sema4
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PATIENT INFORMATION		SPECIMEN DETAILS		PROVIDER INFORMATION
NAME:	**Test Patient**	**SPECIMEN TYPE:**	Blood	Doctor Doctor, MD
ACC #:	12345678PG	**COLLECTION DATE:**	10/18/2019	Practice
DOB:	3/30/1951	**RECEIVED DATE:**	10/19/2019	**PHONE:** (123) 456-7890
SEX:	Male	**REPORT DATE:**	11/14/2019	

ReadyGen Pediatric Pharmacogenetics Panel

Summary

This patient was tested for a panel of pharmacogenetic genes and variants using a combination of targeted genotyping and copy number analysis. Based on available multi-ethnic population databases, it is estimated that ~95% of all individuals will carry at least one clinically actionable pharmacogenetic variant in the ReadyGen Pediatric Pharmacogenetics Panel.
Please note that absence of a detectable pharmacogenetic variant by this test does not rule out the possibility that a patient will have an atypical drug response. Please see the Test Results and Medication Dosing Guidance sections in this report for more details.

Test Results

Gene	Genotype	Phenotype	Alleles Tested
CYP2C19	*1/*17	Rapid Metabolizer	*2, *3, *4, *4B, *5, *6, *7, *8, *9, *10, *16, *17, *19, *22, *24, *25, *26, *35
CYP2C9	*1/*1	Normal Metabolizer	*2, *3, *4, *5, *6, *8, *11, *12, *13, *15, *25, *27, *31
CYP2D6	*2/*2	Normal Metabolizer	*2, *3, *4M, *6, *7, *8, *9, *10, *11, *12, *14A, *14B, *15, *17, *18, *19, *20, *29, *30, *31, *38, *41, *42, *44, *47, *49, *50, *51, *54, *55, *56A, *56B, *57, *58, *62, *72, *100, *101, *5 (gene deletion), XN (gene duplication)
CYP3A5	*3/*3	Poor Metabolizer	*3, *3C, *6, *7
DPYD	Activity Score: 2	Normal Metabolizer	2846A>T, 1679T>G, 1905+1G>A
F5	rs6025 CC	Normal Risk of Thrombosis	rs6025
NUDT15	*1/*1	Normal Metabolizer	*2, *3, *4, *5
SLCO1B1	521T>C T/T	Normal Function	521T>C
TPMT	*1/*3A	Intermediate Metabolizer	*2, *3A, *3B, *3C, *4
UGT1A1	*1/*1	Normal Metabolizer	*6, *27, *28
VKORC1	-1639G>A G/A	Intermediate Warfarin Sensitivity	-1639G>A, rs72547529, Asp36Tyr

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PATIENT INFORMATION

NAME: F-1571935 L-1571935
ACC #: 19225998PG
DOB: 3/30/1951
SEX: Male

Potentially Impacted Medications

CATEGORY	DRUG CLASS	STANDARD PRECAUTIONS	USE WITH CAUTION	CONSIDER ALTERNATIVES
Anticancer Agents	Fluoropyrimidines	Capecitabine (Xeloda®) Fluorouracil (Adrucil® (iv); Carac® (topical); Efudex® (topical))		
	Thiopurines		Azathioprine (Azasan®, Imuran®) Mercaptopurine (Purinethol®, Purixan®) Thioguanine (Tabloid®)	
Cardiovascular	Anticoagulants	Warfarin (Coumadin®)		
	Antiplatelets		Clopidogrel (Plavix®)	
	Statins	Simvastatin (Zocor®)		
Gastrointestinal	Antiemetics	Ondansetron (Zofran®, Zuplenz®)		
Gaucher Disease	Endocrine-Metabolic Agents	Eliglustat (Cerdelga®)		
Hematology	Hemostatic Agents	Eltrombopag (Promacta®)		
Infections	Antifungals			Voriconazole (Vfend®)
	Anti-HIV Agents	Atazanavir (Reyataz®, Evotaz®)		
Pain	NSAIDs	Celecoxib (Celebrex®)		
	Opioids	Codeine (Codeine, Tylenol® with Codeine) Hydrocodone/Acetaminophen (Vicodin®) Oxycodone (Percocet®, Oxycontin®) Tramadol (Ultram®)		
Psychotropic	Anti-ADHD Agents		Atomoxetine (Strattera®)	
	Anticonvulsants	Fosphenytoin (Cerebyx®) Phenytoin (Dilantin®)		
	Antidepressants	Desipramine (Norpramin®) Fluoxetine (Prozac®, Sarafem®) Fluvoxamine (Luvox®) Nortriptyline (Pamelor®) Paroxetine (Paxil®, Brisdelle®)	Sertraline (Zoloft®)	Amitriptyline (Elavil®) Citalopram (Celexa®) Clomipramine (Anafranil®) Doxepin (Silenor®) Escitalopram (Lexapro®) Imipramine (Tofranil®) Trimipramine (Surmontil®)
	Antipsychotics	Aripiprazole (Abilify®, Aristada®) Iloperidone (Fanapt®) Pimozide (Orap®)		
Transplantation	Immunosuppressants	Tacrolimus (Prograf®)		

PATIENT INFORMATION

NAME: F-1571935 L-1571935
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Dosing Guidance

NEONATAL PERIOD	INFANCY	EARLY CHILDHOOD	LATE CHILDHOOD	ADULTHOOD
BIRTH - 4 WEEKS	5 WEEKS - 1 Y	2Y - 5Y	6Y - 17Y	>=18Y

AMITRIPTYLINE *Elavil®*

Decreased Amitriptyline Exposure (CYP2C19: Rapid Metabolizer) **INFORMATIVE**

ADULT The patient's high CYP2C19 activity is likely to result in a significantly increased metabolism of amitriptyline to nortriptyline and a subsequent decrease in amitriptyline exposure leading to therapy failure or increased side effects.

Psychiatric Conditions: Consider an alternative medication. If amitriptyline is warranted, consider therapeutic drug monitoring to guide dose adjustments.

Neuropathic Pain: Consider an alternative medication. If amitriptyline is warranted titrate dose according to the patient's clinical response and tolerability.

PEDIATRIC When used at low dose ranges for neuropathic pain or at higher dose ranges for other indications such as depression, the pharmacogenetic recommendations for daily dosing of amitriptyline based on CYP2C19 genotypes may be used with caution in older children and adolescents and should be accompanied by close monitoring.

Hicks JK, Sangkuhl K, Swen JJ, Ellingrod VL, Müller D, Shimoda K, Bishop JR, Kharasch ED, Skaar TC, Gaedigk A, Dunnenberger HM, Klein TE, Caudle KE, Stingl JC. Clinical pharmacogenetics implementation consortium guideline (CPIC) for CYP2D6 and CYP2C19 genotypes and dosing of tricyclic antidepressants: 2016 update. Clin Pharmacol Ther 2017 07;102(1):37-44.

AGE	Neonatal Period	Infancy	Early Childhood	Late Childhood	Adulthood
SUITABILITY	Not Used	Not Used	Not Used	Caution: See Pediatric Guidelines	See Adult Guidelines

ARIPIPRAZOLE *Abilify®, Aristada®*

Normal Exposure to Aripiprazole (CYP2D6: Normal Metabolizer) **ACTIONABLE**

ADULT The patient's genotype is associated with normal aripiprazole exposure. Consider prescribing aripiprazole at standard label-recommended dosage and administration. Careful titration is recommended until a favorable response is achieved.

Daily dosing (oral): the daily maintenance and maximum recommended doses are 10-15 mg and 30 mg, respectively. Reduce dose by 50% if a strong CYP2D6 inhibitor or a strong CYP3A4 inhibitor is co-administered. Reduce the dose to 25% of the usual dose if both a strong CYP2D6 inhibitor and a strong CYP3A4 inhibitor are co-administered. Double the dose if a strong CYP3A4 inducer is co-administered.

Single dosing (intramuscular): consider one single injection of 675 mg of *Aristada Initio* when initiating treatment with *Aristada*. Avoid using *Aristada Initio* if a strong CYP2D6 inhibitor or a strong CYP3A4 inhibitor or a strong CYP3A4 inducer is co-administered.

Monthly dosing (intramuscular): the starting and maintenance monthly recommended dose is 400 mg for *Abilify Maintena* or 441 mg, 662 mg and 882 mg for *Aristada*. For *Abilify Maintena*, reduce the monthly dose to 300 mg if a strong CYP2D6 inhibitor or a strong CYP3A4 inhibitor is co-administered to patients receiving aripiprazole at 400 mg, and reduce dose to 200 mg in patients receiving aripiprazole at 300 mg. For *Aristada*. reduce the dose to the next lower strength if a strong CYP2D6 inhibitor or a strong CYP3A4 inhibitor is co-administered for more than 14 days. For *Abilify Maintena*, reduce the dose to 2[illegible] if both a strong CYP2D6 inhibitor and a strong CYP3A4 inhibitor are co-administered to patients receiving aripiprazole at 400 mg, and reduce the dose to 160 mg in patients receiving aripiprazole at 300 mg. For *Aristada*. avoid use for patients at 662 mg or 882 mg dose if both a strong CYP2D6 inhibitor and a strong CYP3A4 inhibitor are co-administered. No dosage adjustment is necessary in patients taking 441 mg *Aristada*. if tolerated. If a strong CYP3A4 inducer is co-administered for more than 14 days, avoid using *Abilify Maintena*. For *Aristada*, if a strong CYP3A4 inducer is co-administered for more than 14 days, increase the 441 mg dose to 6[illegible]; no dose adjustment is necessary for 662 mg and 882 mg doses.

