Pharmacogenomic and Pharmacogenetic Testing for Drug Metabolism Status for Non-Cancer Indications

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DESCRIPTION

Drug efficacy and toxicity vary substantially across individuals. Because drugs and doses are typically adjusted, if needed, by trial and error, clinical consequences may include a prolonged time to optimal therapy. In some cases, serious adverse events may result.

Various factors may influence the variability of drug effects, including age, liver function, concomitant diseases, nutrition, smoking, and drug-drug interactions. Inherited (germline) DNA sequence variation in genes coding for drug metabolizing enzymes, drug receptors, drug transporters, and molecules involved in signal transduction pathways also may have major effects on the activity of those molecules and thus on the efficacy or toxicity of a drug.

Pharmacogenomic testing broadly describes how one's genome, or multiple genes, can influence drug response while more targeted pharmacogenetic testing describes genotyping (polymorphisms) a specific gene to predict response to certain medications. This policy addresses pharmacogenomic and pharmacogenetic testing for the purpose of informing medication selection, dosage, and risk of adverse side effects. Potentially, these test results could be used to optimize drug choice and/or dose for more effective therapy, avoid serious adverse effects, and decrease medical costs.

Genetically determined variability in drug response has been traditionally addressed using a trial- and -error approach to prescribing and dosing, along with therapeutic drugs monitoring (TDM) for drugs with a very narrow therapeutic range and/or potential serious adverse effects outside that range. However, TDM is not available for all drugs of interest, and a cautious trial and error approach can lengthen the time to achieving an effective dose.

To definitively show that pharmacogenomic/pharmacogenetic testing have value in clinical practice, it is not enough to demonstrate that drug response varies by genotype. There must be an alternative treatment strategy, and proof that testing for the genotype and subsequently tailoring the treatment strategy based on genetic information are more clinically effective or cost effective (or both) than merely treating everyone in the same manner. Use of test to identify gene variants and affected populations must be more efficient than current practice in preventing serious adverse effects. After taking into account known non-genetic factors that cause variation in response, the remaining variability in patient response can often be managed with appropriate monitoring or can be reversed by withdrawal of the drug by changing drugs or dosage. Adverse effects of available drugs are generally preventable. It has been proposed that testing (genotyping) for genetic variants may assist in tailoring drug selection and drug dosing for an individual based on their gene composition for drug metabolism which could lead to early selection and optimal dosing of the most effective drugs, while minimizing treatment failures and toxicities.

Single Gene Pharmacogenetic Assays

There are many challenges in gathering sufficient evidence to support the clinical utility of pharmacogenetic testing, including the complex interactions between different genetic variants and the large number of confounding factors in medication response across individuals. In addition, there is a high degree of variability in study design, methods, and measured outcomes in the published literature, making comparisons difficult. Other limitations of published studies include conflicts of interest among the researchers and lack of blinding for participants and providers. While genotype-guided drug choice or dosing has been shown to increase efficacy and limit side effects for certain medications, the clinical utility of most pharmacogenetic testing has not yet been established.

As a result, the US Food and Drug Administration (FDA) includes pharmacogenetic testing recommendations with the labeling of many drugs, but the overall number that have genetic testing requirements on the FDA label is relatively small. Many drug/gene

pairs for which testing is mentioned on the FDA label are based on evidence from laboratory studies, case reports, or observational studies rather than randomized controlled trials or large subgroup analyses. Additional recommendations or guidelines are often needed to help clinicians assess the clinical utility of pharmacogenetic testing. In many cases, there is limited evidence that pharmacogenetic testing results in better clinical outcomes. In addition, there is significant variability in the specific alleles that are evaluated by different clinical tests. This complicates result interpretation, especially in ethnically diverse populations. It is important to interpret results of pharmacogenetic testing with these limitations in mind.

The Clinical Pharmacogenetics Implementation Consortium (CPIC) have established guidelines to assist clinicians in guiding drug therapy and dosage based on existing pharmacogenetic results. CPIC guidelines are developed in a standard format after rigorous review and grading of the literature and extensive peer review. They are meant to provide guidance for the use of existing genetic test results, but do not provide recommendations about whether to order specific genetic tests

Cytochrome P450 System
The cytochrome P450 (CYP450) family is a major subset of all drug-metabolizing enzymes; several CYP450 enzymes are involved in the metabolism of a significant proportion of currently administered drugs. CYP2D6 metabolizes approximately 25% of all clinically used medications (e.g., dextromethorphan, β-blockers, antiarrhythmics, antidepressants, morphine derivatives), including most prescribed drugs. CYP2C19 metabolizes several important types of drugs, including proton pump inhibitors, diazepam, propranolol, imipramine, and amitriptyline.

Some CYP450 enzymes are highly polymorphic, resulting in some enzyme variants that have variable metabolic capacities among individuals, and some with little to no impact on activity. Thus, CYP450 enzymes constitute an important group of drug-gene interactions influencing the variability of the effect of some CYP450-metabolized drugs.

Individuals with 2 copies (alleles) of the most common (wild type) DNA sequence of a particular CYP450 enzyme gene resulting in an active molecule are termed extensive metabolizers (EMs; normal). Poor metabolizers (PMs) lack active enzyme gene alleles, and intermediate metabolizers, who have 1 active and 1 inactive enzyme gene allele, may experience to a lesser degree some of the consequences of PMs. Ultrarapid metabolizers (UMs) are individuals with more than 2 alleles of an active enzyme gene. There is pronounced ethnic variability in the population distribution of metabolizer types for a given CYP enzyme.

UMs administered an active drug may not reach therapeutic concentrations at usual recommended doses of active drugs, while PMs may suffer more adverse events at usual doses due to reduced metabolism and increased concentrations. Conversely, for administered prodrugs that must be converted by CYP450 enzymes into active metabolites, UMs may suffer adverse events, and PMs may not respond.

Many drugs are metabolized to varying degrees by more than one enzyme, either within or outside of the CYP450 superfamily. Also, the interaction between different metabolizing genes, the interaction between genes and environment, and interactions among different nongenetic factors also influence CYP450-specific metabolizing functions. Thus, identification of a variant in a single gene in the metabolic pathway may be insufficient in all but a small proportion of drugs to explain interindividual differences in metabolism and consequent efficacy or toxicity.

Determining Genetic Variability in Drug Response
Genetically determined variability in drug response has been traditionally addressed using a trial-and-error approach to prescribing and dosing, along with therapeutic drug monitoring for drugs with a very narrow therapeutic range and/or potentially serious adverse events outside that range. However, therapeutic drug monitoring is not available for all drugs of interest, and a cautious trial-and-error approach can lengthen the time to achieving an effective dose.

CYP450 enzyme phenotyping (identifying metabolizer status) can be accomplished by administering a test enzyme substrate to a patient and monitoring parent substrate and metabolite concentrations over time (e.g., in urine). However, testing and interpretation are time-consuming and inconvenient; as a result, phenotyping is seldom performed.

The clinical utility of *CYP450* genotyping (i.e., the likelihood that genotyping will significantly improve drug choice, dosing, and patient outcomes) may be favored when the drug under consideration has a narrow therapeutic dose range, when the consequences of treatment failure are severe, and/or when serious adverse reactions are more likely in patients with gene sequence variants. Under these circumstances, genotyping may direct early selection of the most effective drug or dose, and/or avoid drugs or doses likely to cause toxicity. For example, warfarin, some neuroleptics, and tricyclic antidepressants have narrow therapeutic windows and can cause serious adverse events when concentrations exceed certain limits, resulting in cautious dosing protocols. The potential severity of the disease condition may call for immediate and sufficient therapy; genotyping might speed up the process of achieving a therapeutic dose and avoiding significant adverse events.

CYP450 Genotype-Guided Treatment Strategy

Clinical Context and Test Purpose
The purpose of a cytochrome P450 (*CYP450*) genotype-guided strategy is to tailor selection and dosing of drugs based on gene composition for drug metabolism. In theory, this should lead to early selection and optimal dosing of the most effective drugs, while minimizing treatment failures or toxicities.

Populations
The relevant populations of interest is patients being considered for treatment with clopidogrel, eliglustat, tetrabenazine, selective serotonin reuptake inhibitors, serotonin-

norepinephrine reuptake inhibitors, tricyclic antidepressants, antipsychotic drugs, codeine, efavirenz and other antiretroviral therapies for HIV infection, immunosuppressants for organ transplantation, β-blockers (e.g., metoprolol), and antitubercular medications.

Interventions
Commercial tests for individual genes or gene panels are available and are listed in the Regulatory Status section. Only those panels that include *CYP450* genes are listed in that section.

Comparators
The following practice is currently being used: standard clinical management without genetic testing.

Outcomes
Specific outcomes of interest

Outcomes	Details
Morbid events	Opioid addiction, adverse events
Health status measures	Pain relief, functional status
Medication use	The number of unsuccessful mediation trials and medications needed, including the dose of medication and dose frequency

Review of Evidence

Selection and/or Dosing of Clopidogrel (Plavix)
Dual antiplatelet therapy with aspirin and a P2Y12 inhibitor (clopidogrel, prasugrel, ticagrelor) is the standard of care for the prevention of subsequent atherothrombotic events such as stent thrombosis or recurrent acute coronary syndrome in patients who undergo a percutaneous intervention or who have an acute coronary syndrome.

Clopidogrel is a prodrug that is converted to its active form by several CYP450 enzymes (particularly CYP2C19). Individuals with genetic variants that inactivate the CYP2C19 enzyme are associated with lack of response to clopidogrel. There are several variants of *CYP2C19,* but the 2 most frequent variants associated with loss of function alleles are *CYP2C19*2* and *CYP2C19*3*. It is hypothesized that such individuals may benefit from other drugs such as prasugrel or ticagrelor or a higher dose of clopidogrel. Approximately 30% of whites and blacks and 65% of Asians carry a nonfunctional *CYP2C19* gene variant. While CYP2C19 is the major enzyme involved in the generation of clopidogrel active metabolite, the variability in clinical response seen with clopidogrel may also result from other factors such as variable absorption, accelerated platelet turnover, reduced CYP3A metabolic activity, increased adenosine diphosphate exposure,

or upregulation of P2Y12 pathways, drug-drug interactions, comorbidities (e.g., diabetes, obesity), and medication adherence.

Pereira et al (2021) reported the results of the open-label randomized TAILOR-PCI trial of 5302 patients undergoing PCI for acute coronary syndromes or stable coronary artery disease. The genotype-guided group underwent point-of-care genotyping for detection of *CYP2C19* carriers and were prescribed ticagrelor (prasugrel was recommended as an alternative for patients who did not tolerate ticagrelor) and noncarriers were prescribed clopidogrel. Patients randomized to the conventional group were prescribed clopidogrel and underwent genotyping after 12 months. Among 5302 patients randomized (median age, 62 years; 25% women), 94% completed the trial. Of 1849 *CYP2C19* carriers, 764 of 903 (85%) assigned to genotype-guided therapy received ticagrelor, and 932 of 946 (99%) assigned to conventional therapy received clopidogrel. The primary end point (a composite of cardiovascular death, myocardial infarction, stroke, stent thrombosis, and severe recurrent ischemia at 12 months) occurred in 35 of 903 *CYP2C19* carriers (4.0%) in the genotype-guided therapy group and 54 of 946 (5.9%) in the conventional therapy group at 12 months (HR, 0.66; 95% CI, 0.43 to 1.02; p=.06). None of the 11 prespecified secondary end points showed significant differences, including major or minor bleeding in *CYP2C19* carriers in the genotype-guided group (1.9%) versus the conventional therapy group (1.6%) at 12 months (HR, 1.22; 95% CI , 0.60 to 2.51; p=.58). Among all randomized patients, the primary end point occurred in 113 of 2641 (4.4%) in the genotype-guided group and 135 of 2635 (5.3%) in the conventional group (HR, 0.84; 95% CI , 0.65 to 1.07; p=.16). The trial failed to meet the pre-specified end point and the authors contend that the trial was underpowered to detect an effect size less than the 50% relative risk after a revised sample calculation. Despite the occurrence of 89 ischemic events observed in this trial, which exceeded the 76 events anticipated to provide adequate power, the observed relative risk reduction was 34% instead of the estimated 50%, hence a borderline p value of.056 was observed. Further, the authors also comment that the potential benefit of genotype guided oral P2Y12 inhibitor therapy may be important early after PCI rather than 12 months after PCI. A post-hoc analysis of the data from the trial showed that a nearly 80% reduction in the rate of adverse events occurred in the first three months of treatment among patients who received genetically guided therapy compared with those who did not.

Claassens et al (2019) reported on the results of the CYP2C19 Genotype Guided Treatment with Antiplatelet Drugs in Patients With ST-segment-elevation Myocardial Infarction Undergoing Immediate PCI With Stent Implantation: Optimization of Treatment (POPular Genetics) trial. In this non-inferiority trial, patients with acute coronary syndrome were randomly assigned to receive standard treatment (prasugrel or ticagrelor) or genotype-guided treatment (clopidogrel in those without *CYP2C19* loss of-function variants; standard treatment otherwise). Results of the primary combined endpoint met the P value for non-inferiority. Thus, one can conclude that a genotype guided strategy led to outcomes that were at least as good as, if not better than, outcomes with the standard approach of prescribing prasugrel or ticagrelor to all patients. However, the trial results do not inform whether using genotype-based strategy for prescribing

clopidogrel results in any incremental net health benefit versus standard treatment with clopidogrel. Furthermore, there was no difference in the incidence of PLATO major bleeding between the genotype-guided group and the standard-treatment group (2.3% in both groups; HR, 0.97; 95% CI, 0.58 to 1.63). The statistically significant difference observed in the primary bleeding outcome was primarily driven by PLATO minor bleeding events in the genotype-guided group versus standard-treatment group (7.6% vs. 10.5%; HR, 0.72; 95% CI, 0.55 to 0.94).

Multiple observational studies in patients undergoing percutaneous coronary intervention (PCI) have reported associations between the presence of loss of function alleles and lower levels of active clopidogrel metabolites, high platelet reactivity, and increased risk of adverse cardiovascular events. However, evidence of publication bias has been reported in these studies where smaller studies have reported larger benefits than larger studies which have reported no effect or smaller effect. Wang et al (2016) reported post hoc analysis of the Clopidogrel in High-Risk Patients with Acute Nondisabling Cerebrovascular Events trial conducted in China; it randomized patients with a transient ischemic attack or minor stroke to clopidogrel plus aspirin or aspirin alone. In a subgroup analysis of patients who did not have the loss of function alleles, clopidogrel plus aspirin versus aspirin alone was associated with statistically significant reduction in the risk of stroke (6.7% vs. 12.4%; hazard ratio [HR], 0.51; 95% confidence interval [CI], 0.35 to 0.75) but not among those who carried loss of function alleles (9.4% vs. 10.8%; HR, 0.93; 95% CI, 0.69 to 1.26). Results of this analysis have contributed to the formulation of the hypothesis of a differential effect of clopidogrel in patients with and without loss of function alleles.

Roberts et al (2012) reported on the results of an RCT that allocated patients undergoing PCI for acute coronary syndrome or stable angina to genotype-guided management to select for treatment with prasugrel (carriers) or clopidogrel (noncarriers) or to standard treatment with clopidogrel.[9,] Among those who received prasugrel and clopidogrel based on genotyping test, 0% and 10%, respectively, exhibited high on-treatment platelet reactivity while 17% patients who received standard treatment with clopidogrel without any genotypes testing exhibited high on-treatment platelet reactivity. This difference was not statistically significant. So et al (2016) reported on the results of an RCT that randomized ST-elevation myocardial infarction patients who were carriers of *CYP2C19*2*, *ABCB1* TT, and *CYP2C19*17* alleles to prasugrel 10 mg daily or an augmented dosing strategy of clopidogrel (150 mg per day for 6 days and subsequently 75 mg per day).[10,] Results showed that (1) carriers did not respond to augmented clopidogrel as well as they did to prasugrel (24% patients with high platelet reactivity vs. 0%) and (2) among noncarriers, physician-directed clopidogrel was effective for most patients (95% did not have high platelet reactivity).

In 2017, the FDA issued a drug safety communication and added a Boxed Warning to the label for clopidogrel (plavix). The Boxed Warning is related to patients who do not effectively metabolize the drug (e.g., “poor metabolizers”) and therefore not receive the full benefits of the drug. Clopidogrel (plavix) is given to reduce the risk of heart attack,

unstable angina, stroke and cardiovascular death in patients with cardiovascular disease. Clopidogrel (Plavix) works by decreasing the activity of blood cells called platelets, making platelets less likely to form blood clots. For clopidogrel (plavix) to work, enzymes in the liver (particularly CYP2C19) must convert (metabolize) the drug to its active form. Patients who are poor metabolizers of the drug, do not effectively convert clopidogrel (plavix) to its active form. In these patients, clopidogrel (plavix) has less effect on platelets, and therefore less ability to prevent heart attack, stroke, and cardiovascular death. It is estimated that 2 to 14% of the population are poor metabolizers; the rate varies based on racial background. Healthcare professionals should be aware that a subgroup of patients are poor metabolizers and do not metabolize clopidogrel (plavix) effectively; this can result in reduced effectiveness of clopidogrel (plavix). Healthcare professionals should consider use of other anti-platelet medications or alternative dosing strategies for Plavix in these patients.

