

Pharmacogenetic Testing

Policy Number: AHS – M2021 – Pharmacogenetic Testing	Prior Policy Name and Number, as applicable: <ul style="list-style-type: none"> • M2021 – Cytochrome P450
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I. Policy Description

Pharmacogenetics aims to study the influence of genetic variation on drug response and drug toxicity, which allows physicians to select a more targeted therapeutic strategy to suit each patient’s genetic profile (Aka et al., 2017). Genetic variations in human proteins, such as, cytochrome P450 enzymes, Thiopurine methyltransferase (*TPMT*), Dihydropyrimidine dehydrogenase (*DPD*), and cell surface proteins, highlights the clinical importance of pharmacogenetic testing.

Cytochrome (CYP) P450 enzymes are a class of enzymes essential in the synthesis and breakdown metabolism of various molecules and chemicals. Found primarily in the liver, these enzymes are also essential for the metabolism of many medications. CYP P450 enzymes, approximately 58 CYP human genes, are essential to produce many biochemical building blocks, such as cholesterol, fatty acids, and bile acids. Additional cytochrome P450 are involved in the metabolism of drugs, carcinogens, and internal substances, such as toxins formed within cells. Mutations in CYP P450 genes can result in the inability to properly metabolize medications and other substances, leading to increased levels of toxic substances in the body (Bains, 2013; Tantisira & Weiss, 2020).

Thiopurine methyltransferase (*TPMT*) is an enzyme that methylates azathioprine, mercaptopurine and thioguanine into active thioguanine nucleotide metabolites. Azathioprine and mercaptopurine are used for treatment of nonmalignant immunologic disorders; mercaptopurine is used for treatment of lymphoid malignancies; and thioguanine is used for treatment of myeloid leukemias (Relling et al., 2011).

Dihydropyrimidine dehydrogenase (*DPD*), encoded by the gene *DPYD*, is a rate-limiting enzyme responsible for fluoropyrimidine catabolism. The fluoropyrimidines (5-fluorouracil and capecitabine) are drugs used in the treatment of solid tumors, such as colorectal, breast, and aerodigestive tract tumors (Amstutz et al., 2018).

A variety of cell surface proteins, such as antigen-presenting molecules and other proteins, are encoded by the human leukocyte antigen genes (*HLAs*). *HLAs* are also known as major histocompatibility complex (*MHC*) (Viatte, 2021).

II. Related Policies

Policy Number	Policy Title
AHS-G2100	In Vitro Chemoresistance and Chemosensitivity Assays
AHS-G2115	Metabolite Markers of Thiopurines Testing
AHS-M2030	Testing for Targeted Therapy of Non-Small-Cell Lung Cancer
AHS-M2067	Therapeutic Drug Monitoring for 5-Fluorouracil
AHS-M2082	Genetic Testing for Lipoprotein A Variant(s) as a Decision Aid for Aspirin Treatment and/or CVD Risk Assessment

III. Indications and/or Limitations of Coverage

Application of coverage criteria is dependent upon an individual's benefit coverage at the time of the request. Specifications pertaining to Medicare and Medicaid can be found in Section VII of this policy document.

- 1) Testing for the cytochrome P450, family 2, subfamily D, polypeptide 6 (*CYP2D6*) genotype once per lifetime (please see policy guideline)* **MEETS COVERAGE CRITERIA** for individuals being considered for therapy with any of the medications listed below, or who are in their course of therapy with a medication listed below, to aid in therapy selection and/or dosing.
 - a) Amphetamine
 - b) Aripiprazole
 - c) Aripiprazole Lauroxil
 - d) Atomoxetine
 - e) Brexpiprazole
 - f) Carvedilol
 - g) Cevimeline
 - h) Clozapine
 - i) Codeine
 - j) Desipramine
 - k) Deutetrabenazine
 - l) Eligustat
 - m) Fluvoxamine

- n) Gefitinib
 - o) Iloperidone
 - p) Lofexidine
 - q) Meclizine
 - r) Metoclopramide
 - s) Nortriptyline
 - t) Oliceridine
 - u) Ondansetron
 - v) Paroxetine
 - w) Perphenazine
 - x) Pimozide
 - y) Pitolisant
 - z) Propafenone
 - aa) Tamoxifen
 - bb) Tetrabenazine
 - cc) Thioridazine
 - dd) Tolterodine
 - ee) Tramadol
 - ff) Tropisetron
 - gg) Valbenazine
 - hh) Venlafaxine
 - ii) Vortioxetine
- 2) Testing for the *CYP2D6* and cytochrome P450 family 2 subfamily C member 19 (*CYP2C19*) genotype once per lifetime (please see policy guideline)* **MEETS COVERAGE CRITERIA** for individuals being considered for therapy with any of the medications listed below, or who are in their course of therapy with these medications, to aid in therapy selection and/or dosing.
- a) Amitriptyline
 - b) Clomipramine
 - c) Doxepin
 - d) Imipramine
 - e) Trimipramine
- 3) Testing for the *CYP2C19* genotype once per lifetime (please see policy guideline)* **MEETS COVERAGE CRITERIA** for individuals being considered for therapy with any of the

medications listed below, or who are in their course of therapy with these medications, to aid in therapy selection and/or dosing.

- a) Brivaracetam
 - b) Citalopram
 - c) Clobazam
 - d) Clopidogrel
 - e) Dexlansoprazole (see Note 1)
 - f) Escitalopram
 - g) Flibanserin
 - h) Lansoprazole (see Note 1)
 - i) Omeprazole (see Note 1)
 - j) Pantoprazole (in pediatric individuals) (see Note 1)
 - k) Sertraline
 - l) Voriconazole (see Note 1)
- 4) Testing for the cytochrome P450 enzyme 2C9 (*CYP2C9*) genotype once per lifetime (please see policy guideline)* **MEETS COVERAGE CRITERIA** for individuals being considered for therapy with any of the medications listed below, or who are in their course of therapy with these medications, to aid in therapy selection and/or dosing.
- a) Celecoxib
 - b) Dronabinol
 - c) Erdafitinib
 - d) Flurbiprofen
 - e) Lornoxicam
 - f) Meloxicam
 - g) Piroxicam
 - h) Siponimod
 - i) Tenoxicam
- 5) Testing for the *CYP2C9*, cytochrome P450 family 4 subfamily F member 2 (*CYP4F2*), vitamin K epoxide reductase complex subunit 1 (*VKORC1*), and rs12777823 genotype once per lifetime **MEETS COVERAGE CRITERIA** for individuals being considered for Warfarin therapy.
- 6) Testing for the thiopurine methyltransferase (*TPMT*) and nucleoside diphosphate-linked moiety X-type motif 15 (*NUDT15*) genotype once per lifetime (please see policy guideline)*

MEETS COVERAGE CRITERIA for individuals being considered for therapy with any of the below medications, or who are in their course of therapy with these medications, to aid in therapy selection and/or dosing.

- a) Azathioprine
 - b) Mercaptopurine
 - c) Thioguanine
- 7) Testing for the dihydropyrimidine dehydrogenase (*DPYD*) genotype once per lifetime (please see policy guideline)* **MEETS COVERAGE CRITERIA** for individuals being considered for therapy with any of the below medications, or who are in their course of therapy with these medications, to aid in therapy selection and/or dosing.
- a) Capecitabine
 - b) Flucytosine
 - c) Fluorouracil
 - d) Tegafur
- 8) Testing for the following Human Leukocyte Antigens (HLAs) genotypes once per lifetime **MEETS COVERAGE CRITERIA** for individuals being considered for therapy with any of the below medications, or who are in their course of therapy with these medications, to aid in therapy selection and/or dosing:
- a) *HLA-B*57:01* before treatment with Abacavir
 - b) *HLA-B*58:01* before treatment with Allopurinol
 - c) *HLA-B*15:02* for treatment with Oxcarbazepine
 - d) *HLA-B*15:02* and *HLA-A*31:01* for treatment with Carbamazepine
- 9) Testing for the *CYP2C9* and *HLA-B*15:02* genotype once per lifetime **MEETS COVERAGE CRITERIA** for individuals being considered for therapy with the below medication, or who are in their course of therapy with this medication, to aid in therapy selection and/or dosing.
- a) Phenytoin/Fosphenytoin
- 10) Testing for the glucose-6-phosphate dehydrogenase (*G6PD*) genotype once per lifetime (please see policy guideline)* **MEETS COVERAGE CRITERIA** for individuals being considered for therapy with any of the medications listed below, or who are in their course of therapy with these medications, to aid in therapy selection and/or dosing.
- a) Pegloticase
 - b) Primaquine
 - c) Rasburicase
 - d) Tafenoquine

- 11) Testing for the following genotypes once per lifetime (please see policy guideline)* **MEETS COVERAGE CRITERIA** for individuals being considered for therapy with any of the below medications, or who are in their course of therapy with a medication listed below, to aid in therapy selection and/or dosing.
 - a) Butyrylcholinesterase enzyme (*BCHE*) for treatment with mivacurium or succinylcholine
 - b) Cystic fibrosis transmembrane conductance regulator (*CFTR*) for treatment with Ivacaftor, Elexacaftor and Tezacaftor, Ivacaftor and Lumacaftor, or Ivacaftor and Tezacaftor
 - c) Cytochrome P450 2B6 (*CYP2B6*) for treatment with Efavirenz
 - d) Cytochrome P450 3A5 (*CYP3A5*) for treatment with Tacrolimus
 - e) Interferon Lambda 3 (*IFNL3*) treatment with Peginterferon alfa-2a, Peginterferon alfa-2b or Ribavirin
 - f) N-acetyltransferase 2 (*NAT2*) for treatment with Amifampridine or Amifampridine Phosphate
 - g) Uridine diphosphate glucuronosyltransferase 1 family, polypeptide A1 (*UGT1A1*) for treatment with Atazanavir, Belinostat, Irinotecan, Nilotinib, Pazopanib, or Sacituzumab govitecan-hziy
- 12) Testing for the ryanodine receptor type 1 (*RYR1*) and calcium channel, voltage-dependent, L-type, alpha 1S subunit (*CACNA1S*) genotype once per lifetime (please see policy guideline)* **MEETS COVERAGE CRITERIA** for individuals being considered for the use of depolarizing muscle relaxants, such as succinylcholine, or halogenated volatile anesthetics.
- 13) Genetic testing for the presence of variants in the solute carrier organic anion transporter family member 1B1 (*SLCO1B1*) gene for the purpose of identifying patients at risk of statin-induced myopathy **DOES NOT MEET COVERAGE CRITERIA**.

The following does not meet coverage criteria due to a lack of available published scientific literature confirming that the test(s) is/are required and beneficial for the diagnosis and treatment of a patient's illness.

- 14) The following pharmacogenetic testing **DOES NOT MEET COVERAGE CRITERIA**:
 - a) Genotyping for any medication therapy more than once per lifetime (please see policy guideline).*
 - b) Testing for the specific genotype for individuals on medications not listed as meeting coverage criteria for testing.
 - c) Testing for all other genotypes including, but not limited to, use of other medication therapy not listed as meeting coverage criteria.
 - d) Genotyping the general population.
 - e) Pharmacogenetic panel testing for individuals not being considered for any of the above conditions.

- 15) All other single nucleotide polymorphism (SNP) testing, either as individual SNPs or as a panel of SNPs, **DOES NOT MEET COVERAGE CRITERIA** for all indications. The list of SNPs includes, but is not limited to, the following:
- a) *5HT2C* (serotonin receptor)
 - b) *5HT2A* (serotonin receptor)
 - c) *SLC6A4* (serotonin transporter)
 - d) *DRD1* (dopamine receptor)
 - e) *DRD2* (dopamine receptor)
 - f) *DRD4* (dopamine receptor)
 - g) *DAT1* or *SLC6A3* (dopamine transporter)
 - h) *DBH* (dopamine beta-hydroxylase)
 - i) *COMT* (catechol-O-methyl-transferase)
 - j) *MTHFR* (methylenetetrahydrofolate reductase)
 - k) γ -Aminobutyric acid (GABA) A receptor
 - l) *OPRM1* (μ -opioid receptor)
 - m) *OPRK1* (κ -opioid receptor)
 - n) *TYMS*
 - o) *UGT2B15* (uridine diphosphate glycosyltransferase 2 family, member 15)
 - p) Cytochrome P450 genes: *CYP3A4*, *CYP1A2*

*Policy Guideline:

Genotyping once per lifetime

Any gene should be tested once per lifetime regardless of the indication (an exception would be for *HLA* where a specific variant is tested for the medication). For example, if *CYP2C19* was tested for therapy with citalopram, additional testing for *CYP2C19* for treatment with clopidogrel is not needed and **DOES NOT MEET COVERAGE CRITERIA**.

Note 1: Pharmacogenetic testing for proton pump inhibitor therapies (PPIs) **ONLY MEETS COVERAGE CRITERIA** if the patient has an active *H. pylori* infection.

IV. Table of Terminology

Term	Definition
AACAP	American Academy of Child and Adolescent Psychiatry
AACC	American Association for Clinical Chemistry
AACF	American College of Cardiology Foundation
AAFP	American Family Physician

AAN	American Academy of Neurology
ACMG	American College of Medical Genetics and Genomics
AHA	American Heart Association
AMP	Association For Molecular Pathology
AS	Activity score
ASCPT	American Society for Clinical Pharmacology and Therapeutics
ASHP	American Society of Health System Pharmacists
BDI	Beck's Depression Inventory
CFTR	Cystic fibrosis transmembrane conductance regulator
COMT	Catechol-O-methyltransferase
CPIC	Clinical Pharmacogenetics Implementation Consortium
CYP	Cytochrome
<i>DBH</i>	<i>Dopamine beta-hydroxylase</i>
DPD	Dihydropyrimidine dehydrogenase
DPWG	Dutch Pharmacogenetics Working Group
<i>DPYD</i>	<i>Dihydropyrimidine dehydrogenase gene</i>
<i>DRD1</i>	<i>Dopamine receptor gene</i>
EMA	European Medicines Agency
FDA	Food and Drug Administration
<i>G6PD</i>	<i>Glucose-6-phosphate dehydrogenase gene</i>
HLAs	Human leukocyte antigen
IM	Intermediate metabolizer
ISPG	The International Society of Psychiatric Genetics
MDD	Major depressive disorder
MHC	Major histocompatibility complex
MP	Mercaptopurine
MTHFR	Methylenetetrahydrofolate reductase
NM	Normal metabolizer
<i>NUDT15</i>	<i>Nudix hydrolase 15</i>
PM	Poor metabolizer
PPIs	Proton pump inhibitor therapies
RM	Rapid metabolizer
<i>RYR1</i>	<i>Ryanodine receptor 1 gene</i>
SJS	Stevens Johnson Syndrome
<i>SLC6A4</i>	<i>Solute carrier family 6 member 4</i>
SNP	Single nucleotide polymorphism
TAU	Treatment as usual
TCAs	Tricyclic antidepressants
TEN	Toxic epidermal necrolysis
TG	Thioguanine

<i>TPMT</i>	<i>Thiopurine methyltransferase</i>
<i>TYMS</i>	<i>Thymidylate synthetase</i>
<i>UGT2B15</i>	<i>Uridine diphosphate glycosyltransferase 2 family, member 15</i>
URM	Ultra-rapid metabolizer

V. Scientific Background

Genetic variations play a potentially large role in an individual’s response to medications. However, drug metabolism and responses are affected by many other factors, including age, sex, interactions with other drugs, and disease states (Tantisira & Weiss, 2020). Nonetheless, inherited differences in the metabolism and disposition of drugs and genetic polymorphisms in the targets of drug therapy can have a significant influence on the efficacy and toxicity of medications potentially even more so than clinical variables such as age and organ function (Kapur et al., 2014; Ting & Schug, 2016). Genetic variation can influence pharmacodynamic factors through variations affecting drug target receptors and downstream signal transduction, or pharmacokinetic factors, affecting drug metabolism and/or elimination (Tantisira & Weiss, 2020).