Every 6 weeks or two months dosing with *Aristada* (intramuscular): depending on individual patient's needs, treatment may be initiated with the 882 mg dose every 6 weeks or 1064 mg dose every two months. Reduce the dose to a lower strength: 441 mg every 4 weeks if a strong CYP2D6 inhibitor or a strong CYP3A4 inhibitor is co-administered for more than 14 days. Reduce the dose to a lower strength: 441 mg every 4 weeks if a strong CYP2D6 inhibitor and a strong CYP3A4 inhibitor are both co-administered for more than 14 days. If a strong CYP3A4 inducer is co-administered for more than 14 days, no dose adjustment is necessary for the 662 mg, 882 mg or 1064 mg doses, whereas 441 mg dose should be increased to 662 mg.

PEDIATRIC The pharmacogenetic recommendations for daily oral dosing of aripiprazole based on CYP2D6 genotypes in adults are suitable for children (6 years and older) and adolescents. Dosing strategies in pediatric patients vary by indication.

Abilify [package insert]. Tokyo, Japan: Otsuka America Pharmaceutical, Inc.; 2012.
Abilify Maintena [package insert]. Tokyo, Japan: Otsuka America Pharmaceutical, Inc.; 2014.
Aristada [package insert]. Waltham, MA: Alkermes; 2017.
Abilify [package insert]. Tokyo, Japan: Otsuka America Pharmaceutical, Inc.; 2017.
Abilify Maintena [package insert]. Tokyo, Japan: Otsuka America Pharmaceutical, Inc.; 2017.
Aristada [package insert]. Waltham, MA: Alkermes; 2018.
Aristada Initio [package insert]. Waltham, MA: Alkermes; 2018.

AGE	Neonatal Period	Infancy	Early Childhood	Late Childhood	Adulthood
SUITABILITY	Not Used	Not Used	See Pediatric Guidelines	See Pediatric Guidelines	See Adult Guidelines

ATAZANAVIR *Reyataz®, Evotaz®*

Normal Risk of Hyperbilirubinemia (UGT1A1: Normal Metabolizer) **ACTIONABLE**

✓ **ADULT** The genotype results predict that the patient has normal UGT1A1 activity. Inform the patient that some patients stop atazanavir because of hyperbilirubinemia or jaundice (yellowing of eyes and skin). However, patients with this genotype are unlikely to develop atazanavir-associated hyperbilirubinemia. Use label-recommended dosage of atazanavir in this patient.

✓ **PEDIATRIC** Although limited data is available on the pharmacogenetics of atazanavir in pediatric patients, the pharmacogenetic recommendations for atazanavir based on UGT1A1 genotypes in adults may be suitable for children 1 year of age or older.

Gammal RS, Court MH, Haidar CE, Iwuchukwu OF, Gaur AH, Alvarellos M, Guillemette C, Lennox JL, Whirl-Carrillo M, Brummel SS, Ratain MJ, Klein TE, Schackman BR, Caudle KE, Haas DW, . Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for UGT1A1 and Atazanavir Prescribing. Clin Pharmacol Ther 2016 Apr;99(4):363-9.

AGE	Neonatal Period	Infancy	Early Childhood	Late Childhood	Adulthood
SUITABILITY	Not Used	Caution: See Pediatric Guidelines	Caution: See Pediatric Guidelines	Caution: See Pediatric Guidelines	See Adult Guidelines

ATOMOXETINE *Strattera®*

Possible Atomoxetine Underexposure Leading to Decreased Response (CYP2D6: Normal Metabolizer) **ACTIONABLE**

⚠ **ADULT** The genotype result indicates that the patient is likely to have an insufficient response due to inadequate drug exposure following standard dosing. Consider the following dosing strategy:

- Initiate treatment at 40 mg/day, increase to 80 mg/day after 3 days and maintain dose.
- If after 2 weeks, optimal clinical response is not observed and adverse events are not present, consider a dose increase to 100 mg/day.
- If after 2 weeks, optimal clinical response is not observed and adverse events are not present, consider therapeutic drug monitoring 1-2 hours post dose. If the plasma concentration is less than 200 ng/ml consider a dose increase to a target of 400 ng/ml. Doses greater than 100 mg/day may be needed to achieve a targeted therapeutic concentration. (Therapeutic range: 200-1000 ng/ml).

⚠ **PEDIATRIC** The pharmacogenetic recommendations for atomoxetine based on CYP2D6 genotypes in adults are suitable for children and adolescents.

Specific CYP2D6-based dosing strategies for children and adolescents up to 70 kg body weight: The genotype results indicates that the patient is likely to have an insufficient response due to inadequate drug exposure following standard dosing. Consider the following dosing strategy:

- Initiate treatment at 0.5 mg/kg/day, increase to 1.2 mg/kg/day after 3 days and maintain dose.
- If after 2 weeks, optimal clinical response is not observed and adverse events are not present, consider therapeutic drug monitoring 1-2 hours post dose. If the plasma concentration is less than 200 ng/ml consider a dose increase to a target of 400 ng/ml. Doses greater than 100 mg/day may be needed to achieve a targeted therapeutic concentration. (Therapeutic range: 200-1000 ng/ml).

CYP2D6-based dosing strategy in adults is applicable to children or adolescents > 70 kg body weight.

Brown JT, Bishop JR, Sangkuhl K, Nurmi EL, Mueller DJ, Dinh JC, Gaedigk A, Klein TE, Caudle KE, McCracken JT, de Leon J, Leeder JS. Clinical Pharmacogenetics Implementation Consortium Guideline for Cytochrome P450 (CYP)2D6 Genotype and Atomoxetine Therapy. Clin Pharmacol Ther 2019 Jul;106(1):94-102.

AGE	Neonatal Period	Infancy	Early Childhood	Late Childhood	Adulthood
SUITABILITY	Not Used	Not Used	Not Used	See Pediatric Guidelines	See Adult Guidelines

AZATHIOPRINE *Azasan®, Imuran®*

Increased Risk of Myelotoxicity (TPMT: Intermediate Metabolizer; NUDT15: Normal Metabolizer) **ACTIONABLE**

ADULT

The TPMT genotype results for this patient are indicative of a *1/*3A predicting intermediate TPMT activity. However, there is a small risk (<1 in 100,000) that this patient's genotype is instead *3B/*3C which would predict a low TPMT activity. A TPMT phenotype test could distinguish between these possible phenotypes.

Evidence shows that 30 to 60% of patients with these genotype results experience severe leukopenia, neutropenia or myelosuppression with standard doses of azathioprine.

Nonmalignant indications
Therapy initiation: if normal starting dose is 2-3mg/kg/day, consider starting with a 30-80% dose reduction and adjust subsequent doses based on disease-specific guidelines and/or myelosuppression, as needed. Allow 2-4 weeks to reach steady state after each dose adjustment. Alternative medications may also be considered.

Malignant indications
Therapy initiation: if normal starting dose is 2-3mg/kg/day, consider starting with a 30-80% dose reduction and adjust subsequent doses based on disease-specific guidelines and myelosuppression. Allow 2-4 weeks to reach steady state after each dose adjustment.

These genotype results cannot be used to assess the patient's risk of thiopurine-related pancreatitis or hepatotoxicity.

PEDIATRIC

The pharmacogenetic recommendations for azathioprine based on TPMT & NUDT15 genotypes in adults are suitable for children and adolescents.

Relling MV, Schwab M, Whirl-Carrillo M, Suarez-Kurtz G, Pui CH, Stein CM, Moyer AM, Evans WE, Klein TE, Antillon-Klussmann FG, Caudle KE, Kato M, Yeoh AEJ, Schmiegelow K, Yang JJ. Clinical Pharmacogenetics Implementation Consortium Guideline for Thiopurine Dosing Based on TPMT and NUDT15 Genotypes: 2018 Update. Clin Pharmacol Ther 2019 May;105(5):1095-1105.

AGE	Neonatal Period	Infancy	Early Childhood	Late Childhood	Adulthood
SUITABILITY	Not Used	See Pediatric Guidelines	See Pediatric Guidelines	See Pediatric Guidelines	See Adult Guidelines

CAPECITABINE *Xeloda®*

Normal Risk for Fluoropyrimidine Toxicity (DPYD: Normal Metabolizer) **ACTIONABLE**

ADULT

The genotype results predict that the patient has a normal Dihydropyrimidine dehydrogenase (DPD) activity. Unless other genetic, environmental, or other risk factors are present, the patient does not have an increased risk for dose-dependent capecitabine toxicity. This genotype however, does not completely exclude toxicities from this drug. Use label-recommended dosage and administration, and titrate the drug according to the patient's response.

