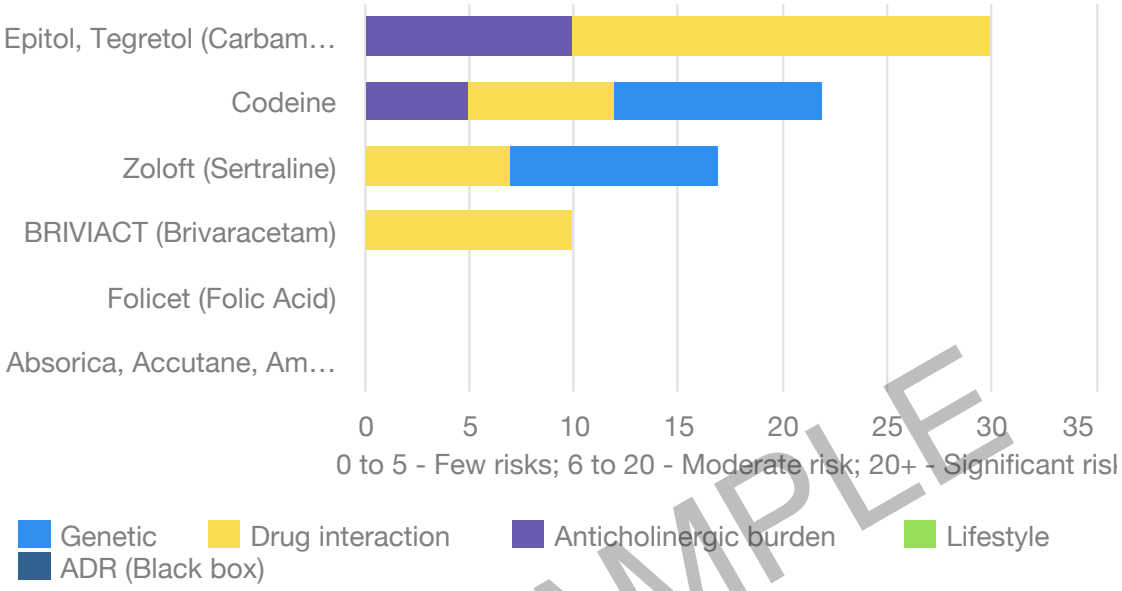
Current Regimen Risk Chart

This chart summarizes the various risk factors associated with each medication entered into GeneDose™ Live for Jane Doe. The length of each colored segment represents the relative contribution of a risk category (detailed in the below legend) to the overall risk associated with the use of a medication. For further information, consult the *Current Regimen Risk Details* Pg. 3 section.



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Current Regimen Risk Detail

Severe Risks

Strong regimen anticholinergic burden

The cumulative effect of taking multiple medicines with anticholinergic properties termed as anticholinergic burden can adversely impact cognition, physical function and increase the risk of mortality.

Major Risks

Genetic warning for Zoloft (Sertraline)

Individuals with poor metabolizer status may have higher plasma concentrations and decreased clearance. Reduce dose by 50%.

Genetic warning for Codeine

For analgesia, select alternative drug (e.g. acetaminophen, NSAID, morphine; not tramadol or oxycodone). Be extra alert to adverse drug events due to increased morphine plasma concentration.

BRIVIACT (Brivaracetam) has its effect decreased by, and increases effect of Epitol, Tegretol (Carbamazepine)

- monitor for signs of drug toxicity
- monitor for altered clinical response to drug therapy
- warn against driving or operating machinery or performing other hazardous tasks until drug effects are known
- dosage reduction may be required

Coadministration with carbamazepine may increase exposure to the active metabolite of carbamazepine, carbamazepine-epoxide. A 26% decrease in the plasma concentration of brivaracetam has also been observed during co-administration.

Moderate Risks

Epitol, Tegretol (Carbamazepine) may decrease concentration of Codeine

- use combination with caution
- monitor for altered clinical response to drug therapy
- adjust drug dosage

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Inducers of CYP3A4 such as carbamazepine, may induce the hepatic metabolism of opiate agonists, which may lead to opiate withdrawal or inadequate pain control. Clinicians should be alert to changes in the effect of the opioid agonist.

