Corporate Medical Policy

Pharmacogenetics Testing AHS – M2021

File Name:	pharmacogenetics_testing
Origination:	01/2019
Last Review:	07/2024

Description of Procedure or Service

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, 2023).

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., 2013).

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 (*HLA*s). HLAs are also known as major histocompatibility complex (MHC) (Viatte, 2023).

Related Policies:
In Vitro Chemoresistance and Chemosensitivity Assays AHS-G2100
Metabolite Markers of Thiopurines Testing AHS-G2115
Genetic Testing for Familial Alzheimer Disease AHS-M2038
Therapeutic Drug Monitoring for 5-Fluorouracil AHS-M2067
Genetic Testing for Lipoprotein A Variant(s) as a Decision Aid for Aspirin Treatment and/or CVD Risk Assessment AHS-M2082

Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.

Policy

BCBSNC will provide coverage for pharmacogenetics testing when it is determined the medical criteria or reimbursement guidelines below are met.

Benefits Application

This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore, member benefit language should be reviewed before applying the terms of this medical policy.

When Pharmacogenetics Testing is covered

1. To aid in therapy selection and/or dosing for individuals being considered for therapy or who are in their course of therapy with any of the medications listed below, testing for the *CYP2D6* genotype once per lifetime (see Note 1) is considered medically necessary.

    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. To aid in therapy selection and/or dosing for individuals being considered for therapy or who are in their course of therapy with any of the medications listed below, testing for the *CYP2D6* and *CYP2C19* genotype once per lifetime (see Note 1) is considered medically necessary.

    a. Amitriptyline
    b. Clomipramine
    c. Doxepin
    d. Imipramine
    e. Trimipramine

3. To aid in therapy selection and/or dosing for individuals being considered for therapy or who are in their course of therapy, testing for the *CYP2C19* genotype once per lifetime (see Note 1) is considered medically necessary.

    a. Abrocitinib
    b. Brivaracetam
    c. Citalopram
    d. Clobazam
    e. Clopidogrel
    f. Dexlansoprazole (see Note 2)
    g. Escitalopram
    h. Flibanserin
    i. Lansoprazole (see Note 2)
    j. Mavacamten
    k. Omeprazole (see Note 2)
    l. Pantoprazole (in pediatric individuals) (see Note 2)
    m. Sertraline
    n. Voriconazole (see Note 2)

4. To aid in therapy selection and/or dosing for individuals being considered for therapy or who are in their course of therapy with any of the medications listed below, testing for the *CYP2C9* genotype once per lifetime (see Note 1) is considered medically necessary.

    a. Celecoxib
    b. Dronabinol
    c. Erdafitinib
    d. Flurbiprofen
    e. Lornoxicam
    f. Meloxicam
    g. Nateglinide
    h. Piroxicam
    i. Siponimod
    j. Tenoxicam

5. For individuals being considered for warfarin therapy, testing for the *CYP2C9, CYP4F2, VKORC1*, and rs12777823 genotype once per lifetime (see Note 1) is considered medically necessary.

6. To aid in therapy selection and/or dosing for individuals being considered for therapy or who are in their course of therapy with the below medications, testing for the *TPMT* and *NUDT15* genotype once per lifetime (see Note 1) is considered medically necessary.

    a. Azathioprine
    b. Mercaptopurine
    c. Thioguanine

7. To aid in therapy selection and/or dosing for individuals being considered for therapy or who are in their course of therapy with the below medications, testing for the *DPYD* genotype once per lifetime (see Note 1) is considered medically necessary.

    a. Capecitabine
    b. Flucytosine
    c. Fluorouracil
    d. Tegafur

8. To aid in therapy selection and/or dosing for individuals being considered for therapy or who are in their course of therapy with the below medications, testing for the following human leukocyte antigens (HLAs) genotypes once per lifetime (see Note 1) is considered medically necessary.

    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. To aid in therapy selection and/or dosing for individuals being considered for therapy or who are in their course of therapy with phenytoin/fosphenytoin, testing for the *CYP2C9* and *HLA-B*15:02* genotype once per lifetime (see Note 1) is considered medically necessary.

10. To aid in therapy selection and/or dosing for individuals being considered for therapy or who are in their course of therapy with the medications listed below, testing for the *G6PD* genotype once per lifetime (see Note 1) is considered medically necessary.

    a. Pegloticase
    b. Primaquine
    c. Rasburicase
    d. Tafenoquine

11. To aid in therapy selection and/or dosing for individuals being considered for therapy or who are in their course of therapy with the below medications, testing for the following genotypes once per lifetime (see Note 1) is considered medically necessary.

    a. *BCHE* for treatment with mivacurium or succinylcholine
    b. *CFTR* for treatment with ivacaftor, elexacaftor and tezacaftor, ivacaftor and lumacaftor, or ivacaftor and tezacaftor
    c. *CYP2B6* for treatment with efavirenz
    d. *CYP3A5* for treatment with tacrolimus
    e. *IFNL3* treatment with peginterferon alfa-2a, peginterferon alfa-2b or ribavirin
    f. *NAT2* for treatment with amifampridine or amifampridine phosphate
    g. *UGT1A1* for treatment with atazanavir, belinostat, irinotecan, nilotinib, or pazopanib, or sacituzumab govitecan-hziy

12. To aid in therapy selection and/or dosing for individuals being considered for therapy or who are in their course of therapy with belzutifan, testing for the *CYP2C19* and *UGT2B17* genotype once per lifetime (see Note 1) is considered medically necessary.

13. For individuals being considered for the use of halogenated volatile anesthetics or depolarizing muscle relaxants, testing for the *RYR1* and *CACNA1S* genotype once per lifetime (see Note 1) is considered medically necessary.

14. When formulary coverage allows a pharmacotherapy that is dependent on a known genetic status (e.g., *APOE* testing prior to lecanemab-irmb treatment), gene specific testing is considered medically necessary.

When Pharmacogenetics Testing is not covered

1. To identify patients at risk of statin-induced myopathy, genetic testing for the presence of variants in the *SLCO1B1* gene is considered not medically necessary.

2. Reimbursement is not allowed for the following pharmacogenetic testing:

   a. Genotyping more than once per lifetime (see Note 1) for any medication therapy.
   b. Genotyping of the general population.
   c. Pharmacogenetic testing (e.g., single nucleotide polymorphism [SNP] testing or SNP panel testing; single gene or multi-gene panel testing [see Note 3]) for all other situations not addressed above.

Notes

Note 1: Any gene may only 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 is considered not medically necessary. Testing in a patient post-liver transplant is not indicated.

Note 2: Pharmacogenetic testing for proton pump inhibitor therapies (PPIs) ONLY MEETS COVERAGE CRITERIA if the patient has an active *H. pylori* infection.

Note 3: For 2 or more gene tests being run on the same platform, please refer to AHS-R2162 Reimbursement Policy.

Policy Guidelines

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, 2023). 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, 2023).

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, 2023).

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, 2023).

ApoE
Apolipoprotein E (*APOE*) is the gene most strongly associated as a genetic risk factor for late-onset Alzheimer disease. *APOE* can have three alleles: ε1, ε2, and ε4 (Sherva & Kowall, 2022). *APOE ε4* is a susceptibility gene, meaning it is associated with increased risk but does not cause Alzheimer disease, and not all patients with Alzheimer disease will carry *APOE ε4.* In one study of 1303 patients, 55% of those homozygous for *ε4* developed Alzheimer disease, while 27% of those heterozygous and 9% with no *ε4* allele also developed Alzheimer disease (Myers et al., 1996). *APOE*, as well as *CYP2D6,* carrier status may have an effect on a patient's response to drugs, "with *CYP2D6*-PMs [poor metabolizers], *CYP2D6*-Ums [ultrarapid metabalizers], and *APOE-4/4* carriers acting as the worst responders" (Cacabelos et al., 2012).

In 2023, the FDA approved Lecanemab (brand name Leqembi), an amyloid beta-directed antibody, for the treatment of Alzheimer disease in adult patients (FDA, 2023). One potential side effect of Leqembi is amyloid related imaging abnormalities (ARIA), which may be more likely to occur in people who are homozygous *APOE ε4* carries (Leqembi, 2024). The FDA includes that "the prescribing information states that testing for ApoE ε4 status should be performed before starting treatment with Leqembi to inform the risk of developing ARIA" (FDA, 2023).

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, 2023).

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, 2023).

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, 2023).

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., 2013).

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, 2024).

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 three 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, 2023).

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 anticontraceptive 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 64 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, 2022). Still, other companies such as Mayo Clinic and Sema4 have developed their own pharmacogenetic panels, each with individually chosen analytes (Mayo, 2023; Sema4, 2022).

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 CYP4502C19 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, three 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 eight 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. A total of 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*. Specifically, 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, nine 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 regiment 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.

Galli et al. (2021) studied the use of guided selection of antiplatelet therapy for patients undergoing percutaneous coronary intervention. The authors conducted a meta-analysis that included 3656 relevant articles with 20743 patients. Overall, "guided selection of antiplatelet therapy was associated with a reduction in major adverse cardiovascular events and reduced bleeding, although not statistically significant." Additionally, cardiovascular death, myocardial infraction, stent thrombosis, and minor bleeding were all reduced with guided therapy compared to standard therapy, but the risks of all-cause death and major bleeding did not differ. The authors concluded that "guided selection of antiplatelet therapy improved both composite and individual efficacy outcomes with a favourable safety profile, driven by a reduction in minor bleeding, supporting the use of platelet function or genetic testing to optimise the choice of agent in patients undergoing PCI" (Galli et al., 2021).