In May 2009, FDA added information about poor metabolizers of clopidogrel (plavix) to the drug label. However, based on additional data reviewed by the agency the Boxed Warning is now being added to highlight the reduced effectiveness of clopidogrel (plavix) in these patients and to recommend that healthcare professionals consider use of other anti-platelet medications or alternative dosing strategies for Plavix in patients identified as poor metabolizers.

A clinical alert in 2010 issued by the American College of Cardiology Foundation (ACCF) and the American Heart Association (AHA) regarding clopidogrel (plavix) boxed warning by the FDA, stated that the boxed warning leaves the issue of whether to perform CYP2C19 testing up to the individual physician. In summary, they indicate that clinicians must be aware that genetic variability in CYP enzymes alter clopidogrel (plavix) metabolism, which in turn can affect its inhibition of platelet function. Diminished responsiveness to clopidogrel (plavix) has been associated with adverse patient outcomes in registry experiences and clinical trials. The evidence base is insufficient to recommend either genetic or platelet function testing at the present time. There is no information that routine testing improves outcome in large subgroups of patients. However, clinical judgement 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 (plavix) metabolism (poor metabolizers) may be considered before starting clopidogrel (plavix) therapy in patients believed to be at moderate or high risk for poor outcomes. This might include individuals undergoing elective high risk percutaneous coronary intervention (PCI) e.g., treatment of extensive and/or very complex disease. Moreover, if a person is identified as a potentially poor metabolizer (PM), other treatments should be considered i.e., alternative dosing of clopidogrel (plavix) or use of other available agents such as prasugrel (effient), if not contraindicated for the individual.

Guidelines from the American Heart Association and the American College of Cardiology recommend the use of dual antiplatelet therapy with aspirin and a P2Y12 inhibitor, such as clopidogrel (plavix), prasugrel or ticagrelor, for the prevention of

atherothrombotic events after acute myocardial infarction (MI). However, a substantial number of subsequent ischemic events still occur, which may be least partly due to interindividual variability in the response to clopidogrel (plavix). Clopidogrel (plavix) is a prodrug which is converted by several CYP450 enzymes, CYP2C19 in particular, to an active metabolite. For this reason, genetic polymorphisms that inactive the CYP2C19 enzyme are associated with impaired pharmacodynamics response in healthy individuals. Previous studies have shown that persistent high platelet reactivity, despite clopidogrel (plavix) treatment at standard dosing, is associated with CYP2C19 variants that code for inactive enzymes, higher loading and/or maintenance doses decrease reactivity even in initial non-responders, presumed to be CYP2C19 PMs. Higher platelet reactivity has been associated with a higher rate of subsequent thrombotic events.

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insufficient to recommend either genetic or platelet function testing at the present time. There is no information that routine testing improves outcome in large subgroups of patients. However, clinical judgement 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 (plavix) metabolism (poor metabolizers) may be considered before starting clopidogrel (plavix) therapy in patients believed to be at moderate or high risk for poor outcomes. This might include individuals undergoing elective high risk percutaneous coronary intervention (PCI) e.g., treatment of extensive and/or very complex disease. Moreover, if a person is identified as a potentially poor metabolizer (PM), other treatments should be considered i.e., alternative dosing of clopidogrel (plavix) or use of other available agents such as prasugrel (effient), if not contraindicated for the individual.

Summary of Evidence

For individuals with a need for antiplatelet therapy who are undergoing or being considered for clopidogrel therapy who receive a *CYP2C19*-guided treatment strategy, includes randomized controlled clinical trials (RCTs), observational studies, systemic reviews, and meta-analyses. Systemic reviews of observational studies report that genetic variant may be associated with modest increase in the rate of stent thrombosis and clinical end points. CYP2C19 genotype testing has been associated with increased risk of thrombosis in patients with coronary disease or cardiac interventions being considered as candidates for clopidogrel (plavix) treatment. This observation is most pronounced for stent thrombosis in patients undergoing percutaneous coronary intervention (PCI). The evidence addressing whether the use of CYP2C19 genotype directed therapy improves outcomes are limited. However, several publications have evaluated outcomes in patients treated with clopidogrel (plavix) according to their CYP2C19 genetic status. These studies showed that patients with genetic variants (poor metabolizers) exhibit higher cardiovascular event rates (worse outcomes) than those patients without genetic variants. This data raises the possibility that the efficacy of clopidogrel (plavix) was reduced in patients with genetic variants. In 2017, the FDA issued a drug safety communication and added a Boxed Warning to the label for clopidogrel (plavix). The Boxed Warning is related to patients who do not effectively metabolize the drug (e.g., “poor metabolizers”) and therefore not receive the full benefits of the drug. Clopidogrel (plavix) is given to reduce the risk of heart attack, unstable angina, stroke, and cardiovascular death in patients with cardiovascular disease. Clopidogrel (Plavix) works by decreasing the activity of blood cells called platelets, making platelets less likely to form blood clots. For clopidogrel (plavix) to work, enzymes in the liver (particularly CYP2C19) must convert (metabolize) the drug to its active form. Patients who are poor metabolizers of the drug, do not effectively convert clopidogrel (plavix) to its active form. In these patients, clopidogrel (plavix) has less effect on platelets, and therefore less ability to prevent heart attack, stroke, and cardiovascular death. Therefore, the evidence is sufficient to determine that this testing results in a meaningful improvement in the net health outcome (consider alternate treatment or dosing strategies) in patients identified as CYP2C19 poor metabolizers.

Selection and/or Dosing of Tetrabenazine and Deutetrabenazine
Huntington's disease is an autosomal dominant genetic neurodegenerative disorder characterized by progressive cognitive and motor dysfunction, including chorea.

In 2008, FDA approved tetrabenazine (xenazine), a centrally acting vesicular monoamine transporter inhibitor, as an orphan drug for the treatment of chorea (abnormal involuntary movement) in Huntington's disease, based on evidence from an RCT of improved chorea symptoms in ambulatory patients with Huntington's disease. Tetrabenazine's primary metabolites are metabolized mainly by CYP2D6. FDA labeling for tetrabenazine includes recommendations for genotyping for CYP2D6 in patients who are being considered for doses over 50mg per day. The labeling states: "Patients requiring doses above 50 mg per day should be genotyped for the drug metabolizing enzyme CYP2D6 to determine if the patient is poor metabolizer (PM), poor metabolizers should not be given daily doses greater than 50 mg."

In 2017, FDA approved deutetrabenazine (austedo), which is a vesicular monoamine transporter2 (VMAT2) inhibitor indicated for the treatment of chorea associated with Huntington's disease. Although the pharmacokinetics of deutetrabenazine and its metabolites have not been systematically evaluated in patient's wo do not express the drug metabolizing enzyme CYP2D6, it is likely that the exposure to a-HTBZ and B-HTBZ would be increased similarly to taking strong CYP2D6 inhibitors (approximately 3-fold). The FDA labeling for deutetrabenazine (austedo) states "in patients receiving strong CYP2D6 inhibitors (i.e., quinidine, antidepressants such as paroxetine, fluoxetine, and bupropion) to total disease of deutetrabenazine (austedo) should not exceed 36 mg (maximum single dose of 18 mg). In patients who are poor CYP2D6 metabolizers the total daily dosage should not exceed 36 mg (maximum single dose of 18 mg)."

The evidence is sufficient to determine the technology results in improvement in the net health outcomes.

Selection and/or Dosing of Eliglustat
Gaucher disease is a rare autosomal recessive lipid storage disease in which deficiency or absence of enzyme B-glucocerebrosidase leads to lysosomal accumulation of the glycosphingolipid glucosylceramide. Untreated, this accumulation can lead to a range of effects, including anemia and thrombocytopenia, splenomegaly, bone disease, pulmonary fibrosis, and central nervous system involvement. Gaucher disease has been treated through enzyme replacement, for which 3 drugs have been FDA approval as orphan drugs (imiglucerase, velaglucerase alfa, and taliglucerase alfa) or substrate reduction therapy, for which 2 drugs have FDA approval as orphan drugs (miglustat and eliglustat tartrate). Eliglustat (cerdelga) is an orally administered selective inhibitor of glucosylceramide synthase that received FDA approval in 2014 and has been found in 3 phase 3 clinical trials to lead to improvements in hematologic metrics and organomegaly.

Eliglustat (cerdelga) is metabolized by CYP2D6 and CYP3A. FDA labeling requires that individuals be selected on the basis of CYP2D6 metabolizer status as determined by

genotype, with recommendations based on genotype about dosage: CYP2D6 Ems (extensive metabolizers) or IMs (intermediate metabolizers) 84 mg orally twice daily; CYP2D6 PMs (poor metabolizers) 84 mg orally once daily. Eliglustat (cerdelga) is not indicated in patients who are CYP2D6 ultra-rapid metabolizers since they may not achieve adequate concentrations of eliglustat (cerdelga) to achieve a therapeutic effect. The evidence is sufficient to determine the technology results in improvement in the net health outcomes.

Selection and Dosing for Mayzent (Siponimod)
In 2019, the FDA approved Mayzent (siponimod) which is a sphingosine 1-phosphatereceptormodulater indicated for the treatment of relapsing forms of multiple sclerosis (MS), to include clinically isolated syndrome, relapsing-remitting disease and active secondary progressive disease in adults. The FDA labeling for Mayzent (siponimod) states "before the initiation of treatment with Mayzent, assess the following: Test patients for CYP2C9 variants to determine CYP2C9 genotype. After treatment titration the recommended maintenance dosage of Mayzent is 2 mg take orally once daily starting on day 6. Dosage adjustment is required in patients with a CYP2C9 1/3 or 2/3 genotype." The evidence is sufficient to determine the technology results in improvement in the net health outcomes.

Selection and/or Dosing of Other Medications
The evidence for cytochrome P450 (CYP450) genotyping in patients with various clinical conditions undergoing or being considered for treatment with a drug metabolized CYP450 enzyme(s) includes prospective and retrospective observational studies reporting associations with CYP450 metabolizer status and medication response or adverse effects. Most published studies of CYP450 pharmacogenomics are retrospective evaluations of CYP450 genotype association with intermediate (e.g., circulating drug concentrations) or, less often, final outcomes (e.g., adverse events or efficacy) and are largely small and underpowered or not designed to examine the clinical effects of homozygous variant poor metabolizers and of ultra-rapid metabolizers, where the strongest effects, if any, would be seen. The hazards associated with different metabolizer status are therefore uncertain. There is limited evidence on the clinical validity of testing for CYP450 genotype. At present, the clinical utility is poorly defined, it is not known whether CYP450 genotyping guided clinical management improves patient outcomes such as therapeutic effect, time to effective dose, and adverse event rate compared to standard clinical management without genotyping. The evidence is insufficient to determine the effects of CYP450 genotyping for various clinical conditions on net health outcomes. Therefore, CYP450 genotyping including but not limited to the following is considered investigational:

- Selection or dose of selective serotonin reuptake inhibitor (SSRI)
- Selection and dosing of serotonin norepinephrine reuptake inhibitors (SNRIs)
- Selection and dosing of tricyclic antidepressant medications
- Selection or dose of antipsychotic medications
- Selection or dosing of opioid analgesics
- Dose of efavirenz (common component of highly active antiretroviral therapy for HIV infection)

- Dose of immunosuppressant for organ transplantation
- Selection or dose of beta blockers
- Dosing and management of antituberculosis medications
- Selection or dosing of Tamoxifen

Summary of Evidence
Testing for genetic polymorphisms has also been proposed for a wide array of other drugs, involving many different conditions and CYP450 enzyme(s). In general, most published CYP450 pharmacogenomic studies consist of retrospective evaluations of CYP450 genotype associations, reporting intermediate outcomes (e.g., circulating drug concentrations) or less often, final outcomes (e.g., adverse effects or efficacy). Many of these studies are small, underpowered and hypothesis generating. Prospective intervention studies, including randomized controlled trials (RCTs) documenting the clinical usefulness of CYP450 genotyping to improve existing clinical decision making to guide dose or drug selection, which may then translate into improvement in patient outcomes, were not identified. The evidence is insufficient to determine the effects of the technology on net health outcomes.

While the potential of pharmacogenomics is intriguing for many clinical applications, it is not yet clear which are most likely to yield clinical benefit. As this field evolves and matures, and if pre-prescription testing can be shown to be of clinical utility for specific drugs and individuals, it will be imperative to establish evidence-based guidelines for healthcare professionals delineating the most effective courses of action based on such genotype testing results.

Genotype-Guided Warfarin (Coumadin) Dosing
Genetic variants in CYP2C9 and VKORC1 genes may impact an individual's ability to metabolize warfarin (Coumadin). It has been proposed that using information regarding an individual's CYP2C9 and VKORC1 genotypes, as well as other characteristics, to determine a personalized starting dose of warfarin (Coumadin), may reduce the time to a stable warfarin (Coumadin) dose and avoid serious bleeding events.

Patients requiring treatment with warfarin (Coumadin) are managed by multiple specialists, including but not limited to cardiologists, cardiovascular surgeons, pulmonologists, internists, critical care physicians, and neurologists based on the clinical indication. Warfarin (Coumadin) is used in both inpatient and outpatient settings.

Warfarin (Coumadin) is indicated for the prevention and treatment of thromboembolic events in high- risk individuals; warfarin (Coumadin) dosing is a challenging process, due to the narrow therapeutic window, variable response to dosing, and serious bleeding events in 5% or more of patients. Patients are typically initiated on a starting dose of 2-5 mg and monitored frequently with dose adjustments until a stable international normalized ratio (INR) value (a standardized indicator of clotting time) between 2 and 3 is achieved. During this period of adjustment, a patient is at high risk for bleeding.

Stable or maintenance warfarin (Coumadin) dose varies among individuals; factors influencing stable dose include body mass index, age, interacting drugs, and indication for therapy. In addition, genetic variants of cytochrome p450 2C9 (CYP2C9) and vitamin K epoxide reductase subunit C1 (VKORC1) genes together account for a substantial proportion of inter-individual variability. More recently, a single nucleotide polymorphism (change in a single base-pair in a DNA sequence) in the CYP4F2 gene has been reported to account for a small proportion of the variability in stable dose; CYP4F2 encodes a protein involved in vitamin K oxidation.

Using the results of CYP2C9 and VKORC1 (and possibly CYP4F2) genetic testing to predict a warfarin (Coumadin) starting dose that approximates the patient's likely maintenance dose may benefit patients by decreasing the risk of serious bleeding events and the time to stable INR. Algorithms have also been developed that incorporate not only genetic variation but also other significant factors to predict the best starting dose.

Clinical Context and Test Purpose
The purpose of genotype-guided warfarin dosing is to guide an individual's initiation and maintenance dose of warfarin by incorporating demographic, clinical, and genotype data. In theory, this should lead to a predicted dose that will decrease the probability of over- or undercoagulation thereby avoiding the downstream consequences of thromboembolism or bleeding.

Populations
The relevant population of interest is patients being considered for treatment with warfarin.

Interventions
Several commercial tests for individual genes or panel tests are available. Numerous algorithms have been developed to guide warfarin dosing based on the results of genetic tests and other demographic and clinical factors.

Comparators
The comparator of interest is standard clinical management without genetic testing.

Outcomes
Specific outcomes of interest are listed in the below table. The interest is in whether genotype-guided warfarin dosing reduces adverse events during the dose adjustment period. Therefore, outcomes in the first 1 to 2 months are relevant.