Epitol, Tegretol (Carbamazepine) reduces effect of Zoloft (Sertraline)

- use combination with caution
- monitor patient clinically

Sertraline is a substrate for CYP3A4 and CYP2C19. Drugs that induce hepatic isoenzymes, such as carbamazepine could decrease sertraline plasma concentrations, potentially causing decreased effectiveness of sertraline.

Minor Risks

Codeine has its effect reduced by Zoloft (Sertraline)

- use combination with caution
- monitor patient clinically

The activity of codeine is due to its conversion to morphine via the cytochrome P450 CYP2D6 hepatic isoenzyme. The analgesic activity of codeinemay be reduced when it is combined with drugs that inhibit CYP2D6, such as sertraline.

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Thrombosis Profile

Tested Gene (Allele)	Genotype	Predicted Phenotype	Clinical Guidance
Prothrombin (F2)	Normal	Variant alleles detected. It is important for individuals possessing this allelic variant to understand the clinical risks and the genetic implications of their result. Patients should be counseled by their physician or genetic counselor	Individuals homozygous for the Factor V Leiden mutation have an approximately 80-fold increased risk of venous thrombosis as compared to individuals without the mutation. Patients who are homozygous for either MTHFR variant may have a further increased risk for venous thrombosis if they also possess the Factor V Leiden 1691A allele.
Factor V Leiden	Homozygous variant		
MTHFR (A1298C)	Homozygous variant		
MTHFR (C677T)	Homozygous variant		

General Description

Genetic analyses of three genes (four alleles) considered to increase the risk for venous thromboembolism were performed using molecular genetic techniques. The presence of the Prothrombin (Factor 2) gene allele c.*97G>A (previously designated as 20210G>A) and Factor V Leiden allele c.1601G>A (previously designated as 1691G>A) are risk factors for venous thromboembolism. This risk may be further increased by the use of estrogen therapy, oral contraceptives, pregnancy, and surgery.

Patients who are homozygous for MTHFR C677T or MTHFR A1298C may have a further increased risk for venous thromboembolism if they also possess the Factor V Leiden c.1601G>A allele. However, the MTHFR alleles alone do not predict a significant risk for venous thromboembolism.

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References

- Zhang S, et al.; ACMG Laboratory Quality Assurance Committee. Venous thromboembolism laboratory testing (factor V Leiden and factor II c.*97G>A), 2018 update: a technical standard of the American College of Medical Genetics and Genomics (ACMG). Genet Med. 2018 Dec;20(12):1489-1498. doi: 10.1038/s41436-018-0322-z. Epub 2018 Oct 5. PMID: 30297698.
- Bhatt S, et al.; ACMG Professional Practice and Guidelines Committee. Addendum: American College of Medical Genetics consensus statement on factor V Leiden mutation testing. Genet Med. 2021 Mar 5. doi: 10.1038/s41436-021-01108-x. Epub ahead of print. PMID: 33674767.
- Lim MY, et al.; Thrombophilic risk of individuals with rare compound factor V Leiden and prothrombin G20210A polymorphisms: an international case series of 100 individuals. Eur J Haematol. 2016 Oct;97(4):353-60. doi: 10.1111/ejh.12738. Epub 2016 Feb 18. PMID: 26773706.
- Saemundsson Y, et al.; Homozygous factor V Leiden and double heterozygosity for factor V Leiden and prothrombin mutation. J Thromb Thrombolysis. 2013 Oct;36(3):324-31. doi: 10.1007/s11239-012-0824-5. PMID: 23054468.
- Stevens SM, et al.; Guidance for the evaluation and treatment of hereditary and acquired thrombophilia. J Thromb Thrombolysis. 2016 Jan;41(1):154-64. doi: 10.1007/s11239-015-1316-1. PMID: 26780744; PMCID: PMC4715840.