Oslin et al. (2022) conducted a randomized clinical trial that compared treatment guided by pharmacogenomic testing vs. usual care "to determine whether pharmacogenomic testing affects Participants of this clinical trial included 676 clinicians and 1944 patients. Criteria for patient enrollment were those with major depressive disorder who were initiating or switching treatment with a single antidepressant and exclusion included those who have active substance use disorder, mania, psychosis, or concurrent treatment with a specified list of medications. Results of this study determined "remission rates over 24 weeks were higher among patients whose care was guided by pharmacogenomic testing than those in usual care (OR, 1.28 [95% CI, 1.05 to 1.57]; P = .02; risk difference, 2.8% [95% CI, 0.6% to 5.1%]) but were not significantly higher at week 24 when 130 patients in the pharmacogenomic-guided group and 126 patients in the usual care group were in remission (estimated risk difference, 1.5% [95%CI, -2.4% to 5.3%]; P = .45)". In conclusion, in provision of pharmacogenomic testing for drug-gene interaction amongst patients with major depressive disorder, pharmacogenomic testing "reduced prescription of medications with predicted drug-gene interactions compared to usual care. Provision test results had small nonpersistent effects on symptom remission" (Oslin et al., 2022). antidepressant medication selection and whether such testing leads to better clinical outcomes". (Oslin et al., 2022).

Ghanbarian et al. (2023) studied the cost-effectiveness of pharmacogenetic testing used to guide prescription of antidepressants. The authors looked at data from patients with major depressive disorder in British Columbia, Canada. The data included unique patient characteristics, including metabolizer phenotypes, incremental costs, life-years, and quality-adjusted life-years. "Pharmacogenomic-guided care was associated with 37% fewer patients with refractory depression over 20 years." The costs of pharmacogenetic testing were estimated to be offset within about two years of use, with an overall saving of 956 million Canadian dollars (4926 Canadian dollars per patient) (Ghanbarian et al., 2023).

The 2023 PREPARE (preemptive pharmacogenomic testing for preventing adverse drug reactions) trial investigated the effects of pre-emptive genotyping using a pharmacogenetic panel on adverse drug reactions. Swen et al. (2023) conducted an "open-label, multicentre, controlled, cluster-randomised, crossover implementation study of a 12-gene pharmacogenetic panel in 18 hospitals, nine community health centres, and 28 community pharmacies in seven European countries." A total of 6944 patients receiving their first prescription for a clinically recommended drug were included in the study. The participants were divided into a study group, which received genotyping and recommended treatment adjustments, and a control group, which received standard care. The primary outcome measured was the occurrence of clinically relevant adverse drug reactions within 12-weeks. A clinically relevant adverse drug reactions occurred in 21.5% of patients in the study group (N=2923), and 28.6% of patients in the control group (N=3270). The authors concluded that "genotype-guided treatment using a 12-gene pharmacogenetic panel significantly reduced the incidence of clinically relevant

adverse drug reactions and was feasible across diverse European health-care system organisations and settings" (Swen et al., 2023)

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, 2023b).

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	*CYP2C9*/ Phenotype	Summary of CPIC Therapeutic Recommendations	Level of Recommendations	Reference
Phenytoin/ fosphenytoin based on *HLA-B*15:02*	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	No adjustments needed from typical dosing strategies. Subsequent doses should be adjusted according to therapeutic drug	Moderate	

	Metabolizer (IM)	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. 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 *CYP2C9*, *VKORC1*, *CYP4F2* 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	Moderate	

		during course of therapy. Alternatively, consider an alternate therapy not metabolized by CYP2C9 or not significantly impacted by CYP2C9 genetic variants in vivo"		
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 treatment goals"	Strong	(Theken et al., 2020)
	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	Moderate	

		variants in vivo or choose an NSAID metabolized by CYP2C9 but with a shorter half-life"		
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 Nortripyline Other TCAs (Tricyclic antidepressants): clomipramine, desipramine, doxepin, imipramine, and trimipramine	Ultra-rapid Metabolizer (URM)	Avoid tricyclic use due to potential lack of efficacy. Consider alternative drug not metabolized by *CYP2D6*. 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., 2016)
	Normal Metabolizer (NM)	Initiate therapy with recommended starting dose.	Strong (Recommendation for other TCAs is Strong)	
	IM	Consider a 25% reduction of recommended starting dose. Utilize therapeutic drug monitoring to guide dose adjustments.	Moderate (Recommendation for other TCAs is Optional)	
	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 (Recommendation for other TCAs is Optional)	
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 because of possibility of diminished analgesia.	Strong	
Paroxetine	URM	Select alternative drug not predominantly metabolized by *CYP2D6*	Moderate	(Bousman et al., 2023)

	M	Initiate therapy with recommended starting dose.	Strong	
	IM	Consider a lower starting dose and slower titration schedule as compared with normal metabolizers	Optional	
	PM	Consider a 50% reduction in recommended starting dose, slower titration schedule, and a 50% lower maintenance dose as compared with normal metabolizers.	Moderate	
Fluvoxamine	URM	No recommendation due to lack of evidence.	No recommendation	(Bousman et al., 2023)
	EM	Initiate therapy with recommended starting dose.	Strong	
	IM	Initiate therapy with recommended starting dose.	Moderate	
	PM	Consider a 25–50% lower starting dose and lower titration schedule as compared with normal metabolizers or consider a clinically appropriate alternative antidepressant not predominantly metabolized by *CYP2D6*.	Optional	
Ondansetron and Tropisetron	URM	Select alternative drug not predominantly metabolized by *CYP2D6* (i.e., granisetron).	Moderate	(Bell et al., 2016)
	NM	Initiate therapy with recommended starting dose.	Strong	
	IM	Insufficient evidence demonstrating clinical impact based on *CYP2D6* genotype. Initiate therapy with recommended starting dose.	No recommendation	
	PM	Insufficient evidence demonstrating clinical impact based on *CYP2D6* genotype. Initiate therapy with recommended starting dose.	No recommendation	
Tamoxifen	URM	Avoid moderate and strong *CYP2D6* inhibitors. Initiate therapy with recommended standard of care dosing (tamoxifen 20 mg/day).	Strong	(Goetz et al., 2018)

	NM	Avoid moderate and strong *CYP2D6* 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 [individuals]or aromatase inhibitor along with ovarian function suppression in premenopausal[individuals}, given that these approaches are superior to tamoxifen regardless of *CYP2D6* 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 *CYP2D6* strong to weak inhibitors.	Optional (Controversy remains)	
	IM	Consider hormonal therapy such as an aromatase inhibitor for postmenopausal [individuals]or aromatase inhibitor along with ovarian function suppression in premenopausal[individuals], given that these approaches are superior to tamoxifen regardless of *CYP2D6* genotype. If aromatase inhibitor use is contraindicated, consideration should be given to use a higher but FDA approved tamoxifen dose (40 mg/day). Avoid *CYP2D6* strong to weak inhibitors.	Moderate	
	PM	Recommend alternative hormonal therapy such as an aromatase inhibitor for postmenopausal [individuals]or aromatase inhibitor along with ovarian function suppression in premenopausal [individuals]given that these approaches are superior to tamoxifen regardless of *CYP2D6* genotype and based on knowledge that *CYP2D6*	Strong	

		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.		
Atomoxetine (for children)	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). If < 200 ng/mL, consider a proportional increase in dose to approach 400 ng/mL	Moderate	(Brown et al., 2019)
	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	
	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,	Strong	

		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		
Atomoxetine (for adults)	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	Moderate	

		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.		
	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	Reference
Amitriptyline and Nortripyline Other TCAs: clomipramine, doxepin, imipramine, and trimipramine	URM, UM	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., 2016)
	NM	Initiate therapy with recommended starting dose.	Strong (Recommendation for other TCAs is Strong)	
	IM	Initiate therapy with recommended starting dose.	Strong (Recommendation for other TCAs is Optional)	
	PM	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. 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 a clinically appropriate alternative antidepressant not predominantly metabolized by *CYP2C19*. If citalopram or escitalopram are clinically appropriate, and adequate efficacy is not achieved at standard maintenance dosing, consider titrating to a higher maintenance dose	Strong	(Bousman et al., 2023)

	EM	Initiate therapy with recommended starting dose.	Strong	
	IM	Initiate therapy with recommended starting dose. Consider a slower titration schedule and lower maintenance dose than normal metabolizers	Moderate	
	PM	Consider a clinically appropriate antidepressant not predominantly metabolized by CYP2C19. If citalopram or escitalopram are clinically appropriate, consider a lower starting dose, slower titration schedule, and 50% reduction of the standard maintenance dose as compared with normal metabolizers	Strong	
Sertraline	URM	Initiate therapy with recommended starting dose.	Strong	(Bousman et al., 2023)
	EM	Initiate therapy with recommended starting dose.	Strong	
	IM	Initiate therapy with recommended starting dose. Consider a slower titration schedule and lower maintenance dose than CYP2C19 normal metabolizers	Moderate	
	PM	Consider a lower starting dose, slower titration schedule, and 50% reduction of standard maintenance dose as compared with CYP2C19 normal metabolizers or select a clinically appropriate alternative antidepressant not predominantly metabolized by *CYP2C19*.	Moderate	
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	Strong	

		ticagrelor at standard dose if no contraindication.		
Voriconazole	URM	Choose an alternative agent that is not dependent on *CYP2C19* 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 *CYP2C19* metabolism as primary therapy in lieu of voriconazole. Such agents include isavuconazole, liposomal amphotericin B, and posaconazole.	Moderate	
	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 *CYP2C19* 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 Helicobacter pylori infection and erosive esophagitis. Daily dose may be given in	Moderate	

		divided doses. Monitor for efficacy"		
	Normal	"Initiate standard starting daily dose. Consider increasing dose by 50–100% for the treatment of H. pylori 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, 2016) for Amitriptyline, Clomipramine, Doxepin, Imipramine, and Trimipramine

Phenotype	***CYP2D6***	***CYP2D6***	***CYP2D6***	***CYP2D6***
CYP2C19	**UM**	**NM**	**IM**	**PM**
URM	Avoid amitriptyline use Recommendation: Optional	Consider alternative drug not metabolized by *CYP2C19*. Recommendation: Optional	Consider alternative drug not metabolized by *CYP2C19*. Recommendation: Optional	Avoid amitriptyline use Recommendation: Optional
NM	Avoid amitriptyline use. If amitriptyline is warranted, consider titrating to a higher target dose (compared to normal metabolizers) Recommendation: Strong	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 recommended starting dose. Recommendation: Strong
IM	Avoid amitriptyline use	Initiate therapy with recommended starting	Consider a 25% reduction of recommended starting dose.	Avoid amitriptyline use. If Amitriptyline is warranted,

	Recommendation: Optional	dose. Recommendation: Strong	Recommendation: Optional This recommendation may also be considered for diplotypes with an activity score of 1.	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	Strong	

		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.		
	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 or NUDT15 status is unknown, monitor closely for toxicity.	Strong	
Azathioprine	NM	Start with normal starting dose (e.g., 2–3 mg/kg/d) and adjust doses of azathioprine based on	Strong	(Relling et al., 2018)

		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.		
	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/m2 /day). Adjust doses of thioguanine (TG) and of other myelosuppressive therapy without any	Strong	(Relling et al., 2013; Relling et al., 2018)

		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.		
	IM	Start with reduced doses (50% to 80% of normal dose) if normal starting dose is ≥40-60 mg/m2 /day (e.g., 20-48 mg/m2 /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	Strong	

		therapy. Consider evaluating erythrocyte TPMT activity to assess TPMT phenotype. If thiopurines are required and TPMT status is unknown, monitor closely for toxicity.		