PEDIATRIC

The pharmacogenetic recommendations for capecitabine based on DPYD genotypes in adults are suitable for children and adolescents.

Amstutz U, Henricks LM, Offer SM, Barbarino J, Schellens JHM, Swen JJ, Klein TE, McLeod HL, Caudle KE, Diasio RB, Schwab M. Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for Dihydropyrimidine Dehydrogenase Genotype and Fluoropyrimidine Dosing: 2017 Update. Clin Pharmacol Ther 2018 02;103(2):210-216.

AGE	Neonatal Period	Infancy	Early Childhood	Late Childhood	Adulthood
SUITABILITY	Not Used	Not Used	See Pediatric Guidelines	Caution: See Pediatric Guidelines	See Adult Guidelines

CELECOXIB *Celebrex®*

Normal Sensitivity to Celecoxib (CYP2C9: Normal Metabolizer) **ACTIONABLE**

PATIENT INFORMATION

NAME: F-1571935 L-1571935
ACC #: 19225998PG
DOB: 3/30/1951
SEX: Male

✓ **ADULT** Celecoxib can be prescribed at standard label-recommended dosage and administration.

✓ **PEDIATRIC** The CYP2C9 enzyme activity in young children is significantly lower than adults with subjects having 50% of adult activity. Adolescents are expected to have a CYP2C9 enzyme activity similar to that found in adults. Therefore, the pharmacogenetic recommendations for celecoxib based on CYP2C9 genotypes in adults should be used with caution in children or adolescents.

Celebrex [package insert]. New York, NY: Pfizer Inc.; 2016.

AGE	Neonatal Period	Infancy	Early Childhood	Late Childhood	Adulthood
SUITABILITY	Not Used	Not Used	Caution: See Pediatric Guidelines	Caution: See Pediatric Guidelines	See Adult Guidelines

CITALOPRAM *Celexa®*

Insufficient Response to Citalopram (CYP2C19: Rapid Metabolizer) **ACTIONABLE**

⊗ **ADULT** At standard label-recommended dosage, citalopram plasma concentrations levels are expected to be low which may result in a loss of efficacy. Consider an alternative medication. If citalopram is warranted, consider increasing the dose to a maximum of 150% and titrate based on the clinical response and tolerability.

⊗ **PEDIATRIC** The pharmacogenetic recommendations for citalopram based on CYP2C19 genotypes in adults may be used with caution in older children and adolescents and should be accompanied by close monitoring.

Hicks JK, Bishop JR, Sangkuhl K, Müller DJ, Ji Y, Leckband SG, Leeder JS, Graham RL, Chiulli DL, LLerena A, Skaar TC, Scott SA, Stingl JC, Klein TE, Caudle KE, Gaedigk A, . Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for CYP2D6 and CYP2C19 Genotypes and Dosing of Selective Serotonin Reuptake Inhibitors. Clin Pharmacol Ther 2015 Aug;98(2):127-34.

AGE	Neonatal Period	Infancy	Early Childhood	Late Childhood	Adulthood
SUITABILITY	Not Used	Not Used	Not Used	Caution: See Pediatric Guidelines	See Adult Guidelines

CLOMIPRAMINE *Anafranil®*

Decreased Clomipramine Exposure (CYP2C19: Rapid Metabolizer) **INFORMATIVE**

⊗ **ADULT** The patient's high CYP2C19 activity is likely to result in a significantly increased metabolism of clomipramine to desmethyl clomipramine and a subsequent decrease in clomipramine exposure leading to therapy failure or increased side effects.

Psychiatric Conditions: Consider an alternative medication. If clomipramine is warranted, consider therapeutic drug monitoring to guide dose adjustments.

⊗ **PEDIATRIC** When used for obsessive compulsive disorder, the pharmacogenetic recommendations for daily dosing of clomipramine based on CYP2C19 genotypes in adults may be used with caution in older children and adolescents and should be accompanied by close monitoring.

Hicks JK, Sangkuhl K, Swen JJ, Ellingrod VL, Müller DJ, Shimoda K, Bishop JR, Kharasch ED, Skaar TC, Gaedigk A, Dunnenberger HM, Klein TE, Caudle KE, Stingl JC. Clinical pharmacogenetics implementation consortium guideline (CPIC) for CYP2D6 and CYP2C19 genotypes and dosing of tricyclic antidepressants: 2016 update. Clin Pharmacol Ther 2017 07;102(1):37-44.

AGE	Neonatal Period	Infancy	Early Childhood	Late Childhood	Adulthood
SUITABILITY	Not Used	Not Used	Not Used	Caution: See Pediatric Guidelines	See Adult Guidelines

CLOPIDOGREL *Plavix®*

Increased Response to Clopidogrel (CYP2C19: Rapid Metabolizer) **ACTIONABLE**

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

⚠ **PEDIATRIC** The pharmacogenetic recommendations for clopidogrel based on CYP2C19 genotypes in adults may be used with caution in children and adolescents and should be accompanied by close monitoring and testing of platelet function.

Scott SA, Sangkuhl K, Stein CM, Hulot JS, Mega JL, Roden DM, Klein TE, Sabatine MS, Johnson JA, Shuldiner AR, . Clinical Pharmacogenetics Implementation Consortium guidelines for CYP2C19 genotype and clopidogrel therapy: 2013 update. Clin Pharmacol Ther 2013 Sep;94(3):317-23.

AGE	Neonatal Period	Infancy	Early Childhood	Late Childhood	Adulthood
SUITABILITY	Not Used	Caution: See Pediatric Guidelines	Caution: See Pediatric Guidelines	Caution: See Pediatric Guidelines	See Adult Guidelines

CODEINE *Codeine; Fioricet® with Codeine*

Normal Response to Codeine (CYP2D6: Normal Metabolizer) **ACTIONABLE**

✓ **ADULT** Codeine can be prescribed at standard label-recommended dosage and administration.

✓ **PEDIATRIC** The pharmacogenetic recommendations for codeine based on CYP2D6 genotypes in adults are suitable for children (12 years and older) and adolescents. Caution: Regardless of their genotype, children ages 12 to 18 who are obese or have obstructive sleep apnea or a weakened respiratory system should not be prescribed codeine. Prescription cough and cold medicines containing codeine are not indicated for use in children, and their use in this age group is not recommended. Warning: Breastfeeding is not recommended when taking codeine due to the risk of serious adverse reactions in breastfed infants.

Crews KR, Gaedigk A, Dunnenberger HM, Leeder JS, Klein TE, Caudle KE, Haidar CE, Shen DD, Callaghan JT, Sadhasivam S, Prows CA, Kharasch ED, Skaar TC, . Clinical Pharmacogenetics Implementation Consortium guidelines for cytochrome P450-2D6 genotype and codeine therapy: 2014 update. Clin Pharmacol Ther 2014 Apr;95(4):376-82.
"FDA requires labeling changes for prescription opioid cough and cold medicines to limit their use to adults 18 years and older." FDA. January 11, 2018. PDF.
"FDA restricts use of prescription codeine pain and cough medicines and tramadol pain medicines in children; recommends against use in breastfeeding women." FDA. April 20, 2017. PDF.
"FDA statement from Douglas Throckmorton, M.D., deputy center director for regulatory programs, Center for Drug Evaluation and Research, on new warnings about the use of codeine and tramadol in children and nursing mothers." FDA. April 20, 2017.

AGE	Neonatal Period	Infancy	Early Childhood	Late Childhood	Adulthood
SUITABILITY	Not Used	Not Used	Not Used	Caution: See Pediatric Guidelines	See Adult Guidelines

DESIPRAMINE *Norpramin®*

Normal Desipramine Exposure (CYP2D6: Normal Metabolizer) **ACTIONABLE**

✓ **ADULT** The patient is predicted to be a normal CYP2D6 metabolizer which is likely to result in normal metabolism of desipramine to less active compounds.

Psychiatric Conditions: Desipramine therapy can be prescribed according to standard recommended dosage and administration.

✓ **PEDIATRIC** When used for depression, the pharmacogenetic recommendations for daily dosing of desipramine based on CYP2D6 genotypes in adults are suitable for older children and adolescents.

Hicks JK, Sangkuhl K, Swen JJ, Ellingrod VL, Müller DJ, Shimoda K, Bishop JR, Kharasch ED, Skaar TC, Gaedigk A, Dunnenberger HM, Klein TE, Caudle KE, Stingl JC. Clinical pharmacogenetics implementation consortium guideline (CPIC) for CYP2D6 and CYP2C19 genotypes and dosing of tricyclic antidepressants: 2016 update. Clin Pharmacol Ther 2017 07;102(1):37-44.