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Medication Summary

Cardiac			
Therapeutic Class	**Standard Precautions**	**Caution / Info**	**Change recommended**
Anticoagulants	Acenocoumarol	Warfarin	

Gastroenterology			
Therapeutic Class	**Standard Precautions**	**Caution / Info**	**Change recommended**
Antidepressants		Nortriptyline	
Proton Pump Inhibitors (PPIs)		Omeprazole	

Infectious Disease			
Therapeutic Class	**Standard Precautions**	**Caution / Info**	**Change recommended**
Antifungals		Voriconazole	

Pain			
Therapeutic Class	**Standard Precautions**	**Caution / Info**	**Change recommended**
Antidepressants		Nortriptyline Venlafaxine Vortioxetine	
Antipsychotics	Olanzapine		
Opioids		Oxycodone	

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Psychotropic

Therapeutic Class	Standard Precautions	Caution / Info	Change recommended
Antidepressants		Nortriptyline Venlafaxine Vortioxetine	
Antipsychotics	Olanzapine	Zuclopenthixol	

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Legend

- Typical response is expected
- Consider alternative therapy
- Change recommended
- Additional information available
- Response is uncertain

Clinical Evidence Level

- Strong
- Moderate
- Emerging

Medication Report Details (by therapeutic class)

Drug	Finding	Recommendation	Concern	Evidence
Anticoagulants				
Acenocoumarol (Sintrom, Acitrom)	CYP2C9: Extensive metabolizer. Two alleles showing normal activity.	Typical response is expected; no additional therapeutic recommendations.		Strong
Warfarin (Coumadin)	Multigenic: VKORC1, CYP2C9: Two alleles showing normal activity.; Extensive metabolizer. Two alleles showing normal activity.	Individuals with this combination of alleles may benefit from an increased dose of Warfarin. The FDA table recommends a therapeutic dose of 5-7 mg/day.		Moderate

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Drug	Finding	Recommendation	Concern	Evidence
Antidepressants				
Nortriptyline (Pamelor)	CYP2D6: Ultrarapid metabolizer. One allele showing normal activity and one duplicated allele showing increased activity.	Individuals with ultrarapid metabolizer status have increased metabolism of tricyclics to less active compounds when compared to extensive metabolizers; the resultant lower plasma concentrations will increase probability of pharmacotherapy failure. Consider alternative therapy--select alternative drug (e.g. citalopram, sertraline) or increase dose by 60% and monitor nortriptyline 10-hydroxynortriptyline plasma concentrations.	Efficacy	
Venlafaxine (Effexor)	CYP2D6: Ultrarapid metabolizer. One allele showing normal activity and one duplicated allele showing increased activity.	Be alert to decreased venlafaxine and increased (O-desmethyl) venlafaxine plasma concentration. Titrate dose to a maximum of 150% of the normal dose or select alternative drug (e.g. citalopram, sertraline).		
Vortioxetine (Brintellix)	CYP2D6: *1|*1x2	Individuals with ultrarapid metabolizer status have increased clearance of vortioxetine; the resultant lower plasma concentrations may increase the probability of pharmacotherapy failure. Consider increasing the dose.	Efficacy	
Antifungals				
Voriconazole	CYP2C19: Poor metabolizer. Two null alleles likely showing reduced activity.	Individuals with poor metabolizer status may have higher voriconazole exposure. Adjust the dose and monitor for adverse events or lack of efficacy.	ADR & Efficacy	