***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/m2 /day or ≥ 1.5 mg/kg/day (e.g., start at 25-60 mg/m2 /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/m2 /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	Strong	

		reducing mercaptopurine over other agents. For nonmalignant conditions, consider alternative nonthiopurine immunosuppressant therapy.		
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)
	IM	Start with reduced doses (50% to 80% of normal dose) if normal starting dose is ≥40-60 mg/m2 /day (e.g., 20-48 mg/m2 /day) and adjust doses	Moderate	

		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.		
	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 dosed with early therapeutic drug monitoring. Activity score 0: Avoid use of 5-fluorouracil or 5-	Strong	

		fluorouracil prodrug-based regimens.		

***HLA-B* Genotypes**

Drug	Phenotype	Summary of CPIC Therapeutic Recommendations	Level of Recommendations	Reference
Abacavir	Noncarrier of *HLA-B*57:01*	Low or reduced risk of abacavir hypersensitivity	Strong	(Martin et al., 2014)
	Carrier of *HLA-B*57:01*	Abacavir is not recommended	Strong	
Allopurinol	Noncarrier of *HLA-B*5801* (*X/*X)	Use allopurinol per standard dosing guidelines	Strong	(Hershfield et al., 2013; Saito et al., 2016)
	Carrier of *HLA-B*5801* (*HLA-B*5801*/*X,b *HLA-B*5801/HLA-B*5801*)	Allopurinol is contraindicated	Strong	
Oxcarbazepine	*HLA-B*15:02* negative	Use oxcarbazepine per standard dosing guidelines	Strong	(Phillips et al., 2018)
	*HLA-B*15:02* positive	If patient is oxcarbazepine naıve, do not use oxcarbazepine.	Strong	
Carbamazepine	*HLA-B*15:02* negative and *HLA-A*31:01* negative	Use carbamazepine per standard dosing guidelines.	Strong	(Phillips et al., 2018)
	*HLA-B*15:02* negative and *HLA-A*31:01* positive	If patient is carbamazepine-naıve and alternative agents are available, do not use carbamazepine.	Strong	
	*HLA-B*15:02* positive and any *HLA-A*31:01* genotype (or *HLA-A*31:01* genotype unknown)	If patient is carbamazepine-naıve, do not use carbamazepine.	Strong	

Additional Genotypes

Drug/Genotype	Phenotype	Summary of CPIC Therapeutic Recommendations	Level of Recommendations	Reference
UGT1A1 for Atazanavir	EM	There is no need to avoid prescribing of atazanavir based on *UGT1A1* 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 *UGT1A1* 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	
UGT1A1 for Irinotecan	N/A	N/A	A, 1B level of evidence	(CPIC, 2023a)
CFTR for Ivacaftor	Homozygous or heterozygous G551D-*CFTR*—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-*CFTR*—e.g.,	Ivacaftor is not recommended	Moderate	

	F508del/R553X, rs75527207 genotype GG			
	Homozygous for F508del-*CFTR* (F508del/F508del), rs113993960, or rs199826652 genotype del/ del	Ivacaftor is not recommended	Moderate	
G6PD for high-risk drugs (rasburicase and pegloticase)	Normal	No reason to avoid high-risk drugs based on *G6PD* status	Strong	(Gammal et al., 2023)
	Deficient or deficient with CNSHA	Avoid use of high-risk drugs	Strong	
	Variable	To ascertain *G6PD* status, enzyme activity must be measured. Drug use should be guided per the recommendations based on the activity-based phenotype.	Moderate	
SLCO1B1 for Simvastatin	SLCO1B1 decreased function or SLCO1B1 possible decreased function	Prescribe an alternative statin depending on the desired potency. If simvastatin therapy is warranted, limit dose to <20mg/day	Strong	(Cooper-DeHoff et al., 2022)
	SLCO1B1 poor function	Prescribe an alternative statin depending on the desired potency	Strong	
CYP3A5 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	
IFNL3 treatment with Peginterferon alfa-2a,	Favorable response genotype	Approximately 90% chance for SVR after 24–48 weeks of treatment. Approximately 80–90% of patients are	Strong	(Muir et al., 2014)

Peginterferon alfa-2b or Ribavirin		eligible for shortened therapy (24–28 weeks vs. 48 weeks). Weighs in favor of using PEG-IFN-α- and RBV-containing regimens.		
	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	
RYR1 and *CACNA1S* genotypes for Potent Volatile Anesthetic Agents and Succinylcholine	Malignant Hyperthermia Susceptible	Halogenated volatile anesthetics or depolarizing muscle relaxants succinylcholine are relatively contraindicated in persons with MHS. They should not be used, except in extraordinary circumstances where 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, 2023a).

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

		therapy if no contraindications	CPIC guidance limits genotype-guided dosing recommendations to patients undergoing percutaneous coronary intervention for acute coronary syndromes (excluding medical management of acute coronary syndromes, stroke, and peripheral artery disease). 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. Alternative antiplatelet therapy not affected by *CYP2C19* variability includes prasugrel (Effient) and ticagrelor (Brilinta).
CYP2C19	Amitriptyline	Poor metabolizer: Consider 50% reduction in recommended starting dose	CPIC guidance is available for *CYP2D6*- and *CYP2C19*-genotype guided tricyclic antidepressant therapy. Although limited data exist for other tricyclic antidepressants, most supporting evidence of clinically relevant gene-drug effects is for amitriptyline and nortriptyline (Pamelor).
CYP2C19	Citalopram (Celexa), escitalopram (Lexapro)	Ultrarapid metabolizer: Consider alternative. Poor metabolizer: Consider 50% starting dose reduction and titrate to response, or use alternative	CPIC guidance is available for *CYP2C19*-genotype guided citalopram and escitalopram therapy. 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 *CYP2C19* poor metabolizers or patients taking cimetidine (Tagamet) or another *CYP2C19* inhibitor.
CYP2C19	Sertraline (Zoloft)	Ultrarapid metabolizer: If patient does not respond to recommended dose, consider alternative. Poor metabolizer: Consider 50% dose reduction or alternative	CPIC guidance is available for *CYP2C19*-genotype guided sertraline therapy.
CYP2D6	Amitriptyline, nortriptyline	Ultrarapid metabolizer: Avoid because of possible lack of effectiveness Poor metabolizer: Avoid because of possible adverse effects; if use is warranted, consider 50% reduction in recommended starting dose	CPIC guidance is available for CYP2D6- and CYP2C19-genotype guided tricyclic antidepressant therapy. Although limited data exist for other tricyclic antidepressants, most supporting evidence of clinically relevant gene-drug effects is for amitriptyline and nortriptyline.
CYP2D6	Aripiprazole (Abilify)	Poor metabolizer: Decrease dose	Quality of supporting evidence is classified as low by PharmGKB 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%.
CYP2D6	Atomoxetine (Strattera)	Poor metabolizer: Adjust dose	Quality of supporting evidence is classified as moderate (Level 2a) by PharmGKB. 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 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.

CYP2D6	Paroxetine (Paxil)	Ultrarapid metabolizer: Select alternative because of possible lack of effectiveness. Poor metabolizer: Select alternative or if use is warranted, consider 50% starting dose reduction	CPIC guidance is available for CYP2D6-genotype guided paroxetine therapy.

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., 2020)."

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, 2022).