The Cytochrome P450 (CYP 450) system is a group of enzymes responsible for the metabolism of many endogenous and exogenous substances, including many pharmaceutical agents. This system may serve to “activate” an inactive form of a drug, as well as inactivate and/or clear a drug from circulation. The CYP 450 enzymes are responsible for the clearance of over half of all drugs, and their activity can be affected by diet, age, and other medications. The genes encoding for the CYP 450 enzymes are highly variable with multiple alleles that confer various levels of metabolic activity for specific substrates. In some cases, alleles can be highly correlated with ethnic background. Generally, there are three categories of metabolizer; ultra-rapid metabolizers, normal metabolizers, and poor metabolizers (Tantisira & Weiss, 2020).

Due to the variations in enzyme activity conferred by allelic differences, some CYP 450 alleles are associated with an increased risk for certain conditions or adverse outcomes with certain drugs. Knowledge of the allele type may assist in the selection of a drug, or in drug dosing. Three CYP 450 enzymes are most often considered regarding clinical use for drug selection and/or dosing. Phenotypes, such as CYP2D6, CYP2C9 and CYP2C19, have been associated with the metabolism of several therapeutic drugs, and various alleles of the *CYP450* gene confer differences in metabolic function. For these CYP 450 enzymes, it is thought that “poor metabolizers” could have less efficient elimination of a drug, and therefore may be at risk for side effects due to drug accumulation. For drugs that require activation by a specific CYP 450 enzyme, lower activity may yield less of the biologically active drug, which could result in lower drug efficacy. Individuals considered as “ultra-rapid metabolizers” may clear the drug more quickly than normal, and therefore may require higher doses to yield the desired therapeutic effect. Likewise, for drugs that require activation, these individuals may produce higher levels of the active drug, potentially causing unwanted side effects. Due to these differences in enzyme activity, some alleles are associated with a higher risk of adverse outcomes depending on the drug prescribed (Tantisira & Weiss, 2020).

CYP2C9

Warfarin (brand name Coumadin) is widely used as an anticoagulant in the treatment and prevention of thrombotic disorders. *CYP2C9* participates in warfarin metabolism, and several *CYP2C9* alleles have reduced activity, resulting in a higher circulating drug concentration. *CYP2C9*2* and *CYP2C9*3* are the most common variants with reduced activity. Variations in a second gene, *VKORC1*, also can impact warfarin's effectiveness. This gene codes for the enzyme that is the target for warfarin. Genotypes resulting in reduced metabolism may need a higher dose to achieve the desired efficacy (Tantisira & Weiss, 2020).

CYP2C19

Clopidogrel (brand name Plavix) is used to inhibit platelet aggregation and is given as a pro-drug that is metabolized to its active form by *CYP2C19*. Alleles *CYP2C19*2* and *CYP2C19*3* are associated with reduced metabolism of clopidogrel. Individuals with the “poor metabolizer” alleles may not benefit from clopidogrel treatment at standard doses (Tantry et al., 2021). Tuteja et al. (2020) studied *CYP2C19* genotyping to guide antiplatelet therapy. A total of 504 participants contributed to this study, with only 249 participants genotyped. The authors noted that genotyping results “significantly influenced antiplatelet drug prescribing; however, almost half of *CYP2C19* LOF [loss-of-function] carriers continued to receive clopidogrel. Interventional cardiologists consider both clinical and genetic factors when selecting antiplatelet therapy following PCI [percutaneous coronary intervention] (Tuteja et al., 2020).”

CYP2D6

Tetrabenazine (brand name Xenazine) is used in the treatment of chorea associated with Huntington disease. This drug is metabolized for clearance primarily by *CYP2D6*. Poor metabolizers are considered to be those individuals with impaired *CYP2D6* function, and dosing is often influenced by how well a patient metabolizes the drug. For example, a poor metabolizer will often have a maximum dose of 50 mg daily whereas an extensive metabolizer has a maximum dose of 100 mg daily (Suchowersky, 2021).

Tamoxifen, a drug commonly used for the treatment and prevention of recurrence of estrogen receptor positive breast cancer, is metabolized by *CYP2D6*. Polymorphisms of *CYP2D6* have been noted to affect the efficacy of tamoxifen by affecting the amount of active metabolite produced. Endoxifen, which is the primary active metabolite of tamoxifen, has a 100-fold affinity for the estrogen receptor compared to tamoxifen, but poor metabolizers have been demonstrated to show lower than expected levels of plasma endoxifen (Ahern et al., 2017).

Codeine, which is commonly used to treat mild to moderate pain, is metabolized to morphine, a much more powerful opioid, by *CYP2D6*. Individuals with varying *CYP2D6* activity may see negative side effects or a shorter duration of pain relief. The effect is significant enough to have caused fatalities in unusual metabolizers; for instance, an ultra-rapid metabolizing toddler was reported to have passed away after being given codeine for a routine dental operation (Kelly et al., 2012; Tantisira & Weiss, 2020).

TPMT

Thiopurine methyltransferase (TPMT) is an enzyme that methylates thiopurines into active thioguanine nucleotides. The *TPMT* gene is inherited as a monogenic co-dominant trait with ethnic differences in the frequencies of low-activity variant alleles. Individuals who inherit two inactive *TPMT* alleles will develop severe myelosuppression. Individuals that inherit only one inactive *TPMT* allele will develop moderate to severe myelosuppression, and those individuals who inherit both active *TPMT* alleles will have a lower risk of myelosuppression. Therefore, genotyping for *TPMT* is critical before starting therapy with thiopurine drugs (Relling et al., 2011).

DPYD

The dihydropyrimidine dehydrogenase (*DPYD*) gene encodes for the rate-limiting enzyme dihydropyrimidine dehydrogenase, which is involved in catabolism of fluoropyrimidine drugs used in the treatment of solid tumors. Decreased DPD activity increases the risk for severe or even fatal drug toxicity when patients are being treated with fluoropyrimidine drugs. Numerous genetic variants in the *DPYD* gene have been identified that alter the protein sequence or mRNA splicing; however, some of these variants have no effect on DPD enzyme activity. The most studied causal variant of *DPYD* haplotype (HapB3) spans intron 5 to exon 11 and affects protein function. The most common variant in Europeans is HapB3 with a c.1129–5923C>G *DPYD* variant which demonstrates decreased function with carrier frequency of 4.7%, followed by c.190511G>A (carrier frequency: 1.6%) and c.2846A>T (carrier frequency: 0.7%). Approximately 7% of Europeans carry at least one decreased function *DPYD* variant. In people with African ancestry, the most common variant is c.557A>G (rs115232898, p.Y186C) and is relatively common (3–5% carrier frequency). Other *DPYD* decreased function variants are rare. Therefore, most available genetic tests focus on identifying the most common variants with well-established risk: (c.190511G>A, c.1679T>G, c.2846A>T, c.1129– 5923C>G) (Amstutz et al., 2018).

TYMS

TYMS (thymidylate synthetase) encodes an enzyme necessary for thymidine production. As with *DPYD*, *TYMS* is thought to be involved with the toxicity of fluoropyrimidines. Fluorouracil (FU)'s primary metabolite inhibits thymidylate synthetase by forming a stable complex with thymidylate synthetase and folate, thereby blocking activity of the enzyme. Polymorphisms in the *TYMS* gene further affect the interaction between *TYMS* and FU, potentially increasing the toxicity of FU. Genotyping of *TYMS* prior to treatment with FU or capecitabine has been suggested for clinical practice, but data has been varied (Krishnamurthi & Kamath, 2022).

Castro-Rojas et al. (2017) evaluated *TYMS* genotypes as predictors of both clinical response and toxicity to fluoropyrimidine-based treatment for colorectal cancer. A total of 105 patients were genotyped. The authors noted that while the 2R/2R genotype was associated with clinical response (odds ratio = 3.45), the genotype was also associated with severe toxicity (odds ratio = 5.21). The genotype was thought to be associated with low *TYMS* expression. The authors further identified the rs2853542 and rs151264360 alleles to be independent predictors of response failure to chemotherapy (Castro-Rojas et al., 2017).

HLAs

Human Leukocyte antigens (HLAs) are divided into 3 regions, such as class I, class II and class III. Each class has many gene loci, expressed genes and pseudogenes. The class I encodes HLA-A, HLA-B, HLA-C and other antigens. The class II encodes HLA-DP, DQ and DR. The class III region is located between class I and class II and does not encode any HLAs, but other immune response proteins (Viatte, 2021).

An article published by van der Wouden et al. (2019) reports on the development of the new PGx-Passport panel (pre-emptive pharmacogenetics-passport panel), which is able to test “58 germline variant alleles, located within 14 genes (*CYP2B6*, *CYP2C9*, *CYP2C19*, *CYP2D6*, *CYP3A5*, *DPYD*, *F5*, *HLA-A*, *HLA-B*, *NUDT15*, *SLCO1B1*, *TPMT*, *UGT1A1*, and *VKORC1*)”; this standardized panel is based on the Dutch Pharmacogenetics Working Group (DPWG) guidelines and will help physicians to optimize drug prescription in 49 common drugs. It is recommended by the authors that commercial and hospital laboratories utilize this panel for personalized medicinal purposes. Drug optimization in the 49 commonly prescribed drugs includes ten antidepressants, five immunosuppressants, five anti-cancer drugs, four anti-infectives, four anticoagulants, four antiepileptics, four antipsychotics, three proton pump inhibitors, two anti-arrhythmics, two analgesics, two antilipidemics, one antihypertensive, one psychostimulant, one contraceptive and one Gaucher disease drug (van der Wouden et al., 2019).

Proprietary Testing

Due to the increase in pharmacogenetic genotyping, proprietary gene panels have become commercially available. Panels encompassing the most common genes that influence drug metabolism have increased in usage. For example, Myriad’s new proprietary panel “GeneSight” proposes it can “predict poorer antidepressant outcomes and to help guide healthcare providers to more genetically optimal medications,” thereby leading to better patient outcomes. The test assesses every known metabolic pathway (CYP450 or otherwise) for a given drug and their metabolites, as well as the pharmacodynamic activity of the compound and its metabolites, any FDA information on that drug, and other validated research on the relevant alleles; this information is then integrated with the genetic test results. This allows the test to categorize the 55 FDA-approved medications into three categories: “green (use as directed), yellow (some moderate gene-drug interaction) and red (significant gene-drug interaction).” Myriad states that this allows every metabolic pathway of a drug to be evaluated instead of the “one gene, one drug” view. Other GeneSight variations, such as GeneSight Psychotropic used for psychotropic medications, exist as well (Myriad, 2016, 2019). Still, other companies such as Mayo Clinic and Sema4 have developed their own pharmacogenetic panels, each with individually chosen analytes (Mayo, 2019; Sema4, 2019).

Benitez et al. (2018) assessed the cost-effectiveness of pharmacogenomics in treating psychiatric disorders. The authors compared 205 members that received guidance from GeneSight’s Psychotropic to 478 members that received “treatment-as-usual” (TAU). Reimbursement costs were calculated over the 12 months pre- and post-index event periods. The authors found a total

post-index cost savings of \$5505, which was equivalent to a savings of \$0.07 per-member-per-month (PMPM). The authors also evaluated the savings at different adoption rates of the GeneSight test. At 5% adoption, commercial payer savings was calculated at \$0.02 PMPM and at 40% adoption, savings was \$0.15 PMPM (Benitez et al., 2018).

The AmpliChip® (Roche Molecular Systems, Inc.) is the FDA-cleared test for CYP450 genotyping. This test genotypes *CYP2D6* and *CYP2C19*. From the FDA website: “The AmpliChip CYP450C19 Test is designed to identify specific nucleic acid sequences and query for the presence of certain known sequence polymorphisms through analysis of the pattern of hybridization to a series of probes that are specifically complementary either to wild-type or mutant sequences (FDA, 2005).” The analytical accuracy was evaluated at 99.6%, or 806 of 809 samples identified correctly. This test assesses a total of 30 alleles, 3 for CYP219 and 27 for *CYP2D6* (FDA, 2005).

The OneOme RightMed Pharmacogenomic Test analyzes more than 100 variants in 27 genes to study how a patient may respond to certain medications. The test covers *CYP1A2*, *CYP2B6*, *CYP2C Cluster*, *CYP2C9*, *CYP2C19*, *CYP2D6*, *CYP3A4*, *CYP3A5*, *CYP4F2*, *COMT*, *DPYD*, *DRD2*, *F2*, *F5*, *GRIK4*, *HLA-A*, *HLA-B*, *HTR2A*, *HTR2C*, *IL28B (IFNL4)*, *MTHFR**, *NUDT15*, *OPRM1*, *SLC6A4*, *SLCO1B1*, *TPMT*, *UGT1A1*, and *VKORC1* (OneOme, 2021). Analytical validity of the test was assessed by comparing RightMed test results with bi-directional Sanger sequencing results, which resulted in 100% concordance. The RightMed test detects *CYP2D6* deletions, duplications, and hybrid alleles, but cannot differentiate duplications in the presence of a deletion (GTR, 2017).

Clinical Utility and Validity

A study evaluating GeneSight Psychotropic’s clinical utility was performed by Greden et al. (2019); a total of 1167 patients with major depressive disorder were split into two randomized groups: treatment as usual (TAU) and pharmacogenetic-guided. Medications were classified as “congruent” (‘use as directed’ or ‘use with caution’ test categories) or “incongruent” (‘use with increased caution and with more frequent monitoring’ test category) with test results. After 8 weeks, the authors found a statistically significant improvement in response and remission; 26% for the pharmacogenetic arm compared 19.9% for TAU and 15.3% for remission compared to 10.1% for TAU (Greden et al., 2019). The authors concluded that pharmacogenetic testing did not improve results, but significantly improved response and remission rates for “difficult-to-treat depression patients over standard of care” (Greden et al., 2019).

Kekic et al. (2020) studied genetic variants that commonly affect supportive care medications, which include, antidepressants, antiemetics, and analgesics, used in oncology practice. 196 cancer patients were genotyped using a multi-gene panel, OneOme RightMed. The panel assessed 27 genes, including *CYP2C9*, *CYP2C19*, *CYP2D6*, *CYP3A4*, *COMT*, *OPRM1*, *GRIK4*, *HTR2A*, *SLC6A4*, associated with pain medications, antidepressants, and antiemetics. Of the 196 patients, 19.9% had prostate cancer, 17.9% had colorectal cancer, 14.8% had melanoma, and 47.4% had other cancer types. All 196 patients had at least one actionable polymorphism related to these supportive care medications, specifically, in *CYP2C19* and *CYP2D6*. 67.3% of the patients had other than normal *CYP2D6* metabolizer phenotype and 57.1% had other than normal

CYP2C19 metabolizer phenotype. Based on the results, 37 patients were recommended an alternative analgesic, 9 were recommended an alternative antiemetic, and 51 were recommended an alternative anti-depressant (Kekic et al., 2020).