AGE	Neonatal Period	Infancy	Early Childhood	Late Childhood	Adulthood
SUITABILITY	Not Used	Not Used	Not Used	See Pediatric Guidelines	See Adult Guidelines

DOXEPIN *Silenor®*

Decreased Doxepin Exposure (CYP2C19: Rapid Metabolizer) **INFORMATIVE**

PATIENT INFORMATION

NAME: F-1571935 L-1571935
ACC #: 19225998PG
DOB: 3/30/1951
SEX: Male

ADULT The patient's high CYP2C19 activity is likely to result in a significantly increased metabolism of doxepin to desmethyl doxepin and a subsequent decrease in doxepin exposure leading to therapy failure or increased side effects.

Psychiatric Conditions: Consider an alternative medication. If doxepin is warranted, consider therapeutic drug monitoring to guide dose adjustments.

Insomnia: Doxepin can be prescribed according to the standard recommended dosage and administration.

PEDIATRIC When used at low dose ranges for insomnia or at larger dose ranges for other indications such as depression or anxiety, the pharmacogenetic recommendations for daily dosing of doxepin based on CYP2C19 genotypes may be used with caution in older children and adolescents and should be accompanied by close monitoring.

Hicks JK, Sangkuhl K, Swen JJ, Ellingrod VL, Müller DJ, Shimoda K, Bishop JR, Kharasch ED, Skaar TC, Gaedigk A, Dunnenberger HM, Klein TE, Caudle KE, Stingl JC. Clinical pharmacogenetics implementation consortium guideline (CPIC) for CYP2D6 and CYP2C19 genotypes and dosing of tricyclic antidepressants: 2016 update. Clin Pharmacol Ther 2017 07;102(1):37-44.

AGE	Neonatal Period	Infancy	Early Childhood	Late Childhood	Adulthood
SUITABILITY	Not Used	Not Used	Not Used	Caution: See Pediatric Guidelines	See Adult Guidelines

ELIGLUSTAT *Cerdelga®*

Normal Exposure to Eliglustat (CYP2D6: Normal Metabolizer) **ACTIONABLE**

ADULT The genotype result indicates that the patient is likely to have a normal eliglustat exposure. Consider prescribing eliglustat at standard label-recommended dosage and administration (84 mg orally twice daily).

Dose adjustments with co-medications: Reduce the dosage of eliglustat to 84 mg once daily if the patient is also taking a strong/moderate CYP2D6 inhibitor or a strong/moderate CYP3A inhibitor. Eliglustat is contraindicated if a strong/moderate CYP2D6 inhibitor AND a strong/moderate CYP3A inhibitor are co-administered. Eliglustat should be avoided if the patient is also taking a CYP3A inducer.

PEDIATRIC Limited data is available regarding the use of eliglustat in adolescents; the pharmacogenetic recommendations for eliglustat based on CYP2D6 genotypes in adults are suitable for adolescents.

Cerdelga [package insert]. Waterford, Ireland: Genzyme Ireland, Ltd.; 2018.

AGE	Neonatal Period	Infancy	Early Childhood	Late Childhood	Adulthood
SUITABILITY	Not Used	Not Used	Not Used	Caution: See Pediatric Guidelines	See Adult Guidelines

ELTROMBOPAG *Promacta®*

Normal Risk of Eltrombopag-Induced Thrombosis (F5: Normal Thrombosis Risk) **ACTIONABLE**

ADULT Venous and arterial thromboses have been reported in adult patients being treated with eltrombopag, more frequently in patients with hepatitis C and chronic liver disease. Other risk factors that can potentially increase the risk of thrombosis include but are not limited to splenectomy, immobilization, surgery, anti-phospholipid antibody syndrome and use of estrogen-containing contraceptives. The absence of the F5 c.1601G>A variant (also known as Factor V Leiden) in this patient indicates that the patient has a typical risk for thrombosis. Use eltrombopag as recommended.

PEDIATRIC Although eltrombopag-associated thrombotic events have been reported predominantly in adult patients with hepatitis C and liver disease, children and adolescents patients may be at similar increased risk of thrombosis than adults in the setting of additional risk factors. Therefore, when used for chronic immune idiopathic thrombocytopenia, the pharmacogenetic recommendations for eltrombopag based on F5 genotype in adults are suitable for pediatric patients.

Promacta [package insert]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; 2017.

Kim TO, Despotovic J, Lambert MP. Eltrombopag for use in children with immune thrombocytope[illegible] Blood Adv 2018 02;2(4):454-461.

Wong RS, Bakshi K, Brainsky A. Thrombophilia in patients with chronic immune thrombocyto[illegible]a. Scand J[illegible]n Lab Invest 2015 Jan;75(1):13-7.

AGE	Neonatal Period	Infancy	Early Childhood	[illegible]e Childhood	Adulthood
SUITABILITY	Not Used	See Pediatric Guidelines	See P[illegible]iatric Guidelines	[illegible]e Pediatric Guidelines	See Adult Guidelines

ESCITALOPRAM *Lexapro®*

Insufficient Response to Escitalopram (CYP2C19: Rapid Metabolizer) ACTIONABLE

ADULT At standard label-recommended dosag[illegible]escita[illegible]ram plasma concentrations levels are expected to be low which may result in a loss of efficacy. Consider[illegible]n [illegible]ternat[illegible]e medication. If escitalopram is warranted, consider increasing the dose to a maximum of 150[illegible]nd titrate ba[illegible]d on the clinical response and tolerability.

PEDIATRIC The pharmacogenetic recommen[illegible]tions [illegible]escitalopram based on CYP2C19 genotypes in adults may be used with caution in children[illegible]nd adolesc[illegible]ts and should be accompanied by close monitoring.

Hicks JK, Bishop JR, Sangkuhl K, M[illegible]252,[illegible]Li Y, Leckb[illegible]d SG, Leeder JS, Graham RL, Chiulli DL, LLerena A, Skaar TC, Scott SA, Stingl JC, Klein TE, Caudle KE, Gaedigk A, . Clinical Pharmacogenetics Implemen[illegible]ion Co[illegible](CPIC) Guideline for CYP2D6 and CYP2C19 Genotypes and Dosing of Selective Serotonin Reuptake Inhibitors. Clin Pharmacol Ther 2015 Aug;98(2):127-3[illegible]

AGE	Neonatal [illegible]eriod	Infancy	Early Childhood	Late Childhood	Adulthood
SUITABILITY	Not Use[illegible]	Not Used	Not Used	Caution: See Pediatric Guidelines	See Adult Guidelines

FLUOROURACIL *Adrucil® (iv); Carac® (topical); Efudex® (topical)*

Normal Risk for Fluoropyrimidine Toxicity (DPYD: Normal Metabolizer) ACTIONABLE

ADULT The genotype results predict that the patient has a normal Dihydropyrimidine dehydrogenase (DPD) activity. Unless other genetic, environmental, or other risk factors are present, the patient does not have an increased risk for dose-dependent fluorouracil toxicity; this genotype however, does not completely exclude toxicities from this drug. Use label-recommended dosage and administration, and titrate the drug according to the patient's response.

PEDIATRIC The pharmacogenetic recommendations for fluorouracil based on DPYD genotypes in adults are suitable for children and adolescents.

Amstutz U, Henricks LM, Offer SM, Barbarino J, Schellens JHM, Swen JJ, Klein TE, McLeod HL, Caudle KE, Diasio RB, Schwab M. Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for Dihydropyrimidine Dehydrogenase Genotype and Fluoropyrimidine Dosing: 2017 Update. Clin Pharmacol Ther 2018 02;103(2):210-216.

AGE	Neonatal Period	Infancy	Early Childhood	Late Childhood	Adulthood
SUITABILITY	Not Used	Not Used	See Pediatric Guidelines	Caution: See Pediatric Guidelines	See Adult Guidelines

FLUOXETINE *Prozac®, Sarafem®*

Normal Sensitivity to Fluoxetine (CYP2D6: Normal Metabolizer) INFORMATIVE

✓ **ADULT** Fluoxetine is metabolized to its active metabolite norfluoxetine and to other metabolites by multiple enzymes including CYP2D6, CYP2C19, CYP2C9, and CYP3A4. Fluoxetine can be prescribed at standard label-recommended dosage and administration.

✓ **PEDIATRIC** The pharmacogenetic recommendations for daily oral dosing of fluoxetine based on CYP2D6 genotypes in adults are suitable for children (7 years and older) and adolescents. Dosing strategies in pediatric patients vary by indication and lower weight children require a longer up-titration period.

Hicks JK, Bishop JR, Sangkuhl K, Müller DJ, Ji Y, Leckband SG, Leeder JS, Graham RL, Chiulli DL, LLerena A, Skaar TC, Scott SA, Stingl JC, Klein TE, Caudle KE, Gaedigk A, . Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for CYP2D6 and CYP2C19 Genotypes and Dosing of Selective Serotonin Reuptake Inhibitors. Clin Pharmacol Ther 2015 Aug;98(2):127-34.

AGE	Neonatal Period	Infancy	Early Childhood	Late Childhood	Adulthood
SUITABILITY	Not Used	Not Used	Not Used	See Pediatric Guidelines	See Adult Guidelines

FLUVOXAMINE *Luvox®*

Normal Sensitivity to Fluvoxamine (CYP2D6: Normal Metabolizer) **ACTIONABLE**

✓ **ADULT** Fluvoxamine can be prescribed at standard label recommended-dosage and administration. Careful titration is recommended until a favorable response is achieved.