Outcomes	Details
Morbid events	Opioid addiction, adverse events
Health status measures	Pain relief, functional status
Medication use	The number of unsuccessful mediation trials and medications needed, including

	the dose of medication and dose frequency

Review of Evidence

Systematic Reviews and Meta-Analyses

All 6 reviews found that the percentage of time the international normalized ratio (INR) was in therapeutic range was higher in patients treated with genotype-guided warfarin therapy; however, the heterogeneity between studies was high for this outcome. In the Belley-Cote et al (2015) review, there was no difference between groups on the composite outcome of thromboembolic events (TEEs), major bleeding, or death. Similarly, Sridharan and Sivaramakrishnan evaluated these outcomes independently in a network meta-analysis and found no significant differences between clinically adjusted warfarin and genotype-guided dosing, except that bleeding risk was lower with cytochrome P450 2C9 (*CYP2C9)*-guided dosing compared with clinically adjusted warfarin. Wang et al (2022) was the only systematic review to find a significant reduction in TEEs with genotype-guided warfarin dosing, driven mainly by the Zhu et al (2020) RCT.[54,] There was also a reduction in major bleeding events but not deaths, in the genotype-guided warfarin group compared to the control group. Meta-analyses in the most recent systematic reviews were heavily weighted by the large Genetics Informatics Trial (GIFT), published in 2017.[4,] Authors of these reviews found no difference between genotype-guided dosing and clinical dosing for mortality, but genotype-guided dosing was associated with a lower risk of major bleeding. For example, the Washington HTA reviewers found a 57% reduction for risk of major bleeding in the pharmacogenetic testing group compared to controls (relative risk [RR], 0.43; 95% confidence interval [CI], 0.22 to 0.84; p=.01).[51,] The absolute number of major bleeding events was low, with an anticipated 8.6 fewer major bleeding events per 1000 people with pharmacogenetic testing (95% CI, 2.7 to 14.4 fewer major bleeding episodes per 1000 people). Subgroup analyses by comparator groups showed this difference was statistically significant only when pharmacogenetic testing was compared to using a clinical algorithm to guide initial dosing (RR, 0.39; 95% CI, 0.19 to 0.81), and not when compared to a fixed dose (RR, 0.70; 95% CI, 0.14 to 3.53). Washington HTA reviewers rated the overall quality of the evidence for major bleeding as moderate due to the imprecision of the estimate.

Belley-Cote et al (2015) used the GRADE approach to evaluate the quality of evidence. A summary of the risk of bias of individual studies is as follows: (1) the trials inconsistently reported allocation concealment; (2) only 1 study blinded participants, clinicians, research personnel, and outcome assessors; (3) patients who died during the trial period were excluded from analysis in 2 trials; (4) the 3 studies with highest loss to follow-up had losses of 12%, 16%, and 23%, respectively; and (5) 5 studies did not report the definitions used for bleeding events. Reviewers found that genotype-guided vitamin K antagonist dosing compared with standard dosing algorithms did not decrease a composite outcome of death, thromboembolism, and major bleeding (n=2223, 87 events; RR=0.85; 95% CI, 0.54 to 1.34; p=.48) but did result in an improved time of INR in the therapeutic range. The improvement in time in therapeutic range was reported in a pooled

analysis of RCTs with fixed dosing algorithms but not with clinical algorithms. Of the 13 trials included in the Washington HTA systematic review, 3 were judged to be at low-risk of bias, 4 at moderate-risk of bias, and 6 at high-risk of bias. Study limitations included inadequate methods of randomization and allocation concealment and lack of blinding of outcomes. Yang et al (2019) also completed a risk of bias assessment of included RCTs. All trials claimed to be randomized in nature; however, the random sequence generation was only explicitly described in 9 studies. Additionally, only 7 studies discussed allocation concealment; blinding was not implemented in most of the included RCTs as administration of an initial fixed warfarin dose would potentially imply to the participants and study personnel that the subject was randomized to the conventional dosing versus genotype-guided arm. Sridharan and Sivaramakrishnan assessed the quality of evidence as follows for the assessed outcomes and comparisons: time to first therapeutic INR with *CYP2C9*: low; time to first therapeutic INR with *CYP2C9* and vitamin K epoxide reductase complex, subunit 1 (*VKORC1)*: moderate; time to stable INR or warfarin dose with *CYP2C9*: very low; time to stable INR with *CYP2C9* and *VKORC1*: very low; and percentage of time the INR was in therapeutic range with *CYP2C9* and *VKORC1*: very low. The quality of evidence was often downgraded because of high risk of bias, potential for publication bias, and imprecision. Wang et al (2022) assessed risk of bias of their included studies. Three studies were identified as unclear on all of the bias assessments because they were conference abstracts with limited data. In the selection bias category, 3 studies were assigned high risk of bias. In the reporting bias category, 4 studies were identified as high risk of bias. For performance bias, 2 studies were assigned high risk. Overall, the majority of trials had a low risk of of detection and attrition bias.

Randomized Controlled Trials

Most randomized controlled trials (RCTs) were single-center studies including fewer than 250 patients. The trials used varying algorithms in both the genotype-guided and clinical dosing arms. Most studies included mixed indications for warfarin use. The trials primarily included patients of European descent. Twenty-seven percent of the participants in the multicenter Clarification of Optimal Anticoagulation through Genetics (COAG) trial were African American.

While a few of the RCTs reported differences in the percentage of time the INR was in therapeutic range or the proportion of patients with an INR greater than 4, none reported statistically significant differences in major bleeding, and only 1 (Zhu et al [2020]) reported significant reduction in TEEs (ischemic stroke) with genotype-guided dosing. However, it is important to note that the event rates were very low in the selected trials and the studies were not powered to show differences in rates of major bleeding or TEEs.

Three multicenter RCTs with more than 400 patients have been reported: COAG, European Pharmacogenetics of Anticoagulant Therapy (EU-PACT), and GIFT. These larger RCTs, along with the large single center trial by Zhu et al (2020), are discussed in the following paragraphs

Two larger RCTs of pharmacogenetic dosing algorithms were published by Kimmel et al (2013) and Pirmohamed et al (2013).[66,67,] The larger of these, the COAG trial, was

conducted in the U.S. by the National Heart, Lung, and Blood Institute,[66,] and the smaller trial was conducted in Sweden and England by the EU-PACT consortium.[67,] In both trials, the intervention period was the first 5 days of dosing; genotyping comprised the *CYP2D6*2* and **3* and *VKORC1* 1639G>A alleles; the primary outcome was the mean percentage of time in the therapeutic INR range of 2.0 to 3.0. Neither trial reported an intention-to-treat analysis.

In the COAG trial, 1015 individuals, 6 to 70 years old, 51% male, and 27% African American were randomized to warfarin doses for the first 5 days of therapy based on their clinical and genetic characteristics or their clinical characteristics alone.[66,] Patients were followed for 4 additional weeks during which time their drug doses were adjusted based on standard protocols. Ninety-four percent (n=955) of patients completed the 5-day intervention period and were included in efficacy analyses. Results showed that INR was within the desired range 45% (p=.91) of the time in both groups during the 28-day monitoring period, based on standardized blood clotting tests. The principal secondary outcome (a composite of INR ≥4, major bleeding [fatal hemorrhage, intracranial bleeding, or symptomatic bleeding requiring overnight hospitalization, transfusion, angiographic intervention, or surgery], or thromboembolism) was also similar in the 2 groups (20% vs 21%, respectively; p=.93). A subgroup analysis of 255 African American patients showed that the clinically guided group fared better than the genotype-guided group (INR was within the desired range 43.5% vs 35.2%, respectively; p=.01).

In the EU-PACT trial, 455 individuals, 24 to 90 years old, 99% white, were randomized to warfarin doses for the first 3 days based on their clinical and genetic characteristics or their clinical characteristics alone.[67,] Patients were followed for 12 additional weeks during which time their drug doses were adjusted based on standard protocols. Ninety-four percent of patients had 13 or more days of INR data and were included in efficacy analyses. Results showed that INR was within the desired range 67% of the time in the genotype-guided dosing group compared with 60% in the clinically guided group (p<.001). There were no differences in secondary outcomes assessed (bleeding or TEEs). However, the percentage of patients with an INR >4 was lower in the genotype-guided group (27%) than in the clinically guided group (37%). The time to achieving therapeutic INR was also shorter in the genotype-guided group (21 days) than in the clinically guided group (29 days).

Gage et al (2017) reported on the results of the GIFT RCT, which evaluated genotype-guided warfarin dosing (n=831) and clinically guided dosing (n=819) in patients aged 65 years or older initiating warfarin for elective hip or knee arthroplasty; the trial was conducted at 6 U.S. medical centers. Patients were genotyped for *VKORC1*-1639G>A, *CYP2C9*2*, *CYP2C9*3*, and *CYP4F2* V433M variants. The primary endpoint was the composite of major bleeding, INR ≥4, venous thromboembolism, or death. The mean age of randomized patients was 72, 64% of participants were women, and 91% were white. Randomized participants who received 1 or more doses of warfarin were included in the analysis (808 in the genotype-guided group vs 789 in the clinically guided group). Eighty-seven (11%) patients in the genotype-guided group vs 116 (15%) patients

in the clinically guided group met at least 1 of the components of the composite outcome (absolute difference, 3.9%; 95% CI, 0.7% to 7.2%; p=.02). The difference in the composite outcome was primarily driven by the difference in the percent of patients with INR ≥4 (56 vs 77; RR=0.71; 95% CI, 0.51 to 0.99). There were 2 versus 8 major bleeding events in the genotype vs clinical groups (RR=0.24; 95% CI, 0.05 to 1.15) and 33 versus 38 venous TEEs (RR=0.85; 95% CI, 0.54 to 1.34). There were no deaths.

Zhu et al (2020) randomized elderly Chinese patients, aged 60 years or greater, with nonvalvular atrial fibrillation to receive their warfarin dose based on an algorithm using genetic and clinical factors (genetic group, n=313) or an algorithm using clinical factors only (n=194). Investigators found that INR time in therapeutic range was improved with genotype-guided dosing based on *CYP2C9* and *VKORC1* compared with clinically guided dosing. Additionally, bleeding events did not differ between groups, but ischemic stroke occurred less frequently with genotype-guided dosing.

Risk of bias and quality of evidence assessments for the RCTs included in the Belley-Cote (2015), Washington HTA (2018), Yang (2019), Sridharan and Sivaramakrishnan (2020), and Wang (2022) systematic reviews were summarized in the previous section.

Summary of Evidence
For individuals with conditions requiring warfarin treatment who receive genotype-guided warfarin dosing, the evidence includes multiple RCTs and systematic reviews of RCTs. Relevant outcomes are morbid events, medication use, and treatment-related mortality and morbidity. Thirty RCTs and 6 recent systematic reviews were identified. Most RCTs were single-center studies including fewer than 250 patients. Systematic reviews found the percentage of time the INR was in therapeutic range was higher in patients treated with genotype-guided warfarin therapy; however, the heterogeneity between studies was high for this outcome. No RCT reported statistically significant differences in major bleeding, and only 1 reported a significant reduction in TEEs with genotype-guided dosing, but studies were not powered to show differences in these outcomes. Meta-analyses of RCTs found no difference between genotype-guided dosing and clinical dosing for mortality, and only 1 found reduction in TEEs, but genotype-guided dosing was associated with a lower risk of major bleeding. Very few trials enrolled sufficient numbers of subpopulations except White participants. In the COAG study, which included 27% African American participants, African Americans fared better in the clinically guided group than in the genotype-guided group. One trial of elderly Chinese patients with atrial fibrillation experienced improved time with INR in the therapeutic range and a reduced risk of ischemic stroke, but no difference in bleeding events. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Testing Panels to Determine Drug Metabolizer Status
While targeted gene testing for variants in some genes has been proposed to predict patient-specific drug metabolism of specific drugs, there still exists a lack of robust evidence to support the clinical utility of panel testing for multiple genes. There are

several clinically available combined pharmacogenomic panel tests designed to evaluate variants within multiple genes to provide guidance for prescribing and dosing various medications which may ultimately aid in addressing the recognized need to alleviate prolonging or complicating the clinical course of a patient's condition due to side effects or lack of response from a trial-and-error approach to medication choice. These panel tests are even marketed as "decision support tools."

The majority of professional society guidelines related to pharmacogenomic testing address specific drug-gene interactions rather than multi-gene panels. Although individual biomarkers may have clinical utility in certain circumstances, clinicians will often choose larger panels due to the increasing availability in the market, without sufficient evidence that panel testing of multiple genes has any benefit over single-gene testing or standard trial-and-error methods.

Several commercial laboratories market multi-test panels for genetic polymorphisms that include analysis of multiple CYP450 mutations and other gene polymorphisms (variants) related to drug metabolizer status. While the use of some individual tests included in these test panels may be reasonable under specific circumstances, the use of all the tests within a panel is rarely justified unless there is clinical evidence that the panel provides information that leads to meaningful impact on treatment.

Pharmacogenomic Testing for Pain Management

Pain is a universal human experience and an important contributor to outpatient and inpatient medical visits. The Institute of Medicine's (IOM) reported in 2011 (revised in 2012) that chronic pain conditions affect at least 100 million adults in the United States. Chronic pain may be related to cancer, or be what is termed chronic non-cancer pain, which may be secondary to a wide range of conditions, such as migraines, low back pain or fibromyalgia. Multiple therapeutic options exist to manage pain, including pharmacotherapies, behavioral modifications, and physical and occupational therapy, and complementary/alternative therapies. Nonetheless, IOM has reported that many individuals receive inadequate pain prevention, assessment, and treatment. Given that pain is an individual and subjective experience, assessing and predicting response to pain interventions, including pain medications, is challenging.

A variety of medication classes are available to manage pain: non-opioid analgesics, including acetaminophen and non-steroidal anti-inflammatory drugs (NSAIDs), opioid analgesics, which target nervous system pain perception, and classes of adjuvants, including anti-epileptic drugs (i.e., gabapentin, pregabalin), and topical analgesics. The management of chronic pain has been driven in part by the World Health Organization's analgesic ladder for pain management, which was developed to manage cancer related pain but has been applied to other forms of pain. The ladder outlines a stepped approach to pain management in the following order: non-opioid analgesia and proceeding to a mild opioid (codeine) with or without an adjuvant for persisting pain, and subsequently to a strong opioid (i.e., fentanyl, morphine), with or without an adjuvant for persisting or worsening pain. Various opioids are available in short and long- acting preparations and

administered through different routes, including oral, intramuscular, subcutaneous, sublingual, and transdermal.

While multiple pharmacologic therapies are available for the management of acute and chronic pain, there is a high degree of heterogeneity in pain response, particularly in the management of chronic pain, and in adverse events. This has prompted interest in better targeting pain therapies based on pharmacogenomics testing of genes relevant to analgesic pharmacokinetics (i.e., how medications are absorbed, distributed, metabolized, or excreted) or pharmacodynamics (i.e. medications effects on the body). Several panel tests have been developed to aid in pain management that includes several genes associated with pharmacokinetics and pharmacodynamics of analgesic medications. Genetic factors may contribute to a range of aspects in pain and pain control, including predisposition to conditions that lead to pain, pain perception, and the development of comorbid conditions that may affect pain perception. Currently available genetic tests relevant to pain management consist of panels of single genetic variants (polymorphisms, or single nucleotide variants (SNVs)) which include but are not limited to the following:

- 5HT2C (serotonin receptor gene)
- 5HT2A (serotonin receptor gene)
- SLC6A4 (serotonin transporter gene)
- DRD1 (dopamine receptor gene)
- DRD2 (dopamine receptor gene)
- DRD4 (dopamine receptor gene)
- DAT1 or SLC6A3 (dopamine transporter gene)
- DBH (dopamine beta-hydroxylase gene)
- COMT (catechol O-methyltransferase gene)
- MTHFR (methylenetetrahydrofolate reductase gene)
- y-aminobutyric acid (GABA) A receptor gene
- OPRM1 (u-opioid receptor gene)
- OPRK1 (k-opioid receptor gene)
- UGT2B15 (uridine diphosphate glycosyltransferase 2 family, member 15)
- Cytochrome P450 genes: CYP2D6, CYP2C19, CYP2C9, CYP3A4, CYP2B6, CYP1A2

Genetic Testing for the Management of Acute and Chronic Pain

The purpose of genetic testing for management of acute and chronic pain is to

- Select appropriate pain medications or avoid use of inappropriate pain medications
- To identify individuals likely or unlikely to respond to a specific medication.
- To identify individuals at a high risk of adverse drug reactions.
- To identify individuals at high risk of opioid addiction or abuse.
- Optimize the dose selection or frequency by
- Identifying individuals who are likely to require higher or lower dose of a drug.

Patients with acute and chronic pain are likely to be managed by a wide variety of specialists such as chiropractors, general physicians, physiatrists (rehabilitation

physicians), rheumatologists, orthopedic surgeons, oncologist, pain management specialist, physical therapist, acupuncturists. Most patients are likely to be tested in an outpatient setting.

Clinical Context and Test Purpose
The purpose of pharmacogenetic testing-guided treatment for the management of acute and chronic pain is to:

- Select appropriate pain medications or avoid the use of inappropriate pain medications, including:
    - To identify individuals likely or unlikely to respond to a specific medication.
    - To identify individuals at high-risk of adverse drug reactions.
    - To identify individuals at high-risk of opioid addiction or abuse.
- Optimize the dose selection or frequency by:
    - Identifying individuals who are likely to require higher or lower doses of a drug.