Plumpton et al. (2019) evaluated the cost-effectiveness of panel tests with various pharmacogenes. The constructed multigene panel included *HLA-A*31:01*, *HLA-B*15:02*, *HLA-B*57:01*, *HLA-B*58:01*, *HLA-B (158T)*, and *HLA-DQB1 (126Q)*, which are involved with various treatments (abacavir, carbamazepine, et al). The constructed multigene panel was found to provide a cost savings of \$491 if all findings for all alleles were acted on, regardless of an allele's individual cost-effectiveness. Testing for patients eligible for abacavir (*HLA-B*57:01*) and clozapine (*HLA-B (158T)* and *HLA-DQB1 (126Q)*) was found to be cost-effective. However, testing for patients eligible for allopurinol (*HLA-B*58:01*) was not found to be cost-effective. Furthermore, testing for *HLA-A*31:01* for carbamazepine was found to be cost-effective, but not testing for *HLA-B*15:02* (Plumpton et al., 2019).

Braten et al. (2020) researched the impact of *CYP2C19* genotyping on the antidepressant drug sertraline, which is metabolized by the polymorphic *CYP2C19* enzyme. A total of 1202 patients participated and submitted 2190 sertraline serum samples. All patients were categorized based on *CYP2C19* genotype-predicted phenotype subgroups; these groups include normal (NM), ultra-rapid (UM), intermediate (IM), and poor metabolizer (PM). Serum samples showed that *CYP2C19* IM and PM patients had significantly higher sertraline concentrations compared to NMs; “Based on the relative differences in serum concentrations compared to NMs, dose reductions of 60% and 25% should be considered in PMs and IMs, respectively, to reduce the risk of sertraline overexposure in these patients (Braten et al., 2020).”

Roscizewski et al. (2021) conducted a retrospective observational study to determine what effect pharmacogenomic testing had on “treatment decisions in patients with depressive symptoms in an interprofessional primary care setting.” From April 2019 to March 2021, they identified 78 patients who underwent pharmacogenomic testing for psychotropic medications. They found that 53.8% of patients “experienced a change to their antidepressant regimen after [pharmacogenomic] testing,” with the most cited change being addition of another antidepressant, followed by switching the antidepressant, then increased dose. This demonstrated how pharmacogenomic testing could be useful in informing clinical decision making at the beginning of treatment or “in those who experience an inadequate response to their prescribed regimen” and ensuring optimal patient recovery.

Stevenson et al. (2021) aimed to assess the potential impact of multigene pharmacogenomic testing among those hospitalized with COVID-19 in the United States. Through a cross-sectional analysis with electronic health records, researchers “characterized medication orders, focusing on medications with actionable guidance related to 14 commonly assayed genes (*CYP2C19*, *CYP2C9*, *CYP2D6*, *CYP3A5*, *DPYD*, *G6PD*, *HLA-A*, *HLA-B*, *IFNL3*, *NUDT15*, *SLCO1B1*, *TPMT*, *UGT1A1*, and *VKORC1*).” From their cohort, they found that 64 unique medications with pharmacogenomic guidance were ordered at least once, and about 89.7% of patients “had at least one order for a medication with PGx guidance and... (23.1%) had orders for 4 or more actionable

medications.” Through a simulation analysis, they estimated that “17 treatment modifications per 100 patients would be enabled if [pharmacogenomic] results were available,” and that the genes *CYP2D6* and *CYP2C19* were responsible for most of the treatment modifications. Medications most affected included ondansetron, oxycodone, and clopidogrel. With additional investigations that support these findings, pharmacogenomic testing would better inform the curation of individualized treatment plans for patients suffering from severe COVID-19.

VI. Guidelines and Recommendations

Clinical Pharmacogenetics Implementation Consortium (CPIC)

CPIC guidelines provide guidance to physicians on how to use genetic testing to help them to optimize drug therapy. The guidelines and projects were endorsed by several professional societies including The Association for Molecular Pathology (AMP), The American Society for Clinical Pharmacology and Therapeutics (ASCPT) and The American Society of Health-System Pharmacists (ASHP) (CPIC, 2019).

In their list of guidelines, CPIC provides specific therapeutic recommendations for drugs metabolized by Cytochrome P450 enzymes and other important metabolic enzymes.

CYP2C9 Genotypes

Drug	<i>CYP2C9</i> /Phenotype	Summary of CPIC Therapeutic Recommendations	Level of Recommendations	Reference
Phenytoin/fosphenytoin based on <i>HLA-B*15:02</i>	HLA-B*15:02 Positive- Normal Metabolizer (NM), Intermediate Metabolizer (EM), and Poor Metabolism (M)	If patient is phenytoin-naïve, do not use phenytoin/fosphenytoin. Avoid carbamazepine and oxcarbazepine. If the patient has previously used phenytoin continuously for longer than three months without incidence of cutaneous adverse reactions, cautiously consider use of phenytoin in the future.	Strong	(Caudle et al., 2014; Karnes et al., 2021)
	HLA-B*15:02 Negative- Normal Metabolizer (NM)	No adjustments needed from typical dosing strategies. Subsequent doses should be adjusted according to therapeutic drug monitoring, response, and side effects. An HLA-B*15:02 negative test does not eliminate the risk of phenytoin-induced SJS/TEN, and patients should be carefully monitored according to standard practice.	Strong	
	HLA-B*15:02 Negative- Intermediate Metabolizer (IM)	No adjustments needed from typical dosing strategies. Subsequent doses should be adjusted according to therapeutic drug monitoring, response and side effects. An HLA-B*15:02 negative test does not eliminate the risk of phenytoin-induced SJS/TEN, and patients should be carefully monitored according to standard	Moderate	

		practice. For first dose, use typical initial or loading dose. For subsequent doses, use approximately 25% less than typical maintenance dose. Subsequent doses should be adjusted according to therapeutic drug monitoring, response and side effects.		
	HLA-B*15:02 Negative-Poor Metabolizer (PM)	For first dose, use typical initial or loading dose. For subsequent doses use approximately 50% less than typical maintenance dose. Subsequent doses should be adjusted according to therapeutic drug monitoring, response, and side effects. An HLA-B*15:02 negative test does not eliminate the risk of phenytoin-induced SJS/TEN, and patients should be carefully monitored according to standard practice.	Strong	
Warfarin	Various phenotypes	Genotype-guided warfarin dosing is very complex and involves a combination of <i>CYP2C9</i> , <i>VKORC1</i> , <i>CYP4F2</i> and rs12777823 as well as an algorithm including ancestry information.	Multiple	(Johnson et al., 2017)
Celecoxib, flurbiprofen, ibuprofen, lornoxicam	NM	“In accordance with the prescribing information, use the lowest effective dosage for shortest duration consistent with individual patient treatment goals”	Strong	(Theken et al., 2020)
	IM (Activity Score [AS] = 1.5)	“Initiate therapy with recommended starting dose. In accordance with the prescribing information, use the lowest effective dosage for shortest duration consistent with individual patient treatment goals.”	Moderate	
	IM (AS = 1)	“Initiate therapy with lowest recommended starting dose. Titrate dose upward to clinical effect or maximum recommended dose with caution. In accordance with the prescribing information, use the lowest effective dosage for shortest duration consistent with individual patient treatment goals. Carefully monitor adverse events, such as blood pressure and kidney function during course of therapy.”	Moderate	
	PM	“Initiate therapy with 25–50% of the lowest recommended starting dose. Titrate dose upward to clinical effect or 25–50% of the maximum recommended dose with caution. In accordance with the prescribing information, use the lowest effective dosage for shortest duration consistent with individual patient treatment goals. Upward dose titration should not occur until after steady-state is reached (at least 8 days for celecoxib and 5 days for ibuprofen, flurbiprofen, and lornoxicam after first dose in PMs). Carefully monitor adverse events such as blood pressure and kidney function during course of therapy. Alternatively, consider an alternate therapy not metabolized by CYP2C9 or not significantly impacted by CYP2C9 genetic variants in vivo”	Moderate	
Meloxicam	NM	“Initiate therapy with recommended starting dose. In accordance with the prescribing information, use the lowest effective dosage for shortest duration consistent with individual patient	Strong	(Theken et al., 2020)

		treatment goals”		
	IM, AS 1.5	See NM	Moderate	
	IM, AS 1	“Initiate therapy with recommended starting dose. In accordance with the prescribing information, use the lowest effective dosage for shortest duration consistent with individual patient treatment goals. Upward dose titration should not occur until after steady-state is reached (at least 7 days). Carefully monitor adverse events, such as blood pressure and kidney function during course of therapy. Alternatively, consider alternative therapy. Choose an alternative therapy not metabolized by CYP2C9 or not significantly impacted by CYP2C9 genetic variants in vivo or choose an NSAID metabolized by CYP2C9 but with a shorter half-life”	Moderate	
	PM	“Choose an alternative therapy not metabolized by CYP2C9 or not significantly impacted by CYP2C9 genetic variants in vivo or choose an NSAID metabolized by CYP2C9 but with a shorter half-life”	Moderate	
Piroxicam/Tenoxicam	NM	“Initiate therapy with recommended starting dose. In accordance with the prescribing information, use the lowest effective dosage for shortest duration consistent with individual patient treatment goals.”	Strong	(Theken et al., 2020)
	IM AS 1.5	“Initiate therapy with recommended starting dose. In accordance with the prescribing information, use the lowest effective dosage for shortest duration consistent with individual patient treatment goals.”	Moderate	
	IM AS 1	“Choose an alternative therapy not metabolized by CYP2C9 or not significantly impacted by CYP2C9 genetic variants in vivo or choose an NSAID metabolized by CYP2C9 but with a shorter half-life”	Moderate (Optional for Tenoxicam)	
	PM	“Choose an alternative therapy not metabolized by CYP2C9 or not significantly impacted by CYP2C9 genetic variants in vivo or choose an NSAID metabolized by CYP2C9 but with a shorter half-life”	Moderate (Optional for Tenoxicam)	

CYP2D6 Genotype

Drug	CYP2D6 Phenotype	Summary of CPIC Therapeutic Recommendations	Level of Recommendations	Reference
Amitriptyline and Nortriptyline	Ultra-rapid Metabolizer (UM)	Avoid tricyclic use due to potential lack of efficacy. Consider alternative drug not metabolized by <i>CYP2D6</i> . If a TCA is warranted, consider titrating to a higher target dose (compared to normal metabolizers). Utilize therapeutic drug monitoring to guide dose adjustments.	Strong (recommendation for other TCAs is Optional)	(Hicks et al., 2017)

Drug	CYP2D6 Phenotype	Summary of CPIC Therapeutic Recommendations	Level of Recommendations	Reference
Other TCAs (tricyclic antidepressants): clomipramine, desipramine, doxepin, imipramine, and trimipramine	Normal Metabolizer (NM)	Initiate therapy with recommended starting dose.	Strong <small>(recommendation for other TCAs is Strong)</small>	
	IM	Consider a 25% reduction of recommended starting dose. Utilize therapeutic drug monitoring to guide dose adjustments.	Moderate <small>(recommendation for other TCAs is Optional)</small>	
	PM	Avoid tricyclic use due to potential for side effects. Consider alternative drug not metabolized by CYP2D6. If a TCA is warranted, consider a 50% reduction of recommended starting dose. Utilize therapeutic drug monitoring to guide dose adjustments.	Strong <small>(recommendation for other TCAs is Optional)</small>	
Codeine	URM	Avoid codeine use due to potential for toxicity.	Strong	(Crews et al., 2021)
	EM	Use label-recommended age or weight-specific dosing.	Strong	
	IM	Use label-recommended age or weight-specific dosing. If no response, consider alternative analgesics such as morphine or a nonopioid.	Moderate	
	PM	Avoid codeine use due to lack of efficacy.	Strong	
Paroxetine	URM	Select alternative drug not predominantly metabolized by CYP2D6	Strong	(Hicks et al., 2015)
	EM	Initiate therapy with recommended starting dose.	Strong	
	IM	Initiate therapy with recommended starting dose.	Moderate	
	PM	Select alternative drug not predominantly metabolized by CYP2D6b or if paroxetine use warranted, consider a 50% reduction of recommended starting dose and titrate to response.	Optional	
Fluvoxamine	UM	No recommendation due to lack of evidence.	Optional	(Hicks et al., 2015)
	EM	Initiate therapy with recommended starting dose.	Strong	
	IM	Initiate therapy with recommended starting dose.	Moderate	
	PM	Consider a 25–50% reduction of recommended starting dose and titrate to response or use an alternative drug not metabolized by CYP2D6.	Optional	
	URM	Select alternative drug not predominantly metabolized by CYP2D6 (i.e., granisetron).	Moderate	(Bell et al., 2017)
	NM	Initiate therapy with recommended starting dose.	Strong	

Drug	CYP2D6 Phenotype	Summary of CPIC Therapeutic Recommendations	Level of Recommendations	Reference
Ondansetron and Tropisetron	IM	Insufficient evidence demonstrating clinical impact based on <i>CYP2D6</i> genotype. Initiate therapy with recommended starting dose.	No recommendation	
	PM	Insufficient evidence demonstrating clinical impact based on <i>CYP2D6</i> genotype. Initiate therapy with recommended starting dose.	No recommendation	
Tamoxifen	URM	Avoid moderate and strong <i>CYP2D6</i> inhibitors. Initiate therapy with recommended standard of care dosing (tamoxifen 20 mg/day).	Strong	(Goetz et al., 2018)
	NM	Avoid moderate and strong <i>CYP2D6</i> inhibitors. Initiate therapy with recommended standard of care dosing (tamoxifen 20 mg/day).	Strong	
	NM/IM	Consider hormonal therapy such as an aromatase inhibitor for postmenopausal women or aromatase inhibitor along with ovarian function suppression in premenopausal women, given that these approaches are superior to tamoxifen regardless of <i>CYP2D6</i> genotype. If aromatase inhibitor use is contraindicated, consideration should be given to use a higher but FDA approved tamoxifen dose (40 mg/day). ⁴⁵ Avoid <i>CYP2D6</i> strong to weak inhibitors.	Optional (Controversy remains)	
	IM	Consider hormonal therapy such as an aromatase inhibitor for postmenopausal women or aromatase inhibitor along with ovarian function suppression in premenopausal women, given that these approaches are superior to tamoxifen regardless of <i>CYP2D6</i> genotype. If aromatase inhibitor use is contraindicated, consideration should be given to use a higher but FDA approved tamoxifen dose (40 mg/day). Avoid <i>CYP2D6</i> strong to weak inhibitors.	Moderate	
	PM	Recommend alternative hormonal therapy such as an aromatase inhibitor for postmenopausal women or aromatase inhibitor along with ovarian function suppression in premenopausal women given that these approaches are superior to tamoxifen regardless of <i>CYP2D6</i> genotype and based on knowledge that <i>CYP2D6</i> poor metabolizers switched from tamoxifen to anastrozole do not have an increased risk of recurrence. Note, higher dose tamoxifen (40 mg/day) increases but does not normalize endoxifen concentrations and can be considered if there are contraindications to aromatase inhibitor therapy.	Strong	
	URM	Initiate with a dose of 0.5 mg/kg/day and increase to 1.2 mg/kg/day after 3 days. If no clinical response and in the absence of adverse events after 2 weeks, consider obtaining a peak plasma concentration (1–2 hours after dose administered).	Moderate	(Brown et al., 2019)