✓ **PEDIATRIC** When used for depression, anxiety or obsessive-compulsive disorder, the pharmacogenetic recommendations for fluvoxamine based on CYP2D6 genotypes in adults are suitable for children and adolescents. Dosing strategies in pediatric patients vary by indication.

Hicks JK, Bishop JR, Sangkuhl K, Müller DJ, Ji Y, Leckband SG, Leeder JS, Graham RL, Chiulli DL, LLerena A, Skaar TC, Scott SA, Stingl JC, Klein TE, Caudle KE, Gaedigk A, . Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for CYP2D6 and CYP2C19 Genotypes and Dosing of Selective Serotonin Reuptake Inhibitors. Clin Pharmacol Ther 2015 Aug;98(2):127-34.

AGE	Neonatal Period	Infancy	Early Childhood	Late Childhood	Adulthood
SUITABILITY	Not Used	Not Used	Not Used	See Pediatric Guidelines	See Adult Guidelines

FOSPHENYTOIN *Cerebyx®*

Normal Sensitivity to Fosphenytoin (CYP2C9: Normal Metabolizer) **ACTIONABLE**

✓ **ADULT** Fosphenytoin is a prodrug of phenytoin. The genotype results indicate that the patient is a CYP2C9 normal metabolizer. Fosphenytoin can be prescribed at a standard loading dose and a standard maintenance dose. Evaluate response and serum concentrations 7-10 days after starting therapy.

✓ **PEDIATRIC** Phenytoin metabolism is highly variable during the first 5 months of age, and the maximal rate of phenytoin metabolism is inversely related with age. Therefore, the pharmacogenetic recommendations for fosphenytoin based on CYP2C9 genotypes in adults should be used with caution in neonates, infants and children and should be accompanied by therapeutic drug monitoring.

Caudle KE, Rettie AE, Whirl-Carrillo M, Smith LH, Mintzer S, Lee MT, Klein TE, Callaghan JT, . Clinical pharmacogenetics implementation consortium guidelines for CYP2C9 and HLA-B genotypes and phenytoin dosing. Clin Pharmacol Ther 2014 Nov;96(5):542-8.
Veeravigrom M, Jaroonvanichkul V, Netbaramee W, Phaisarn P, Uyathanarat T. Phenytoin toxicity in two-month-old Thai infant with CYP2C9 gene polymorphism--A case report. Brain Dev 2016 Jan;38(1):136-8.
Dorado P, López-Torres E, Peñas-Lledó EM, Martínez-Antón J, Llerena A. Neurological toxicity after phenytoin infusion in a pediatric patient with epilepsy: influence of CYP2C9, CYP2C19 and ABCB1 genetic polymorphisms. Pharmacogenomics J 2013 Aug;13(4):359-61.

AGE	Neonatal Period	Infancy	Early Childhood	Late Childhood	Adulthood
SUITABILITY	Not Used	Caution: See Pediatric Guidelines	Caution: See Pediatric Guidelines	Caution: See Pediatric Guidelines	See Adult Guidelines

HYDROCODONE *Vicodin®*

Normal Response to Hydrocodone (CYP2D6: Normal Metabolizer) **INFORMATIVE**

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

PEDIATRIC Analgesia: the pharmacogenetic recommendations for hydrocodone based on CYP2D6 genotypes in adults are suitable for children (2 years and older) and adolescents. **Caution:** Prescription cough and cold medicines containing hydrocodone are not indicated for use in children, and their use in this age group is not recommended.

Crews KR, Gaedigk A, Dunnenberger HM, Leeder JS, Klein TE, Caudle KE, Haidar CE, Shen DD, Callaghan JT, Sadhasivam S, Prows CA, Kharasch ED, Skaar TC, . Clinical Pharmacogenetics Implementation Consortium guidelines for cytochrome P450 2D6 genotype and codeine therapy: 2014 update. Clin Pharmacol Ther 2014 Apr;95(4):376-82.
"FDA requires labeling changes for prescription opioid cough and cold medicines to limit their use to adults 18 years and older." FDA. January 11, 2018. PDF.

AGE	Neonatal Period	Infancy	Early Childhood	Late Childhood	Adulthood
SUITABILITY	Not Used	Not Used	Caution: See Pediatric Guidelines	Caution: See Pediatric Guidelines	See Adult Guidelines

ILOPERIDONE *Fanapt®*

Normal Sensitivity to Iloperidone (CYP2D6: Normal Metabolizer) **ACTIONABLE**

ADULT Iloperidone can be prescribed at standard label-recommended dosage and administration. Iloperidone must be titrated slowly from a low starting dose to avoid orthostatic hypotension. If patients taking iloperidone experience symptoms that could indicate the occurrence of cardiac arrhythmias (e.g., dizziness, palpitations, or syncope), the prescriber should initiate further evaluation, including cardiac monitoring.

PEDIATRIC The pharmacogenetic recommendations for iloperidone based on CYP2D6 genotypes in adults are suitable for adolescents.

Fanapt [package insert]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; 2012.

AGE	Neonatal Period	Infancy	Early Childhood	Late Childhood	Adulthood
SUITABILITY	Not Used	Not Used	Not Used	See Pediatric Guidelines	See Adult Guidelines

IMIPRAMINE *Tofranil®*

Decreased Imipramine Exposure (CYP2C19: Rapid Metabolizer) **INFORMATIVE**

ADULT The patient's high CYP2C19 activity is likely to result in a significantly increased metabolism of imipramine to desipramine and a subsequent decrease in imipramine exposure leading to therapy failure or increased side effects.

Psychiatric Conditions: Consider an alternative medication. If imipramine is warranted, consider therapeutic drug monitoring to guide dose adjustments.

PEDIATRIC When used at low dose ranges for childhood enuresis or at larger dose ranges for other indications such as depression, the pharmacogenetic recommendations for daily dosing of imipramine based on CYP2C19 genotypes may be used with caution in children and adolescents and should be accompanied by close monitoring.

Hicks JK, Sangkuhl K, Swen JJ, Ellingrod VL, Müller DJ, Shimoda K, Bishop JR, Kharasch ED, Skaar TC, Gaedigk A, Dunnenberger HM, Klein TE, Caudle KE, Stingl JC. Clinical pharmacogenetics implementation consortium guideline (CPIC) for CYP2D6 and CYP2C19 genotypes and dosing of tricyclic antidepressants: 2016 update. Clin Pharmacol Ther 2017 07;102(1):37-44.

AGE	Neonatal Period	Infancy	Early Childhood	Late Childhood	Adulthood
SUITABILITY	Not Used	Not Used	Not Used	See Pediatric Guidelines	See Adult Guidelines

MERCAPTOPURINE *Purinethol®, Purixan®*

Increased Risk of Myelotoxicity (TPMT: Intermediate Metabolizer; NUDT15: Normal Metabolizer) **ACTIONABLE**

PATIENT INFORMATION

NAME: F-1571935 L-1571935
ACC #: 19225998PG
DOB: 3/30/1951
SEX: Male

ADULT

The TPMT genotype results for this patient are indicative of a *1/*3A predicting intermediate TPMT activity. However, there is a small risk (<1 in 100,000) that this patient's genotype is instead *3B/*3C which would predict a low TPMT activity. A TPMT phenotype test could distinguish between these possible phenotypes.

Evidence shows that 30 to 60% of patients with these genotype results experience severe leukopenia, neutropenia or myelosuppression with standard doses of mercaptopurine.

Nonmalignant indications
Therapy initiation: if normal starting dose is 1.5mg/kg/day, consider starting with a 30-80% dose reduction and adjust subsequent doses based on disease-specific guidelines and/or myelosuppression, as needed. Allow 2-4 weeks to reach steady state after each dose adjustment. A dose reduction may not be needed when the initiation dose considered is below 1.5mg/kg/day. Alternative medications may also be considered.

Malignant indications
Therapy initiation: if normal starting dose is 75mg/m^2/day (1.5 mg/kg/day), consider starting with a 30-80% dose reduction and adjust subsequent doses based on disease-specific guidelines and myelosuppression. Allow 2-4 weeks to reach steady state after each dose adjustment.

These genotype results cannot be used to assess the patient's risk for thiopurine-related pancreatitis or hepatotoxicity.

PEDIATRIC

The pharmacogenetic recommendations for mercaptopurine based on TPMT & NUDT15 genotypes in adults are suitable for children and adolescents.

Relling MV, Schwab M, Whirl-Carrillo M, Suarez-Kurtz G, Pui CH, Stein CM, Moyer AM, Evans WE, Klein TE, Antillon-Klussmann FG, Caudle KE, Kato M, Yeoh AEJ, Schmiegelow K, Yang JJ. Clinical Pharmacogenetics Implementation Consortium Guideline for Thiopurine Dosing Based on TPMT and NUDT15 Genotypes: 2018 Update. Clin Pharmacol Ther 2019 May;105(5):1095-1105.