Populations
The relevant population of interest is patients with chronic and acute pain, including conditions such as cancer, migraine, low back pain, and fibromyalgia.

Interventions
Testing for individual genes is available for most, or all, of the genes listed in Table 2, as well as for a wider range of genes. Because of a large number of potential genes, panel testing is available from a number of genetic companies. These panels include a variable number of genes that broadly test potential response to relevant medication classes such as opioids, nonsteroidal anti-inflammatory drugs (NSAIDs), selective serotonin reuptake inhibitors, and tricyclic antidepressants. Several test labs market panel or individual tests designed to address 1 or more aspects of pain management, including but not limited to drug selection, drug dosing, or prediction of adverse events.

Commercially Available Genetic Panels for Pain Management

- Advanced Pain Care Pharmacogenetic panel
- Aeon Pain Management PGX Profile
- ARUP Pain Management
- Focused Pharmacogenomics Panel Mayo Clinic
- GeneDose Analgesic Appropriateness Report
- GeneSight Analgesic
- GeneTrait Pain Management Drug Metabolism and Risk Factor Profile
- IDgenetix Pain Tests
- Kailos Testing for Pain Medication (Kailos Genetics)
- Millennium Pharmacogenetic Testing PGT – Millennium Analysis of Patient Phenotype (MAPP) report
- NeuroIDgenetix test
- Pain Management Panel

- Pain Medication DNA Insight
- Pain Panel
- PersonaGene Pain Management
- PgxOne Plus Pain Management
- Pharmacogenomic Comprehensive Panel – Opioids
- Proove Addiction Risk Test
- Proove Drug Metabolism
- Proove Opioid Response Profile
- Proove Opioid Risk
- Proove Pain Perception
- Proove Non-Opioid Response
- Proove NSAID Risk Profile
- RightMed PGx16 Test
- RightMed Comprehensive Test Exclude F2 and F5
- RightMed Comprehensive Test
- RightMed Gene
- RESPONSEpain
- YouScript Analgesic

Genes Included in Commercially Available Genetic Panels for Pain Management

- 5HT2C (serotonin receptor gene)
- 5HT2A (serotonin receptor gene)
- SLC6A4 (serotonin transporter gene)
- DRD1 (dopamine receptor gene)
- DRD2 (dopamine receptor gene)
- DRD4 (dopamine receptor gene)
- DAT1 or SLC6A3 (dopamine transporter gene)
- DBH (dopamine beta-hydroxylase gene)
- COMT (catechol O-methyltransferase gene)
- MTHFR (methylenetetrahydrofolate reductase gene)
- y-aminobutyric acid (GABA) A receptor gene
- OPRM1 (u-opioid receptor gene)
- OPRK1 (k-opioid receptor gene)
- UGT2B15 (uridine diphosphate glycosyltransferase 2 family, member 15)
- Cytochrome P450 genes: CYP2D6, CYP2C19, CYP2C9, CYP3A4, CYP2B6, CYP1A2

Comparators

The following practice is currently being used to treat chronic and acute pain: standard pain management without genetic testing. For chronic pain management, a multimodal, multidisciplinary approach that is individualized to the patient is recommended. A multimodal approach to pain management consists of using treatments (i.e., nonpharmacologic and pharmacologic) from 1 or more clinical disciplines incorporated

into an overall treatment plan. This allows for different avenues to address the pain condition, often enabling a synergistic approach that impacts various aspects of pain, including functionality. The efficacy of such a coordinated, integrated approach has been documented to reduce pain severity, improve mood and overall quality of life, and increase function. Patients with pain are likely to be managed by a wide variety of specialties such as chiropractors, primary care physicians, physiatrists (rehabilitation physicians), neurologists, rheumatologists, orthopedic surgeons, oncologists, pain management specialists, physical therapists, and acupuncturists. Most patients are likely to be tested in an outpatient setting.

Outcomes
Specific outcomes of interest for patients with acute or chronic pain are listed in the table below. The potential beneficial outcomes of primary interest would be improvements in pain, functioning, and quality of life. The potential harmful outcomes are those resulting from a false test result. False-positive or -negative test results can lead to the initiation of unnecessary treatment and associated adverse events or under-treatment.

Outcomes	Details
Morbid events	Opioid addiction, adverse events
Health status measures	Pain relief, functional status
Medication use	The number of unsuccessful medication trials and medications needed, including the dose of medication and dose frequency

Review of Evidence

Randomized Study
Thomas et. al. (2021) completed a hybrid implementation-effectiveness randomized trial of CYP2D6-guided postoperative pain management versus usual care in 260 adults undergoing joint arthroplasty. In this open-label trial, the authors evaluated the feasibility of clinically implementing CYP2D6-guided post-surgical pain management via the collection of feasibility metrics and pain control through measures of opioid consumption and pain intensity. In the genotype-guided arm, 20% had a high-risk phenotype (intermediate, poor, or ultrarapid metabolizer). Of these, 72% were administered an alternative opioid versus 0% of usual care participants ($p<.001$). Effectiveness outcomes were collected 2 weeks post-surgery and results of the exploratory analysis revealed reduced opioid consumption and similar pain intensity between the 2 groups.

Nonrandomized Studies
One prospective cohort study using historical controls and 1 prospective non-randomized pragmatic trial have assessed genotype-guided management of pain.

Smith et al (2019) reported a prospective non-randomized pragmatic trial of 375 patients who either underwent a CYP2D6-guided approach to opioid prescribing for pain control

at 4 primary care clinics or standard of care pain management at 3 clinics without assessment of CYP2D6.[12,] Based on genotyping alone, 10% of the CYP2D6-guided group were considered intermediate or poor metabolizers (IM/PM). The percentage of patients who were considered IM or PM increased to 35% after drug interactions were considered. In the CYP2D6-guided IM/PM group, there was a more frequent change to a nonopioid therapy. The reduction in pain was statistically significant, though modest, compared to the standard of care group**.**

Senagore et al (2017) reported on the results of a prospective cohort study of 63 consecutive patients undergoing open or laparoscopic colorectal and major ventral hernia surgery. The authors compared the findings with a historical cohort of 47 patients who underwent similar surgeries but were managed with a standard enhanced recovery protocol. Results showed that the overall benefit of analgesia score was statistically significantly lower in patients in whom the analgesia protocol was initiated based on results of genotype testing versus the historical control on postoperative days 1 and day 5 (all $p<.05$). The need for narcotic-equivalent analgesics was also statistically significantly lower in the genotype-tested group versus historical controls.

Because of the lack of established clinical validity, it is not possible to establish the clinical utility of genetic testing for pain management through a chain of evidence.

Summary of Evidence

For individuals who have a need for pharmacologic pain management who receive pharmacogenetic testing to target therapy, the evidence includes a hybrid implementation-effectiveness randomized trial, prospective cohort study with historical controls that assessed genotype-guided management of postoperative pain, and a prospective non-randomized pragmatic trial that evaluated chronic pain control when treatment occurred via a CYP2D6-guided approach to opioid prescribing versus standard management. Relevant outcomes are symptoms, health status measures, medication use, and treatment-related morbidity. The randomized trial concluded that preemptive CYP2D6-guided opioid selection is feasible in an elective surgery setting and that this approach may decrease postoperative opioid utilization with similar pain control as compared to usual care; however, these results were only exploratory in nature. The prospective cohort study reported on the use of genetic panel test results to guide the selection of analgesics in a postoperative setting and reported statistically significant improvement in total scores of a composite endpoint that measured analgesia, patient satisfaction, and the impact of drug-associated side effects versus historical controls. However, methodologic limitations precluded assessment of the effects on outcomes. The prospective non-randomized pragmatic trial evaluated a CYP2D6-guided approach finding a statistically significant but modest improvement in chronic pain control in the intermediate and poor metabolizers. The effect of pharmacogenetic testing alone cannot be determined from this trial. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Pharmacogenomic Testing for Mental Health Conditions
Psychiatric disorders cover a wide range of clinical phenotypes and are generally classified by symptomology in systems such as the classification outlined in the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5). In addition to counseling and other forms of behavioral treatment, treatment commonly involves 1 or more psychotropic medications that are aimed at alleviating symptoms of the disorder. Although there are a wide variety of effective medications, treatment of psychiatric disease is characterized by relatively high rates of inadequate response. This often necessitates numerous trials of individual agents and combinations of medications to achieve optimal response.

Knowledge of the physiologic and genetic basis of psychiatric disorders is advancing rapidly and may substantially alter the way in which these disorders are classified and treated. Genetic testing could potentially be used in several ways including stratifying patients' risks of developing a particular disorder, aiding diagnosis, targeting medication therapy, and optimally dosing medication. Better understanding of these factors may lead to an improved ability to target medications to the specific underlying abnormalities, with potential improvement in the efficiency and efficacy of treatment (pharmacogenomics). Several labs offer commercially available genetic tests either as panels or individual tests relevant for mental health disorders.

Mental health disorders encompass a wide range of conditions: the DSM-5 includes more than 300 different disorders. However, currently available genetic testing for mental health disorders is primarily related to several clinical situations:

- Risk stratifying patients for one of several mental health conditions, including schizophrenia and related psychotic disorders, bipolar and related disorders, depressive disorders, obsessive-compulsive and related disorders, and substance-related and addictive disorders.
- Pharmacogenomics - predicting patient's response to, dose requirement for, or adverse effects from one of several medications (or classes of medications) used to treat mental health conditions, including: typical and atypical antipsychotic agents, serotonin and serotonin/norepinephrine reuptake inhibitors (SSRIs), and medications used to treat addiction, such as disulfiram.

Clinical Context and Test Purpose
The purpose of testing for genes associated with increased risk of mental illness in individuals who are currently asymptomatic is to identify those for whom an early intervention during a presymptomatic phase of the illness might facilitate improved outcomes.

Populations
The relevant population of interest is asymptomatic individuals who would consider intervention if a genetic variant were detected.

Interventions
The intervention being considered is testing for genes associated with increased risk of mental illness, either as a panel or single gene.

Individual genes have been shown to be associated with risk of psychiatric disorders. Commercially available testing panels include several of these genes which are outlined below:

- Serotonin Transporter (SLC6A4): The serotonin transporter gene (SLC6A4) is responsible for coding the protein that clears serotonin metabolites (5-HT) from the synaptic spaces in the central nervous system (CNS). This protein is the principal target for many of the SSRIs. By inhibiting the activity of the SLC6A4 protein, the concentration of 5-HT in the synaptic spaces is increased. A common polymorphism in this gene consists of insertion or deletion of 44 base pairs in the serotonin-transporter-linked polymorphic region (5-HTTLPR), leading to the terminology of the long (L) and short (S) variants of this gene. These polymorphisms have been studied in relation to a variety of psychiatric and non-psychiatric conditions, including anxiety, obsessive compulsive disorder, and response to SSRIs.
- Serotonin Receptor (5HT2C): This gene codes for 1 of at least 6 subtypes of the serotonin receptor that is involved in the release of dopamine and norepinephrine. These receptors play a role in controlling mood, motor function, appetite, and endocrine secretion. Alterations in functional status have been associated with affective disorders such as anxiety and depression. Certain antidepressants, e.g., mirtazapine and nefazodone, are direct antagonists of this receptor. There is also interest in developing agonists of the 5HT2C receptor as treatment for obesity and schizophrenia, but no such medications are commercially available at present.
- Serotonin Receptor (5HT2A): The 5HT2A gene codes for another subtype of the serotonin receptor. Variations in the 5HT2A gene have been associated with susceptibility to schizophrenia and obsessive- compulsive disorder (OCD)_ and response to certain antidepressants.
- Sulfotransferase Family 4A, Member 1 (SULT4A1): SULT4A1 encodes a protein that is involved in the metabolism of monoamines, particularly dopamine and norepinephrine. This has been studied in schizotypical personality disorder and schizophrenia.
- Dopamine Receptors (DRD1, DRD2, DRD4): The DRD2 gene codes for a subtype of the dopamine receptor, called the D2 subtype. The activity of this receptor is modulated by G-proteins, which inhibit adenyl cyclase. These receptors are involved in a variety of physiologic functions related to motor and endocrine processes. The D2 receptor is the target of certain antipsychotic drugs. Mutations in this gene have been associated with schizophrenia and myoclonic dystonia. Polymorphisms of the DRD2 gene have been associated with addictive behaviors, such as smoking and alcoholism.
    - The DRD1 gene encodes another G protein coupled receptor that interacts with dopamine to mediate some behavioral responses and modulate D2

receptor-mediated events. Polymorphisms of the DRD1 gene have been associated with nicotine dependence and schizophrenia.
    - The DRD4 gene encodes a dopamine receptor with a similar structure; DRD4 polymorphisms have been associated with risk-taking behavior and attention deficit hyperactivity disorder.
- Dopamine Transporter (DAT1 or SLC6A3): Similar to the SCL6A4 gene, the dopamine transporter gene (DAT1 or SLC6A3) encodes a transporter that mediates the active reuptake of dopamine from the synaptic spaces in the CNS. Polymorphisms in this gene are associated with Parkinson disease, Tourette syndrome, and addictive behaviors.
- Dopamine Beta-Hydroxylase (DBH): The dopamine beta-hydroxylase protein encoded by this gene catalyzes the hydroxylase of dopamine to norepinephrine. It is primarily located in the adrenal medulla and in postganglionic sympathetic neurons. Variation in DBH gene has been investigated as a modular of psychotic symptoms in psychiatric disorders and in tobacco addiction.
- Gated Calcium Channel (CACNA1C): The gated calcium channel gene (CACNA1C) is responsible for coding of a protein that controls activation of voltage-sensitive calcium channels. Receptors for this protein are found widely throughout the body, including skeletal muscle, cardiac muscle, and in neurons in the CNS. In the brain, different modes of calcium entry into neurons determine which signaling pathways are activated, thus modulating excitatory cellular mechanisms. Associations of polymorphisms of this gene have been most frequently studied in related to cardiac disorders. However, a large- scale genetic analysis conducted in 2008 shows the possibility that CACNA1C has been associated with bipolar disorder and subsequently also with schizophrenia.
- Ankyrin 3 (ANK3): Ankyrins are proteins that are components of the cell membrane and interconnect with the spectrum-based cell membrane skeleton. The ANK3 gene codes for the protein Ankyrin G, which has a role in regulating sodium channels in neurons. Alterations of this gene have been associated with cardiac arrhythmias such as Brugada syndrome. Polymorphisms of this gene have also been associated with bipolar disorder, cyclothymic depression, and schizophrenia.
- Catechol O-Methyltransferase (COMT): The catechol O-methyltransferase gene (COMT) codes for the COMT enzyme that is responsible for the metabolism of the catecholamine neurotransmitters, dopamine, epinephrine, and norepinephrine. COMT inhibitors, such as entacapone are currently used in the treatment of Parkinson disease. A polymorphism of the COMT gene, the Val158Met polymorphism, has been associated with alterations in emotional processing and executive function and has also been implicated in increasing susceptibility to schizophrenia.
- Methylenetetrahydrofolate Reductase (MTHFR): The Methylenetetrahydrofolate Reductase gene (MTHFR) is a widely studied gene that codes for the protein that converts folic acid to methylfolate. Methylfolate is a precursor for the synthesis of norepinephrine, dopamine and serotonin. It is a key step in the metabolism of homocysteine to methionine, and deficiency of MTHFR can cause hyperhomocysteinemia and homocystinuria. The MTHFR protein also plays a

major role in the epigenetics, through methylation of somatic genes. A number of polymorphisms have been identified that a result in altered activity of the MTHFR enzyme. These polymorphisms have been associated with a wide variety of clinical disorders, including vascular disease, neural tube defects, dementia, colon cancer and leukemia.

- y-Aminobutyric Acid A Receptor: This gene encodes a ligand-gated chloride channel composed of 5 subunits that responds to GABA, a major inhibitory neurotransmitter. Mutations in the y-aminobutyric acid (GABA) receptor have been associated with several epilepsy syndromes.
- u and k Opioid Receptors: OPRM1 encode the u-opioid receptor, which is a G-protein coupled receptor that is the primary site of action for commonly used opioids, including morphine, heroin, fentanyl, and methadone. Polymorphisms in the OPRM1 gene have been associated with differences in dose requirements for opioids. OPRK1 encodes the k-opioid receptor, which binds the natural ligand dynorphin and a number of synthetic ligands.
- Cytochrome p450 Genes: CYP2D6, CYP2C19, CYP3A4, CYP1A2, CYP2C9, and CYP2B6 code for hepatic enzymes that are members of the cytochrome p450 family and are responsible for the metabolism of a wide variety of medications, including many psychotropic agents. For each of these genes, polymorphisms exist that impact the rate of activity, and therefore the rapidity of elimination of drugs and their metabolites. Based on the presence or absence of polymorphisms, patients can be classified as rapid metabolizers (RM), intermediate metabolizers (IM), and poor metabolizers (PM).
- P-Glycoprotein Gene: The ABCB1 gene, also known as the MDR1 gene, encodes P-glycoprotein which is involved in the transport of most antidepressants across the blood-brain barrier. ABCB1 polymorphisms have been associated with differential response to antidepressants that are substrates of P-glycoprotein, but not to antidepressants that are not P-glycoprotein substrates.
- UDP-Glucuronosyltransferase Gene: The UDP-glucuronosyltransferase gene, UGT1A4, encodes an enzyme of the glucuronidation pathway that transforms small lipophilic molecules into water-soluble molecules. Polymorphisms in UGT1A4 have been associated with variation in drug metabolism, including some drugs used for mental health disorders.