Drug	CYP2D6 Phenotype	Summary of CPIC Therapeutic Recommendations	Level of Recommendations	Reference
Atomoxetine (for children)		If < 200 ng/mL, consider a proportional increase in dose to approach 400 ng/mL		
	NM	Initiate with a dose of 0.5 mg/kg and increase to 1.2 mg/kg/day after 3 days. If no clinical response and in the absence of adverse events after 2 weeks, consider obtaining a peak plasma concentration (1–2 hours after dose administered). If < 200 ng/mL, consider a proportional increase in dose to approach 400 ng/mL.	Moderate	
	IM	Initiate with a dose of 0.5 mg/kg/day and if no clinical response and in the absence of adverse events after 2 weeks, consider obtaining a plasma concentration 2–4 hours after dosing. If response is inadequate and concentration is < 200 ng/mL, consider a proportional dose increase to achieve a concentration to approach 400 ng/mL.b,c If unacceptable side effects are present at any time, consider a reduction in dose	Moderate	
Atomoxetine (for adults)	PM	Initiate with a dose of 0.5 mg/kg/day and if no clinical response and in the absence of adverse events after 2 weeks, consider obtaining a plasma concentration 4 hours after dosing. If response is inadequate and concentration is < 200 ng/mL, consider a proportional dose increase to achieve a concentration to approach 400 ng/mL.b,c If unacceptable side effects are present at any time, consider a reduction in dose	Moderate	
	URM	Initiate with a dose of 40 mg/day and increase to 80 mg/ day after 3 days. If no clinical response and in the absence of adverse events after 2 weeks, consider increasing dose to 100 mg/day. If no clinical response observed after 2 weeks, consider obtaining a peak plasma concentration (1–2 hours after dose administered). If < 200 ng/mL, consider a proportional increase in dose to approach 400 ng/mL.b,c Dosages > 100 mg/day may be needed to achieve target concentrations.	Moderate	
	NM	Initiate with a dose of 40 mg/day and increase to 80 mg/ day after 3 days. If no clinical response and in the absence of adverse events after 2 weeks, consider increasing dose to 100 mg/day. If no clinical response observed after 2 weeks, consider obtaining a peak plasma concentration (1–2 hours after dose administered). If < 200 ng/mL, consider a proportional increase in dose to approach 400 ng/mL.b,c Dosages > 100 mg/day may be needed to achieve target concentrations.	Moderate	
	IM	Initiate with a dose of 40 mg/day and if no clinical response and in the absence of adverse events after 2 weeks increase dose to 80 mg/day. If response is inadequate after 2 weeks consider obtaining a plasma concentration 2–4 hours after dosing. If concentration is < 200 ng/mL, consider a proportional dose increase to achieve a concentration to approach 400 ng/mL.b,c If	Moderate	

Drug	CYP2D6 Phenotype	Summary of CPIC Therapeutic Recommendations	Level of Recommendations	Reference
		unacceptable side effects are present at any time, consider a reduction in dose.		
	PM	Initiate with a dose of 40 mg/day and if no clinical response and in the absence of adverse events after 2 weeks increase dose to 80 mg/day. If response is inadequate after 2 weeks, consider obtaining a plasma concentration 2–4 hours after dosing. If concentration is < 200 ng/mL, consider a proportional dose increase to achieve a concentration to approach 400 ng/mL. ^{b,c} If unacceptable side effects are present at any time, consider a reduction in dose	Moderate	

CYP2B6 Genotypes

Drug	CYP2B6 Phenotype	Summary of CPIC Therapeutic Recommendations	Level of Recommendations	Reference
Efavirenz (for children >40 kg and adults)	URM	Initiate efavirenz with standard dosing (600 mg/day)	Strong	(Desta et al., 2019)
	Rapid Metabolizer (RM)	Initiate efavirenz with standard dosing (600 mg/day)	Strong	
	NM	Initiate efavirenz with standard dosing (600 mg/day)	Strong	
	IM	Consider initiating efavirenz with decreased dose of 400 mg/day	Moderate	
	PM	Consider initiating efavirenz with decreased dose of 400 or 200 mg/ day.	Moderate	

CYP2C19 Genotype

Drug	Phenotype	Summary of CPIC Therapeutic Recommendations	Level of Recommendations for amitriptyline	Reference
Amitriptyline and Nortriptyline	URM, RM	Avoid tertiary amine use due to potential for sub-optimal response. Consider alternative drug not metabolized by CYP2C19. TCAs without major CYP2C19 metabolism include the secondary amines nortriptyline and desipramine. If a tertiary amine is warranted, utilize therapeutic drug monitoring to guide dose adjustments.	Optional (recommendation for other TCAs is Optional)	(Hicks et al., 2017)
Other TCAs: clomipramine, doxepin, imipramine,	NM	Initiate therapy with recommended starting dose.	Strong (recommendation for other TCAs is Strong)	
	IM	Initiate therapy with recommended starting dose.	Strong	

Drug	Phenotype	Summary of CPIC Therapeutic Recommendations	Level of Recommendations for amitriptyline	Reference
and trimipramine			(recommendation for other TCAs is Optional)	
	PM	Avoid tertiary amine use due to potential for sub-optimal response. Consider alternative drug not metabolized by <i>CYP2C19</i> . TCAs without major <i>CYP2C19</i> metabolism include the secondary amines nortriptyline and desipramine. For tertiary amines, consider a 50% reduction of the recommended starting dose. Utilize therapeutic drug monitoring to guide dose adjustments.	Moderate (recommendation for other TCAs is Optional)	
Citalopram and Escitalopram	URM	Consider an alternative drug not predominantly metabolized by <i>CYP2C19</i> .	Moderate	(Hicks et al., 2015)
	EM	Initiate therapy with recommended starting dose.	Strong	
	IM	Initiate therapy with recommended starting dose.	Strong	
	PM	Consider a 50% reduction of recommended starting dose and titrate to response or select alternative drug not predominantly metabolized by <i>CYP2C19</i> .	Moderate	
Sertraline	URM	Initiate therapy with recommended starting dose. If patient does not respond to recommended maintenance dosing, consider alternative drug not predominantly metabolized by <i>CYP2C19</i> .	Optional	(Hicks et al., 2015)
	EM	Initiate therapy with recommended starting dose.	Strong	
	IM	Initiate therapy with recommended starting dose.	Strong	
	PM	Consider a 50% reduction of recommended starting dose and titrate to response or select alternative drug not predominantly metabolized by <i>CYP2C19</i> .	Optional	
Clopidogrel	URM, RM, NM	If considering clopidogrel, use at standard dose (75 mg/day)	Strong	(Lee et al., 2022)
	IM, Likely IM	Avoid standard dose clopidogrel (75mg) if possible. Use prasugrel or ticagrelor at standard dose if no contraindication.	Strong	
	PM, Likely PM	Avoid clopidogrel if possible. Use prasugrel or ticagrelor at standard dose if no contraindication.	Strong	
Voriconazole	URM	Choose an alternative agent that is not dependent on <i>CYP2C19</i> metabolism as primary therapy in lieu of voriconazole. Such agents include isavuconazole, liposomal amphotericin B, and posaconazole.	Moderate	(Moriyama et al., 2017)
	RM	Choose an alternative agent that is not dependent on <i>CYP2C19</i> metabolism as primary therapy in lieu of voriconazole. Such agents include isavuconazole, liposomal amphotericin B, and posaconazole.	Moderate	

Drug	Phenotype	Summary of CPIC Therapeutic Recommendations	Level of Recommendations for amitriptyline	Reference
	NM	Initiate therapy with recommended starting dose.	Strong	
	IM	Initiate therapy with recommended starting dose.	Moderate	
	PM	Choose an alternative agent that is not dependent on <i>CYP2C19</i> metabolism as primary therapy in lieu of voriconazole. Such agents include isavuconazole, liposomal amphotericin B, and posaconazole. In the event that voriconazole is considered to be the most appropriate agent, based on clinical advice, for a patient with poor metabolizer genotype, voriconazole should be administered at a preferably lower than standard dosage with careful therapeutic drug monitoring.	Moderate	
Proton Pump Inhibitors (omeprazole, lansoprazole, and pantoprazole) All recommendations here are “Optional” for dexlansoprazole	URM	“Increase starting daily dose by 100%. Daily dose may be given in divided doses. Monitor for efficacy”	Optional	(Lima et al., 2020)
	RM	“Initiate standard starting daily dose. Consider increasing dose by 50–100% for the treatment of <i>Helicobacter pylori</i> infection and erosive esophagitis. Daily dose may be given in divided doses. Monitor for efficacy”	Moderate	
	Normal	“Initiate standard starting daily dose. Consider increasing dose by 50–100% for the treatment of <i>H. pylori</i> infection and erosive esophagitis. Daily dose may be given in divided doses. Monitor for efficacy”	Moderate	
	Likely IM/IM	“Initiate standard starting daily dose. For chronic therapy (> 12 weeks) and efficacy achieved, consider 50% reduction in daily dose and monitor for continued efficacy”	Optional	
	Likely PM/PM	“Initiate standard starting daily dose. For chronic therapy (> 12 weeks) and efficacy achieved, consider 50% reduction in daily dose and monitor for continued efficacy”	Moderate	

***CYP2D6* and *CYP2C19* Genotypes (Caudle et al., 2020; Hicks et al., 2017) for Amitriptyline, Clomipramine, Doxepin, Imipramine, and Trimipramine**

Phenotype	<i>CYP2D6</i>	<i>CYP2D6</i>	<i>CYP2D6</i>	<i>CYP2D6</i>
<i>CYP2C19</i>	UM	NM	IM	PM
URM	Avoid amitriptyline use. Recommendation: Optional	Consider alternative drug not metabolized by <i>CYP2C19</i> . Recommendation: Optional	Consider alternative drug not metabolized by <i>CYP2C19</i> . Recommendation: Optional	Avoid amitriptyline use. Recommendation: Optional
NM	Avoid amitriptyline use. If amitriptyline is warranted, consider titrating to a higher	Initiate therapy with recommended starting dose. Recommendation: Strong	Consider a 25% reduction of recommended starting dose. Recommendation: Moderate	Avoid amitriptyline use. If Amitriptyline is warranted, consider a 50% reduction of

	target dose (compared to normal metabolizers) Recommendation: Strong			recommended starting dose. Recommendation: Strong
IM	Avoid amitriptyline use Recommendation: Optional	Initiate therapy with recommended starting dose. Recommendation: Strong	Consider a 25% reduction of recommended starting dose. Recommendation: Optional This recommendation may also be considered for diplotypes with an activity score of 1.	Avoid amitriptyline use. If Amitriptyline is warranted, consider a 50% reduction of recommended starting dose. Recommendation: Optional
PM	Avoid amitriptyline use Recommendation: Optional	Avoid amitriptyline use. If Amitriptyline is warranted, consider a 50% reduction of recommended starting dose. Recommendation: Moderate	Avoid amitriptyline use Recommendation: Optional	Avoid amitriptyline use Recommendation: Optional

TPMT Genotype

Drug	TPMT Phenotype	Summary of CPIC Therapeutic Recommendations	Level of Recommendations	Reference
Mercaptopurine (MP)	NM	Start with normal starting dose (e.g., 75 mg/m ² /d or 1.5 mg/kg/d) and adjust doses of MP (and of any other myelosuppressive therapy) without any special emphasis on MP compared to other agents. Allow 2 weeks to reach steady state after each dose adjustment. Consider evaluating TPMT erythrocyte activity to assess TPMT phenotype. If thiopurines are required and either TPMT or NUDT15 status is unknown, monitor closely for toxicity.	Strong	(Relling et al., 2018)
	IM	Start with reduced doses (start at 30–70% of full dose: e.g., at 50 mg/m ² /d or 0.75 mg/kg/d) and adjust doses of MP based on degree of myelosuppression and disease-specific guidelines. Allow 2–4 weeks to reach steady state after each dose adjustment. In those who require a dosage reduction based on myelosuppression, the median dose may be ~40% lower (44 mg/m ²) than that tolerated in wild-type patients (75 mg/m ²). In setting of myelosuppression, and depending on other therapy, emphasis should be on reducing MP over other agents. Consider evaluating TPMT erythrocyte activity to assess TPMT phenotype. If thiopurines are required and either TPMT or NUDT15 status is unknown, monitor closely for toxicity.	Strong	
	PM	For malignancy, start with drastically reduced doses (reduce daily dose by 10-fold and reduce frequency to thrice weekly instead of daily, e.g., 10 mg/m ² /d given just 3 days/week) and adjust doses of MP based on degree of myelosuppression and disease-specific guidelines. Allow 4–6 weeks to reach steady state after each dose adjustment. In setting of myelosuppression, emphasis should be on reducing MP over other agents. For nonmalignant conditions, consider alternative nonthiopurine immunosuppressant therapy. Consider evaluating TPMT erythrocyte activity to assess TPMT phenotype. If thiopurines are required and either TPMT	Strong	

		or NUDT15 status is unknown, monitor closely for toxicity.		
Azathioprine	NM	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. Consider evaluating erythrocyte TPMT activity to assess TPMT phenotype. If thiopurines are required and TPMT status is unknown, monitor closely for toxicity.	Strong	(Relling et al., 2018)
	IM	Start with reduced starting doses (30%-80% of normal dose) if normal starting dose is 2-3 mg/kg/day, (e.g. 0.6 – 2.4 mg/kg/day), and adjust doses of azathioprine based on degree of myelosuppression and disease-specific guidelines. Allow 2-4 weeks to reach steady-state after each dose adjustment. Consider evaluating erythrocyte TPMT activity to assess TPMT phenotype. If thiopurines are required and TPMT status is unknown, monitor closely for toxicity.	Strong	
	PM	For non-malignant conditions, consider alternative-nonthiopurine immunosuppressant therapy or malignancy, start with drastically reduced doses (reduce daily dose by 10-fold and dose thrice weekly instead of daily) and adjust doses of azathioprine based on degree of myelosuppression and disease specific guidelines. Allow 4-6 weeks to reach steady state after each dose adjustment. Consider evaluating erythrocyte TPMT activity to assess TPMT phenotype. If thiopurines are required and TPMT status is unknown, monitor closely for toxicity.	Strong	
Thioguanine	NM	Start with normal starting dose (e.g. 40-60 mg/m ² /day). Adjust doses of thioguanine (TG) and of other myelosuppressive therapy without any special emphasis on TG. Allow 2 weeks to reach steady state after each dose adjustment. Consider evaluating erythrocyte TPMT activity to assess TPMT phenotype. If thiopurines are required and TPMT status is unknown, monitor closely for toxicity.	Strong	(Relling et al., 2011; Relling et al., 2018)
	IM	Start with reduced doses (50% to 80% of normal dose) if normal starting dose is ≥40-60 mg/m ² /day (e.g. 20-48 mg/m ² /day) and adjust doses of TG based on degree of myelosuppression and disease-specific guidelines. Allow 2–4 weeks to reach steady state after each dose adjustment. In setting of myelosuppression, and depending on other therapy, emphasis should be on reducing TG over other agents. Consider evaluating erythrocyte TPMT activity to assess TPMT phenotype. If thiopurines are required and TPMT status is unknown, monitor closely for toxicity.	Moderate	
	PM	Start with drastically reduced doses (reduce daily dose by 10-fold and dose thrice weekly instead of daily) and adjust doses of TG based on degree of myelosuppression and disease-specific guidelines. Allow 4–6 weeks to reach steady state after each dose adjustment. In setting of myelosuppression, emphasis should be on reducing TG over other agents. For nonmalignant conditions, consider alternative nonthiopurine immunosuppressant therapy. Consider evaluating erythrocyte TPMT activity to assess TPMT phenotype. If thiopurines are required and TPMT status is unknown, monitor closely for toxicity.	Strong	