Drug	Gene	Affected Subgroups	Description of Gene-Drug Interaction
Abacavir	*HLA-B*	*57:01 allele positive	Results in higher adverse reaction risk (hypersensitivity reactions). Do not use abacavir in patients positive for HLA-B*57:01.
Abrocitinib	*CYP2C19*	poor metabolizers	Results in higher systemic concentrations and may result in higher adverse reaction risk. Dosage adjustment is recommended. Refer to FDA labeling for specific dosing recommendations.
Amifampridine	*NAT2*	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	*NAT2*	poor metabolizers	Results in higher systemic concentrations. Use lowest recommended starting dosage (15 mg/day) and monitor for adverse reactions.
Amphetamine	*CYP2D6*	poor metabolizers	May affect systemic concentrations and adverse reaction risk. Consider lower starting dosage or use alternative agent.
Aripiprazole	*CYP2D6*	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	*CYP2D6*	poor metabolizers	Results in higher systemic concentrations. Dosage adjustment is recommended. Refer to FDA labeling for specific dosing recommendations.
Atomoxetine	*CYP2D6*	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	*TPMT* and/or *NUDT15*	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 NUDT15 or TPMT. Intermediate metabolizers for both genes may require more substantial dosage reductions. Refer to FDA labeling for specific dosing recommendations.
Belinostat	*UGT1A1*	*28/*28 (poor metabolizers)	May result in higher systemic concentrations and higher adverse reaction risk. Reduce starting dose to 750 mg/m2 in poor metabolizers.
Belzutifan	*CYP2C19 and/or UGT2B17*	poor metabolizers	Results in higher systemic concentrations and may result in higher adverse reaction risk (anemia, hypoxia). Monitor patients who are poor metabolizers for both genes for adverse reactions.
Brexpiprazole	*CYP2D6*	poor metabolizers	Results in higher systemic concentrations. Dosage adjustment is recommended. Refer to FDA labeling for specific dosing recommendations.
Brivaracetam	*CYP2C19*	intermediate or poor metabolizers	Results in higher systemic concentrations and higher adverse reaction risk. Consider dosage reductions in poor metabolizers.
Capecitabine	*DPYD*	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	*HLA-B*	*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 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.
Celecoxib	*CYP2C9*	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	*CYP2C19*	poor metabolizers	Results in higher systemic concentrations and adverse reaction risk (QT prolongation). The maximum recommended dose is 20 mg.
Clobazam	*CYP2C19*	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	*CYP2C19*	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	*CYP2D6*	poor metabolizers	Results in higher systemic concentrations. Dosage reductions may be necessary.
Codeine	*CYP2D6*	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	*CYP2D6*	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	*CYP2C9*	intermediate or poor metabolizers	May result in higher systemic concentrations and higher adverse reaction risk. Monitor for adverse reactions.
Eliglustat	*CYP2D6*	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	*CYP2C9*	*3/*3 (poor metabolizers)	May result in higher systemic concentrations and higher adverse reaction risk. Monitor for adverse reactions.
Flibanserin	*CYP2C19*	poor metabolizers	May result in higher systemic concentrations and higher adverse reaction risk. Monitor patients for adverse reactions.
Flurbiprofen	*CYP2C9*	poor metabolizers	Results in higher systemic concentrations. Use a reduced dosage.
Fluorouracil	*DPYD*	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	*CYP2C9*	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 CYP2C9*3 alleles may be at increased risk of severe cutaneous adverse reactions. Consider avoiding fosphenytoin as an alternative to carbamazepine in patients who are CYP2C9*3 carriers. Genotyping is not a substitute for clinical vigilance and patient management.
Fosphenytoin	*HLA-B*	*15:02 allele positive	May result in higher adverse reaction risk (severe cutaneous reactions). Patients positive for HLA-B*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 HLA-B*15:02. Genotyping is not a substitute for clinical vigilance and patient management.
Gefitinib	*CYP2D6*	poor metabolizers	Results in higher systemic concentrations and higher adverse reaction risk. Monitor for adverse reactions.
Iloperidone	*CYP2D6*	poor metabolizers	Results in higher systemic concentrations and higher adverse reaction risk (QT prolongation). Reduce dosage by 50%.
Irinotecan	*UGT1A1*	*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	*CYP2D6*	poor metabolizers	Results in higher systemic concentrations and higher adverse reaction risk. Monitor for orthostatic hypotension and bradycardia.
Meclizine	*CYP2D6*	ultrarapid, intermediate, or poor metabolizers	May affect systemic concentrations. Monitor for adverse reactions and clinical effect.
Meloxicam	*CYP2C9*	Poor metabolizers or *3 carriers	Results in higher systemic concentrations. Consider dose reductions in poor metabolizers. Monitor patients for adverse reactions.
Metoclopramide	*CYP2D6*	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	*TPMT* and/or *NUDT15*	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	*BCHE*	intermediate or poor metabolizers	Results in higher systemic concentrations and higher adverse reaction risk (prolonged neuromuscular blockade). Avoid use in poor metabolizers.
Nateglinide	*CYP2C9*	poor metabolizers	Results in higher systemic concentrations and may result in higher adverse reaction risk (hypoglycemia). Dosage reduction is recommended. Increase monitoring frequency for adverse reactions. Refer to FDA labeling for specific dosing recommendations.
Oliceridine	*CYP2D6*	Poor metabolizers	Results in higher systemic concentrations and higher adverse reaction risk (respiratory depression and sedation). May require less frequent dosing.

Pantoprazole	*CYP2C19*	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	*CYP2C9*	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 CYP2C9*3 alleles may be at increased risk of severe cutaneous adverse reactions. Consider avoiding phenytoin as an alternative to carbamazepine in patients who are CYP2C9*3 carriers. Genotyping is not a substitute for clinical vigilance and patient management.
Phenytoin	*HLA-B*	*15:02 allele positive	May result in higher adverse reaction risk (severe cutaneous reactions). Patients positive for HLA-B*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 HLA-B*15:02. Genotyping is not a substitute for clinical vigilance and patient management.
Pimozide	*CYP2D6*	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	*CYP2C9*	intermediate or poor metabolizers	Results in higher systemic concentrations. Consider reducing dosage in poor metabolizers.
Pitolisant	*CYP2D6*	Poor metabolizers	Results in higher systemic concentrations. Use lowest recommended starting dosage. Refer to FDA labeling for specific dosing recommendations.
Propafenone	*CYP2D6*	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	*UGT1A1*	*28/*28 (poor metabolizers)	May result in higher systemic concentrations and adverse reaction risk (neutropenia). Monitor for adverse reactions and tolerance to treatment.
Siponimod	*CYP2C9*	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	*BCHE*	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	*CYP3A5*	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	*CYP2D6*	poor metabolizers	Results in higher systemic concentrations. The maximum recommended single dose is 25 mg and should not exceed 50 mg/day.
Thioguanine	*TPMT* and/or *NUDT15*	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	*CYP2D6*	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	*CYP2D6*	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	*CYP2D6*	poor metabolizers	Results in higher systemic active metabolite concentrations and higher adverse reaction risk (QT prolongation). Dosage reductions may be necessary.
Venlafaxine	*CYP2D6*	poor metabolizers	Alters systemic parent drug and metabolite concentrations. Consider dosage reductions.
Vortioxetine	*CYP2D6*	poor metabolizers	Results in higher systemic concentrations. The maximum recommended dose is 10 mg.
Warfarin	*CYP2C9*	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	*CYP4F2*	V433M variant carriers	May affect dosage requirements. Monitor and adjust doses based on INR.
Warfarin	*VKORC1*	-1639G>A variant carriers	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, 2022).

Drug	Gene	Affected Subgroups	Description of Gene-Drug Interaction
Allopurinol	*HLA-B*	*58:01 allele positive	Results in higher adverse reaction risk (severe skin reactions).
Carbamazepine	*HLA-A*	*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	*CYP2D6*	poor metabolizers	Results in higher systemic concentrations and higher adverse reaction risk (dizziness).
Cevimeline	*CYP2D6*	poor metabolizers	May result in higher adverse reaction risk. Use with caution.
Codeine	*CYP2D6*	poor metabolizers	Results in lower systemic active metabolite concentrations and may result in reduced efficacy.
Efavirenz	*CYP2B6*	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	*HLA-DRB1*	*07:01 allele positive	Results in higher adverse reaction risk (hepatotoxicity). Monitor liver function tests regardless of genotype.
Lapatinib	*HLA-DQA1*	*02:01 allele positive	Results in higher adverse reaction risk (hepatotoxicity). Monitor liver function tests regardless of genotype.
Mavacamten	*CYP2C19*	Intermediate or poor metabolizers	Results in higher systemic concentrations and may have higher adverse reaction risk (heart failure). Dosage is based on individual response. The dose titration and monitoring schedule accounts for differences due to CYP2C19 genetic variation, so adjustments based on CYP2C19 genotype are not necessary. Refer to FDA labeling for specific dosing recommendations and monitoring.
Nilotinib	*UGT1A1*	*28/*28 (poor metabolizers)	Results in higher adverse reaction risk (hyperbilirubinemia).
Oxcarbazepine	*HLA-B*	*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	*HLA-B*	*57:01 allele positive	May result in higher adverse reaction risk (liver enzyme elevations). Monitor liver function tests regardless of genotype.
Pazopanib	*UGT1A1*	*28/*28 (poor metabolizers)	Results in higher adverse reaction risk (hyperbilirubinemia).
Perphenazine	*CYP2D6*	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	*SLCO1B1*	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	*CYP2D6*	poor metabolizers	Results in higher systemic concentrations and higher adverse reaction risk (QT prolongation).
Tramadol	*CYP2D6*	poor metabolizers	Results in lower systemic active metabolite concentrations and may result in reduced efficacy.
Voriconazole	*CYP2C19*	Intermediate or poor metabolizers	Results in higher systemic concentrations and may result in higher adverse reaction risk.

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).

State and Federal Regulations, as applicable

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), Gentris Rapid Genotyping Assay-CYP2C9&VKORCI (ParagonDx, LLC), INFINITI 2C9 & VKORC1 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, 2022).

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, 2021b).

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, 2021b).

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). LDTs are not approved or cleared by the U. S. Food and Drug Administration; however, FDA clearance or approval is not currently required for clinical use.

Billing/Coding/Physician Documentation Information

This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at www.bcbsnc.com. They are listed in the Category Search on the Medical Policy search page.