Comparators

The following practices are currently being used to make decisions about management of mental illness: diagnosis and risk assessment without genetic testing.

At present, decisions about the management of mental illnesses are made when patients present with symptoms and are typically diagnosed based on clinical evaluation according to standard criteria (i.e., Diagnostic and Statistical Manual of Mental Disorders).

Outcomes
The general outcomes of interest are change in disease state, morbid events, functional outcomes, health status measures, quality of life and treatment-related morbidity.

The primary outcome of interest is change in disease outcomes, which would result directly from changes in management that could be instituted because of earlier disease detection. Standardized outcome measures are available for many mental illnesses. Commonly used measures for the evaluation of depression in clinical trials are described in the next section.

Review of Evidence
In 2018, Numberger et. al., the International Society of Psychiatric Genetics (ISPG) created a Residency Education Committee with the purpose of identifying key genetic knowledge that should be taught in psychiatric training programs. Thirteen committee members were appointed by the ISPG Board of Directors, based on varied training, expertise, gender, and national origin. The Committee has met quarterly for the past 2 years, with periodic reports to the Board and to the members of the Society. The information summarized includes the existing literature in the field of psychiatric genetics and the output of ongoing large genomics consortia. An outline of clinically relevant areas of genetic knowledge was developed, circulated, and approved. This document was expanded and annotated with appropriate references, and the manuscript was developed. Specific information regarding the contribution of common and rare genetic variants to major psychiatric disorders and treatment response is now available. Current challenges include the following: (1) Genetic testing is recommended in the evaluation of autism and intellectual disability, but its use is limited in current clinical practice. (2) Commercial pharmacogenomic testing is widely available, but its utility has not yet been clearly established. (3) Other methods, such as whole exome and whole genome sequencing, will soon be clinically applicable. The need for informed genetic counseling in psychiatry is greater than ever before, knowledge in the field is rapidly growing, and genetic education should become an integral part of psychiatric training.

Panels of genetic tests have been developed and have been proposed for the use of predicting a patient's response to, dose requirement for, or adverse effects from one of several medications (or classes of medications) (pharmacogenomics) used to treat mental health conditions.

Pharmacogenomic testing in patients who are being treated with or considered for therapy with several different medications used to treat mental illness is to inform a decision whether to start a particular drug, set or adjust dose, or change drugs when a therapy fails. Interventions of interest include testing for genes associated with medication pharmacokinetics and/or pharmacodynamics, either as single genes or as a panel. Currently decisions about medication management for mental illnesses are typically based on clinical response. The primary outcome of interest is change in disease outcomes resulting from more appropriate selection of specific drugs or doses for the

patient's condition. In addition, avoidance of adverse effects is an important outcome. Testing would generally occur in the primary care or mental health practice setting.

Genetic variants may alter medications pharmacokinetics (i.e., how medications are absorbed, distributed, metabolized or excreted) or pharmacodynamics (i.e. medications effects on the body); therefore, individual genetic differences may lead to variability in the effectiveness of medications used to treat mental health disorders. To distinguish genes predictive of treatment response, versus those prognostic (predictive of outcome independent of treatment), it is usually necessary for studies to evaluate outcomes in patients receiving treatment and in patients not receiving treatment (or receiving alternative treatment). A gene that is predictive will result in a study demonstrating an interaction between genotype and treatment. In many studies claiming to evaluate genotype and treatment response, only patients receiving treatment have been evaluated.

Based on review of the literature no studies were identified addressing analytic validity of commercially available tests for mental health panels or specific genes. Genetic variants appear to have some association with response to medication, particularly for SLC6A4 variants and response to antidepressants. However, because many studies did not include untreated patients or patients treated with alternative therapies, one cannot determine from many of these studies whether the identified genes are predictive of treatment response or are simply prognostic factors (predictive of outcome independent of treatment).

Management changes that might be made in response to genetic testing information include selection of specific medications according to test results, discontinuation of medications, and change in dosing of medications. However, management changes made in response to genetic testing information are not well defined and may vary according to the judgement of the treating clinician. Currently there are no specific recommended changes in management linked to specific test results, making it difficult to assess whether test results lead to improvements in net health outcomes.

Pharmacogenomic Testing to Inform Medication Selection for Antidepressants
Despite guideline recommendations and expert opinions over 35 commercial entities provide combinatorial pharmacogenomic (PGx) test for depression in the United States, with claims of predicting antidepressant response and tolerability based on an individual's pharmacokinetic and pharmacodynamics gene variants. The largest randomized controlled trial (RCT), the GUIDED study, was unable to predict antidepressant tolerability despite including CYP2D6 and CYP2C19 polymorphisms (genotyping). Candidate gene polymorphisms selected to predict efficacy, such as the serotonin transporter and serotonin receptors, have also not been informative. There has been much debate about the clinical utility and validity of this testing, and the conclusion of both a meta-analysis and expert opinion is that there is insufficient evidence that any of these tests can predict either antidepressant efficacy or tolerability.

Clinical Context and Test Purpose
The purpose of pharmacogenetic testing in patients with depression is to inform antidepressant selection in order to improve symptoms (i.e., clinical response) and, preferably, to achieve remission of depression.

Major Depressive Disorder (MDD) is a mood disorder characterized by pervasive sadness, lack of interest and enjoyment in most activities, feelings of low self-worth, sleep disturbance, over-or under-eating, suicidal thoughts, and suicide attempts. The goal of treatment is remission of depression. While response to treatment is defined as 50% or greater reduction of symptoms; the patient who has responded, but is not in remission, may still bear a considerable burden of depression. Moreover, the risk of recurrence is greater than when remission is achieved. The main categories of treatment for MDD are psychotherapy, pharmacotherapy, and brain stimulation therapies. These may be used in combination. First-generation antidepressants are tricyclic antidepressants and monoamine oxidase inhibitors. Classes of second-generation antidepressants are: selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors and atypical agents.

Individuals who fail to achieve remission of MDD after 2 vigorous trials of antidepressant medications have a poor prognosis. The Sequenced Treatment Alternatives to Relieve Depression * (STAR*D) found that only about half of patients reached remission after 2 treatments. Individuals may stop treatment due to side effects of antidepressants, which can include drowsiness; insomnia/agitation; orthostatic hypotension; QTc prolongation; gastrointestinal toxicity; weight gain; and sexual dysfunction.

Pharmacogenomic testing is proposed to identify which antidepressant medications would be most effective or have the least side effects based on genetic variants that affect drug metabolism.

Populations
The relevant population of interest is adult individuals who have a diagnosis of MDD.

MDD is defined by the presence of 5 or more of the symptoms below for a period of at least 2 weeks. At least 1 symptom must be: (1) lack of interest or enjoyment in most activities, almost every day; or (2) depressed mood almost every day for most of the day. In addition, at least 4 of the symptoms below must be present almost every day.

- Sleep disturbance, insomnia, or excessive sleepiness
- Over-or under-eating with significant weight gain or loss
- Observable psychomotor agitation or retardation
- Fatigue or loss of energy
- Difficulty concentrating or making decisions
- Feelings of worthlessness or inappropriate guilt
- Thoughts of death or suicide, or suicide attempt.

The symptoms are not attributable to another medical condition, or behavioral disorder or substance abuse.

Interventions
The interventions being considered are commercially available pharmacogenetic tests to inform medication selection.

Three commercially available pharmacogenetic tests for antidepressant selection are reviewed here: Each test has its own proprietary algorithm for assessing genes associated with drug pharmacokinetics and pharmacodynamics. Each of these tests also has a proprietary format for reporting results and categorizing likely responsiveness or intolerance to available antidepressants.

All laboratory developed tests may not subject to U.S. Food and Drug Administration (FDA) regulation. However, recently, the FDA has raised concerns about pharmacogenetic tests that claim to predict medication response where drug labeling does not describe a predictive relationship between genetic variation and drug response. The FDA has reportedly reached out to firms marketing such tests, including tests of antidepressant response, with concerns about claims of clinical benefit.

Comparators
The following practices are currently being used to make decisions about antidepressant drug selection: antidepressant selection without pharmacogenetic testing.

At present, there is no definitive algorithm for selecting next line treatment after failure to respond to initial treatment.

Outcomes
The general outcomes of interest are symptoms, change in disease state, morbid events, functional outcomes, health status measures, quality of life, and treatment-related morbidity.

This evidence review assesses whether genetic testing for the management of depression is clinically useful. The balance of benefits and harms must be better when the test is used to manage the condition than when no test is used. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid adverse events.

There are standardized outcome measures for depression (e.g., Hamilton Rating Scale for Depression [HAM-D], Montgomery-Asberg Depression Rating Scale [MADRS], and Beck's Depression Inventory [BDI]). Scoring for the HAM-D and MADRS.

HAM-D and MADRS are physician scored scales that rate the presence and intensity of attributes of depression. The HAM-D, introduced by Max Hamilton in 1960, is the progenitor of depression measurement scales. Attributes rated include depressive mood,

guilt feelings, insomnia, suicidal ideas or attempts, work, and activity. However, shortcomings of HAM-D are incomplete overlap with DSM criteria for MDD and weak item-level inter-rarer reliability. Nonetheless, HAM-D has moderate to high correlation with other depression scales. Various versions have been developed, intended to make the instrument easier to use. The 17-item HAM-D (HAM-D17) is the most commonly used instrument in trials of depression drugs. The MADRS is the next most commonly used instrument in trials of depression drugs. Attributes scored include sadness, pessimism, inability to feel, and suicidal thoughts. As with HAM-D, MADRS has incomplete overlap with DSM criteria for MDD. MADRS is reported to correlate to other depression scales, including the HAM-D17. MADRS is generally reported to be more sensitive to treatment related change and to have better inter-rater reliability than HAM-D17; perhaps because of its more uniform structure.

Review of Evidence
A recent meta-analysis of five RCTs demonstrated that, overall, individuals with PGx-guided antidepressant treatment were 1.7 times more likely to achieve remission than usual care. At face value, this seems promising. However, there are several concerns with this conclusion. First, remission of symptoms was not the primary outcome measure in any of the studies, and the GUIDED study failed to meet its primary outcome. Also, the population included in the meta-analysis was composed predominately of white women aged 40-50 years. Many patients do not fit this description, which leads to question the generalizability of the studies. Additionally, the meta-analysis was unable to inform at what point in antidepressant treatment PGx testing is most beneficial. As a whole, the five studies have also been criticized because of a lack of transparency in their algorithms and a lack of blinding in most of the studies.

One of the criticisms of universal PGx testing to predict antidepressant response is the variability in the gene variants comprising each company's panel. Of the four companies that have published RCTs of PGx-guided treatment versus usual care, each company tests for a different panel of pharmacokinetic and pharmacodynamic candidate genes and SNVs. These differences lead to varying antidepressant recommendations in the proprietary PGx report. Therefore, a positive finding in one study does not indicate that all pharmacogenetic testing is useful. Unfortunately, no head-to-head trials of different PGx testing platforms have been conducted, therefore, at this time there is no conclusion on whether any one company yields superior results. In 2019, the International Society of Psychiatric Genetics updated their statement regarding genetic testing for psychiatric disorders which includes the following "expanded research efforts are needed to clarify the proper role of genetic testing and its clinical utility in psychiatric care." The field of pharmacogenomics (PGx) is advancing quickly, but evidence of its utility is inadequate. There is insufficient evidence to support the use of PGx testing to guide treatment decisions.

GeneSight® Test
GeneSight evaluates 8 genes (59 variants) in relation to 38 psychotropic medications and the potential for gene-drug interactions. Based on results from the genotype test, the

medications are categorized as either congruent ('use as directed' or 'use with caution') or incongruent ('use with increased caution and with more frequent monitoring') for a particular individual.

Systematic Reviews
Several publications have reported pooled analyses assessing the clinical utility of the GeneSight test to inform treatment decisions for individuals with MDD. The methods and studies included in these analyses varied. The review by Brown et al included a mix of randomized and nonrandomized studies, the Ontario Health review[18,] did not include the most recently published RCT (GAPP-MDD), and the analysis included in the GAPP-MDD publication did not include assessment of study quality or risk of bias according to established systematic review methods (e.g., the GRADE approach). Due to these limitations, the results from these publications are not discussed here.

Randomized Controlled Trials
Three randomized controlled trials (RCTs) compared response and remission with antidepressant therapy informed by GeneSight test results to antidepressant therapy selected without gene test results (i.e., SOC).

Two similarly designed RCTs (GUIDED and GAPP-MDD) compared 8-week outcomes in individuals who received treatment for MDD guided by GeneSight testing or SOC. In both GUIDED (N=1,799) and GAPP-MDD (N=437), the primary outcome was symptom improvement, measured by a change in HAM-D. Secondary outcomes were response and remission. Neither trial found a significant difference between GeneSight guided treatment and SOC in symptom improvement. The GUIDED trial found treatment guided by GeneSight associated with a statistically significant benefit for response and remission compared with treatment as usual, while there were no significant differences between GeneSight and TAU groups in the GAPP-MDD trial for response or remission. Due to limitations in both trials, no conclusions can be drawn from these trials about the differential effect of treatment guided by GeneSight versus SOC.

A serious methodological limitation of both trials is failure to account for all randomized participants in outcome analyses. The GUIDED trial randomized 1,799 individuals. After post-randomization exclusions, according to the text, 1,541 individuals remained, in what was labeled the intention to treat (ITT) cohort, but the ITT results reported included only 1,299 participants. The publication text also describes a per protocol cohort that included 1,398 participants, yet only 1,167 of these participants are accounted for in the study results reported of the text. The participant flow chart included in the Supplement describes missing data as occurring because of loss to follow-up, or study withdrawal due to inclusion/exclusion violations, HAM-D or Quick Inventory of Depressive Symptomatology (QIDS) scores, out of window visits, withdrawal of consent, or other reasons. Depending on the population (ITT or per protocol), up to one third of GUIDED randomized participants were missing from the reported results. The GAPP-MDD trial had similar limitations. The trial initially randomized 437 individuals, and the publication supplement indicates an ITT population of 363 individuals and a per protocol population

of 202 individuals at 8 weeks. Reasons given for post-randomization exclusions were similar to those in the GUIDED trial: loss to follow-up, or study withdrawal due to inclusion/exclusion violations, QIDS score, withdrawal of consent or "other." The GAPP-MDD publication reported symptom improvement for 203 individuals in the ITT population and for 134 individuals in the per protocol population; data from 308 ITT and 196 per protocol individuals were reported for response and remission. Depending on the population (ITT or per protocol) and the outcome analyzed, data from 30% to 69% of randomized individuals were missing. In both trials, the post-randomization exclusions and analysis methods do not conform with definitions of intent-to-treat and there were no sensitivity analyses for the missing data provided. In addition to these limitations, enrollment in the GAPP-MDD trial was stopped early due to a determination that it would not be possible to enroll enough participants to adequately power the trial. Although initially designed to enroll 570 participants, GAPP-MDD investigators revised that calculation based on results from the GUIDED trial, subsequently determining that a sample size of 4,000 would be required to achieve 90% power. Based on the recalculation, the GAPP-MDD results would have been powered at less than 25% probability to detect a difference between treatment groups even if the full, planned enrollment of 570 had been achieved.

A pilot RCT by Winner et al (2013) evaluated the effect of providing the GeneSight test on the management of psychotropic medications used for MDD in a single outpatient psychiatric practice. Fifty-one patients were enrolled and randomized to treatment as usual, or treatment guided by GeneSight testing. All patients underwent GeneSight testing, though results were not given to the physicians in the treatment as a usual group until after study completion. At 10-week follow-up, treating physicians' dose-adjusted patients' medication regimens with the same likelihood in the GeneSight group (53%) and the treatment as usual group (58%; p=.66). However, patients in the GeneSight group who were initially on a medication classified as "use with caution and with more frequent monitoring" were more likely than those with the same classification in the unguided group to have a medication change or dose adjustment (100% vs. 50% respectively; p=.02). Depression outcomes, measured by the HAM-D17 score, did not differ significantly between groups at the 10-week follow-up. This trial's small size may have limited the ability to detect a significant effect, as the authors estimated that 92 patients per arm would be required. The GeneSight directed arm and the SOC arm included 26 and 25 patients, respectively, in this pilot study for a larger trial.