NUDT15 Genotype

Drug	NUDT15 Phenotype	Summary of CPIC Therapeutic Recommendations	Level of Recommendations	Reference
Mercaptopurine	NM	Start with normal starting dose (e.g., 75 mg/m ² /d or 1.5 mg/kg/d) and adjust doses of MP (and of any other myelosuppressive therapy) without any special emphasis on MP compared to other agents. Allow 2 weeks to reach steady state after each dose adjustment.	Strong	(Relling et al., 2018)
	IM	Start with reduced doses (start at 30–80% of normal dose: if normal starting dose is ≥75 mg/m ² /day or ≥ 1.5 mg/kg/day (e.g. start at 25-60 mg/m ² /day or 0.45-1.2 mg/kg/day) and adjust doses of MP based on degree of myelosuppression and disease-specific guidelines. Allow 2–4 weeks to reach steady state after each dose adjustment. If myelosuppression occurs, and depending on other therapy, emphasis should be on reducing mercaptopurine over other agents. If normal starting dose is already < 1.5mg/kg/day, dose reduction may not be recommended.	Strong	
	PM	For malignancy, initiate dose at 10 mg/m ² /day and adjust dose based on myelosuppression and disease specific guidelines. Allow 4-6 weeks to reach steady state after each dose adjustment. If myelosuppression occurs, emphasis should be on reducing mercaptopurine over other agents. For nonmalignant conditions, consider alternative nonthiopurine immunosuppressant therapy.	Strong	
Azathioprine	NM	Start with normal starting dose (e.g., 2–3 mg/kg/day) and adjust doses of azathioprine based on disease-specific guidelines. Allow 2 weeks to reach steady state after each dose adjustment.	Strong	(Relling et al., 2018)
	IM	Start with reduced doses (start at 30–80% of normal dose: if normal starting dose is 2-3 mg/kg/day, (e.g. 0.6 – 2.4 mg/kg/day) and adjust doses of MP based on degree of myelosuppression and disease-specific guidelines. Allow 2–4 weeks to reach steady state after each dose adjustment.	Strong	
	PM	For nonmalignant conditions, consider alternative nonthiopurine immunosuppressant therapy. For malignant conditions, start with drastically reduced normal daily doses (reduce daily dose by 10-fold) and adjust doses of azathioprine based on degree of myelosuppression and disease specific guidelines. Allow 4-6 weeks to reach steady-state after each dose adjustment.	Strong	
Thioguanine	NM	Start with normal starting dose (40- 60 mg/day). 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	Strong	(Relling et al., 2018)

Drug	<i>NUDT15</i> Phenotype	Summary of CPIC Therapeutic Recommendations	Level of Recommendations	Reference
	IM	Start with reduced doses (50% to 80% of normal dose) if normal starting dose is ≥ 40 -60 mg/m ² /day (e.g. 20-48 mg/m ² /day) and adjust doses of thioguanine based on degree of myelosuppression and disease specific guidelines. Allow 2-4 weeks to reach steady-state after each dose adjustment. If myelosuppression occurs, and depending on other therapy, emphasis should be on reducing thioguanine over other agents.	Moderate	
	PM	Reduce doses to 25% of normal dose and adjust doses of thioguanine based on degree of myelosuppression and disease specific guidelines. Allow 4-6 weeks to reach steady-state after each dose adjustment. In setting of myelosuppression, emphasis should be on reducing thioguanine over other agents. For non-malignant conditions, consider alternative nonthiopurine immunosuppressant therapy.	Strong	

DPYD Genotypes

Drug	Phenotype	Summary of CPIC Therapeutic Recommendations	Level of Recommendations	Reference
5-Fluorouracil Capecitabine	NM	Based on genotype, there is no indication to change dose or therapy. Use label recommended dosage and administration.	Strong	(Amstutz et al., 2018)
	IM	Reduce starting dose based on activity score followed by titration of dose based on toxicity or therapeutic drug monitoring (if available). Activity score 1: Reduce dose by 50% Activity score 1.5: Reduce dose by 25% to 50%	Activity score 1: Strong Activity score 1.5: Moderate	
	PM	Activity score 0.5: Avoid use of 5-fluorouracil or 5-fluorouracil prodrug-based regimens. In the event, based on clinical advice, alternative agents are not considered a suitable therapeutic option, 5-fluorouracil should be administered at a strongly reduced dose with early therapeutic drug monitoring. Activity score 0: Avoid use of 5-fluorouracil or 5-fluorouracil prodrug-based regimens.	Strong	

HLA-B Genotypes

Drug	Phenotype	Summary of CPIC Therapeutic Recommendations	Level of Recommendations	Reference
Abacavir	Noncarrier of <i>HLA-B*57:01</i>	Low or reduced risk of abacavir hypersensitivity	Strong	(Martin et al., 2014)

Drug	Phenotype	Summary of CPIC Therapeutic Recommendations	Level of Recommendations	Reference
	Carrier of <i>HLA-B*57:01</i>	Abacavir is not recommended	Strong	
Allopurinol	Noncarrier of <i>HLA-B*5801</i> (*X/*X)	Use allopurinol per standard dosing guidelines	Strong	(Hershfield et al., 2013; Saito et al., 2016)
	Carrier of <i>HLA-B*5801</i> (<i>HLA-B*5801</i> /*X, b <i>HLA-B*5801/HLA-A-B*5801</i>)	Allopurinol is contraindicated	Strong	
Oxcarbazepine	<i>HLA-B*15:02</i> negative	Use oxcarbazepine per standard dosing guidelines	Strong	(Phillips et al., 2018)
	<i>HLA-B*15:02</i> positive	If patient is oxcarbazepine naive, do not use oxcarbazepine.	Strong	
Carbamazepine	<i>HLA-B*15:02</i> negative and <i>HLA-A*31:01</i> negative	Use carbamazepine per standard dosing guidelines.	Strong	(Phillips et al., 2018)
	<i>HLA-B*15:02</i> negative and <i>HLA-A*31:01</i> positive	If patient is carbamazepine-naive and alternative agents are available, do not use carbamazepine.	Strong	
	<i>HLA-B*15:02</i> positive and	If patient is carbamazepine-naive, do not use carbamazepine.	Strong	

Drug	Phenotype	Summary of CPIC Therapeutic Recommendations	Level of Recommendations	Reference
	any <i>HLA-A*31:01</i> genotype (or <i>HLA-A*31:01</i> genotype unknown)			

Additional Genotypes

Drug/Genotype	Phenotype	Summary of CPIC Therapeutic Recommendations	Level of Recommendations	Reference
<i>UGT1A1</i> for Atazanavir	EM	There is no need to avoid prescribing of atazanavir based on <i>UGT1A1</i> genetic test result. Inform the patient that some patients stop atazanavir because of jaundice (yellow eyes and skin), but that this patient's genotype makes this unlikely (less than about a 1 in 20 chance of stopping atazanavir because of jaundice).	Strong	(Gammal et al., 2016)
	IM	There is no need to avoid prescribing of atazanavir based on <i>UGT1A1</i> genetic test result. Inform the patient that some patients stop atazanavir because of jaundice (yellow eyes and skin), but that this patient's genotype makes this unlikely (less than about a 1 in 20 chance of stopping atazanavir because of jaundice).	Strong	
	PM	Consider an alternative agent particularly where jaundice would be of concern to the patient. If atazanavir is to be prescribed, there is a high likelihood of developing jaundice that will result in atazanavir discontinuation (at least 20% and as high as 60%).	Strong	
<i>UGT1A1</i> for Irinotecan	N/A	N/A	A, 1A level of evidence	(CPIC, 2021)

Drug/Genotype	Phenotype	Summary of CPIC Therapeutic Recommendations	Level of Recommendations	Reference
<i>CFTR</i> for Ivacaftor	Homozygous or heterozygous G551D- <i>CFTR</i> —e.g. G551D/F508del, G551D/G551D, rs75527207 genotype AA or AG	Use ivacaftor according to the product label (e.g., 150 mg every 12h for patients aged 6 years and older without other diseases; modify dose in patients with hepatic impairment)	Strong	(Clancy et al., 2014)
	Noncarrier of G551D- <i>CFTR</i> — e.g. F508del/R553X, rs75527207 genotype GG	Ivacaftor is not recommended	Moderate	
	Homozygous for F508del- <i>CFTR</i> (F508del/F508del), rs113993960, or rs199826652 genotype del/ del	Ivacaftor is not recommended	Moderate	
<i>G6PD</i> for Rasburicase	Normal	No reason to withhold rasburicase based on <i>G6PD</i> status	Strong	(Relling et al., 2014)
	Deficient or deficient with CNSHA	Rasburicase is contraindicated; alternatives include allopurinol	Strong	
	Variable	To ascertain that <i>G6PD</i> status is normal, enzyme activity must be measured; alternatives include allopurinol	Moderate	
<i>SLCO1B1</i> for Simvastatin	Normal function	Prescribe desired starting dose and adjust doses of simvastatin based on disease-specific guidelines	Strong	(Ramsey et al., 2014)
	Intermediate function	Prescribe a lower dose or consider an alternative statin (e.g., pravastatin or rosuvastatin); consider routine CK surveillance	Strong	
	Low function	Prescribe a lower dose or consider an alternative statin (e.g., pravastatin or rosuvastatin); consider routine CK surveillance	Strong	

Drug/Genotype	Phenotype	Summary of CPIC Therapeutic Recommendations	Level of Recommendations	Reference
<i>CYP3A5</i> for treatment with Tacrolimus	EM	Increase starting dose 1.5–2 times recommended starting dose. Total starting dose should not exceed 0.3 mg/kg/day. Use therapeutic drug monitoring to guide dose adjustments.	Strong	(Birdwell et al., 2015)
	IM	Increase starting dose 1.5–2 times recommended starting dose. Total starting dose should not exceed 0.3 mg/kg/day. Use therapeutic drug monitoring to guide dose adjustments.	Strong	
	PM	Initiate therapy with standard recommended dose. Use therapeutic drug monitoring to guide dose adjustments.	Strong	
<i>IFNL3</i> treatment with Peginterferon alfa-2a, Peginterferon alfa-2b or Ribavirin	Favorable response genotype	Approximately 90% chance for SVR after 24–48 weeks of treatment. Approximately 80–90% of patients are eligible for shortened therapy (24–28 weeks vs. 48 weeks). Weighs in favor of using PEG-IFN- α - and RBV- containing regimens.	Strong	(Muir et al., 2014)
	Unfavorable response genotype	Approximately 60% chance of SVR after 24–48 weeks of treatment. Approximately 50% of patients are eligible for shortened therapy regimens (24–28 weeks). Consider implications before initiating PEG-IFN- α - and RBV- containing regimens.	Strong	
<i>RYR1</i> and <i>CACNA1S</i> genotypes for Potent Volatile Anesthetic Agents and Succinylcholine	Malignant Hyperthermia Susceptible	Halogenated volatile anesthetics or depolarizing Halogenated volatile anesthetics or depolarizing muscle relaxants succinylcholine are relatively contraindicated in persons with MHS. They should not be used, except in extraordinary circumstances in which the benefits outweigh the risks. In general, alternative anesthetics are widely available and effective in patients with MHS	Strong	(Gonsalves et al., 2019)
	Uncertain susceptibility	Clinical findings, family history, further genetic testing and other laboratory data should guide use of halogenated volatile anesthetics or depolarizing muscle relaxants.	Strong	

CPIC notes that evidence for *TYMS* testing is unclear or weak and have assigned *TYMS* a “D” level recommendation. CPIC does not recommend any change in prescription based on *TYMS* genotype (CPIC, 2021).

American College of Medical Genetics and Genomics (ACMG)

ACMG notes that *CYP2C9* and *VKORC1* testing may be useful for assessing unusual responses to warfarin, but cannot recommend for or against routine genotyping (ACMG, 2007).

American College of Cardiology Foundation (ACCF) and the American Heart Association (AHA) Joint Guidelines

A report by the ACCF and the AHA on genetic testing for selection and dosing of clopidogrel provided the following recommendations for practice:

- “Clinicians must be aware that genetic variability in CYP enzymes alter clopidogrel metabolism, which in turn can affect its inhibition of platelet function. Diminished responsiveness to clopidogrel has been associated with adverse patient outcomes in registry experiences and clinical trials.”
- “The specific impact of the individual genetic polymorphisms on clinical outcome remains to be determined (e.g., the importance of *CYP2C19**2 versus *3 or *4 for a specific patient), and the frequency of genetic variability differs among ethnic groups.”
- “Information regarding the predictive value of pharmacogenomic testing is very limited at this time; resolution of this issue is the focus of multiple ongoing studies.”
- “The evidence base is insufficient to recommend either routine genetic or platelet function testing at the present time. There is no information that routine testing improves outcome in large subgroups of patients. In addition, the clinical course of the majority of patients treated with clopidogrel without either genetic testing or functional testing is excellent. Clinical judgment is required to assess clinical risk and variability in patients considered to be at increased risk. Genetic testing to determine if a patient is predisposed to poor clopidogrel metabolism (“poor metabolizers”) may be considered before starting clopidogrel therapy in patients believed to be at moderate or high risk for poor outcomes. This might include, among others, patients undergoing elective high-risk PCI procedures (e.g., treatment of extensive and/or very complex disease). If such testing identifies a potential poor metabolizer, other therapies, particularly prasugrel for coronary patients, should be considered. (Holmes et al., 2010).

American Academy of Neurology (AAN)

The AAN published a position paper on the use of opioids for chronic non-cancer pain. Regarding pharmacogenetic testing, the guidelines state “genotyping to determine whether response to opioid therapy can/should be more individualized will require critical original research to determine effectiveness and appropriateness of use” (Franklin, 2014).

American Association for Clinical Chemistry (AACC) Academy Laboratory Medicine Practice Guidelines

AACC Academy issued laboratory medicine practice guidelines on using clinical laboratory tests to monitor drug therapy in pain management. Their guidelines have a total of 26 recommendations and 7 expert opinions. Regarding pharmacogenetic testing for pain management, they stated in the recommendation #20 (Level A, II) that: “While the current evidence in the literature doesn’t support routine genetic testing for all pain management patients, it should be considered to predict or explain variant pharmacokinetics, and/ or pharmacodynamics of specific drugs as evidenced by repeated treatment failures, and/or adverse drug reactions/toxicity (AACC, 2017).”