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Drug	Finding	Recommendation	Concern	Evidence
Antipsychotics				
Olanzapine (Zalasta, Zyprexa)	CYP2D6: Ultrarapid metabolizer. One allele showing normal activity and one duplicated allele showing increased activity.	Typical response is expected; no additional therapeutic recommendations.		
Zuclopenthixol	CYP2D6: Ultrarapid metabolizer. One allele showing normal activity and one duplicated allele showing increased activity.	Individuals with ultrarapid metabolizer status have increased metabolism to less active compounds; the resultant decreased plasma concentrations may increase the probability of pharmacotherapy failure. Insufficient evidence to allow calculation of dose adjustment. Be alert to low zuclopenthixol plasma concentrations or select alternative drug (e.g. flupenthixol, quetiapine, olanzapine, clozapine).	Efficacy	
Opioids				
Oxycodone (Oxycontin)	CYP2D6: Ultrarapid metabolizer. One allele showing normal activity and one duplicated allele showing increased activity.	Individuals with ultrarapid metabolizer status are at risk of possible adverse drug reaction. Insufficient evidence to allow calculation of dose adjustment. Select alternative drug (not tramadol or codeine) or be alert to adverse drug events (e.g. nausea; vomiting; constipation; respiratory depression; confusion; urinary retention).	ADR	

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Drug	Finding	Recommendation	Concern	Evidence
Proton Pump Inhibitors (PPIs)				
Omeprazole (Prilosec, Zegerid)	CYP2C19: Poor metabolizer. Two null alleles showing reduced activity.	Individuals with poor metabolizer status have decreased metabolism to less active compounds; the resultant increased concentrations may increase drug efficacy. Individual is expected to respond well to PPI treatment; no additional therapeutic recommendations.	Efficacy	

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Clinical Evidence Levels

Strong

- Includes gene-drug pairs approved by the Coriell Institute for Medical Research Pharmacogenomics Advisory Group.
- Includes gene-drug pairs supported by multiple studies documenting consistent effects of specific genetic variant(s) on clinical outcomes.
- Includes gene-drug pairs approved by the Dutch Pharmacogenetics Working Group (DPWG) and/or guidelines published in Clinical Pharmacology and Therapeutics by the Clinical Pharmacogenetics Implementation Consortium (CPIC).

Moderate

- Includes gene-drug pairs supported by pharmacokinetic, pharmacodynamic, or molecular/cellular functional studies showing consistent effects of genetic variant(s).
- Includes Drug product information (e.g. This interpretation is based on guidance available in the FDA (Food and Drug Administration) drug label for ABILIFY® (10/2013).
- Includes gene-drug pairs for which potential clinical outcomes are inferred from similar gene-drug interactions approved by the Dutch Pharmacogenetics Working Group (DPWG), and/or guidelines published in Clinical Pharmacology and Therapeutics by the Clinical Pharmacogenetics Implementation Consortium (CPIC), and/or pharmacogenomic reports and submission from the Coriell Institute for Medical Research.

Emerging

- Includes gene-drug pairs supported by published studies of the drug, related drug, or a probing compound of interest involving limited data and/or inconsistent findings.

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Patient Information Card

This card contains an abbreviated genetic summary.
It is not intended as a replacement for the complete GeneDose™ report.

TruDiagnostic, Inc.
https://trudiagnostic.com/

Patient: Doe, Jane
DOB: 1990-01-01
Sample ID: example

This card shows information about your genetics that relate to drug metabolism. Show to your doctors before being prescribed new medications.

Pharmacogenomic Summary		
ApoE	ε3|ε3	See full GeneDose report
CYP2C19	*8|*8	Poor metabolizer
CYP2C9	*1|*1	Normal metabolizer
CYP2D6	*1|*1x2	Ultrarapid metabolizer
CYP3A4	*1B|*1B	Ultrarapid metabolizer
CYP3A5	*1A|*1A; or *1A|*1D; or *1D|*1D	Normal metabolizer
CYP4F2	*1|*1	Normal (with respect to Warfarin)
Factor V Leiden	Variant	See full GeneDose report
HLA-B*1502	WT|WT	Negative
MTHFR (A1298C)	Variant	See full GeneDose report
MTHFR (C677T)	Variant	See full GeneDose report
Prothrombin (F2)	Normal	See full GeneDose report
SLCO1B1	*1|*1	Normal liver uptake activity
TPMT	*1|*1	Normal metabolizer
VKORC1	*1|*1	Normal (with respect to Warfarin)

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