Applicable service codes: 81220, 81225, 81226, 81227, 81230, 81231, 81232, 81346, 81247, 81283, 81291, 81306, 81328, 81335, 81350, 81355, 81381, 81405, 81406, 81418, 81479, 0029U, 0030U, 0031U, 0032U, 0033U, 0034U, 0070U, 0071U, 0072U, 0073U, 0074U, 0075U, 0076U, 0169U, 0286U, 0345U, 0347U, 0348U, 0349U, 0350U, 0380U, 0392U, 0411U, 0419U, 0423U, 0434U, 0437U, 0438U, 0460U, 0461U, 0476U, 0477U, 0516U, G9143

BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

Scientific Background and Reference Sources

AACAP. (2020). Clinical Use of Pharmacogenetic Tests in Prescribing Psychotropic Medications for Children and Adolescents. https://www.aacap.org/aacap/Policy_Statements/2020/Clinical-Use-Pharmacogenetic-Tests-Prescribing-Psychotropic-Medications-for-Children-Adolescents.aspx

AACC. (2017, 01/01/2017). *Using Clinical Laboratory Tests to Monitor Drug Therapy in Pain Management Patients*. https://www.aacc.org/science-and-practice/practice-guidelines/using-clinical-laboratory-tests-to-monitor-drug-therapy-in-pain-management-patients

ACMG. (2007). *Pharmacogenetic testing of CYP2C9 and VKORC1 alleles for warfarin*. http://www.acmg.net/PDFLibrary/CYP2C9-VKORC1-Parmacogenetic-Testing.pdf

Ahern, T. P., Hertz, D. L., Damkier, P., Ejlertsen, B., Hamilton-Dutoit, S. J., Rae, J. M., Regan, M. M., Thompson, A. M., Lash, T. L., & Cronin-Fenton, D. P. (2017). Cytochrome P-450 2D6 (CYP2D6) Genotype and Breast Cancer Recurrence in Tamoxifen-Treated Patients: Evaluating the Importance of Loss of Heterozygosity. *Am J Epidemiol*, *185*(2), 75-85. https://doi.org/10.1093/aje/kww178

Aka, I., Bernal, C. J., Carroll, R., Maxwell-Horn, A., Oshikoya, K. A., & Van Driest, S. L. (2017). Clinical Pharmacogenetics of Cytochrome P450-Associated Drugs in Children. *J Pers Med*, *7*(4). https://doi.org/10.3390/jpm7040014

Amstutz, U., Henricks, L. M., Offer, S. M., Barbarino, J., Schellens, J. H. M., Swen, J. J., Klein, T. E., McLeod, H. L., Caudle, K. E., Diasio, R. B., & Schwab, M. (2018). Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for Dihydropyrimidine Dehydrogenase Genotype and Fluoropyrimidine Dosing: 2017 Update. *Clin Pharmacol Ther*, *103*(2), 210-216. https://doi.org/10.1002/cpt.911

Bains, R. K. (2013). African variation at Cytochrome P450 genesEvolutionary aspects and the implications for the treatment of infectious diseases. *Evolution, Medicine, and Public Health*, *2013*(1), 118-134. https://doi.org/10.1093/emph/eot010

Bell, G. C., Caudle, K. E., Whirl-Carrillo, M., Gordon, R. J., Hikino, K., Prows, C. A., Gaedigk, A., Agundez, J., Sadhasivam, S., Klein, T. E., & Schwab, M. (2016). Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline for CYP2D6 genotype and use of ondansetron and tropisetron. *Clin Pharmacol Ther*, *102*(2), 213-218. https://doi.org/10.1002/cpt.598

Benitez, J., Cool, C. L., & Scotti, D. J. (2018). Use of combinatorial pharmacogenomic guidance in treating psychiatric disorders. *Per Med*, *15*(6), 481-494. https://doi.org/10.2217/pme-2018-0074

Birdwell, K. A., Decker, B., Barbarino, J. M., Peterson, J. F., Stein, C. M., Sadee, W., Wang, D., Vinks, A. A., He, Y., Swen, J. J., Leeder, J. S., van Schaik, R., Thummel, K. E., Klein, T. E., Caudle, K. E., & MacPhee, I. A. (2015). Clinical Pharmacogenetics Implementation Consortium (CPIC) Guidelines for CYP3A5 Genotype and Tacrolimus Dosing. *Clin Pharmacol Ther*, *98*(1), 19-24. https://doi.org/10.1002/cpt.113

Bousman, C. A., Stevenson, J. M., Ramsey, L. B., Sangkuhl, K., Hicks, J. K., Strawn, J. R., Singh, A. B., Ruaño, G., Mueller, D. J., Tsermpini, E. E., Brown, J. T., Bell, G. C., Leeder, J. S., Gaedigk, A., Scott, S. A., Klein, T. E., Caudle, K. E., & Bishop, J. R. (2023). Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for CYP2D6, CYP2C19, CYP2B6, SLC6A4, and HTR2A Genotypes and Serotonin Reuptake Inhibitor Antidepressants. *Clin Pharmacol Ther*, *114*(1), 51-68. https://doi.org/10.1002/cpt.2903

Braten, L. S., Haslemo, T., Jukic, M. M., Ingelman-Sundberg, M., Molden, E., & Kringen, M. K. (2020). Impact of CYP2C19 genotype on sertraline exposure in 1200 Scandinavian patients. *Neuropsychopharmacology*, *45*(3), 570-576. https://doi.org/10.1038/s41386-019-0554-x

Brown, J. T., Bishop, J. R., Sangkuhl, K., Nurmi, E. L., Mueller, D. J., Dinh, J. C., Gaedigk, A., Klein, T. E., Caudle, K. E., McCracken, J. T., de Leon, J., & Leeder, J. S. (2019). Clinical Pharmacogenetics Implementation Consortium Guideline for Cytochrome P450 (CYP)2D6 Genotype and Atomoxetine Therapy. *Clin Pharmacol Ther*, *106*(1), 94-102. https://doi.org/10.1002/cpt.1409

Cacabelos, R., Martinez, R., Fernandez-Novoa, L., Carril, J. C., Lombardi, V., Carrera, I., Corzo, L., Tellado, I., Leszek, J., McKay, A., & Takeda, M. (2012). Genomics of Dementia: APOE- and CYP2D6-Related Pharmacogenetics. *Int J Alzheimers Dis*, *2012*, 518901. https://doi.org/10.1155/2012/518901

Castro-Rojas, C. A., Esparza-Mota, A. R., Hernandez-Cabrera, F., Romero-Diaz, V. J., Gonzalez-Guerrero, J. F., Maldonado-Garza, H., Garcia-Gonzalez, I. S., Buenaventura-Cisneros, S., Sanchez-Lopez, J. Y., Ortiz-Lopez, R., Camacho-Morales, A., Barboza-Quintana, O., & Rojas-Martinez, A. (2017). Thymidylate synthase gene variants as predictors of clinical response and toxicity to fluoropyrimidine-based chemotherapy for colorectal cancer. *Drug Metab Pers Ther*, *32*(4), 209-218. https://doi.org/10.1515/dmpt-2017-0028

Caudle, K. E., Rettie, A. E., Whirl-Carrillo, M., Smith, L. H., Mintzer, S., Lee, M. T., Klein, T. E., & Callaghan, J. T. (2014). Clinical pharmacogenetics implementation consortium guidelines for CYP2C9 and HLA-B genotypes and phenytoin dosing. *Clin Pharmacol Ther*, *96*(5), 542-548. https://doi.org/10.1038/clpt.2014.159

Caudle, K. E., Sangkuhl, K., Whirl-Carrillo, M., Swen, J. J., Haidar, C. E., Klein, T. E., Gammal, R. S., Relling, M. V., Scott, S. A., Hertz, D. L., Guchelaar, H. J., & Gaedigk, A. (2020). Standardizing CYP2D6 Genotype to Phenotype Translation: Consensus Recommendations from the Clinical Pharmacogenetics Implementation Consortium and Dutch Pharmacogenetics Working Group. *Clin Transl Sci*, *13*(1), 116-124. https://doi.org/10.1111/cts.12692

Chang, K. L., Weitzel, K., & Schmidt, S. (2015). Pharmacogenetics: Using Genetic Information to Guide Drug Therapy. *Am Fam Physician*, *92*(7), 588-594. https://www.aafp.org/afp/2015/1001/p588.html

Clancy, J. P., Johnson, S. G., Yee, S. W., McDonagh, E. M., Caudle, K. E., Klein, T. E., Cannavo, M., & Giacomini, K. M. (2014). Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines for ivacaftor therapy in the context of CFTR genotype. *Clin Pharmacol Ther*, *95*(6), 592-597. https://doi.org/10.1038/clpt.2014.54

Cooper-DeHoff, R. M., Niemi, M., Ramsey, L. B., Luzum, J. A., Tarkiainen, E. K., Straka, R. J., Gong, L., Tuteja, S., Wilke, R. A., Wadelius, M., Larson, E. A., Roden, D. M., Klein, T. E., Yee, S. W., Krauss, R. M., Turner, R. M., Palaniappan, L., Gaedigk, A., Giacomini, K. M., . . . Voora, D. (2022). The Clinical Pharmacogenetics Implementation Consortium Guideline for SLCO1B1, ABCG2, and CYP2C9 genotypes and Statin-Associated Musculoskeletal Symptoms. *Clin Pharmacol Ther*, *111*(5), 1007-1021. https://doi.org/10.1002/cpt.2557

CPIC. (2023a, 06/15/2021). *Genes-Drugs*. Retrieved 02/05/2023 from https://cpicpgx.org/genes-drugs/

CPIC. (2023b). *What is CPIC?* https://cpicpgx.org/

Crews, K. R., Monte, A. A., Huddart, R., Caudle, K. E., Kharasch, E. D., Gaedigk, A., Dunnenberger, H. M., Leeder, J. S., Callaghan, J. T., Samer, C. F., Klein, T. E., Haidar, C. E., Van Driest, S. L., Ruano, G., Sangkuhl, K., Cavallari, L. H., Müller, D. J., Prows, C. A., Nagy, M., . . . Skaar, T. C. (2021). Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline for CYP2D6, OPRM1, and COMT genotype and select opioid therapy. *Clinical Pharmacology & Therapeutics*, *n/a*(n/a). https://doi.org/https://doi.org/10.1002/cpt.2149

Desta, Z., Gammal, R. S., Gong, L., Whirl-Carrillo, M., Gaur, A. H., Sukasem, C., Hockings, J., Myers, A., Swart, M., Tyndale, R. F., Masimirembwa, C., Iwuchukwu, O. F., Chirwa, S., Lennox, J., Gaedigk, A., Klein, T. E., & Haas, D. W. (2019). Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for CYP2B6 and Efavirenz-Containing Antiretroviral Therapy. *Clin Pharmacol Ther*, *106*(4), 726-733. https://doi.org/10.1002/cpt.1477

EMA. (2020). Test before fluorouracil, capecitabine, tegafur or flucytosine therapy. *Reactions Weekly*, *1804*(1), 6-6. https://doi.org/10.1007/s40278-020-78435-3