American Family Physician (AAFP)

The AAFP has published guidelines on pharmacogenetics: using genetic information to guide drug therapy. CPIC guidelines are cited for many medication/allele combinations in this article. The recommendations by the AAFP are listed in the table below taken from Chang et al. (2015):

Allele	Medications	Test Results and Clinical Implications	Comments
<i>CYP2D6</i>	Codeine, hydrocodone, oxycodone, tramadol	<p>Ultrarapid metabolizer: Avoid codeine because of potential for toxicity</p> <p>Poor metabolizer: Avoid codeine and possibly tramadol because of possible lack of effectiveness</p>	<p>CPIC guidance limits genotype-guided dosing recommendations to codeine.</p> <p>Alternative analgesics not affected by <i>CYP2D6</i> variability include morphine, oxymorphone, and nonopioid analgesics.</p> <p>Oxycodone may also have reduced effectiveness in poor <i>CYP2D6</i> metabolizers.</p>
<i>CYP2C19</i>	Clopidogrel (Plavix)	<p>Intermediate metabolizer: Use alternative antiplatelet therapy if no contraindications</p> <p>Poor metabolizer: Use alternative antiplatelet therapy if no contraindications</p>	<p>Clopidogrel prescribing information states that <i>CYP2C19</i> tests can be used as an aid to determine therapeutic strategy in patients with acute coronary syndromes who are undergoing percutaneous coronary intervention.</p> <p>CPIC guidance limits genotype-guided dosing recommendations to patients undergoing percutaneous coronary intervention for acute coronary syndromes (excluding medical management of acute</p>

			<p>coronary syndromes, stroke, and peripheral artery disease).</p> <p>ACCF/AHA guidelines state that genotyping may be considered in patients with unstable angina/non-ST segment elevation myocardial infarction (or after percutaneous coronary intervention for acute coronary syndromes) if test results could alter management.</p> <p>Alternative antiplatelet therapy not affected by <i>CYP2C19</i> variability includes prasugrel (Effient) and ticagrelor (Brilinta).</p>
<i>CYP2C19</i>	Amitriptyline	<p>Poor metabolizer: Consider 50% reduction in recommended starting dose</p>	<p>CPIC guidance is available for <i>CYP2D6</i>- and <i>CYP2C19</i>-genotype guided tricyclic antidepressant therapy.</p> <p>Although limited data exist for other tricyclic antidepressants, most supporting evidence of clinically relevant gene-drug effects is for amitriptyline and nortriptyline (Pamelor).</p>
<i>CYP2C19</i>	Citalopram (Celexa), escitalopram (Lexapro)	<p>Ultrarapid metabolizer: Consider alternative</p> <p>Poor metabolizer: Consider 50% starting dose reduction and titrate to response, or use alternative</p>	<p>CPIC guidance is available for <i>CYP2C19</i>-genotype guided citalopram and escitalopram therapy.</p> <p>FDA label for citalopram states that 20 mg per day is the maximum recommended dosage for patients older than 60 years, patients with hepatic impairment, and <i>CYP2C19</i> poor metabolizers or patients taking cimetidine (Tagamet) or another <i>CYP2C19</i> inhibitor.</p>
<i>CYP2C19</i>	Sertraline (Zoloft)	<p>Ultrarapid metabolizer: If patient does not respond to recommended dose, consider alternative</p> <p>Poor metabolizer: Consider 50% dose</p>	<p>CPIC guidance is available for <i>CYP2C19</i>-genotype guided sertraline therapy.</p>

		reduction or alternative	
<i>CYP2D6</i>	Amitriptyline, nortriptyline	<p>Ultrarapid metabolizer: Avoid because of possible lack of effectiveness</p> <p>Poor metabolizer: Avoid because of possible adverse effects; if use is warranted, consider 50% reduction in recommended starting dose</p>	<p>CPIC guidance is available for CYP2D6- and CYP2C19-genotype guided tricyclic antidepressant therapy.</p> <p>Although limited data exist for other tricyclic antidepressants, most supporting evidence of clinically relevant gene-drug effects is for amitriptyline and nortriptyline.</p>
<i>CYP2D6</i>	Aripiprazole (Abilify)	<p>Poor metabolizer: Decrease dose</p>	<p>Quality of supporting evidence is classified as low by PharmGKB</p> <p>FDA label for aripiprazole states that in poor metabolizers, the usual dose should initially be reduced to 50% and then adjusted to achieve a favorable clinical response; in poor metabolizers receiving a strong CYP3A4 inhibitor, the usual dose should be reduced to 25%.</p>
<i>CYP2D6</i>	Atomoxetine (Strattera)	<p>Poor metabolizer: Adjust dose</p>	<p>Quality of supporting evidence is classified as moderate (Level 2a) by PharmGKB.</p> <p>FDA label for atomoxetine states that in poor metabolizers, the initial dosage should be 0.5 mg per kg per day and then increased to the the usual target dosage of 1.2 mg per kg per day only if symptoms do not improve after 4 weeks and the initial dose is well tolerated.</p>
<i>CYP2D6</i>	Paroxetine (Paxil)	<p>Ultrarapid metabolizer: Select alternative because of possible lack of effectiveness.</p> <p>Poor metabolizer: Select alternative or if use is warranted,</p>	<p>CPIC guidance is available for CYP2D6-genotype guided paroxetine therapy.</p>

		consider 50% starting dose reduction	
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Dutch Pharmacogenetics Working Group (DPWG)

The DPWG has published guidelines for the gene-drug interaction of *DPYD* and fluoropyrimidines. Conclusions state that “four variants have sufficient evidence to be implemented into clinical care: *DPYD**2A (c.1905+1G>A, IVS14+1G>A), *DPYD**13 (c.1679T>G), c.2846A>T and c.1236G>A (in linkage disequilibrium with c.1129–5923C>G). The current guideline only reports recommendations for these four variants; no recommendations are provided for other variants in *DPYD* or other genes (Lunenburg et al., 2019).”

Food and Drug Administration

The FDA published several tables of pharmacogenetic associations with “sufficient scientific evidence to suggest that subgroups of patients with certain genetic variants, or genetic variant-inferred phenotypes (i.e., affected subgroup in the table below), are likely to have altered drug metabolism, and in certain cases, differential therapeutic effects, including differences in risks of adverse events”.

The table below lists associations “for which the data support therapeutic management recommendations” (FDA, 2021b).

Drug	Gene	Affected Subgroups	Description of Gene-Drug Interaction
Abacavir	<i>HLA-B</i>	*57:01 allele positive	Results in higher adverse reaction risk (hypersensitivity reactions). Do not use abacavir in patients positive for <i>HLA-B</i> *57:01.
Amifampridine	<i>NAT2</i>	poor metabolizers	Results in higher systemic concentrations and higher adverse reaction risk. Use lowest recommended starting dosage and monitor for adverse reactions. Refer to FDA labeling for specific dosing recommendations.
Amifampridine Phosphate	<i>NAT2</i>	poor metabolizers	Results in higher systemic concentrations. Use lowest recommended starting dosage (15 mg/day) and monitor for adverse reactions.
Amphetamine	<i>CYP2D6</i>	poor metabolizers	May affect systemic concentrations and adverse reaction risk. Consider lower starting dosage or use alternative agent.
Aripiprazole	<i>CYP2D6</i>	poor metabolizers	Results in higher systemic concentrations and higher adverse reaction risk. Dosage adjustment is recommended. Refer to FDA labeling for specific dosing recommendations.

Aripiprazole Lauroxil	<i>CYP2D6</i>	poor metabolizers	Results in higher systemic concentrations. Dosage adjustment is recommended. Refer to FDA labeling for specific dosing recommendations.
Atomoxetine	<i>CYP2D6</i>	poor metabolizers	Results in higher systemic concentrations and higher adverse reaction risk. Adjust titration interval and increase dosage if tolerated. Refer to FDA labeling for specific dosing recommendations.
Azathioprine	<i>TPMT</i> and/or <i>NUDT15</i>	intermediate or poor metabolizers	Alters systemic active metabolite concentration and dosage requirements. Results in higher adverse reaction risk (myelosuppression). Consider alternative therapy in poor metabolizers. Dosage reduction is recommended in intermediate metabolizers for <i>NUDT15</i> or <i>TPMT</i> . Intermediate metabolizers for both genes may require more substantial dosage reductions. Refer to FDA labeling for specific dosing recommendations.
Belinostat	<i>UGT1A1</i>	*28/*28 (poor metabolizers)	May result in higher systemic concentrations and higher adverse reaction risk. Reduce starting dose to 750 mg/m ² in poor metabolizers.
Brexpiprazole	<i>CYP2D6</i>	poor metabolizers	Results in higher systemic concentrations. Dosage adjustment is recommended. Refer to FDA labeling for specific dosing recommendations.
Brivaracetam	<i>CYP2C19</i>	intermediate or poor metabolizers	Results in higher systemic concentrations and higher adverse reaction risk. Consider dosage reductions in poor metabolizers.
Capecitabine	<i>DPYD</i>	intermediate or poor metabolizers	Results in higher adverse reaction risk (severe, life-threatening, or fatal toxicities). No dosage has proven safe in poor metabolizers, and insufficient data are available to recommend a dosage in intermediate metabolizers. Withhold or discontinue in the presence of early-onset or unusually severe toxicity.
Carbamazepine	<i>HLA-B</i>	*15:02 allele positive	Results in higher adverse reaction risk (severe skin reactions). Avoid use unless potential benefits outweigh risks and consider risks of alternative therapies. Patients positive for <i>HLA-B</i> *15:02 may be at increased risk of severe skin reactions with other drugs that are associated with a risk of Stevens Johnson Syndrome/Toxic Epidermal necrolysis (SJS/TEN). Genotyping is not a substitute for clinical vigilance.
Celecoxib	<i>CYP2C9</i>	poor metabolizers	Results in higher systemic concentrations. Reduce starting dose to half of the lowest recommended dose in poor metabolizers. Consider alternative therapy in patients with juvenile rheumatoid arthritis.

Citalopram	<i>CYP2C19</i>	poor metabolizers	Results in higher systemic concentrations and adverse reaction risk (QT prolongation). The maximum recommended dose is 20 mg.
Clobazam	<i>CYP2C19</i>	intermediate or poor metabolizers	Results in higher systemic active metabolite concentrations. Poor metabolism results in higher adverse reaction risk. Dosage adjustment is recommended. Refer to FDA labeling for specific dosing recommendations.
Clopidogrel	<i>CYP2C19</i>	intermediate or poor metabolizers	Results in lower systemic active metabolite concentrations, lower antiplatelet response, and may result in higher cardiovascular risk. Consider use of another platelet P2Y12 inhibitor.
Clozapine	<i>CYP2D6</i>	poor metabolizers	Results in higher systemic concentrations. Dosage reductions may be necessary.
Codeine	<i>CYP2D6</i>	ultrarapid metabolizers	Results in higher systemic active metabolite concentrations and higher adverse reaction risk (life-threatening respiratory depression and death). Codeine is contraindicated in children under 12 years of age.
Deutetrabenazine	<i>CYP2D6</i>	poor metabolizers	Results in higher systemic concentrations and adverse reaction risk (QT prolongation). The maximum recommended dosage should not exceed 36 mg (maximum single dose of 18 mg).
Dronabinol	<i>CYP2C9</i>	intermediate or poor metabolizers	May result in higher systemic concentrations and higher adverse reaction risk. Monitor for adverse reactions.
Eliglustat	<i>CYP2D6</i>	ultrarapid, normal, intermediate, or poor metabolizers	Alters systemic concentrations, effectiveness, and adverse reaction risk (QT prolongation). Indicated for normal, intermediate, and poor metabolizer patients. Ultrarapid metabolizers may not achieve adequate concentrations to achieve a therapeutic effect. The recommended dosages are based on CYP2D6 metabolizer status. Coadministration with strong CYP3A inhibitors is contraindicated in intermediate and poor CYP2D6 metabolizers. Refer to FDA labeling for specific dosing recommendations.
Erdafitinib	<i>CYP2C9</i>	*3/*3 (poor metabolizers)	May result in higher systemic concentrations and higher adverse reaction risk. Monitor for adverse reactions.
Flibanserin	<i>CYP2C19</i>	poor metabolizers	May result in higher systemic concentrations and higher adverse reaction risk. Monitor patients for adverse reactions.
Flurbiprofen	<i>CYP2C9</i>	poor metabolizers	Results in higher systemic concentrations. Use a reduced dosage.

Fluorouracil	<i>DPYD</i>	intermediate or poor metabolizer	Results in higher adverse reaction risk (severe, life-threatening, or fatal toxicities). No dosage has proven safe in poor metabolizers and insufficient data are available to recommend a dosage in intermediate metabolizers. Withhold or discontinue in the presence of early-onset or unusually severe toxicity.
Fosphenytoin	<i>CYP2C9</i>	Intermediate or poor metabolizers	May result in higher systemic concentrations and higher adverse reaction risk (central nervous system toxicity). Consider starting at the lower end of the dosage range and monitor serum concentrations. Refer to FDA labeling for specific dosing recommendations. Carriers of <i>CYP2C9</i> *3 alleles may be at increased risk of severe cutaneous adverse reactions. Consider avoiding fosphenytoin as an alternative to carbamazepine in patients who are <i>CYP2C9</i> *3 carriers. Genotyping is not a substitute for clinical vigilance and patient management.
Fosphenytoin	<i>HLA-B</i>	*15:02 allele positive	May result in higher adverse reaction risk (severe cutaneous reactions). Patients positive for <i>HLA-B</i> *15:02 may be at increased risk of Stevens Johnson Syndrome/Toxic Epidermal necrolysis (SJS/TEN). Consider avoiding fosphenytoin as an alternative to carbamazepine in patients who are positive for <i>HLA-B</i> *15:02. Genotyping is not a substitute for clinical vigilance and patient management.
Gefitinib	<i>CYP2D6</i>	poor metabolizers	Results in higher systemic concentrations and higher adverse reaction risk. Monitor for adverse reactions.
Iloperidone	<i>CYP2D6</i>	poor metabolizers	Results in higher systemic concentrations and higher adverse reaction risk (QT prolongation). Reduce dosage by 50%.
Irinotecan	<i>UGT1A1</i>	*28/*28 (poor metabolizers)	Results in higher systemic active metabolite concentrations and higher adverse reaction risk (severe neutropenia). Consider reducing the starting dosage by one level and modify the dosage based on individual patient tolerance.
Lofexidine	<i>CYP2D6</i>	poor metabolizers	Results in higher systemic concentrations and higher adverse reaction risk. Monitor for orthostatic hypotension and bradycardia.
Meclizine	<i>CYP2D6</i>	ultrarapid, intermediate, or poor metabolizers	May affect systemic concentrations. Monitor for adverse reactions and clinical effect.
Meloxicam	<i>CYP2C9</i>	Poor metabolizers or *3 carriers	Results in higher systemic concentrations. Consider dose reductions in poor metabolizers. Monitor patients for adverse reactions.
Metoclopramide	<i>CYP2D6</i>	poor metabolizers	Results in higher systemic concentrations and higher adverse reaction risk. The recommended dosage is