AGE	Neonatal Period	Infancy	Early Childhood	Late Childhood	Adulthood
SUITABILITY	Not Used	Not Used	See Pediatric Guidelines	See Pediatric Guidelines	See Adult Guidelines

NORTRIPTYLINE *Pamelor®*

Normal Nortriptyline Exposure (CYP2D6: Normal Metabolizer) — **ACTIONABLE**

ADULT

The patient is predicted to be a normal CYP2D6 metabolizer which is likely to result in normal metabolism of nortriptyline to less active compounds.

Psychiatric Conditions: Nortriptyline therapy can be prescribed according to standard recommended dosage and administration.

PEDIATRIC

When used at low doses for neuropathic pain, no genotype-based effect is expected and standard pediatric dosing is applicable with close monitoring and a slow titration. When used at larger dose ranges for depression, the pharmacogenetic recommendations for daily dosing of nortriptyline based on CYP2D6 genotypes in adults are suitable for children and adolescents.

Hicks JK, Sangkuhl K, Swen JJ, Ellingrod VL, Müller DJ, Shimoda K, Bishop JR, Kharasch ED, Skaar TC, Gaedigk A, Dunnenberger HM, Klein TE, Caudle KE, Stingl JC. Clinical pharmacogenetics implementation consortium guideline (CPIC) for CYP2D6 and CYP2C19 genotypes and dosing of tricyclic antidepressants: 2016 update. Clin Pharmacol Ther 2017 07;102(1):37-44.

AGE	Neonatal Period	Infancy	Early Childhood	Late Childhood	Adulthood
SUITABILITY	Not Used	Not Used	Caution: See Pediatric Guidelines	Caution: See Pediatric Guidelines	See Adult Guidelines

ONDANSETRON *Zofran®, Zuplenz®*

Normal Response to Ondansetron (CYP2D6: Normal Metabolizer) — **ACTIONABLE**

✓ **ADULT** Ondansetron can be prescribed at standard label-recommended dosage and administration.

✓ **PEDIATRIC** The pharmacogenetic recommendations for ondansetron based on CYP2D6 genotypes in adults are suitable for infants (at least 1 month old), children and adolescents.

Bell GC, Caudle KE, Whirl-Carrillo M, Gordon RJ, Hikino K, Prows CA, Gaedigk A, Agundez J, Sadhasivam S, Klein TE, Schwab M. Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline for CYP2D6 genotype and use of ondansetron and tropisetron. Clin Pharmacol Ther 2017 08;102(2):213-218.

AGE	Neonatal Period	Infancy	Early Childhood	Late Childhood	Adulthood
SUITABILITY	Not Used	See Pediatric Guidelines	See Pediatric Guidelines	See Pediatric Guidelines	See Adult Guidelines

OXYCODONE *Percocet®, Oxycontin®*

Normal Response to Oxycodone (CYP2D6: Normal Metabolizer) **ACTIONABLE**

✓ **ADULT** Oxycodone can be prescribed at standard label-recommended dosage and administration.

✓ **PEDIATRIC** The pharmacogenetic recommendations for oxycodone based on CYP2D6 genotypes in adults are suitable for children (2 years and older) and adolescents.

Crews KR, Gaedigk A, Dunnenberger HM, Leeder JS, Klein TE, Caudle KE, Haidar CE, Shen DD, Callaghan JT, Sadhasivam S, Prows CA, Kharasch ED, Skaar TC, . Clinical Pharmacogenetics Implementation Consortium guidelines for cytochrome P450 2D6 genotype and codeine therapy: 2014 update. Clin Pharmacol Ther 2014 Apr;95(4):376-82.
Balyan R, Mecoli M, Venkatasubramanian R, Chidambaran V, Kamos N, Clay S, Moore DL, Mavi J, Glover C, Szmuk P, Vinks A, Sadhasivam S. CYP2D6 pharmacogenetic and oxycodone pharmacokinetic association study in pediatric surgical patients. Pharmacogenomics 2017 Mar;18(4):337-348.

AGE	Neonatal Period	Infancy	Early Childhood	Late Childhood	Adulthood
SUITABILITY	Not Used	Not Used	See Pediatric Guidelines	See Pediatric Guidelines	See Adult Guidelines

PAROXETINE *Paxil®, Brisdelle®*

Normal Sensitivity to Paroxetine (CYP2D6: Normal Metabolizer) **ACTIONABLE**

✓ **ADULT** Paroxetine can be prescribed at standard label-recommended dosage and administration. Careful titration is recommended until a favorable response is achieved.

✓ **PEDIATRIC** When used for depression, anxiety or obsessive compulsive disorder, the pharmacogenetic recommendations for paroxetine based on CYP2D6 genotypes in adults are suitable for children and adolescents.

Hicks JK, Bishop JR, Sangkuhl K, Müller DJ, Ji Y, Leckband SG, Leeder JS, Graham RL, Chiulli DL, LLerena A, Skaar TC, Scott SA, Stingl JC, Klein TE, Caudle KE, Gaedigk A, . Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for CYP2D6 and CYP2C19 Genotypes and Dosing of Selective Serotonin Reuptake Inhibitors. Clin Pharmacol Ther 2015 Aug;98(2):127-34.

AGE	Neonatal Period	Infancy	Early Childhood	Late Childhood	Adulthood
SUITABILITY	Not Used	Not Used	Not Used	See Pediatric Guidelines	See Adult Guidelines

PHENYTOIN *Dilantin®*

Normal Sensitivity to Phenytoin (CYP2C9: Normal Metabolizer) **ACTIONABLE**

✓ **ADULT** The genotype results indicate that the patient is a CYP2C9 substrate normal metabolizer. Phenytoin can be prescribed at a standard loading dose and a standard maintenance dose. Evaluate response and serum concentrations 7-10 days after starting therapy.

✓ **PEDIATRIC** Phenytoin metabolism is highly variable during the first 5 months of age, and the maximal rate of phenytoin metabolism is inversely related with age. Therefore, the pharmacogenetic recommendations for phenytoin based on CYP2C9 genotypes in adults should be used with caution in neonates, infants and children and should be accompanied by therapeutic drug monitoring.

Caudle KE, Rettie AE, Whirl-Carrillo M, Smith LH, Mintzer S, Lee MT, Klein TE, Callaghan JT, . Clinical pharmacogenetics implementation consortium guidelines for CYP2C9 and HLA-B genotypes and phenytoin dosing. Clin Pharmacol Ther 2014 Nov;96(5):542-8.
Veeravigrom M, Jaroonvanichkul V, Netbaramee W, Phaisarn P, Uyathanarat T. Phenytoin toxicity in two-month-old Thai infant with CYP2C9 gene polymorphism--A case report. Brain Dev 2016 Jan;38(1):136-8.
Dorado P, López-Torres E, Peñas-Lledó EM, Martínez-Antón J, Llerena A. Neurological toxicity after phenytoin infusion in a pediatric patient with epilepsy: influence of CYP2C9, CYP2C19 and ABCB1 genetic polymorphisms. Pharmacogenomics J 2013 Aug;13(4):359-61.

PATIENT INFORMATION

NAME: **F-1571935 L-1571935**
ACC #: 19225998PG
DOB: 3/30/1951
SEX: Male

AGE	Neonatal Period	Infancy	Early Childhood	Late Childhood	Adulthood
SUITABILITY	Not Used	Caution: See Pediatric Guidelines	Caution: See Pediatric Guidelines	Caution: See Pediatric Guidelines	See Adult Guidelines

PIMOZIDE *Orap®*

Normal Exposure to Pimozide (CYP2D6: Normal Metabolizer) **ACTIONABLE**

✓ **ADULT** Consider prescribing pimozide at standard label-recommended dosage and administration. Standard starting dose: 1 to 2 mg/day. Doses may be increased to a maximum of 10 mg/day.

Concomitant use of pimozide with strong CYP2D6 or strong CYP3A inhibitors is contraindicated. Cautions should be taken when pimozide is administered with other drugs that prolong QT.

✓ **PEDIATRIC** The pharmacogenetic recommendations for pimozide based on CYP2D6 genotypes in adults are suitable for children (2 years and older) and adolescents. Consider prescribing pimozide at a starting dose: 0.05 mg/kg/day (children). Doses may be increased to a maximum of 0.2 mg/kg/day.

Orap [package insert]. Sellersville, PA: Gate Pharmaceuticals; 2011.

Rogers HL, Bhattaram A, Zineh I, Gobburu J, Mathis M, Laughren TP, Pacanowski M. CYP2D6 genotype information to guide pimozide treatment in adult and pediatric patients: basis for the U.S. Food and Drug Administration's new dosing recommendations. J Clin Psychiatry 2012 Sep;73(9):1187-90.

Preskorn SH. Changes in the product label for pimozide illustrate both the promises and the challenges of personalized medicine. J Clin Psychiatry 2012 Sep;73(9):1191-3.