FDA. *HIGHLIGHTS OF PRESCRIBING INFORMATION*. https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/009218s107lbl.pdf

FDA. (2005). *510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION DECISION SUMMARY ASSAY ONLY TEMPLATE*. https://www.accessdata.fda.gov/cdrh_docs/reviews/K043576.pdf

FDA. (2008). *HIGHLIGHTS OF PRESCRIBING INFORMATION*. https://www.lundbeck.com/upload/us/files/pdf/Products/Xenazine_PI_US_EN.pdf

FDA. (2014). *HIGHLIGHTS OF PRESCRIBING INFORMATION*. https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/205494s003lbl.pdf

FDA. (2016). *SUPPLEMENT APPROVAL*. https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2016/020839Orig1s062,s064ltr.pdf

FDA. (2021a). *Nucleic Acid Based Tests*. Retrieved 1/20/2021 from https://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/InVitroDiagnostics/ucm330711.htm

FDA. (2021b). Table of Pharmacogenomic Biomarkers in Drug Labeling. https://www.fda.gov/drugs/science-and-research-drugs/table-pharmacogenomic-biomarkers-drug-labeling

FDA. (2022, 11/08/2021). *Table of Pharmacogenetic Associations*. https://www.fda.gov/medical-devices/precision-medicine/table-pharmacogenetic-associations

FDA. (2023). FDA Converts Novel Alzheimer's Disease Treatment to Traditional Approval. https://www.fda.gov/news-events/press-announcements/fda-converts-novel-alzheimers-disease-treatment-traditional-approval

Franklin, G. M. (2014). Opioids for chronic noncancer pain: a position paper of the American Academy of Neurology. *Neurology*, *83*(14), 1277-1284. https://doi.org/10.1212/wnl.0000000000000839

Galli, M., Benenati, S., Capodanno, D., Franchi, F., Rollini, F., D'Amario, D., Porto, I., & Angiolillo, D. J. (2021). Guided versus standard antiplatelet therapy in patients undergoing percutaneous coronary intervention: a systematic review and meta-analysis. *The Lancet*, *397*(10283), 1470-1483.

Gammal, R. S., Court, M. H., Haidar, C. E., Iwuchukwu, O. F., Gaur, A. H., Alvarellos, M., Guillemette, C., Lennox, J. L., Whirl-Carrillo, M., Brummel, S. S., Ratain, M. J., Klein, T. E., Schackman, B. R., Caudle, K. E., & Haas, D. W. (2016). Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for UGT1A1 and Atazanavir Prescribing. *Clin Pharmacol Ther*, *99*(4), 363-369. https://doi.org/10.1002/cpt.269

Gammal, R. S., Pirmohamed, M., Somogyi, A. A., Morris, S. A., Formea, C. M., Elchynski, A. L., Oshikoya, K. A., McLeod, H. L., Haidar, C. E., Whirl-Carrillo, M., Klein, T. E., Caudle, K. E., & Relling, M. V. (2023). Expanded Clinical Pharmacogenetics Implementation Consortium Guideline for Medication Use in the Context of G6PD Genotype. *Clin Pharmacol Ther*, *113*(5), 973-985. https://doi.org/10.1002/cpt.2735

Ghanbarian, S., Wong, G. W. K., Bunka, M., Edwards, L., Cressman, S., Conte, T., Price, M., Schuetz, C., Riches, L., Landry, G., Erickson, D., McGrail, K., Peterson, S., Vijh, R., Hoens, A. M., Austin, J., & Bryan, S. (2023). Cost-effectiveness of pharmacogenomic-guided treatment for major depression. *Cmaj*, *195*(44), E1499-e1508. https://doi.org/10.1503/cmaj.221785

Goetz, M. P., Sangkuhl, K., Guchelaar, H. J., Schwab, M., Province, M., Whirl-Carrillo, M., Symmans, W. F., McLeod, H. L., Ratain, M. J., Zembutsu, H., Gaedigk, A., van Schaik, R. H., Ingle, J. N., Caudle, K. E., & Klein, T. E. (2018). Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for CYP2D6 and Tamoxifen Therapy. *Clin Pharmacol Ther*, *103*(5), 770-777. https://doi.org/10.1002/cpt.1007

Gonsalves, S. G., Dirksen, R. T., Sangkuhl, K., Pulk, R., Alvarellos, M., Vo, T., Hikino, K., Roden, D., Klein, T. E., Poler, S. M., Patel, S., Caudle, K. E., Gordon, R., Brandom, B., & Biesecker, L. G. (2019). Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for the Use of Potent Volatile Anesthetic Agents and Succinylcholine in the Context of RYR1 or CACNA1S Genotypes. *Clin Pharmacol Ther*, *105*(6), 1338-1344. https://doi.org/10.1002/cpt.1319

Greden, J. F., Parikh, S. V., Rothschild, A. J., Thase, M. E., Dunlop, B. W., DeBattista, C., Conway, C. R., Forester, B. P., Mondimore, F. M., Shelton, R. C., Macaluso, M., Li, J., Brown, K., Gilbert, A., Burns, L., Jablonski, M. R., & Dechairo, B. (2019). Impact of pharmacogenomics on clinical outcomes in major depressive disorder in the GUIDED trial: A large, patient- and rater-blinded, randomized, controlled study. *Journal of Psychiatric Research*. https://doi.org/https://doi.org/10.1016/j.jpsychires.2019.01.003

GTR. (2017). OneOme RightMed pharmacogenomic test. https://www.ncbi.nlm.nih.gov/gtr/tests/552110.3/performance-characteristics/

Hershfield, M. S., Callaghan, J. T., Tassaneeyakul, W., Mushiroda, T., Thorn, C. F., Klein, T. E., & Lee, M. T. (2013). Clinical Pharmacogenetics Implementation Consortium guidelines for human leukocyte antigen-B genotype and allopurinol dosing. *Clin Pharmacol Ther*, *93*(2), 153-158. https://doi.org/10.1038/clpt.2012.209

Hicks, J. K., Sangkuhl, K., Swen, J. J., Ellingrod, V. L., Muller, D. J., Shimoda, K., Bishop, J. R., Kharasch, E. D., Skaar, T. C., Gaedigk, A., Dunnenberger, H. M., Klein, T. E., Caudle, K. E., & Stingl, J. C. (2016). Clinical pharmacogenetics implementation consortium guideline (CPIC) for CYP2D6 and CYP2C19 genotypes and dosing of tricyclic antidepressants: 2016 update. *Clin Pharmacol Ther*, *102*(1), 37-44. https://doi.org/10.1002/cpt.597

Holmes, D. R., Jr., Dehmer, G. J., Kaul, S., Leifer, D., O'Gara, P. T., & Stein, C. M. (2010). ACCF/AHA clopidogrel clinical alert: approaches to the FDA "boxed warning": a report of the American College of Cardiology Foundation Task Force on clinical expert consensus documents and the American Heart Association endorsed by the Society for Cardiovascular Angiography and Interventions and the Society of Thoracic Surgeons. *J Am Coll Cardiol*, *56*(4), 321-341. https://doi.org/10.1016/j.jacc.2010.05.013

ISPG. (2019). A Statement from the International Society of Psychiatric Genetics. https://ispg.net/genetic-testing-statement/

Johnson, J. A., Caudle, K. E., Gong, L., Whirl-Carrillo, M., Stein, C. M., Scott, S. A., Lee, M. T., Gage, B. F., Kimmel, S. E., Perera, M. A., Anderson, J. L., Pirmohamed, M., Klein, T. E., Limdi, N. A., Cavallari, L. H., & Wadelius, M. (2017). Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for Pharmacogenetics-Guided Warfarin Dosing: 2017 Update. *Clin Pharmacol Ther*, *102*(3), 397-404. https://doi.org/10.1002/cpt.668

Kapur, B. M., Lala, P. K., & Shaw, J. L. (2014). Pharmacogenetics of chronic pain management. *Clin Biochem*, *47*(13-14), 1169-1187. https://doi.org/10.1016/j.clinbiochem.2014.05.065

Karnes, J. H., Rettie, A. E., Somogyi, A. A., Huddart, R., Fohner, A. E., Formea, C. M., Ta Michael Lee, M., Llerena, A., Whirl-Carrillo, M., Klein, T. E., Phillips, E. J., Mintzer, S., Gaedigk, A., Caudle, K. E., & Callaghan, J. T. (2021). Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for CYP2C9 and HLA-B Genotypes and Phenytoin Dosing: 2020 Update. *Clinical Pharmacology & Therapeutics*, *109*(2), 302-309. https://doi.org/https://doi.org/10.1002/cpt.2008

Kekic, A., Seetharam, M., Singh, P., Kunze, K., Golafshar, M. A., Azevedo, C., Welp, S., Bofferding, A., Koep, T., Ross, J., Nelson, E., Grilli, C., & Samadder, J. (2020). Integrating pharmacogenomics panel testing for supportive care medications in patients with solid tumors. *Journal of Clinical Oncology*, *38*(15_suppl), e24114-e24114. https://doi.org/10.1200/JCO.2020.38.15_suppl.e24114

Kelly, L. E., Rieder, M., van den Anker, J., Malkin, B., Ross, C., Neely, M. N., Carleton, B., Hayden, M. R., Madadi, P., & Koren, G. (2012). More codeine fatalities after tonsillectomy in North American children. *Pediatrics*, *129*(5), e1343-1347. https://doi.org/10.1542/peds.2011-2538

Krishnamurthi, S., & Kamath, S. (2024, May 8). *Clinical presentation and risk factors for chemotherapy-associated diarrhea, constipation, and intestinal perforation*. https://www.uptodate.com/contents/clinical-presentation-and-risk-factors-for-chemotherapy-associated-diarrhea-constipation-and-intestinal-perforation