			lower. Refer to FDA labeling for specific dosing recommendations.
Mercaptopurine	<i>TPMT</i> and/or <i>NUDT15</i>	intermediate or poor metabolizers	Alters systemic active metabolite concentration and dosage requirements. Results in higher adverse reaction risk (myelosuppression). Initial dosages should be reduced in poor metabolizers; poor metabolizers generally tolerate 10% or less of the recommended dosage. Intermediate metabolizers may require dosage reductions based on tolerability. Intermediate metabolizers for both genes may require more substantial dosage reductions. Refer to FDA labeling for specific dosing recommendations.
Mivacurium	<i>BCHE</i>	intermediate or poor metabolizers	Results in higher systemic concentrations and higher adverse reaction risk (prolonged neuromuscular blockade). Avoid use in poor metabolizers.
Oliceridine	<i>CYP2D6</i>	Poor metabolizers	Results in higher systemic concentrations and higher adverse reaction risk (respiratory depression and sedation). May require less frequent dosing.
Pantoprazole	<i>CYP2C19</i>	poor metabolizers	Results in higher systemic concentrations. Consider dosage reduction in children who are poor metabolizers. No dosage adjustment is needed for adult patients who are poor metabolizers.
Phenytoin	<i>CYP2C9</i>	Intermediate or poor metabolizers	May result in higher systemic concentrations and higher adverse reaction risk (central nervous system toxicity). Refer to FDA labeling for specific dosing recommendations. Carriers of <i>CYP2C9</i> *3 alleles may be at increased risk of severe cutaneous adverse reactions. Consider avoiding phenytoin as an alternative to carbamazepine in patients who are <i>CYP2C9</i> *3 carriers. Genotyping is not a substitute for clinical vigilance and patient management.
Phenytoin	<i>HLA-B</i>	*15:02 allele positive	May result in higher adverse reaction risk (severe cutaneous reactions). Patients positive for <i>HLA-B</i> *15:02 may be at increased risk of Stevens Johnson Syndrome/Toxic Epidermal necrolysis (SJS/TEN). Consider avoiding phenytoin as an alternative to carbamazepine in patients who are positive for <i>HLA-B</i> *15:02. Genotyping is not a substitute for clinical vigilance and patient management.
Pimozide	<i>CYP2D6</i>	poor metabolizers	Results in higher systemic concentrations. Dosages should not exceed 0.05 mg/kg in children or 4 mg/day in adults who are poor metabolizers and dosages should not be increased earlier than 14 days.
Piroxicam	<i>CYP2C9</i>	intermediate or poor metabolizers	Results in higher systemic concentrations. Consider reducing dosage in poor metabolizers.

Pitolisant	<i>CYP2D6</i>	Poor metabolizers	Results in higher systemic concentrations. Use lowest recommended starting dosage. Refer to FDA labeling for specific dosing recommendations.
Propafenone	<i>CYP2D6</i>	poor metabolizers	Results in higher systemic concentrations and higher adverse reaction risk (arrhythmia). Avoid use in poor metabolizers taking a CYP3A4 inhibitor.
Sacituzumab Govitecan-hziy	<i>UGT1A1</i>	*28/*28 (poor metabolizers)	May result in higher systemic concentrations and adverse reaction risk (neutropenia). Monitor for adverse reactions and tolerance to treatment.
Siponimod	<i>CYP2C9</i>	intermediate or poor metabolizers	Results in higher systemic concentrations. Adjust dosage based on genotype. Do not use in patients with CYP2C9 *3/*3 genotype. Refer to FDA labeling for specific dosing recommendations.
Succinylcholine	<i>BCHE</i>	intermediate or poor metabolizers	Results in higher systemic concentrations and higher adverse reaction risk (prolonged neuromuscular blockade). Avoid use in poor metabolizers. May administer test dose to assess sensitivity and administer cautiously via slow infusion.
Tacrolimus	<i>CYP3A5</i>	intermediate or normal metabolizers	Results in lower systemic concentrations and lower probability of achieving target concentrations. Measure drug concentrations and adjust dosage based on trough whole blood tacrolimus concentrations.
Tetrabenazine	<i>CYP2D6</i>	poor metabolizers	Results in higher systemic concentrations. The maximum recommended single dose is 25 mg and should not exceed 50 mg/day.
Thioguanine	<i>TPMT</i> and/or <i>NUDT15</i>	intermediate or poor metabolizers	Alters systemic active metabolite concentration and dosage requirements. Results in higher adverse reaction risk (myelosuppression). Initial dosages should be reduced in poor metabolizers; poor metabolizers generally tolerate 10% or less of the recommended dosage. Intermediate metabolizers may require dosage reductions based on tolerability. Intermediate metabolizers for both genes may require more substantial dosage reductions. Refer to FDA labeling for specific dosing recommendations.
Thioridazine	<i>CYP2D6</i>	poor metabolizers	Results in higher systemic concentrations and higher adverse reaction risk (QT prolongation). Predicted effect based on experience with CYP2D6 inhibitors. Contraindicated in poor metabolizers.
Tramadol	<i>CYP2D6</i>	Ultrarapid metabolizers	Results in higher systemic and breast milk active metabolite concentrations, which may result in respiratory depression and death. Contraindicated in children under 12 and in adolescents following tonsillectomy/adenoidectomy. Breastfeeding is not recommended during treatment.

Valbenazine	<i>CYP2D6</i>	poor metabolizers	Results in higher systemic active metabolite concentrations and higher adverse reaction risk (QT prolongation). Dosage reductions may be necessary.
Venlafaxine	<i>CYP2D6</i>	poor metabolizers	Alters systemic parent drug and metabolite concentrations. Consider dosage reductions.
Vortioxetine	<i>CYP2D6</i>	poor metabolizers	Results in higher systemic concentrations. The maximum recommended dose is 10 mg.
Warfarin	<i>CYP2C9</i>	intermediate or poor metabolizers	Alters systemic concentrations and dosage requirements. Select initial dosage, taking into account clinical and genetic factors. Monitor and adjust dosages based on INR.
Warfarin	<i>CYP4F2</i>	V433M carriers variant	May affect dosage requirements. Monitor and adjust doses based on INR.
Warfarin	<i>VKORC1</i>	-1639G>A carriers variant	Alters dosage requirements. Select initial dosage, taking into account clinical and genetic factors. Monitor and adjust dosages based on INR.

The table below lists associations “for which the data indicate a potential impact on safety or response” (FDA, 2021b).

Drug	Gene	Affected Subgroups	Description of Gene-Drug Interaction
Allopurinol	<i>HLA-B</i>	*58:01 allele positive	Results in higher adverse reaction risk (severe skin reactions).
Carbamazepine	<i>HLA-A</i>	*31:01 allele positive	Results in higher adverse reaction risk (severe skin reactions). Consider risk and benefit of carbamazepine use in patients positive for HLA-A*31:01. Genotyping is not a substitute for clinical vigilance.
Carvedilol	<i>CYP2D6</i>	poor metabolizers	Results in higher systemic concentrations and higher adverse reaction risk (dizziness).
Cevimeline	<i>CYP2D6</i>	poor metabolizers	May result in higher adverse reaction risk. Use with caution.
Codeine	<i>CYP2D6</i>	poor metabolizers	Results in lower systemic active metabolite concentrations and may result in reduced efficacy.
Efavirenz	<i>CYP2B6</i>	poor metabolizers	Results in higher systemic concentrations and higher adverse reaction risk (QT prolongation).
Isoniazid	Nonspecific (NAT)	poor metabolizers	May result in higher systemic concentrations and adverse reaction risk.

Lapatinib	<i>HLA-DRB1</i>	*07:01 allele positive	Results in higher adverse reaction risk (hepatotoxicity). Monitor liver function tests regardless of genotype.
Lapatinib	<i>HLA-DQA1</i>	*02:01 allele positive	Results in higher adverse reaction risk (hepatotoxicity). Monitor liver function tests regardless of genotype.
Nilotinib	<i>UGT1A1</i>	*28/*28 (poor metabolizers)	Results in higher adverse reaction risk (hyperbilirubinemia).
Oxcarbazepine	<i>HLA-B</i>	*15:02 allele positive	Results in higher adverse reaction risk (severe skin reactions). Patients positive for HLA-B*15:02 may be at increased risk of severe skin reactions with other drugs that are associated with a risk of Stevens Johnson Syndrome/Toxic Epidermal necrolysis (SJS/TEN). Genotyping is not a substitute for clinical vigilance.
Pazopanib	<i>HLA-B</i>	*57:01 allele positive	May result in higher adverse reaction risk (liver enzyme elevations). Monitor liver function tests regardless of genotype.
Pazopanib	<i>UGT1A1</i>	*28/*28 (poor metabolizers)	Results in higher adverse reaction risk (hyperbilirubinemia).
Perphenazine	<i>CYP2D6</i>	poor metabolizers	Results in higher systemic concentrations and higher adverse reaction risk.
Procainamide	Nonspecific (NAT)	poor metabolizers	Alters systemic parent drug and metabolite concentrations. May result in higher adverse reaction risk.
Simvastatin	<i>SLCO1B1</i>	521 TC or 521 CC (intermediate or poor function transporters)	Results in higher systemic concentrations and higher adverse reaction risk (myopathy). The risk of adverse reaction (myopathy) is higher for patients on 80 mg than for those on lower doses.
Sulfamethoxazole and Trimethoprim	Nonspecific (NAT)	poor metabolizers	May result in higher adverse reaction risk.
Sulfasalazine	Nonspecific (NAT)	poor metabolizers	Results in higher systemic metabolite concentrations and higher adverse reaction risk.
Tolterodine	<i>CYP2D6</i>	poor metabolizers	Results in higher systemic concentrations and higher adverse reaction risk (QT prolongation).

The International Society of Psychiatric Genetics

The International Society of Psychiatric Genetics (ISPG) released recommendations on the use of pharmacogenetic testing to guide psychiatric treatment. ISPG recommends that pharmacogenetic testing should be used as a decision-support tool. *HLA-A* and *HLA-B* testing is recommended before the use of carbamazepine and oxcarbazepine. *CYP2C19* and *CYP2D6*

testing would be beneficial for those who experienced an inadequate response or adverse reaction to a previous antidepressant or antipsychotic medication (ISPG, 2019).

The American Academy of Child and Adolescent Psychiatry

AACAP does not recommend the use of pharmacogenetic testing to select psychotropic medications for children and adolescents (AACAP, 2020)

Association for Molecular Pathology PGx Working Group (AMP)

AMP released clinical practice guidelines to define a minimum set of *CYP2C19* allele variants that should be included in the pharmacogenomic genotyping assay. Tier 1 represents alleles that have been shown to affect drug response and should be included, while Tier 2 represents alleles which meet at least one but not all the criteria for inclusion in Tier 1 and are considered optional for inclusion in expanded clinical genotyping panels. Those in Tier 1 include alleles *2, *3, and *17. The following *CYP2C19* alleles were recommended as Tier 2: *4A, *4B, *5, *6, *7, *8, *9, *10, and *35 (Pratt et al., 2018). Regarding *CYP2C9* variant alleles, Tier 1 alleles include *CYP2C9* *2, *3, *5, *6, *8, and *11. The following *CYP2C9* alleles are recommended for inclusion in Tier 2: *CYP2C9**12, *13, and *15 (Pratt et al., 2019). For testing genes and alleles specific to warfarin, AMP recommends including *VKORC1* c.-1639G>A in Tier 1 and *VKORC1* c.196G>A and c.106G>A in Tier 2 (Pratt et al., 2020). In a joint recommendation endorsed by the AMP, College of American Pathologists, Dutch Pharmacogenetics Working Group of the Royal Dutch Pharmacists Association, and the European Society for Pharmacogenomics and Personalized Therapy, *CYP2D6* variant alleles were elucidated. Tier 1 alleles include *CYP2D6* *2 to *6, *9, *10, *17, *29, and *41. Tier 2 *CYP2D6* alleles include *CYP2D6* *7, *8, *12, *14, *15, *21, *31, *40, *42, *49, *56, and *59, and hybrid genes containing portions of *CYP2D6* and *CYP2D7* (Pratt et al., 2021). These recommendations should help to standardize testing and genotyping concordance among laboratories.

European Medicines Agency

EMA released recommendations on *DPD* testing before treatment with fluorouracil, capecitabine, tegafur, and flucytosine. EMA recommends testing for the lack of *DPD* before starting cancer treatment with fluorouracil, capecitabine, or tegafur. Patients who completely lack *DPD* should not be given these medications. For patients with partial deficiency, the physician may consider beginning treatment at a lower dose and terminating treatment if severe side effects occur. These recommendations do not apply to fluorouracil medications used for skin conditions or flucytosine used for fungal infection (EMA, 2020).

VII. Applicable State and Federal Regulations

DISCLAIMER: If there is a conflict between this Policy and any relevant, applicable government policy for a particular member [e.g., Local Coverage Determinations (LCDs) or National Coverage Determinations (NCDs) for Medicare and/or state coverage for Medicaid], then the government policy will be used to make the determination. For the most up-to-date Medicare policies and coverage, please visit the Medicare search website: <http://www.cms.gov/medicare-coverage-database/overview-and-quick-search.aspx>. For the most up-to-date Medicaid policies and coverage, visit the applicable state Medicaid website.

A. Food and Drug Administration (FDA)

Diagnostic genotyping tests for certain drug metabolizing enzymes are FDA-approved. Many labs have developed specific tests that they must validate and perform in house. These laboratory-developed tests (LDTs) are regulated by the Centers for Medicare and Medicaid (CMS) as high-complexity tests under the Clinical Laboratory Improvement Amendments of 1988 (CLIA '88). As an LDT, the U. S. Food and Drug Administration has not approved or cleared this test; however, FDA clearance or approval is not currently required for clinical use.

Currently, there are over 14 other FDA-approved tests for the drug metabolizing enzymes that are nucleic acid-based tests including xTAG *CYP2D6* Kit v3 and XTAG *CYP2C19* KIT V3 (Luminex Molecular Diagnostics, Inc), Spartan RX *CYP2C19* Test System (Spartan Bioscience, Inc), Verigene *CYP2C19* Nucleic Acid Test (Nanosphere, Inc), INFINITI *CYP2C19* Assay (AutoGenomics, Inc), Invader *UGT1A1* (Third Wave Technologies Inc.), eSensor Warfarin Sensitivity Saliva Test (GenMark Diagnostics), eQ-PCR LC Warfarin Genotyping kit (TrimGen Corporation), eSensor Warfarin Sensitivity Test and XT-8 Instrument (Osmetech Molecular Diagnostics), Gentriss Rapid Genotyping Assay-*CYP2C9*&*VKORCI* (ParagonDx, LLC), INFINITI 2C9 & *VKORCI* Multiplex Assay for Warfarin (AutoGenomics, Inc), Verigene Warfarin Metabolism Nucleic Acid Test and Verigene System (Nanosphere, Inc), TruDiagnosis System (Akonni Systems, Inc), Roche AmpliChip *CYP450* microassay (Roche Molecular Systems, Inc) (FDA, 2021a).

FDA Notes

The Office of Clinical Pharmacology within FDA includes The Genomics and Targeted Therapy Group responsible for applying pharmacogenomics and other biomarkers in drug development and clinical practice. The FDA scientists review current pharmacogenomic information and ensure that pharmacogenomic strategies are utilized appropriately in all phases of drug development (FDA, 2018).