Summary of Evidence

For adult individuals with MDD who receive GeneSight testing guided drug treatment, the evidence includes 3 RCTs. Relevant outcomes are symptoms, change in disease status, morbid events, functional outcomes, health status measures, quality of life, and treatment-related morbidity. The RCTs compared response (≥50% decrease in HAM-D17), remission (HAM-D17 ≤7), and symptom improvement (mean % change in HAM-D17) with antidepressant therapy informed by GeneSight test results to antidepressant therapy selected without GeneSight test results (ie, SOC). The GUIDED trial reported statistically significant improvements in response and remission in the GeneSight arm

compared to SOC at 8 weeks among individuals with MDD. However, depending on the population (ITT or per protocol), up to one-third of GUIDED randomized participants were missing from the reported results; the extent of missing data following randomization precludes conclusions on outcomes at 8 weeks. The GAPP-MDD trial, also comparing GeneSight guided treatment with SOC, found no statistically significant differences between groups in response, remission, or symptom improvement at 8 weeks follow-up, although like the GUIDED trial, a high proportion (up to 69%) of randomized participants were excluded from outcome analysis and the study was not adequately powered to detect between-group differences. In the third trial, a small, single-center pilot study by Winner et al (2013), depression outcomes did not differ significantly between GeneSight-guided care and SOC groups at the 10-week follow-up, though the study was underpowered to detect significant differences in outcomes between study arms. All these trials have major limitations in design and conduct and in consistency and precision, thus none provided adequate evidence. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For adult individuals with MDD who receive Neuropharmagen testing guided drug treatment, the evidence includes 2 RCTs. Relevant outcomes are symptoms, changes in disease status, morbid events, functional outcomes, health status measures, quality of life, and treatment-related morbidity. The 2 RCTs compared response (≥50% decrease in HAM-D17) and remission (HAM-D17 ≤7) with antidepressant therapy informed by Neuropharmagen test results to antidepressant therapy selected without Neuropharmagen test results (ie, SOC). The single-blinded RCT by Han et al (2018) reported statistically significant improvement in response (72% of 52 vs. 44% of 48; p=.01) but no statistically significant improvement in remission (46% of 52 vs. 26% of 48; p=.07) in the Neuropharmagen arm compared to SOC at 8 weeks among patients with MDD. The study reported an early dropout of 25% in guided-care and 38% in the standard care arm and used the LOCF approach in the ITT analysis of effectiveness. Use of LOCF assumes data are missing completely at random, which is unlikely to hold in this analysis. Also, the study did not report registration in any clinical trial database. The single-blinded RCT by Perez et al (2017) reported non-statistically significant improvement in response (45% of 141 vs. 40% of 139; p=.39) and remission (34% of 141 vs. 33% of 139; p=.87) in the Neuropharmagen arm compared to SOC at 12 weeks among individuals with MDD. Response and remission data were missing for 9% of individuals in the guided care group and 14% in the standard care group. None of these trials provided adequate evidence. Both studies have major limitations in design and conduct and in consistency and precision. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Genetic Testing to Inform Medication Selection for Patients with a Mental Illness other than Depression

Clinical Context and Test Purpose
The purpose of pharmacogenetic testing in individuals diagnosed with a mental illness other than depression is to inform management decisions such as starting a particular drug, determining, or adjusting a dose, or changing drugs when therapy fails.

Populations
The relevant population of interest is individuals with a mental illness other than depression.

Interventions
Interventions of interest include testing for genes (single or as part of a panel) associated with medication pharmacokinetics and/or pharmacodynamics.

Comparators
Currently, decisions about medication management for patients with mental illnesses are based on clinical response, potentially informed by studies such as the STAR*D study, which evaluated specific medication sequences.

Outcomes
The evidence review assesses whether genetic testing for the management of mental health conditions is clinically useful. To make a clinical management decision that improves the net health outcome; the balance of benefits and harms must be better when the test is used to manage the condition than when another test or no test is used. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

The primary outcome of interest is change in disease outcomes resulting from a more appropriate selection of specific drugs or doses for the patient's condition. Also, avoidance of adverse events is an important outcome.

Review of Evidence

Systematic Review
Hartwell et. al. (2020) conducted a systematic review and meta-analysis of the moderating effect of rs1799971, a single nucleotide polymorphism (SNP) that encodes a non-synonymous substitution (Asn40Asp) in the mu-opioid receptor gene, *OPRM1* on response to naltrexone treatment of alcohol use disorder. The meta-analysis included 7 RCTs (659 patients randomly assigned to receive naltrexone and 597 received placebo). Of the 5 alcohol consumption outcomes considered, there was a nominally significant moderating effect of the Asn40Asp SNP only on drinks per day (d=−0.18, 95% CI, −0.32 to −0.03; p=.02). However, the effect was not significant when multiple comparisons were considered. There was no statistically significant heterogeneity (I^2=33.8%, p=.18).

Randomized Controlled Trials
Kampangkaew et al (2019) conducted a study among cocaine and opioid codependent individuals randomized into disulfiram (n=32) and placebo (n=35) groups for 12 weeks of treatment and evaluated the role of SLC6A3 (DAT1) 40 bp 3′-untranslated region variable number tandem repeat variant in moderating disulfiram efficacy for cocaine dependence. Study reported better treatment outcomes with disulfiram pharmacotherapy of cocaine dependence among individuals with genetically higher dopamine transporter (DAT) levels compared to those with lower DAT levels.

Naumova el al (2019) conducted a randomized pharmacodynamic investigation to evaluate the effect of DRD4 exon 3 polymorphisms on child behaviors in response to treatment of attention deficit hyperactivity disorder (ADHD) with methylphenidate. In this 2-week prospective within-subject, placebo-controlled, crossover trial, there was significant interaction between DRD4 genotype and treatment when the child's behavior was evaluated by the parents (p=.035, effect size of 0.014), driven by a better treatment response in children homozygous for long 7-repeat allele.

Bradley et. al. (2018) conducted a double-blind RCT in which 685 individuals with depression and/or anxiety disorders were randomized to treatment guided by either NeuroIDgenetix or SOC. Among the participants, 115 in the experimental arm and 120 in the SOC arm had only anxiety. Outcomes included percent reduction in HAM-A and response (50% reduction in HAM-A) rate. Trained and blinded clinicians conducted interviews using the HAM-A. Response results were only reported for 224 moderate and severe anxiety (Anxiety Only HAM-A ≥18) group of patients (109 in the experimental arm and 115 in the SOC arm). Among the randomized moderate and severe anxiety patients with only anxiety, 25% in the experimental arm and 17% in the SOC arm were lost to follow up over the 12-week period. Response rate was significantly higher in the NeuroIDgenetix-guided group as compared to the control group at 12 weeks (63% vs. 50%; p=.04). The study does not report clearly if the analysis was based on the ITT population. Reporting is incomplete and suggestive of selective reporting.

Section Summary
Evidence for the use of pharmacogenetic testing in individuals with mental health conditions other than depression includes a meta-analysis on alcohol use disorder and an RCT on anxiety disorder. The meta-analysis found no significant effect of Asn40Asp on the response to naltrexone treatment of heavy drinking or alcohol use. The single available trial did not provide adequate or supportive evidence effect of pharmacogenetic testing on managing moderate to severe anxiety. The study had major limitations in design and conduct and precision.

No other studies performed a direct intervention study. Jukic et al (2019) conducted a retrospective cohort study using patient data from a routine therapeutic drug monitoring database and showed that CYP2D6 genetic variability had a significant effect on risperidone and aripiprazole exposure and treatment and lower doses should be

administered to CYP2D6 poor metabolizers to avoid overdosing and dose-dependent side-effects.

Summary of Evidence
For individuals with a mental illness other than depression who are undergoing drug treatment who receive genetic testing for genes associated with medication pharmacokinetics and pharmacodynamics, the evidence includes a systematic review and meta-analysis and RCTs evaluating associations between specific genes and outcomes of drug treatment. Relevant outcomes are symptoms, changes in disease status, morbid events, functional outcomes, health status measures, quality of life, and treatment-related morbidity. The systematic review and meta-analysis by Hartwell et al (2020) included 7 RCTs and reported no significant moderating effect of rs1799971, a single nucleotide polymorphism (SNP) that encodes a non-synonymous substitution (Asn40Asp) in the mu-opioid receptor gene, *OPRM1* on response to naltrexone treatment of alcohol use disorder. Bradley et al (2018) conducted a double-blind RCT among individuals with anxiety disorders and reported statistically significant improvement in response (≥50% decrease in HAM-A) in the NeuroIDgenetix arm (63% of 82) compared to SOC (50% of 95) at 12 weeks among a moderate and severe group of patients (p=.04). There was evidence of reporting bias and,e it was unclear if the analysis was based on theITT population. Furthermore, among the randomized moderate and severe anxiety patients with only anxiety, 25% in the experimental arm and 17% in the SOC arm were lost to follow-up over the 12-week period. The field of pharmacogenomics (PGx) is advancing quickly, but evidence of its utility is inadequate. There is insufficient evidence to support the use of PGx testing to guide treatment decisions. The evidence is insufficient to determine the effects of this technology on net health outcomes.

Practice Guidelines and Position Statements

American Academy of Neurology (AAN)
In 2014, the American Academy of Neurology published a position paper on the use of opioids for chronic non-cancer pain. Regarding pharmacogenomics testing, the guidelines stated that genotyping to determine whether the response to opioid therapy can or should be more individualized is an emerging issue that "will require original research to determine effectiveness and appropriateness of use."

American College of Cardiology Foundation (ACCF) and American Heart Association (AHA)
In 2010, the American College of Cardiology Foundation (ACCF) and the American Heart Association (AHA) issued a consensus statement on genetic testing for selection and dosing of clopidogrel, and their recommendation for practice included the following statements:

- Adherence to existing ACCF/AHA guidelines for the use of antiplatelet therapy should remain the foundation for therapy. Careful clinical judgment is required to assess the importance of the variability in response to clopidogrel for an individual patient and its associated risk to the patient.

- 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.
- 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 selection of the specific test, as well as the issue of reimbursement, is both important additional considerations.
- The evidence base is insufficient to recommend either routine genetic or platelet function testing at the present time. Clinical judgement 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.
- There are several possible therapeutic options for patients who experience an adverse event while taking clopidogrel in the absence of any concern about medication compliance

American College of Chest Physicians
The 9th Edition of the American College of Chest Physicians Evidence Based Clinical Practice Guidelines on Antithrombotic Therapy and Prevention of Thrombosis, published in 2012, states: "For patients initiating VKA (vitamin K antagonist) therapy, the expert panel recommends against the routine use of pharmacogenetic testing for guiding doses of VKA." (Grade 1B)

Clinical Pharmacogenetics Implementation Consortium
In 2012, the Clinical Pharmacogenetics Implementation Consortium (CPIC) issued a guideline for cytochrome P450 2D6 genotype and codeine therapy, which was updated in 2014 to reflect U.S. Food and Drug Administration (FDA) labeling about codeine in children status post tonsillectomy with or without adenoidectomy and to include other opioids metabolized by CYP2D6. These guidelines did not specifically recommend CYP2D6 genotyping individuals, although they did provide the following codeine therapy recommendations based on CYP2D6 phenotype.

- Ultrarapid metabolizer – avoid codeine use due to potential for toxicity.
- Extensive metabolizer- use label recommended age or weight specific dosing.
- Intermediate metabolizer – use label recommended age or weight specific dosing. If no response, consider alternative analgesics (e.g., morphine or a non-opioid).
- Poor metabolizer – avoid codeine use due to lack of efficacy.

In 2015, the Clinical Pharmacogenetics Implementation Consortium (CPIC) conducted a systematic literature review on the influence of *CYP2D6* and *CYP2C19* genotyping on selective serotonin reuptake inhibitor (SSRI) therapy. The CPIC provided dosing recommendations for SSRIs based on phenotypes that classified patients as ultra-rapid metabolizers, extensive metabolizers, intermediate metabolizers, and poor metabolizers. However, CPIC noted that patients on an effective and stable dose of SSRIs would not benefit from dose modifications based on CYP2D6 and CYP2C19 genotype results. Additionally, CPIC asserted that genetic testing is only one factor among several clinical factors that should be considered when determining a therapeutic approach.

In 2016, the Clinical Pharmacogenetics Implementation Consortium (CPIC) conducted a systematic literature review on the influence of *CYP2D6* and *CYP2C19* genotype on the dosing of tricyclic antidepressants. Dosing recommendations for tricyclic antidepressants were provided, based on patient classifications of ultrarapid metabolizers, extensive metabolizers, intermediate metabolizers, and poor metabolizers

In 2017, the Clinical Pharmacogenetics Implementation Consortium (CPIC) issued an updated guideline for pharmacogenetics guided warfarin dosing in 2017. The guideline provides recommendations for genotype-guided warfarin dosing to achieve a target international normalized ratio of 2-3 for adult and pediatric patients specific to continental ancestry. The guideline also states that "Although there is substantial evidence associating CYP2C9 and VKORC1 variants with warfarin dosing, randomized clinical trials have demonstrated inconsistent results in terms of clinical outcomes."

International Society of Psychiatric Genetics
In 2019, the International Society of Psychiatric Genetics updated their statement regarding genetic testing for psychiatric disorders which states the following:

Pharmacogenetic Tests to Guide Optimal Treatment
Current guidelines provide no advice on when, or to whom, genetic testing should be offered. Clinical trials to date have suggested testing might be most beneficial for individuals who have experienced an adverse drug reaction or inadequate response to a previous antidepressant trial.

Pharmacogenetic testing should be viewed as a decision-support tool to assist in thoughtful implementation of good clinical care, enhancing rather than offering an alternative to standard protocols. In this context, genetic markers can supplement demographic (e.g., age, sex, family history), clinical (e.g., concomitant medications), and lifestyle (e.g., diet, smoking) information to help guide treatment decisions. Genetic testing for HLA-B*15:02 has become mandatory by way of national regulations in Taiwan and Hong Kong while testing is freely available in Thailand in order to avoid serious side effects (e.g., Stevens-Johnson Syndrome) to carbamazepine. At this time, evidence does not support widespread use of other pharmacogenetic testing, but when genetic information is available, we recommend that such information should be considered when making medication selection and dosing decisions. We also recommend

that clinicians and patients educate themselves or consult an expert prior to ordering a pharmacogenetic test and encourage the use of freely available resources to assist in the interpretation and implementation of test results.

Summary Recommendations

- Common genetic variants are not sufficient to cause psychiatric disorders such as depression, bipolar disorder, substance dependence, or schizophrenia. Genotypes from large numbers of common variants can be combined to produce an overall genetic risk score which can identify individuals at higher or lower risk, but at present it is not clear that this has clinical value.
- There is growing evidence that rare, pathogenic variants with large effects on brain function play a causative role in a significant minority of individuals with psychiatric disorders and may be a major cause of illness in some families. Identification of known pathogenic variants may help diagnose rare conditions that have important medical and psychiatric implications for individual patients and may inform family counseling. Identification of de novo mutations and copy number variants (CNVs) may also have a place in the management of serious psychiatric disorders. CNV testing may also prove useful for persons requesting counseling on familial risk. While the Committee did not reach consensus on widespread use of CNV testing in adult-onset disorders, most agreed that such tests may have value in cases that present atypically or in the context of intellectual disability, autism spectrum disorder, learning disorders, or certain medical syndromes.
- Professional counseling can play an important role in the decision to undergo genetic testing and in the interpretation of genetic test results. We recommend that diagnostic and genome-wide genetic testing should include counseling by a professional with expertise in both mental health and in the interpretation of genetic tests. Consultation with a medical geneticist is recommended, if available, when a recognized genetic disorder or other findings with reproductive or other broad health implications.
- Whenever genome-wide testing is performed, the possibility of incidental (secondary) findings must be communicated in a clear and open manner. Procedures for dealing with such findings should be made explicit and should be agreed with the patient or study participant in advance. The autonomy of competent patients regarding preferences for notification of incidental findings should be respected.
- Genetic test results, like all medical records, are private data and must be safeguarded against unauthorized disclosure with advanced encryption and computer security systems.
- We advocate the development and dissemination of education programs and curricula to enhance knowledge of genetic medicine among trainees and mental health professionals, increase public awareness of genetics and genetic testing, and reduce stigma.
- Expanded research efforts are needed to clarify the proper role of genetic testing and its clinical utility in psychiatric care.