Lee, C. R., Luzum, J. A., Sangkuhl, K., Gammal, R. S., Sabatine, M. S., Stein, C. M., Kisor, D. F., Limdi, N. A., Lee, Y. M., Scott, S. A., Hulot, J. S., Roden, D. M., Gaedigk, A., Caudle, K. E., Klein, T. E., Johnson, J. A., & Shuldiner, A. R. (2022). Clinical Pharmacogenetics Implementation Consortium Guideline for CYP2C19 Genotype and Clopidogrel Therapy: 2022 Update. *Clin Pharmacol Ther*. https://doi.org/10.1002/cpt.2526

Lima, J. J., Thomas, C. D., Barbarino, J., Desta, Z., Van Driest, S. L., El Rouby, N., Johnson, J. A., Cavallari, L. H., Shakhnovich, V., Thacker, D. L., Scott, S. A., Schwab, M., Uppugunduri, C. R. S., Formea, C. M., Franciosi, J. P., Sangkuhl, K., Gaedigk, A., Klein, T. E., Gammal, R. S., & Furuta, T. (2020). Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for CYP2C19 and Proton Pump Inhibitor Dosing. *Clin Pharmacol Ther*. https://doi.org/10.1002/cpt.2015

Lunenburg, C., van der Wouden, C. H., Nijenhuis, M., Crommentuijn-van Rhenen, M. H., de Boer-Veger, N. J., Buunk, A. M., Houwink, E. J. F., Mulder, H., Rongen, G. A., van Schaik, R. H. N., van der Weide, J., Wilffert, B., Deneer, V. H. M., Swen, J. J., & Guchelaar, H. J. (2020). Dutch Pharmacogenetics Working Group (DPWG) guideline for the gene-drug interaction of DPYD and fluoropyrimidines. *Eur J Hum Genet*. https://doi.org/10.1038/s41431-019-0540-0

Martin, M. A., Hoffman, J. M., Freimuth, R. R., Klein, T. E., Dong, B. J., Pirmohamed, M., Hicks, J. K., Wilkinson, M. R., Haas, D. W., & Kroetz, D. L. (2014). Clinical Pharmacogenetics Implementation Consortium Guidelines for HLA-B Genotype and Abacavir Dosing: 2014 update. *Clin Pharmacol Ther*, *95*(5), 499-500. https://doi.org/10.1038/clpt.2014.38

Mayo. (2023). Focused Pharmacogenomics Panel, Varies. https://www.mayocliniclabs.com/test-catalog/Overview/610057

Moriyama, B., Obeng, A. O., Barbarino, J., Penzak, S. R., Henning, S. A., Scott, S. A., Agundez, J., Wingard, J. R., McLeod, H. L., Klein, T. E., Cross, S. J., Caudle, K. E., & Walsh, T. J. (2017). Clinical Pharmacogenetics Implementation Consortium (CPIC) Guidelines for CYP2C19 and Voriconazole Therapy. *Clin Pharmacol Ther*, *102*(1), 45-51. https://doi.org/10.1002/cpt.583

Muir, A. J., Gong, L., Johnson, S. G., Lee, M. T., Williams, M. S., Klein, T. E., Caudle, K. E., & Nelson, D. R. (2014). Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines for IFNL3 (IL28B) genotype and PEG interferon-alpha-based regimens. *Clin Pharmacol Ther*, *95*(2), 141-146. https://doi.org/10.1038/clpt.2013.203

Myers, R. H., Schaefer, E. J., Wilson, P. W., D'Agostino, R., Ordovas, J. M., Espino, A., Au, R., White, R. F., Knoefel, J. E., Cobb, J. L., McNulty, K. A., Beiser, A., & Wolf, P. A. (1996). Apolipoprotein E epsilon4 association with dementia in a population-based study: The Framingham study. *Neurology*, *46*(3), 673-677. https://doi.org/10.1212/wnl.46.3.673

Myriad. (2016). *What is the difference between traditional "single-gene" testing and the GeneSight® test's proprietary CPGx® approach?* https://s3.amazonaws.com/myriad-web/Managed+Care/CPGx-approach.pdf

Myriad. (2019). *GeneSight*. https://s3.amazonaws.com/myriad-web/Managed+Care/GeneSight-ExecutiveSummary.pdf

Myriad. (2022). Myriad Genetics Announces Upgrades to the GeneSight® Test. https://genesight.com/news-and-press/myriad-genetics-announces-upgrades-to-the-genesight-test/

OneOme. (2021). The RightMed® Test. https://oneome.com/rightmed-test/#genes-covered

Oslin, D. W., Lynch, K. G., Shih, M. C., Ingram, E. P., Wray, L. O., Chapman, S. R., Kranzler, H. R., Gelernter, J., Pyne, J. M., Stone, A., DuVall, S. L., Lehmann, L. S., Thase, M. E., Aslam, M., Batki, S. L., Bjork, J. M., Blow, F. C., Brenner, L. A., Chen, P., . . . Wood, A. E. (2022). Effect of Pharmacogenomic Testing for Drug-Gene Interactions on Medication Selection and Remission of Symptoms in Major Depressive Disorder: The PRIME Care Randomized Clinical Trial. *Jama*, *328*(2), 151-161. https://doi.org/10.1001/jama.2022.9805

Phillips, E. J., Sukasem, C., Whirl-Carrillo, M., Muller, D. J., Dunnenberger, H. M., Chantratita, W., Goldspiel, B., Chen, Y. T., Carleton, B. C., George, A. L., Jr., Mushiroda, T., Klein, T., Gammal, R. S., & Pirmohamed, M. (2018). Clinical Pharmacogenetics Implementation Consortium

Guideline for HLA Genotype and Use of Carbamazepine and Oxcarbazepine: 2017 Update. *Clin Pharmacol Ther*, *103*(4), 574-581. https://doi.org/10.1002/cpt.1004

Plumpton, C. O., Pirmohamed, M., & Hughes, D. A. (2019). Cost-Effectiveness of Panel Tests for Multiple Pharmacogenes Associated With Adverse Drug Reactions: An Evaluation Framework. *Clin Pharmacol Ther*, *105*(6), 1429-1438. https://doi.org/10.1002/cpt.1312

Pratt, V. M., Cavallari, L. H., Del Tredici, A. L., Gaedigk, A., Hachad, H., Ji, Y., Kalman, L. V., Ly, R. C., Moyer, A. M., Scott, S. A., van Schaik, R. H. N., Whirl-Carrillo, M., & Weck, K. E. (2021). Recommendations for Clinical CYP2D6 Genotyping Allele Selection: A Joint Consensus Recommendation of the Association for Molecular Pathology, College of American Pathologists, Dutch Pharmacogenetics Working Group of the Royal Dutch Pharmacists Association, and the European Society for Pharmacogenomics and Personalized Therapy. *J Mol Diagn*, *23*(9), 1047-1064. https://doi.org/10.1016/j.jmoldx.2021.05.013

Pratt, V. M., Cavallari, L. H., Del Tredici, A. L., Hachad, H., Ji, Y., Kalman, L. V., Ly, R. C., Moyer, A. M., Scott, S. A., Whirl-Carrillo, M., & Weck, K. E. (2020). Recommendations for Clinical Warfarin Genotyping Allele Selection: A Report of the Association for Molecular Pathology and the College of American Pathologists. *J Mol Diagn*, *22*(7), 847-859. https://doi.org/10.1016/j.jmoldx.2020.04.204

Pratt, V. M., Cavallari, L. H., Del Tredici, A. L., Hachad, H., Ji, Y., Moyer, A. M., Scott, S. A., Whirl-Carrillo, M., & Weck, K. E. (2019). Recommendations for Clinical CYP2C9 Genotyping Allele Selection: A Joint Recommendation of the Association for Molecular Pathology and College of American Pathologists. *The Journal of Molecular Diagnostics*, *21*(5), 746-755. https://doi.org/10.1016/j.jmoldx.2019.04.003

Pratt, V. M., Del Tredici, A. L., Hachad, H., Ji, Y., Kalman, L. V., Scott, S. A., & Weck, K. E. (2018). Recommendations for Clinical CYP2C19 Genotyping Allele Selection: A Report of the Association for Molecular Pathology. *The Journal of Molecular Diagnostics*, *20*(3), 269-276. https://doi.org/https://doi.org/10.1016/j.jmoldx.2018.01.011

Relling, M. V., Gardner, E. E., Sandborn, W. J., Schmiegelow, K., Pui, C. H., Yee, S. W., Stein, C. M., Carrillo, M., Evans, W. E., & Klein, T. E. (2013). Clinical Pharmacogenetics Implementation Consortium guidelines for thiopurine methyltransferase genotype and thiopurine dosing. *Clin Pharmacol Ther*, *89*(3), 387-391. https://doi.org/10.1038/clpt.2010.320

Relling, M. V., Schwab, M., Whirl-Carrillo, M., Suarez-Kurtz, G., Pui, C. H., Stein, C. M., Moyer, A. M., Evans, W. E., Klein, T. E., Antillon-Klussmann, F. G., Caudle, K. E., Kato, M., Yeoh, A. E. J., Schmiegelow, K., & Yang, J. J. (2018). Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline for thiopurine dosing based on TPMT and NUDT15 genotypes: 2018 update. *Clin Pharmacol Ther*. https://doi.org/10.1002/cpt.1304

Roscizewski, L., Henneman, A., & Snyder, T. (2021). Effect of pharmacogenomic testing on pharmacotherapy decision making in patients with symptoms of depression in an interprofessional primary care clinic. *J Am Pharm Assoc (2003)*. https://doi.org/10.1016/j.japh.2021.10.033

Saito, Y., Stamp, L. K., Caudle, K. E., Hershfield, M. S., McDonagh, E. M., Callaghan, J. T., Tassaneeyakul, W., Mushiroda, T., Kamatani, N., Goldspiel, B. R., Phillips, E. J., Klein, T. E., & Lee, M. T. (2016). Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines for human leukocyte antigen B (HLA-B) genotype and allopurinol dosing: 2015 update. *Clin Pharmacol Ther*, *99*(1), 36-37. https://doi.org/10.1002/cpt.161