The current list of pharmacogenomic biomarkers in drug labeling by FDA contain numerous medications that have genotypes related to metabolism dosage recommendations or warnings. These medications are involved in different therapeutic areas and the list includes the following genes and medications:

CYP1A2: Rucaparib

CYP2B6: Efavirenz, Prasugrel, Ospemifene

CYP2C19 contains 22 different medications: Clopidogrel, Prasugrel, Ticagrelor, Lansoprazole, Omeprazole, Esomeprazole, Rabeprazole, Pantoprazole, Dexlansoprazole, Flibanserin, Drospirenone and Ethinyl Estradiol, Voriconazole, Lacosamide, Brivaracetam, Clobazam, Phenytoin, Diazepam, Citalopram, Escitalopram, Doxepin, Formoterol, Carisoprodol

CYP2C9 contains 15 different medications: Prasugrel, Dronabinol, Flibanserin, Warfarin, Phenytoin, Celecoxib, Piroxicam, Flurbiprofen, Lesinurad, Avatrombopag, Erdafitinib, Ospemifene, Siponimod, Meloxicam, Rimegepant

CYP2D6 contains 70 different medications: Tramadol, Metoprolol, Nebivolol, Propafenone, Propranolol, Ondansetron, Palonosetron, Flibanserin, Eliglustat, Deutetrabenazine, Dextromethorphan and Quinidine, Galantamine, Tetrabenazine, Valbenazine, Rucaparib, Aripiprazole, Aripiprazole Lauroxil, Atomoxetine, Brexpiprazole, Cariprazine, Citalopram, Clozapine, Desvenlafaxine, Doxepin, Escitalopram, Fluoxetine, Fluvoxamine, Iloperidone, Modafinil, Paroxetine, Perphenazine, Risperidone, Venlafaxine, Vortioxetine, Arformoterol, Formoterol, Umeclidinium, Darifenacin, Mirabegron, Tolterodine, Amphetamine, Donepezil, Fesoterodine, Gefitinib, Metoclopramide, Paliperidone, Tamoxifen, Carvedilol, Amitriptyline, Amoxapine, Clomipramine, Codeine, Desipramine, Duloxetine, Imipramine, Meclizine, Metoclopramide, Nefazodone, Nortriptyline, Pimozide, Protriptyline, Quinine Sulfate, Tamsulosin, Thioridazine, Trimipramine, Pitolisant, Upadacitinib, Bupropion.

CYP3A5: Prasugrel

TPMT: Thioguanine, Azathioprine, Mercaptopurine, Cisplatin

NUDT15: Thioguanine, Azathioprine, Mercaptopurine

UGT1A1: Arformoterol, Belinostat, Binimetinib, Dolutegravir, Indacaterol, Irinotecan, Nilotinib, Pazopanib, Raltegravir, Sacituzumab Govitecan-hziy (FDA, 2021c).

FDA Recommendations

The FDA package insert for Plavix (clopidogrel) carries the following “Black Box” warning: “The effectiveness of Plavix results from its antiplatelet activity which is dependent on its conversion to an active metabolite by the cytochrome P450 (CYP) system, principally *CYP2C19*. Plavix at recommended doses forms less of the active metabolite and so has a reduced effect on platelet activity in patients who are homozygous for nonfunctional alleles of the *CYP2C19* gene, (termed “*CYP2C19* poor metabolizers”). Tests are available to identify patients who are *CYP2C19* poor metabolizers. Consider another platelet P2Y₁₂ inhibitor in patients identified as *CYP2C19* poor metabolizers.” (FDA, 2016)

The FDA package insert for Xenazine (tetrabenazine) indicates, “Patients who require doses of Xenazine greater than 50 mg per day should be first tested and genotyped to determine if they are poor metabolizers (PMs) or extensive metabolizers (EMs) by their ability to express the drug metabolizing enzyme, *CYP2D6*. The dose of XENAZINE should then be individualized accordingly to their status as PMs or EMs. (FDA, 2008)

The Coumadin (warfarin) highlights of prescription information notes that “The appropriate initial dosing of COUMADIN varies widely for different patients. Not all factors responsible for warfarin dose variability are known, and the initial dose is influenced by: Genetic factors (*CYP2C9* and *VKORC1* genotypes).” Although dosage suggestions based on *CYP2C9* and *VKORC1* genotypes are provided in the package insert, the requirement for genetic testing is not included (FDA)

The eligibility and dosing of Eliglustat is dependent on cytochrome P450 *CYP2D6* genotype as eliglustat is extensively metabolized by *CYP2D6*. The FDA contraindicates this medication in the following patients due “to the risk of cardiac arrhythmias from prolongation of the PR, QTc, and/or QRS cardiac Intervals”:

EMs of *CYP2D6*

- Taking a strong or moderate *CYP2D6* inhibitor concomitantly with a strong or moderate *CYP3A* inhibitor
- Moderate or severe hepatic impairment
- Mild hepatic impairment and taking a strong or moderate *CYP2D6* inhibitor

IMs

- Taking a strong or moderate *CYP2D6* inhibitor concomitantly with a strong or moderate *CYP3A* inhibitor
- Taking a strong *CYP3A* inhibitor
- Any degree of hepatic impairment

PMs

- Taking a strong *CYP3A* inhibitor
- Any degree of hepatic impairment (FDA, 2014)

The FDA also includes a warning for irinotecan’s interaction with *UGT1A1*, stating “When administered in combination with other agents, or as a single-agent, a reduction in the starting dose by at least one level of CAMPTOSAR [irinotecan] should be considered for patients known to be homozygous for the *UGT1A1**28 allele” (FDA, 2021c).

B. Centers for Medicare & Medicaid Services (CMS)

- L38294 MolDX: Pharmacogenomics Testing: <https://www.cms.gov/medicare-coverage-database/view/lcd.aspx?lcdid=38294&ver=16&bc=0>

- A58318 Billing and Coding: MolDX: Pharmacogenomics Testing: <https://www.cms.gov/medicare-coverage-database/view/article.aspx?articleid=58318&ver=34&bc=0>
- L35025 MolDX: Molecular Diagnostic Tests (MDT): <https://www.cms.gov/medicare-coverage-database/view/lcd.aspx?lcdid=35025&ver=91&bc=0>
- A56853 Billing and Coding: MolDX: Molecular Diagnostic Tests (MDT): <https://www.cms.gov/medicare-coverage-database/view/article.aspx?articleId=56853&ver=43>

VIII. Applicable CPT/HCPCS Procedure Codes

CPT	Code Description
81220	CFTR (cystic fibrosis transmembrane conductance regulator) (eg, cystic fibrosis) gene analysis; common variants (eg, ACMG/ACOG guidelines)
81225	CYP2C19 (cytochrome P450, family 2, subfamily C, polypeptide 19) (eg, drug metabolism), gene analysis, common variants (eg, *2, *3, *4, *8, *17)
81226	CYP2D6 (cytochrome P450, family 2, subfamily D, polypeptide 6) (eg, drug metabolism), gene analysis, common variants (eg, *2, *3, *4, *5, *6, *9, *10, *17, *19, *29, *35, *41, *1XN, *2XN, *4XN)
81227	CYP2C9 (cytochrome P450, family 2, subfamily C, polypeptide 9) (eg, drug metabolism), gene analysis, common variants (eg, *2, *3, *5, *6)
81230	CYP3A4 (cytochrome P450 family 3 subfamily A member 4) (eg, drug metabolism), gene analysis, common variant(s) (eg, *2, *22)
81231	CYP3A5 (cytochrome P450 family 3 subfamily A member 5) (eg, drug metabolism), gene analysis, common variants (eg, *2, *3, *4, *5, *6, *7)
81232	DPYD (dihydropyrimidine dehydrogenase) (eg, 5-fluorouracil/5-FU and capecitabine drug metabolism), gene analysis, common variant(s) (eg, *2A, *4, *5, *6)
81247	G6PD (glucose-6-phosphate dehydrogenase) (eg, hemolytic anemia, jaundice), gene analysis; common variant(s) (eg, A, A-)
81283	IFNL3 (interferon, lambda 3) (eg, drug response), gene analysis, rs12979860 variant
81291	MTHFR (5,10-methylenetetrahydrofolate reductase) (eg, hereditary hypercoagulability) gene analysis, common variants (eg, 677T, 1298C)
81306	NUDT15 (nudix hydrolase 15) (eg, drug metabolism) gene analysis, common variant(s) (eg, *2, *3, *4, *5, *6)
81328	SLCO1B1 (solute carrier organic anion transporter family, member 1B1) (eg, adverse drug reaction), gene analysis, common variant(s) (eg, *5)
81335	TPMT (thiopurine S-methyltransferase) (eg, drug metabolism), gene analysis, common variants (eg, *2, *3)
81346	TYMS (thymidylate synthetase) (eg, 5-fluorouracil/5-FU drug metabolism), gene analysis, common variant(s) (eg, tandem repeat variant)

81350	UGT1A1 (UDP glucuronosyltransferase 1 family, polypeptide A1) (eg, drug metabolism, hereditary unconjugated hyperbilirubinemia [Gilbert syndrome]) gene analysis, common variants (eg, *28, *36, *37)
81355	VKORC1 (vitamin K epoxide reductase complex, subunit 1) (eg, warfarin metabolism), gene analysis, common variant(s) (eg, -1639G>A, c.173+1000C>T)
81381	HLA Class I typing, high resolution (ie, alleles or allele groups); one allele or allele group (eg, B*57:01P), each
81405	Molecular pathology procedure, Level 6 (eg, analysis of 6-10 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 11-25 exons, regionally targeted cytogenomic array analysis)
81479	Unlisted molecular pathology procedure
0029U	Drug metabolism (adverse drug reactions and drug response), targeted sequence analysis (ie, CYP1A2, CYP2C19, CYP2C9, CYP2D6, CYP3A4, CYP3A5, CYP4F2, SLCO1B1, VKORC1 and rs12777823) Proprietary test: Focused Pharmacogenomics Panel Lab/Manufacturer: Mayo Clinic
0030U	Drug metabolism (warfarin drug response), targeted sequence analysis (ie, CYP2C9, CYP4F2, VKORC1, rs12777823) Proprietary test: Warfarin Response Genotype Lab/Manufacturer: Mayo Clinic
0031U	CYP1A2 (cytochrome P450 family 1, subfamily A, member 2) (eg, drug metabolism) gene analysis, common variants (ie, *1F, *1K, *6, *7) Proprietary test: Cytochrome P450 1A2 Genotype Lab/Manufacturer: Mayo Clinic
0032U	COMT (catechol-O-methyltransferase)(eg, drug metabolism) gene analysis, c.472G>A (rs4680) variant Proprietary test: Catechol-O-Methyltransferase (COMT) Genotype Lab/Manufacturer: Mayo Clinic
0033U	HTR2A (5-hydroxytryptamine receptor 2A), HTR2C (5-hydroxytryptamine receptor 2C) (eg, citalopram metabolism) gene analysis, common variants (ie, HTR2A rs7997012 [c.614-2211T>C], HTR2C rs3813929 [c.-759C>T] and rs1414334 [c.551-3008C>G]) Proprietary test: Serotonin Receptor Genotype (HTR2A and HTR2C) Lab/Manufacturer: Mayo Clinic
0034U	TPMT (thiopurine S-methyltransferase), NUDT15 (nudix hydroxylase 15) (eg, thiopurine metabolism) gene analysis, common variants (ie, TPMT *2, *3A, *3B, *3C, *4, *5, *6, *8, *12; NUDT15 *3, *4, *5) Proprietary test: Thiopurine Methyltransferase (TPMT) and Nudix Hydrolase (NUDT15) Genotyping Lab/Manufacturer: Mayo Clinic
0070U	CYP2D6 (cytochrome P450, family 2, subfamily D, polypeptide 6) (eg, drug metabolism) gene analysis, common and select rare variants (ie, *2, *3, *4, *4N, *5, *6, *7, *8, *9, *10, *11, *12, *13, *14A, *14B, *15, *17, *29, *35, *36, *41, *57, *61, *63, *68, *83, *xN)

	Proprietary test: CYP2D6 Common Variants and Copy Number Lab/Manufacturer: Mayo Clinic
0071U	CYP2D6 (cytochrome P450, family 2, subfamily D, polypeptide 6) (eg, drug metabolism) gene analysis, full gene sequence (List separately in addition to code for primary procedure) Proprietary test: CYP2D6 Full Gene Sequencing Lab/Manufacturer: Mayo Clinic
0072U	CYP2D6 (cytochrome P450, family 2, subfamily D, polypeptide 6) (eg, drug metabolism) gene analysis, targeted sequence analysis (ie, CYP2D6-2D7 hybrid gene) (List separately in addition to code for primary procedure) Proprietary test: CYP2D6-2D7 Hybrid Gene Targeted Sequence Analysis Lab/Manufacturer: Mayo Clinic
0073U	CYP2D6 (cytochrome P450, family 2, subfamily D, polypeptide 6) (eg, drug metabolism) gene analysis, targeted sequence analysis (ie, CYP2D7-2D6 hybrid gene) (List separately in addition to code for primary procedure) Proprietary test: CYP2D7-2D6 Hybrid Gene Targeted Sequence Analysis Lab/Manufacturer: Mayo Clinic
0074U	CYP2D6 (cytochrome P450, family 2, subfamily D, polypeptide 6) (eg, drug metabolism) gene analysis, targeted sequence analysis (ie, non-duplicated gene when duplication/multiplication is trans) (List separately in addition to code for primary procedure) Proprietary test: CYP2D6 trans-duplication/multiplication non-duplicated gene targeted sequence analysis Lab/Manufacturer: Mayo Clinic
0075U	CYP2D6 (cytochrome P450, family 2, subfamily D, polypeptide 6) (eg, drug metabolism) gene analysis, targeted sequence analysis (ie, 5' gene duplication/multiplication) (List separately in addition to code for primary procedure) Proprietary test: CYP2D6 5' gene duplication/multiplication targeted sequence analysis Lab/Manufacturer: Mayo Clinic
0076U	CYP2D6 (cytochrome P450, family 2, subfamily D, polypeptide 6) (eg, drug metabolism) gene analysis, targeted sequence analysis (ie, 3' gene duplication/multiplication) (List separately in addition to code for primary procedure) Proprietary test: CYP2D6 3' gene duplication/multiplication targeted sequence analysis Lab/Manufacturer: Mayo Clinic
0169U	NUDT15 (nudix hydrolase 15) and TPMT (thiopurine S-methyltransferase) (eg, drug metabolism) gene analysis, common variants Proprietary test: NT (NUDT15 and TPMT) genotyping panel Lab/Manufacturer: RPRD Diagnostics
0286U	CEP72 (centrosomal protein, 72-KDa), NUDT15 (nudix hydrolase 15) and TPMT (thiopurine S-methyltransferase) (eg, drug metabolism) gene analysis, common variants

	Proprietary test: CNT (CEP72, TPMT and NUDT15) genotyping panel Lab/Manufacturer: RPRD Diagnostics
G9143	Warfarin responsiveness testing by genetic technique using any method, any number of specimen(s)

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Procedure codes appearing in Medical Policy documents are included only as a general reference tool for each policy. They may not be all-inclusive.

IX. Evidence-based Scientific References

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