- Pharmacogenetic testing should be viewed as a decision-support tool to assist in thoughtful implementation of good clinical care. We recommend HLA-A and HLA-B testing prior to use of carbamazepine and oxcarbazepine, in alignment with regulatory agencies and expert groups. Evidence to support widespread use of other pharmacogenetic tests at this time is still inconclusive, but when pharmacogenetic testing results are already available, providers are encouraged to integrate this information into their medication selection and dosing decisions. Genetic information for CYP2C19 and CYP2D6 would likely be most beneficial for individuals who have experienced an inadequate response or adverse reaction to a previous antidepressant or antipsychotic trial.

American Academy of Neurology (AAN)
In 2014, the American Academy of Neurology published a position paper on the use of opioids for chronic non-cancer pain. Regarding pharmacogenomics testing, the guidelines stated that genotyping to determine whether the response to opioid therapy can or should be more individualized is an emerging issue that "will require original research to determine effectiveness and appropriateness of use."

National Comprehensive Cancer Network (NCCN)
Breast Cancer Version 4.2022
CYP2D6 genotype testing is not recommended for patients considering tamoxifen.

Regulatory Status

CYP450 Genotyping to Determine Drug Metabolizer Status
Diagnostic genotyping tests for certain CYP450 enzymes are now available. Some tests are offered as in-house laboratory developed test services, which do not require U.S. Food and Drug Administration (FDA) approval, but which must meet Clinical Laboratory Improvement (CLIA) quality standards.

Several test kits for CYP450 genotyping have been cleared for marketing by the FDA (FDA product code: NTI). These include:

- The AmpliChip® (Roche Molecular Systems, Inc.) is an FDA-cleared test for CYP450 genotyping. The AmpliChip® is a microarray consisting of many DNA sequences complementary to 2 *CYP450* genes and applied in microscopic quantities at ordered locations on a solid surface (chip). The AmpliChip® tests the DNA from a patient's white blood cells collected in a standard anticoagulated blood sample for 29 polymorphisms and mutations for the *CYP2D6* gene and 2 polymorphisms for the *CYP2C19* gene. CYP2D6 metabolizes approximately 25% of all clinically used medications (e.g., dextromethorphan, beta-blockers, antiarrhythmics, antidepressants, and morphine derivatives), including many of the most prescribed drugs. CYP2C19 metabolizes several important types of drugs, including proton-pump inhibitors, diazepam, propranolol, imipramine, and amitriptyline. FDA cleared the test "based on results of a study conducted by the manufacturers of hundreds of DNA samples as well as on a broad range of supporting peer-reviewed

literature." According to FDA labeling, "Information about CYP2D6 genotype may be used as an aid to clinicians in determining therapeutic strategy and treatment doses for therapeutics that are metabolized by the CYP2D6 product."

- The xTAG® CYP2D6 Kit (Luminex Molecular Diagnostics, Toronto, ON) was cleared for marketing in August 2010 based on substantial equivalence to the AmpliChip CYP450 test. It is designed to identify a panel of nucleotide variants within the polymorphic *CYP2D6* gene on chromosome 22.
- The INFINITI CYP2C19 Assay (AutoGenomics Inc., Vista, CA) was cleared for marketing in October 2010 based on substantial equivalence to the AmpliChip CYP450 test. It is designed to identify variants within the *CYP2C19* gene (*2, *3, and *17)
- Verigene CYP2C19 Nucleic Acid Test (Nanosphere Inc., Northbrook, IL) , designed to identify variants within the *CYP2C19* gene, was cleared for marketing in November 2013 based on substantial equivalence to the INFINITI CYP2C19 Assay.
- The Spartan RX CYP2C19 Test System Spartan Bioscience, Redwood Shores, CA), designed to identify variants in the CYP2C19 gene (*2, *3, and *17 alleles), was cleared for marketing in August 2013 based on substantial equivalence to the INFINITI CYP2C19 Assay.
- The xTAG® CYP2C19 Kit v3 (Luminex Molecular Diagnostics, Toronto, ON), designed to identify variants in the *CYP2C19* gene (*2, *3, and *17 alleles) was cleared for marketing in September 2013 based on substantial equivalence to the INFINITI CYP2C19 Assay.

Food and Drug Administration (FDA) Labeling on CYP450 Genotyping

The FDA maintains online compendia of pharmacogenetic associations online under 3 categories: 1. pharmacogenetic associations for which the data support therapeutic management recommendations; 2. pharmacogenetic associations for which the data indicate a potential impact on safety or response and 3. pharmacogenetic associations for which the data demonstrate a potential impact on pharmacokinetic properties only.[1]

The FDA has included pharmacogenomics information in the physician prescribing information (drug labels) of multiple drugs. In most cases, this information is general and lacks specific directives for clinical decision making. In the following examples, the FDA has given clear and specific directives on either use of a specific dose (e.g., eliglustat, tetrabenazine) or when a drug may not be used at all (e.g., codeine) and therefore evidence in such cases is not reviewed in the Rationale section.

Tetrabenazine

FDA approval 2008 Tetrabenazine (xanazine): Patients requiring doses above 50 mg per day should be genotyped for the drug metabolizing enzyme CYP2D6 to determine if the patient is a poor metabolizer (PM) or an extensive metabolizer (EM). Maximum daily dose in PMs: 50 mg with a maximum single dose of 25 mg; Maximum daily dose in Ems and intermediate metabolizers (IMs): 100 mg with a maximum single dose of 37.5 mg.

Eliglustat
FDA Approval 2014 Cerdelga (eliglustat): Select patients using an FDA cleared test for determining CYP2D6 genotype: CYP2D6 Ems or IMs: 84 mg orally twice daily. CYP2D6 PMs: 84 mg orally once daily.

In 2017, FDA approved deutetrabenazine (austedo), which is a vesicular monoamine transporter2 (VMAT2) inhibitor indicated for the treatment of chorea associated with Huntington's disease. Although the pharmacokinetics of deutetrabenazine and its metabolites have not been systematically evaluated in individuals wo do not express the drug metabolizing enzyme CYP2D6, it is likely that the exposure to a-HTBZ and B-HTBZ would be increased similarly to taking strong CYP2D6 inhibitors (approximately 3-fold). The FDA labeling for deutetrabenazine (austedo) states "in patients receiving strong CYP2D6 inhibitors (e.g., quinidine, antidepressants such as paroxetine, fluoxetine and bupropion) to total disease of deutetrabenazine (austedo) should not exceed 36 mg (maximum single dose of 18 mg). In patients who are poor CYP2D6 metabolizers the total daily dosage should not exceed 36 mg (maximum single dose of 18 mg)."

Siponimod
In 2019, the FDA approved Mayzent (siponimod) which is a sphingosine 1-phosphatereceptormodulater indicated for the treatment of relapsing forms of multiple sclerosis (MS), to include clinically isolated syndrome, relapsing-remitting disease and active secondary progressive disease in adults. The FDA labeling for mayzent (siponimod) states "before the initiation of treatment with Mayzent, assess the following: Test patients for CYP2C9 variants to determine CYP2C9 genotype. After treatment titration the recommended maintenance dosage of Mayzent is 2 mg take orally once daily starting on day 6. Dosage adjustment is required in patients with a CYP2C9 1/3 or 2/3 genotype."

Codeine
The FDA does not recommend genotyping before prescribing codeine. The FDA has contraindicated codeine for treating pain or cough in children under 12 years of age and codeine is not recommended for use in adolescents ages 12 to 18 years who are obese or have conditions such as obstructive sleep apnea or severe lung disease. There is an additional warning to mothers not to breastfeed when taking codeine.

Genetic Testing for Warfarin (Coumadin) Sensitivity
Several tests to help assess warfarin sensitivity, by determining the presence or absence of the relevant *CYP2C9*, *VKORC1*, and *CYP4F2* variants, have been cleared by the U.S. Food and Drug Administration (FDA) for marketing. Similar tests also may be available as laboratory-developed services; laboratory-developed tests must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments. The tests are not identical in terms of the specific variants and number of variants detected. Generally, such tests are not intended as stand-alone tools to determine optimum drug dosage but should be used with clinical evaluation and other tools, including the international

normalized ratio, to predict the initial dose that best approximates the maintenance dose for patients.

FDA Cleared Warfarin Tests

Test (Laboratories)	Alleles Tested	Estimated Time to Completion, h
eSensor® Warfarin Sensitivity Test (GenMark Dx)[a]	CYP2C9*2 and *3, VKORC1 1639G >A	3-4
Rapid Genotyping Assay (ParagonDx)	CYP2C9*2 and *3, VKORC1 1173C >T	Not reported[b]
Verigene® Warfarin Metabolism Nucleic Acid Test (Nanosphere)	CYP2C9*2 and *3, VKORC1 1173C >T	≤2
Infiniti® 2C9-VKORC1 Multiplex Assay for Warfarin (AutoGenomics)[c]	CYP2C9*2 and *3, VKORC1 1639G >A	6-8
eQ-PCR™ LightCycler® Warfarin Genotyping Kit (TrimGen)	CYP2C9*2 and *3, VKORC1 1639G >A	≤2

CYP2C9: cytochrome P450 2C9 enzyme; FDA: Food and Drug Administration; VKORC1: vitamin K epoxide reductase complex, subunit 1.
[a] eSensor Warfarin Plus Test offers testing for *CYP2C9*2*, *3, *5, *6, *11, *14, *15, and *16, *VKORC1* 1639G>A, and *CYP4F2*.
[b] Langley et al (2009) reported a turnaround time of 1.5 hours for the ParagonDx SmartCycler, which may be a precursor assay.[22,]
[c] The expanded Infiniti *CYP450* 2C9 assay offers testing for *CYP2C9*2, *3, *4, *5, *6*, and *11, *VKORC1* 1639G>A, and 6 other *VKORC* variants.

In August 2007, FDA approved updated labeling for Coumadin® to include information on testing for gene variants that may help "personalize" the starting dose for each patient and reduce the number of serious bleeding events. The label was updated again in January 2010. With each update, manufacturers of warfarin (generic for Coumadin®) were directed to add similar information to their products' labels. The 2010 update added information on personalizing initial dose by genotyping results for *CYP2C9* and *VKORC1*, providing a table of genotypes, and suggested initial dose ranges for each. However, suggested starting doses are also provided when genotyping information is unavailable, indicating that genetic testing is not required. Furthermore, FDA did not include information on genetic variation in the label's black box warning on bleeding risk.

Pharmacogenomic Testing for Mental Health Conditions

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests (LDTs) must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments (CLIA). The tests discussed in this section are available under the auspices of CLIA. Laboratories that offer LDTs must be licensed by CLIA for high-complexity testing. To date, the U.S. Food and Drug Administration has chosen not to require any regulatory review of this test.

Examples of commercially available panels include but are not limited to the following:

- Ally Diagnostics Genetic Testing Panel
- Alpha Genomix Psychiatry/ADHD Panel
- AltheaDX IDgenetix branded tests – IDgenetix, NeuroIDgenetix
- Antidepressants and Antipsychotics Pharmacogenetics Panel
- Anxiety, Insomnia and Severe Agitation Panel
- Focused Pharmacogenomics Panel Mayo Clinic
- Genecept Assay
- GeneDose ADHD Medication Appropriateness Reporting
- GeneDose Behavioral Health Medication Appropriateness Reporting
- GeneSight Psychotropic Panel
- GeneSight ADHD
- GeneSight MTHFR
- Genetic Technological Innovations Pharmacogenetic Testing
- GeneTrait Anti-ADHD Drug Metabolism and Risk Factor Profile
- GeneTrait Psychotropic Drug Metabolism and Risk Factor Profile
- Genomind Professional PGx Express Core Anxiety and Depression Report
- Genomind Professional PGx Express Full Mental Health Report
- Kailos Test for Antidressants
- Mental Health DNA Insight
- Millennium Pharmacogenetic Testing (PGT) in Mental Health
- Molecular Testing Labs Psychotropic Medication Panel
- NeuroIDgenetix test
- PersonaGene Panel PsychiaGene
- PGXL Multi-Drug Panel
- PGxOne Plus Psychiatry
- Pharmacogenomic Comprehensive Panel for Antidepressants and Antipsychotics
- Proove Psychiatric Profile
- Proove Psychiatric Risk and Response Panel
- PsychiaGene Panel
- Psych HealthPGx Panel, RPRD Diagnostics
- Psychiatric Dosing Panel
- Psychiatry/ADHD
- RightMed PGx16 Test
- RightMed Comprehensive Test Exclude F2 and F5
- RightMed Comprehensive Test
- RightMed Gene
- RESPONSEpsych/ADHD
- SureGene Test for antypsychotic and antidepressant Response Gene Panel (STAR2)
- YouScript Panel (YouScript Psychotropic, YouScript Psychotropic Plus, YouScript ADHD)

Pharmacogenomic Testing for Pain Management
Clinical laboratories may develop and validate tests in-house and market them as laboratory service; laboratory-developed tests (LDTs) must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments (CLIA). Test for Pain Management are available under the auspices of CLIA. Laboratories that offer LDTs must be licensed by CLIA for high-complexity testing. To date, the U.S. Food and Drug Administration (FDA) has chosen not to require any regulatory review of this test.

PRIOR APPROVAL

Not applicable.

POLICY

CYP450 Genotyping to Determine Drug Metabolizer Status
CYP450 genotyping for CYP2C19 for the purpose of aiding in the choice of clopidogrel (plavix) versus alternative antiplatelet agents or in decisions on the optimal dosing, for an individual at risk for adverse events and therefore requires assessment for CYP2C19 before undergoing treatment with clopidogrel (plavix) in order to identify his or her risk of poorly metabolizing clopidogrel (plavix) and his or her likelihood of exhibiting poor response to this drug is considered medically necessary for any one of the following indications:

- Patient with unstable angina; **or**
- Patient with non-ST-elevation myocardial infarction; **or**
- Patient who experiences recurrent acute coronary syndromes (unstable angina/myocardial infarction) despite ongoing therapy with clopidogrel (plavix); **or**
- Patients undergoing high risk percutaneous coronary interventions (PCI) with extensive and/or very complex disease.

Note: Per American Heart Association: Acute Coronary Syndrome is defined as those situations where the blood supplied to the heart muscle is suddenly blocked.

CYP450 genotyping for CYP2D6 to determine drug metabolizer status is considered **medically necessary** for individuals with the following:

- Diagnosed with Huntington's disease and being considered for treatment with a dosage of tetrabenazine (xenazine) greater than 50mg/day; **or**
- Diagnosed with Huntington's disease and being considered for treatment with a dosage of deutetrabenazine (austedo) greater than 36mg/day; **or**
- Diagnosed with Gaucher disease type I being considered for treatment with eliglustat (cerdelga)

CYP450 genotyping for CYP2C9 to determine drug metabolizer status is considered **medically necessary** for individuals diagnosed with a relapsing form of multiple sclerosis (MS) (including clinically isolated syndrome, relapsing remitting disease or active secondary progressive disease) before the initiation of treatment with Mayzent (Siponimod) as dosage adjustment is required in patients with CYP2C9 1/3 or 2/3 genotype.

Repeat CYP450 genotype testing for CYP2C19, CYP2D6 and CYP2C9 for the above medically necessary indications is considered **not medically necessary**.

CYP450 genotyping for the purpose of aiding in the choice of drug or dose to increase efficacy and/or avoid toxicity not meeting the above criteria and including but not limited to the following drugs is considered **investigational** because the evidence is insufficient to determine the effects of the technology on net health outcomes:

- Selection or dosing of selective serotonin reuptake inhibitors (SSRI)
- Selection or dosing of antipsychotic drugs
- Selection or dosing of opioid analgesics
- Selection and dosing of selective norepinephrine reuptake inhibitors (SNRIs)
- Selection and dosing of tricyclic antidepressants
- Dosing of efavirenz (common component of highly active antiretroviral therapy for HIV)
- Dosing of immunosuppressants for organ transplantation
- Selection or dose of beta blockers
- Dosing and management of antituberculosis medications
- Selection or dosing of Tamoxifen
- Selection or dosing of Clopidogrel (Plavix) except as indicated above
- Dosing of Tetrabenzine (Xenazine) except as indicated above
- Dosing of Eliglustat (Cerdelga) except as indicated above
- Dosing of Deutetrabenazine (Austedo) except as indicated above
- Dosing of Mayzent (Siponimod) except as indicated above

Genotyping for Warfarin (Coumadin) Response and Dosing
Genotyping to determine cytochrome P450 2C9 (CYP2C9), P450 4F2 (CYP4F2), and vitamin K epoxide reductase subunit C1 (VKORC1) genetic variants is considered **investigational** for the purpose of managing the administration and dosing of warfarin (Coumadin), including use in guiding initial warfarin (Coumadin) dose to decrease time to stable international normalized ratio (INR) and reduce the risk of serious bleeding**.** The evidence is insufficient to determine the effects of the technology on net health outcomes.