AGE	Neonatal Period	Infancy	Early Childhood	Late Childhood	Adulthood
SUITABILITY	Not Used	Not Used	See Pediatric Guidelines	See Pediatric Guidelines	See Adult Guidelines

SERTRALINE *Zoloft®*

Possible Reduced Response to Sertraline (CYP2C19: Rapid Metabolizer) **INFORMATIVE**

⚠ **ADULT** Sertraline can be prescribed at standard label-recommended dosage and administration. If patient does not respond to recommended maintenance dosing, consider an alternative medication.

⚠ **PEDIATRIC** The pharmacogenetic recommendations for sertraline based on CYP2C19 genotypes in adults may be used with caution in children and adolescents and should be accompanied by close monitoring.

Hicks JK, Bishop JR, Sangkuhl K, Müller DJ, Ji Y, Leckband SG, Leeder JS, Graham RL, Chiulli DL, LLerena A, Skaar TC, Scott SA, Stingl JC, Klein TE, Caudle KE, Gaedigk A, . Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for CYP2D6 and CYP2C19 Genotypes and Dosing of Selective Serotonin Reuptake Inhibitors. Clin Pharmacol Ther 2015 Aug;98(2):127-3

AGE	Neonatal Period	Infancy	Early Childhood	Late Childhood	Adulthood
SUITABILITY	Not Used	Not Used	Not Used	Caution: See Pediatric Guidelines	See Adult Guidelines

SIMVASTATIN *Zocor®*

Normal Myopathy Risk (SLCO1B1: Normal Function) **ACTIONABLE**

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

⚠ **PEDIATRIC** The pharmacogenetic recommendations based on SLCO1B1 genotypes in adults may not be suitable in children or adolescents. If simvastatin is prescribed to adolescents with familial heterozygous hypercholesterolemia, treatment should be initiated at the lowest recommended dose (10 mg/day) and up-titrated according to lipid lowering response and tolerability. Adjustments should be made at intervals of 4 weeks or more and the maximum recommended dose is 40 mg/day.

Wilke RA, Ramsey LB, Johnson SG, Maxwell WD, McLeod HL, Voora D, Krauss RM, Roden DM, Feng Q, Cooper-Dehoff RM, Gong L, Klein TE, Wadelius M, Niemi M, . The clinical pharmacogenomics implementation consortium: CPIC guideline for SLCO1B1 and simvastatin-induced myopathy. Clin Pharmacol Ther 2012 Jul;92(1):112-7.

AGE	Neonatal Period	Infancy	Early Childhood	Late Childhood	Adulthood
SUITABILITY	Not Used	Not Used	Not Used	Caution: See Pediatric Guidelines	See Adult Guidelines

TACROLIMUS *Prograf®*

Typical response to Tacrolimus (CYP3A5: Poor Metabolizer) **ACTIONABLE**

✓ **ADULT** The genotype result predicts that the patient does not express the CYP3A5 protein. Therefore, there is no risk that the patient may metabolize tacrolimus at a rapid rate. Careful titration of tacrolimus in response to therapeutic drug monitoring is recommended until a favorable response is achieved.

✓ **PEDIATRIC** The pharmacogenetic recommendations for tacrolimus based on CYP3A5 genotypes in adults are suitable for children and adolescents. Please note that pubertal renal transplant patients (age > 12 years) have higher dose-corrected tacrolimus concentrations compared with younger children over the first year posttransplant, indicating a lower dose requirement to achieve a comparable target concentration.

Birdwell KA, Decker B, Barbarino JM, Peterson JF, Stein CM, Sadee W, Wang D, Vinks AA, He Y, Swen JJ, Leeder JS, van Schaik R, Thummel KE, Klein TE, Caudle KE, MacPhee IA. Clinical Pharmacogenetics Implementation Consortium (CPIC) Guidelines for CYP3A5 Genotype and Tacrolimus Dosing. Clin Pharmacol Ther 2015 Jul;98(1):19-24.

AGE	Neonatal Period	Infancy	Early Childhood	Late Childhood	Adulthood
SUITABILITY	Not Used	Not Used	See Pediatric Guidelines	See Pediatric Guidelines	See Adult Guidelines

THIOGUANINE *Tabloid®*

Increased Risk of Myelotoxicity (TPMT: Intermediate Metabolizer; NUDT15: Normal Metabolizer) **ACTIONABLE**

PATIENT INFORMATION

NAME: **F-1571935 L-1571935**
ACC #: 19225998PG
DOB: 3/30/1951
SEX: Male

ADULT

The TPMT genotype results for this patient are indicative of a *1/*3A predicting intermediate TPMT activity. However, there is a small risk (<1 in 100,000) that this patient's genotype is instead *3B/*3C which would predict a low TPMT activity. A TPMT phenotype test could distinguish between these possible phenotypes.

Evidence shows that 30 to 60% of patients with these genotype results experience severe leukopenia, neutropenia or myelosuppression with standard doses of thioguanine.

Nonmalignant indications

Therapy initiation: if normal starting dose is ≥ 40-60mg/m^2/day, consider starting with a 50-80% dose reduction and adjust subsequent doses based on disease-specific guidelines and/or myelosuppression, as needed. Allow 2-4 weeks to reach steady state after each dose adjustment. Alternative medications may also be considered.

Malignant indications

Therapy initiation: if normal starting dose is ≥ 40-60mg/m^2/day, consider starting with a 50-80% dose reduction and adjust subsequent doses based on disease-specific guidelines and myelosuppression. Allow 2-4 weeks to reach steady state after each dose adjustment.

These genotype results cannot be used to assess the patient's risk of thiopurine-related pancreatitis or hepatotoxicity.

PEDIATRIC

The pharmacogenetic recommendations for thioguanine based on TPMT & NUDT15 genotypes in adults are suitable for children and adolescents.

Relling MV, Schwab M, Whirl-Carrillo M, Suarez-Kurtz G, Pui C, Stein CM, Moyer AM, Evans WE, Klein TE, Antillon-Klussmann FG, Caudle KE, Kato M, Yeoh AEJ, Schmiegelow K, Yang JJ. Clinical Pharmacogenetics Implementation Consortium Guideline for Thiopurine Dosing Based on TPMT and NUDT15 Genotypes: 2018 Update. Clin Pharmacol Ther 2019 May;105(5):1095-1105.

AGE	Neonatal Period	Infancy	Early Childhood	Late Childhood	Adulthood
SUITABILITY	Not Used	Not Used	See Pediatric Guidelines	See Pediatric Guidelines	See Adult Guidelines

TRAMADOL *Ultram®*

Normal Exposure to Tramadol (CYP2D6: Normal Metabolizer) — **ACTIONABLE**

ADULT

The patient's genotype is not expected to alter tramadol exposure. Consider prescribing tramadol at standard label-recommended dosage and administration. Individualization of dose with careful weekly titration is recommended.

PEDIATRIC

The pharmacogenetic recommendations for tramadol based on CYP2D6 genotypes in adults are suitable for children (12 years and older) and adolescents.

Caution: Regardless of their genotype, children ages 12 to 18 who are obese or have obstructive sleep apnea or a weakened respiratory system should not be prescribed tramadol.

Warning: Breastfeeding is not recommended when taking tramadol due to the risk of serious adverse reactions in breastfed infants.

"FDA restricts use of prescription codeine pain and cough medicines and tramadol pain medicines in children; recommends against use in breastfeeding women." FDA. April 20, 2017. PDF.

"FDA statement from Douglas Throckmorton, M.D., deputy center director for regulatory programs, Center for Drug Evaluation and Research, on new warnings about the use of codeine and tramadol in children & nursing mothers." FDA. April 20, 2017.

The Royal Dutch Pharmacists Association of the KNMP. (2019). Pharmacogenetic Recommendations 2019 [PDF file]. Retrieved from https://www.knmp.nl/downloads/pharmacogenetic-recommendations-august-2019.pdf (Accessed August 21, 2019).

AGE	Neonatal Period	Infancy	Early Childhood	Late Childhood	Adulthood
SUITABILITY	Not Used	Not Used	Not Used	Caution: See Pediatric Guidelines	See Adult Guidelines

TRIMIPRAMINE *Surmontil®*

Decreased Trimipramine Exposure (CYP2C19: Rapid Metabolizer) — **INFORMATIVE**

PATIENT INFORMATION

NAME: F-1571935 L-1571935
ACC #: 19225998PG
DOB: 3/30/1951
SEX: Male

ADULT The patient's high CYP2C19 activity is likely to result in a significantly increased metabolism of trimipramine to desmethyl trimipramine and a subsequent decrease in trimipramine exposure leading to therapy failure or increased side effects.

Psychiatric Conditions: Consider an alternative medication. If trimipramine is warranted, consider therapeutic drug monitoring to guide dose adjustments.

PEDIATRIC When used for depression, the pharmacogenetic recommendations for daily dosing of trimipramine based on CYP2C19 genotypes in adults may be used with caution in adolescents and should be accompanied by close monitoring.