Sema4. (2022). Comprehensive Pharmacogenetic Genotyping Panel. https://sema4.com/products/test-catalog/comprehensive-pharmacogenetic-genotyping-panel/#

Sherva, R., & Kowall, N. W. (2022, May 19). *Genetics of Alzheimer disease*. https://www.uptodate.com/contents/genetics-of-alzheimer-disease

Stevenson, J. M., Alexander, G. C., Palamuttam, N., & Mehta, H. B. (2021). Projected Utility of Pharmacogenomic Testing Among Individuals Hospitalized With COVID-19: A Retrospective Multicenter Study in the United States. *Clin Transl Sci*, *14*(1), 153-162. https://doi.org/10.1111/cts.12919

Suchowersky, O. (2023, October 25). *Huntington disease: Management*. https://www.uptodate.com/contents/huntington-disease-management

Swen, J. J., van der Wouden, C. H., Manson, L. E., Abdullah-Koolmees, H., Blagec, K., Blagus, T., Böhringer, S., Cambon-Thomsen, A., Cecchin, E., Cheung, K. C., Deneer, V. H., Dupui, M.,

Ingelman-Sundberg, M., Jonsson, S., Joefield-Roka, C., Just, K. S., Karlsson, M. O., Konta, L., Koopmann, R., . . . Guchelaar, H. J. (2023). A 12-gene pharmacogenetic panel to prevent adverse drug reactions: an open-label, multicentre, controlled, cluster-randomised crossover implementation study. *Lancet*, *401*(10374), 347-356. https://doi.org/10.1016/s0140-6736(22)01841-4

Tantisira, K., & Weiss, S. T. (2023, September 6). *Overview of pharmacogenomics*. https://www.uptodate.com/contents/overview-of-pharmacogenomics

Tantry, U., Hennekens, C., Zehnder, J., & Gurbel, P. (2021, 11/09/2021). *Clopidogrel resistance and clopidogrel treatment failure*. Wolters Kluwer. https://www.uptodate.com/contents/clopidogrel-resistance-and-clopidogrel-treatment-failure

Theken, K. N., Lee, C. R., Gong, L., Caudle, K. E., Formea, C. M., Gaedigk, A., Klein, T. E., Agúndez, J. A. G., & Grosser, T. (2020). Clinical Pharmacogenetics Implementation Consortium Guideline (CPIC) for CYP2C9 and Nonsteroidal Anti-Inflammatory Drugs. *Clin Pharmacol Ther*, *108*(2), 191-200. https://doi.org/10.1002/cpt.1830

Ting, S., & Schug, S. (2016). The pharmacogenomics of pain management: prospects for personalized medicine. *J Pain Res*, *9*, 49-56. https://doi.org/10.2147/jpr.s55595

Tuteja, S., Glick, H., Matthai, W., Nachamkin, I., Nathan, A., Monono, K., Carcuffe, C., Maslowski, K., Chang, G., Kobayashi, T., Anwaruddin, S., Hirshfeld, J., Jr., Wilensky, R. L., Herrmann, H. C., Kolansky, D. M., Rader, D. J., & Giri, J. (2020). Prospective CYP2C19 Genotyping to Guide Antiplatelet Therapy Following Percutaneous Coronary Intervention: A Pragmatic Randomized Clinical Trial. *Circ Genom Precis Med*. https://doi.org/10.1161/circgen.119.002640

van der Wouden, C. H., van Rhenen, M. H., Jama, W. O. M., Ingelman-Sundberg, M., Lauschke, V. M., Konta, L., Schwab, M., Swen, J. J., & Guchelaar, H. J. (2019). Development of the PGx-Passport: A Panel of Actionable Germline Genetic Variants for Pre-Emptive Pharmacogenetic Testing. *Clin Pharmacol Ther*, *106*(4), 866-873. https://doi.org/10.1002/cpt.1489

Viatte, S. (2023, September 8). *Human leukocyte antigens (HLA): A roadmap*. https://www.uptodate.com/contents/human-leukocyte-antigens-hla-a-roadmap

Specialty Matched Consultant Advisory Panel review 7/2019

Medical Director review 7/2019

Specialty Matched Consultant Advisory Panel review 7/2020

Medical Director review 7/2020

Medical Director review 4/2023

Medical Director review 7/2024

Policy Implementation/Update Information

1/1/2019 BCBSNC will provide coverage for pharmacogenetics testing when it is determined to be medically necessary because the criteria and guidelines are met. Medical Director review 1/1/2019. Policy noticed 1/1/2019 for effective date 4/1/2019. (jd)

4/1/2019 Billing/Coding section updated. (jd)

6/11/2019 Reviewed by Avalon 1st Quarter 2019 CAB. Related Policies added to Description section with minor revisions. Under the When Covered section, added NUDT15 to item #2 and item #5 was added to the section. Policy Guidelines extensively revised. Billing/Coding section: added code 81306 for NUDT15. The following PLA codes were also added for effective date of 7/1/19: 0029U, 0030U. 0031U, 0032U 0033U, 0034U, 0070U, 0071U, 0072U, 0073U, 0074U, 0075U, 0076U. References updated. Medical Director review. (jd)

8/13/19 Removed the *Policy Guideline statement and "NOTE" from the bottom of the When Not Covered section regarding Genotype once per lifetime. No change to policy intent. Specialty Matched Consultant Advisory Panel review 7/2019. Medical Director review 7/2019. (jd)

11/12/19 Wording in the Policy, When Covered, and/or Not Covered section(s) changed from Medical Necessity to Reimbursement language, where needed. (hb)

1/28/20 Updated non-covered criteria to include "Genomind "as non-covered test. (gm)

5/12/20 Reviewed by Avalon 1st Quarter 2020 CAB. Related Policies section updated with title changes to listed policies. Minor revisions to When Covered section and added "Policy Guideline" statement to the When Covered section, no change to policy intent. Minor update to the Background section. The following codes were removed from the Billing/Coding section: 81221, 81222, 81223, 81224, 81248, 81249; 0169U and G9143 were added. Medical Director review. (jd)

6/12/20 Wording in the Policy under the When Not Covered section changed to Reimbursement language under items #2 and #3; item #4 revised to include the following statement: "Proprietary Lab tests, including panel tests for any of the genotypes listed in this policy are considered investigational." (jd)

8/25/20 Specialty Matched Consultant Advisory Panel review 7/2020. Medical Director review 7/2020. (jd)

3/31/21 Item #7 added to the When Covered section as follows: "Testing for CYP2C19 genotype once per lifetime is considered medically necessary for individuals considered for therapy with clopidogrel." Specialty Matched Consultant Advisory Panel review 3/2021. Medical Director review 3/2021. (jd)

5/4/21 Reviewed by Avalon 1st Quarter 2021 CAB. Policy guidelines and references updated. CPT code 81220 requires PPA, and code 81346 was added to the Billing/Coding section. Medical Director review 4/2021. (jd)

5/17/22 Reviewed by Avalon 1st Quarter 2022 CAB. Description section with minor revisions. When covered section extensively revised as follows: Item #1revised to include a-ii; item #2 revised to include a-e; item #3 added for testing for the CYP2C19 genotype, including a-l; item #4 added for testing for the *CYP2C9* genotype, including a-i; item # 6 added for testing for the *TPMT* and *NUDT15* genotype, including a-c; item #7 added for testing for the *DPYD* genotype, including a-d; item #8 for testing for the following Human Leukocyte Antigens (HLAs) genotypes, including a-d; item #9 for added for testing for the *CYP2C9* and *HLA-B*15:02* genotype, including a; item #10 added for testing for the *G6PD* genotype, including a-d; item #11 added for testing for the following genotypes, including a-g; item #12 added. Under the When Not Covered section, item 2-b and item 4 were removed. Policy guidelines and references updated. Added code 0286U to the Billing/Coding section. Medical Director review 4/2022. (jd)

9/30/22 Added CPT codes 0345U, 0347U, 0348U, 0349U and 0350U to Billing/Coding section. (tm)

12/30/22 Updated Billing/Coding section to add 81418 effective 1/2023. (tm)

3/31/23 Updated Billing/Coding section to add code 0380U effective 4/1/23. (tm)

5/16/23	Reviewed by Avalon 1st Quarter 2023 CAB. Description section, Policy Guidelines and References updated. Related Policies section removed. When Covered section revised as follows: Added Abrocitinib (item a) and Mavacamten (item j) to coverage criteria #3, added Nateglinide (item g) to coverage criteria #4, item #12 added "To aid in therapy selection and/or dosing for individuals being considered for therapy or who are in their course of therapy with belzutifan, testing for the CYP2C19 and UGT2B17 genotype once per lifetime (see Note 1) is considered medically necessary." Under the Not Covered section, previous item 2-b removed and item c edited to state "Pharmacogenetic testing (e.g., single nucleotide polymorphism [SNP] testing or SNP panel testing; single gene or multi-gene panel testing [see Note 3]) for all other situations not addressed above.", item 3 removed as all other testing types are now addressed in the edit of item #2-c. Added notes 1, 2, 3. Medical Director review 4/2023. (tm)
6/30/23	Code 0392U added to Billing/Coding section, effective 7/1/23. (tm)
9/29/23	Codes 0411U and 0419U added to Billing/Coding section, effective 10/1/23. (tm)
12/29/23	Table of Terminology removed. Codes 0423U, 0434U, 0437U, and 0438U added to Billing/Coding section, effective 1/1/2024. (tm)
7/17/24	Codes 0460U and 0461U added to Billing/Coding section, effective 7/1/24. (tm)
9/4/24	Reviewed by Avalon 2nd Quarter 2024 CAB. Description, Policy Guidelines and References sections updated. New coverage criteria number 14 added to When Covered section: “When formulary coverage allows a pharmacotherapy that is dependent on a known genetic status (e.g., *APOE* testing prior to lecanemab-irmb treatment), gene specific testing is considered medically necessary.” Code 81406 added to Billing/Coding section. Medical Director review 7/2024. (tm)
10/1/24	Codes 0476U, 0477U, and 0516U added to Billing/Coding section, effective 10/1/24. (tm)