Pharmacogenomic Panel Testing to Determine Drug Metabolizer Status

Pharmacogenomic Testing for Pain Management
Pharmacogenomic panel testing for multi-genes for pain management treatment, including but not limited to the following to determine drug-metabolizer status (to inform

the selection and/or dose of medication(s)) is considered **investigational because** the evidence is insufficient to determine the effects of the technology on net health outcomes**:**

- Advanced Pain Care Pharmacogenetic panel
- Aeon Pain Management PGX Profile
- ARUP Pain Management
- Focused Pharmacogenomics Panel Mayo Clinic
- GeneDose Analgesic Appropriateness Report
- GeneSight Analgesic
- GeneTrait Pain Management Drug Metabolism and Risk Factor Profile
- IDgenetix Pain Tests
- Kailos Testing for Pain Medication (Kailos Genetics)
- Millennium Pharmacogenetic Testing PGT – Millennium Analysis of Patient Phenotype (MAPP) report
- NeuroIDgenetix test
- Pain Management Panel
- Pain Medication DNA Insight
- Pain Panel
- PersonaGene Pain Management
- PGxOne Plus Pain Management
- Pharmacogenomic Comprehensive Panel - Opioids
- Proove Addiction Risk Test
- Proove Drug Metabolism
- Proove Opioid Response Profile
- Proove Opioid Risk
- Proove Pain Perception
- Proove Non-Opioid Response
- Proove NSAID Risk Profile
- RESPONSEpain
- RightMed Comprehensive Test
- RightMed Comprehensive Test Exclude F2 and F5
- RightMed Gene
- RightMed PGx16 Test
- YouScript Analgesic

Single-nucleotide variants (SNVs) implicated in pain management include but are not limited to the following is considered **investigational**:

- 5HT2C (serotonin receptor gene)
- 5HT2A (serotonin receptor gene)
- SLC6A4 (serotonin transporter gene)
- DRD1 (dopamine receptor gene)
- DRD2 (dopamine receptor gene)
- DRD4 (dopamine receptor gene)

- DAT1 or SLC6A3 (dopamine receptor gene)
- DBH (dopamine beta-hydroxylase gene)
- COMT (catechol O-methyltransferase gene)
- MTHFR (methylenetetrahydrofolate reductase gene)
- y-aminobutyric acid (GABA) A receptor gene
- OPRM1 (u-opioid receptor gene)
- OPRK1 (k-opioid receptor gene)
- UGT2B15 (uridine diphosphate glycosyltransferase 2 family, member 15)
- Cytochrome p450 genes: CYP2D6, CYP2C19, CYP2C9, CYP3A4, CYP2B6, CYP1A2

Based on review of the peer reviewed medical literature the clinical utility and benefit to net health outcomes for single genetic variants and panel testing for pain management has not been established. There is insufficient evidence in the peer reviewed medical literature to validate the effectiveness of this testing to inform on drug metabolism, dosing considerations or to demonstrate improved clinical outcomes. Further, there is lack of published professional consensus guidelines to demonstrate that use of such tests is a standard of care in routine clinical practice. The evidence is sufficient to determine the effects of this testing on net health outcomes.

Pharmacogenomic and Genetic Testing for Mental Health Conditions
Pharmacogenomic panel testing for multi-genes associated with mental health disorders (to inform the selection and/or dose of medication(s)) is considered investigational in all situations, including but not limited to the following:

- To confirm a diagnosis of a mental health disorder in an affected individual
- To predict future risk of a mental health disorder in an asymptomatic individual
- In an affected individual to inform the selection or dose of medications used to treat mental health disorders

***Note**: Genetic mutations associated with mental health disorders include but are not limited to the following: SULT4A1, SLC6A4, 5HT2C, 5HT2A, DRD1, DRD2, DRD4, DAT1, DA beta-hydroxylase, CACNA1C, ANK3, COMPT, MTHFR, GABA, OPRK1, OPRM1, UGT1A4, ABCB1, CYP450 genes: CYP2D6, CYP2C19, CYP3A4, CYP3A5, CYP1A2, CYP2C9, CYP2B6*

Pharmacogenomic panel testing for multi-genes to inform the selection or dose of medication(s) for mental health disorders including but not limited to the following are considered **investigational** because the evidence is sufficient to determine the effects of this testing on net health outcomes:

- Ally Diagnostics Genetic Testing Panel
- Alpha Genomix Psychiatry/ADHD Panel
- AltheaDX IDgenetix branded tests – IDgenetix, NeuroIDgenetix
- Antidepressants and Antipsychotics Pharmacogenetics Panel
- Anxiety, Insomnia and Severe Agitation Panel

- Focused Pharmacogenomics Panel Mayo Clinic
- Genecept Assay
- GeneDose ADHD Medication Appropriateness Reporting
- GeneDose Behavioral Health Medication Appropriateness Reporting
- GeneSight Psychotropic Panel
- GeneSight ADHD
- GeneSight MTHFR
- Genetic Technological Innovations Pharmacogenetic Testing
- GeneTrait Anti-ADHD Drug Metabolism and Risk Factor Profile
- GeneTrait Psychotropic Drug Metabolism and Risk Factor Profile
- Genomind Professional PGx Express Core Anxiety and Depression Report
- Genomind Professional PGx Express Full Mental Health Report
- Kailos Test for Antidressants
- Mental Health DNA Insight
- Millennium Pharmacogenetic Testing (PGT) in Mental Health
- Molecular Testing Labs Psychotropic Medication Panel
- PersonaGene Panel PsychiaGene
- PGXL Multi-Drug Panel
- PGxOne Plus Psychiatry
- Pharmacogenomic Comprehensive Panel for Antidepressants and Antipsychotics
- Proove Psychiatric Profile
- Proove Psychiatric Risk and Response Panel
- PsychiaGene Panel
- Psych HealthPGx Panel, RPRD Diagnostics
- Psychiatric Dosing Panel
- Psychiatry/ADHD
- RightMed Comprehensive Test
- RightMed Comprehensive Test Exclude F2 and F5
- RightMed Gene
- RightMed PGx16 Test
- RESPONSEpsych/ADHD
- SureGene Test for antypsychotic and antidepressant Response Gene Panel (STAR2)
- YouScript Panel (YouScript Psychotropic, YouScript Psychotropic Plus, YouScript ADHD)

PROCEDURE CODES AND BILLING GUIDELINES

To report provider services, use appropriate CPT* codes, Alpha Numeric (HCPCS level 2) codes, Revenue codes, and/or ICD diagnosis codes.

- 0029U Drug metabolism (adverse drug reactions and drug response), targeted sequence analysis (i.e. CYP1A2, CYP2C19, CYP2C9, CYP2D6, CYP3A4, CYP4F2, SLCO1B1, VKORC1, and rs12777823)
- 0030U Drug metabolism (warfarin drug response), targeted sequence analysis (i.e. CYP2C9, CYP4F2, VKORC1, rs12777823)
- 0031U CYP1A2 (cytochrome P450 family 1, subfamily A, member 2) (e.g. drug metabolism) gene analysis common variants (i.e. *1, *1K, *6, *7)
- 0032U COMT (catechol-O-methyltransferase) gene analysis, c.471G>A (rs4680) variant
- 0033U HTR2A (5-hydroxytryptamine receptor 2A), HTR2C (5-hydroxytryptamine receptor 2C) (e.g., citalopram metabolism) gene analysis, common variants (ie, HTR2A rs7997012 [c.614-2211T>C], HTR2C rs3813929 [c.-759C>T] and rs1414334 [c.551-3008C>G]). Includes Serotonin Receptor Genotype (*HTR2A* and *HTR2C*), Mayo Clinic, Mayo Clinic
- 0070U CYP2D6 (cytochrome P450, family 2, subfamily D, polypeptide 6) (eg, drug metabolism) gene analysis, common and select rare variants (ie, *2, *3, *4, *4N, *5, *6, *7, *8, *9, *10, *11, *12, *13, *14A, *14B, *15, *17, *29, *35, *36, *41, *57, *61, *63, *68, *83, *xN)
- 0071U CYP2D6 (cytochrome P450, family 2, subfamily D, polypeptide 6) (eg, drug metabolism) gene analysis, full gene sequence (List separately in addition to code for primary procedure)
- 0072U CYP2D6 (cytochrome P450, family 2, subfamily D, polypeptide 6) (eg, drug metabolism) gene analysis, targeted sequence analysis (i.e., CYP2D6-2D7 hybrid gene) (List separately in addition to code for primary procedure)
- 0073U CYP2D6 (cytochrome P450, family 2, subfamily D, polypeptide 6) (eg, drug metabolism) gene analysis, targeted sequence analysis (i.e., CYP2D7-2D6 hybrid gene) (List separately in addition to code for primary procedure)
- 0074U CYP2D6 (cytochrome P450, family 2, subfamily D, polypeptide 6) (eg, drug metabolism) gene analysis, targeted sequence analysis (i.e., non-duplicated gene when duplication/multiplication is trans) (List separately in addition to code for primary procedure)
- 0075U CYP2D6 (cytochrome P450, family 2, subfamily D, polypeptide 6) (eg, drug metabolism) gene analysis, targeted sequence analysis (i.e., 5' gene duplication/multiplication) (List separately in addition to code for primary procedure)
- 0076U CYP2D6 (cytochrome P450, family 2, subfamily D, polypeptide 6) (eg, drug metabolism) gene analysis, targeted sequence analysis (i.e., 3' gene duplication/ multiplication) (List separately in addition to code for primary procedure)
- 0078U Pain management (opioid-use disorder) genotyping panel, 16 common variants (i.e., ABCB1, COMT, DAT1, DBH, DOR, DRD1, DRD2, DRD4, GABA, GAL, HTR2A, HTTLPR, MTHFR, MUOR, OPRK1, OPRM1), buccal swab or other germline tissue sample, algorithm reported as positive or negative risk of opioid-use disorder

- 0173U Psychiatry (i.e., depression, anxiety), genomic analysis panel, includes variant analysis of 14 genes
- 0175U Psychiatry (e.g., depression, anxiety) genomic analysis panel, variant analysis of 15 genes
- 0345U Psychiatry (e.g., depression, anxiety, attention deficit hyperactivity disorder [ADHD]), genomic analysis panel, variant analysis of 15 genes, including deletion/duplication analysis of CYP2D6 (GeneSight Psychotropic)
- 0347U Drug metabolism or processing (multiple conditions), whole blood or buccal specimen, DNA analysis, 16 gene report, with variant analysis and reported phenotypes (RightMed PGx16 Test)
- 0348U Drug metabolism or processing (multiple conditions), whole blood or buccal specimen, DNA analysis, 25 gene report, with variant analysis and reported phenotypes (RightMed Comprehensive Test Exclude F2 and F5)
- 0349U Drug metabolism or processing (multiple conditions), whole blood or buccal specimen, DNA analysis, 27 gene report, with variant analysis including reported phenotypes and impacted gene-drug interactions (RightMed Comprehensive Test)
- 0350U Drug metabolism or processing (multiple conditions), whole blood or buccal specimen, DNA analysis, 27 gene report, with variant analysis and reported phenotypes (RightMed Gene)
- 81225 CYP2C19 (cytochrome P450, family 2, subfamily C, polypeptide 19) (eg, drug metabolism), gene analysis common variants (e.g., *2, *3, *4, *8, *17)
- 81226 CYP2D6 (cytochrome P450, family 2, subfamily D, polypeptide 6) (eg. drug metabolism), gene analysis common variants (e.g., *2, *3, *4, *5, *6, *9, *10, *17, *19, *29, *35, *41, *1XN, *2XN, *4XN)
- 81227 CYP2C9 (cytochrome P450, family 2, subfamily C, polypeptide 9) (eg, drug metabolism), gene analysis, common variants (e.g., *2, *3, *5, *6)
- 81230 CYP3A4 (cytochrome P450 family 3, subfamily A, member 4) (e.g., drug metabolism), gene analysis, common variant(s) (e.g. *2, *22)
- 81231 CYP3A5 (cytochrome P450 family, subfamily A, member 5) (e.g., drug metabolism), gene analysis common variant(s) (e.g. *2, 3, *4, *5, *6, *7)
- 81291 MTHFR (5, 10-methylenetetrahydrofolate reductase) (eg, hereditary hypercoagulability) gene analysis; common variants (e.g., 677T, 1298C)
- 81350 UGT1A1 (UDP glucuronosyltransferase 1 family, polypeptide A1) (eg, irinotecan metabolism), gene analysis, common variants (eg, *28, *36, *37)
- 81355- VKORC1 (vitamin K epoxide reductase complex, subunit 1) (eg, warfarin metabolism), gene analysis, common variants (e.g., -1639G.A, c.173+1000C>T)
- 81401 Molecular pathology procedure, level 2 (e.g., 2-10 SNPs, 1 methylated variant or 1 somatic variant (typically using non-sequencing target variant analysis], or detection of a dynamic mutation disorder/triplet repeat) includes:
    - CYP3A4 (cytochrome P450, family 3, subfamily A, polypeptide 4) (e.g., drug metabolism), common variants (e.g., *2, *3, *4, *5, *6)
    - CYP3A5 (cytochrome P450, family 3, subfamily A, polypeptide 5) (e.g., drug metabolism), common variants (e.g., *2, *3, *4, *5, *6)

- 81402 Molecular pathology procedure, Level 3 (e.g., > 10 SNPs, 2-10 methylated variants, or 2-10 somatic variants [typically using non-sequencing target variant analysis], immunoglobulin and T-cell receptor gene rearrangements, duplication/deletion variants of 1 exon, loss of heterozygosity [LOH], uniparental disomy [UPD] includes:
    - CYP21A2 (cytochrome P450, family 21, subfamily A, polypeptide 2) (e.g., congenital adrenal hyperplasia, 21 hydroxylase deficiency), common variants (e.g., IVS2-13G, P3OL, I172N, exon 6 mutation cluster [I235N, V236E, M238K,], V281L, L307FfsX6, Q318X, R356W, P453S, G110VfsX21, 30-kb deletion variant)
- 81404 Molecular pathology procedure, Level 5 (e.g., analysis of 2-5 exons by DNA sequencing analysis, mutation scanning or duplication/deletion variants of 6-10 exons, or characterization of a dynamic mutation disorder/triplet repeat by Southern blot analysis) includes:
    - CYP1B1 (cytochrome P450, family 1, subfamily B, polypeptide 1), e.g., primary congenital glaucoma), full gene sequence
- 81405 Molecular pathology procedure Level 6 (e.g., analysis of 6-10 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 11-25 exons, regionally targeted cytogenomic array analysis) includes:
    - Full gene sequence CYP11B1 (cytochrome P450, family 11, subfamily B, polypeptide 1) (e.g., congenital adrenal hyperplasia)
    - Full gene sequence CYP17A1 (cytochrome P450, family 17, subfamily A, polypeptide 2) (e.g., congenital adrenal hyperplasia), full gene sequence
    - Full gene sequence CYP21A2 (cytochrome P450, family 21, subfamily A, polypeptide 2) e.g., steroid 21-hydroxylase isoform, congenital adrenal hyperplasia)
- 81418 Drug metabolism (e.g., pharmacogenomics) genomic sequence analysis panel, must include testing of at least 6 genes, including CYP2C19, CYP2D6, and CYP2D6 duplication/deletion analysis
- 81479 Unlisted molecular pathology procedure
- 81599 Unlisted multi-analyte assays with algorithmic analysis
- G9143 Warfarin responsiveness testing by genetic technique using any method, any number of specimen(s)

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- Ally Clinical Diagnostic http://allyclinicaldiagnostics.com
- Molecular Testing Labs Psychotropic Medication Panel https://moleculartestinglabs.com
- PGXL Drug Sensitivity Panel PGXL Laboratories http://www.pgxlab.com
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POLICY HISTORY		
Date	**Reason**	**Action**
August 2022	Annual Review	Policy Revised
August 2021	Annual Review	Policy Revised
August 2020	Annual Review	Policy Revised
August 2019	Annual Review	Policy Renewed
August 2018	Annual Review	Policy Revised
August 2017	This policy will replace the following policies: • 02.04.48 CYP450 Genotyping to • Determine Drug Metabolizer Status • 02.01.33 Genetic Testing for • Warfarin Sensitivity • 02.04.54 Genetic Testing for • Mental Health Conditions	New Policy

New information or technology that would be relevant for Wellmark to consider when this policy is next reviewed may be submitted to:

Wellmark Blue Cross and Blue Shield
Medical Policy Analyst
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