Hicks JK, Sangkuhl K, Swen JJ, Ellingrod VL, Müller DJ, Shimoda K, Bishop JR, Kharasch ED, Skaar TC, Gaedigk A, Dunnenberger HM, Klein TE, Caudle KE, Stingl JC. Clinical pharmacogenetics implementation consortium guideline (CPIC) for CYP2D6 and CYP2C19 genotypes and dosing of tricyclic antidepressants: 2016 update. Clin Pharmacol Ther 2017 07;102(1):37-44.

AGE	Neonatal Period	Infancy	Early Childhood	Late Childhood	Adulthood
SUITABILITY	Not Used	Not Used	Not Used	Caution: See Pediatric Guidelines	See Adult Guidelines

VORICONAZOLE *Vfend®*

Non-Response to Voriconazole (CYP2C19: Rapid Metabolizer) **ACTIONABLE**

ADULT Voriconazole plasma concentrations are expected to be low if standard dose is used, increasing the risk of loss of response and effectiveness and subsequent disease progression. Consider an alternative medication that is not dependent on CYP2C19 metabolism, such as isavuconazole, liposomal amphotericin B or posaconazole.

PEDIATRIC In pediatric patients, there is insufficient evidence to distinguish a CYP2C19 rapid metabolizer from a normal metabolizer due to large variability in voriconazole trough concentrations. Achieving voriconazole therapeutic concentrations in the pediatric population with the rapid metabolizer phenotype in a timely manner is difficult. Voriconazole may be prescribed at standard label-recommended dosage and administration and dosing should be titrated in this population based on close therapeutic monitoring of trough voriconazole concentrations. As critical time may be lost in achieving therapeutic concentrations, an alternative antifungal agent (like liposomal amphotericin B or posaconazole) may also be considered.

Moriyama B, Obeng AO, Barbarino J, Penzak SR, Henning SA, Scott SA, Agúndez J, Wingard JR, McLeod HL, Klein TE, Cross SJ, Caudle KE, Walsh TJ. Clinical Pharmacogenetics Implementation Consortium (CPIC) Guidelines for CYP2C19 and Voriconazole Therapy. Clin Pharmacol Ther 2017 07;102(1):45-51.

AGE	Neonatal Period	Infancy	Early Childhood	Late Childhood	Adulthood
SUITABILITY	Not Used	Caution: See Pediatric Guidelines	Caution: See Pediatric Guidelines	Caution: See Pediatric Guidelines	See Adult Guidelines

WARFARIN *Coumadin®*

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

PATIENT INFORMATION

NAME: F-1571935 L-1571935
ACC #: 19225998PG
DOB: 3/30/1951
SEX: Male

ADULT

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

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

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

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

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

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

PEDIATRIC

The pharmacogenetic recommendations based on CYP2C9 and VKORC1 genotypes in adults are not suitable for children or adolescents. Based on the current evidence, (1) in children of European ancestry initial warfarin dose can be calculated based on validated published pediatric pharmacogenetics algorithms (appendix). (2) In children of Non-European Ancestry, initial warfarin dose can be defined with a standard dosing approach or with a clinical algorithm without the use of the patient's genotype results.

Johnson JA, Caudle KE, Gong L, Whirl-Carrillo M, Stein CM, Scott SA, Lee MT, Gage BF, Kimmel SE, Perera MA, Anderson JL, Pirmohamed M, Klein TE, Limdi NA, Cavallari LH, Wadelius M. Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for Pharmacogenetics-Guided Warfarin Dosing: 2017 Update. Clin Pharmacol Ther 2017 Sep;102(3):397-404.

AGE	Neonatal Period	Infancy	Early Childhood	Late Childhood	Adulthood
SUITABILITY	See Pediatric Guidelines	See Pediatric Guidelines	See Pediatric Guidelines	See Pediatric Guidelines	See Adult Guidelines

A medication has potentially reduced efficacy, increased toxicity or the patient has an increased risk for the indicated condition.

Guidelines exist for adjusting dosage, increased vigilance or the patient has a moderate risk for the indicated condition.

The medication can be prescribed according to standard regimens or the patient's risk for the indicated condition is not increased.

ACTIONABLE Recommendations based upon publications by international pharmacogenetic expert groups, consortia or regulatory bodies (CPIC, DPWG, FDA, EMA). Recommendations are suitable for implementation in a clinical setting. Guidelines may change as knowledge arises.

INFORMATIVE There are insufficient or contradictory findings documenting the impact of a given genetic polymorphism or drug interaction. Recommendations are informative and implementation in a clinical setting is optional.

PATIENT INFORMATION

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Methods

*Targeted genotyping was performed using multiplex Polymerase Chain Reaction (PCR) and Single Base Extension (SBE) assays with Agena® SpectroCHIP® II on a MassARRAY® Analyzer 4 system. The copy number of CYP2C19, CYP2C9, CYP2D6, and CYP3A5 was determined by multiplex ligation-dependent probe amplification (MLPA) using the SALSA® MLPA® P128-C1 probemix (MRC Holland). The UGT1A1 rs8175347 (*28) variant was genotyped by PCR and capillary electrophoresis, and the mitochondrial MT-RNR1 rs267606617 (m.1555A>G) variant was also interrogated by next-generation sequencing (NGS) using an Agilent SureSelect™QXT custom capture library that targeted rs267606617, followed by sequencing on an Illumina HiSeq 2500 or NovaSeq 6000 system with 100 bp paired-end reads.*

Limitations

*This type of analysis generally provides highly accurate genotype information. Despite this high level of accuracy, it should be kept in mind that there are many potential sources of diagnostic error, including misidentification of samples, polymorphisms, or other rare genetic variants that can interfere with analysis. Individuals should understand that rare diagnostic errors may occur for these reasons. This test does not interrogate all variant alleles of the tested genes. Absence of a detectable genetic variant by this test does not rule out the possibility that a patient will have an atypical drug response. Drug responses could be influenced by genetic variants that are not included in this test and/or other clinical factors, including drug-drug interactions, comorbidities, and other variables. Please note that positive control samples for the validation of this pharmacogenetic genotyping panel were not available for the following rare alleles: CYP2C19 *5, *7, *9, *25, *26; CYP2C9*4, *15, *25; CYP2D6*12, *15, *19, *20, *38, *42, *44, *47, *49, *50, *51, *54, *55, *56, *57, *100, *101. In addition, please note that the Sema4 pharmacogenetic genotyping tests cannot distinguish the related CYP2D6*30 and *40 (rs553846709) alleles.*

Absence of the MT-RNR1 m.1555A>G variant by this test does not exclude the presence of m.1555A>G in other tissues of this patient. The presence of the m.1555A>G variant at less than 20 percent heteroplasmy may not be detected.

Disclaimer

The content of this test report is not intended to be a substitute for professional medical advice, diagnosis, or treatment. Only a physician, pharmacist or other healthcare professional should advise a patient on the use of prescribed medications. It remains the responsibility of the healthcare provider to determine the best course of treatment for a patient. Adherence to dose guidelines does not necessarily assure a successful medical outcome. Please note this test was developed and its performance characteristics were determined by Sema4 and were considered acceptable for patient testing. It has not been cleared or approved by the FDA. The FDA has determined that such clearance or approval is not necessary.

Translational Software Disclaimer

The information presented on this report is provided as general educational health information. The content is not intended to be a substitute for professional medical advice, diagnosis, or treatment. Only a physician, pharmacist or other healthcare professional should advise a patient on the use of the medications prescribed. The pharmacogenetic assay involves use of reporting software and genotype-phenotype associations performed by Translational Software (www.translationalsoftware.com). The software has not been evaluated by the Food and Drug Administration. The software, and the report generated by the software, is not intended to diagnose, treat, cure, or

prevent any disease. A qualified designee within the lab uses Translational Software to generate and subsequently review the report. The pharmacogenetic report is one of multiple pieces of information that clinicians should consider in guiding their therapeutic choice for each patient. It remains the responsibility of the health-care provider to determine the best course of treatment for a patient. Adherence to dose guidelines does not necessarily assure a successful medical outcome

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This case has been reviewed and electronically signed by

INOVA Genomics Laboratory *Portions of this report developed and funded in partnership with Inova Genomics Laboratory.*

PATIENT INFORMATION

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DOB: 3/30/1951
SEX: Male

Patient Information Card

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

sema4
a Mount Sinai venture

REPORT DETAILS
Name: F-1571935 L-1571935
DOB: 3/30/1951
ACC #: 19225998PG

Pharmacogenetic Test Summary

CYP2C19	*1/*17	Rapid Metabolizer
CYP2C9	*1/*1	Normal Metabolizer
CYP2D6	*2/*2	Normal Metaboliz
CYP3A5	*3/*3	Poor Metabolizer
DPYD	Activity Score: 2	Normal Metabolizer
Factor V Leiden	rs6025 CC	Normal Th bosis Risk
NUDT15	*1/*1	N etab zer
SLCO1B1	521T>C T/T	Normal F nction
TPMT	*1/*3A	erm diate Metabolizer
UGT1A1	*1/*1	Nor l Metabolizer
VKORC1	-1639G>A G/	termed ate Warfarin Sensitivity

For a comp a re t contact Sema4
ww ma4.c

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