

Clinical Appropriateness Guidelines

Pharmacogenomic Testing

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Scope

Pharmacogenomic testing broadly describes how one's genome, or multiple genes, can influence drug response while more targeted pharmacogenetic testing describes genotyping a specific gene to predict response to certain medications. This document addresses pharmacogenomic testing for the purpose of informing medication selection, dosage, and risk of adverse side effects. This guideline does not address tumor testing (see Clinical Appropriateness Guideline Molecular Testing of Solid and Hematologic Tumors and Malignancies), germline testing (See Clinical Appropriateness Guideline Genetic Testing for Hereditary Cancer Susceptibility) or gene expression classifiers as well as genetic testing to generate polygenic risk scores (see Clinical Appropriateness Guideline for Genetic Testing for Single-Gene and Multifactorial Conditions). All tests listed in these guidelines may not require prior authorization; please refer to the health plan.

Appropriate Use Criteria

Pharmacogenomic Testing

Pharmacogenetic testing of common variants associated with drug metabolism is medically necessary when all of the following criteria are met:

- All of the following:
 - The individual is a candidate for a targeted drug therapy associated with a specific genotype
 - The results of the pharmacogenetic test will directly impact clinical decision-making and clinical outcome for the individual
 - Published, peer-reviewed studies have proven that identifying the specific genetic variant improves clinical outcomes
- Identification of the genetic variant is required or recommended in a specific population prior to initiating therapy with the target drug as noted by the U.S. Food and Drug Administration (FDA)-approved prescribing label
- The clinical benefit of testing outweighs the potential risk of psychological or medical harm to the individual being tested
- The test is as targeted as possible for the clinical situation (e.g., genes related to phenotype)

Multi-gene pharmacogenomic genotyping assays in which each included target does not meet the above criteria are not medically necessary.

Warfarin Administration

Testing of *CYP2C9* and/or *VKORC1* is medically necessary for individuals being treated with warfarin who have not achieved a stable dose AND either of the following:

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- An unusually low maintenance dose of warfarin (<0.5mg)
- An international normalized ratio (INR) >4.0 during standard dosing

CPT Codes

The following codes are associated with the guidelines in the document. This list is not all inclusive. Medical plans may have additional coverage policies that supersede these guidelines.

Covered when medical necessity criteria are met:

81225	CYP2C19 (cytochrome P450, family 2, subfamily C, polypeptide 19) (eg, drug metabolism), gene analysis, common variants (eg, *2, *3, *4, *8, *17)
81226	CYP2D6 (cytochrome P450, family 2, subfamily D, polypeptide 6) (eg, drug metabolism), gene analysis, common variants (eg, *2, *3, *4, *5, *6, *9, *10, *17, *19, *29, *35, *41, *1XN, *2XN, *4XN)
81227	CYP2C9 (cytochrome P450, family 2, subfamily C, polypeptide 9) (eg, drug metabolism), gene analysis, common variants (eg, *2, *3, *5, *6)
81231	CYP3A5 (cytochrome P450 family 3 subfamily A member 5) (eg, drug metabolism), gene analysis, common variants (eg, *2, *3, *4, *5, *6, *7)
81232	DPYD (dihydropyrimidine dehydrogenase) (eg, 5-fluorouracil/5-FU and capecitabine drug metabolism), gene analysis, common variant(s) (eg, *2A, *4, *5, *6)
81306	NUDT15 (nudix hydrolase 15) (eg, drug metabolism) gene analysis, common variant(s) (eg, *2, *3, *4, *5, *6)
81335	TPMT (thiopurine S-methyltransferase) (eg, drug metabolism), gene analysis, common variants (eg, *2, *3)
81350	UGT1A1 (UDP glucuronosyltransferase 1 family, polypeptide A1) (eg, drug metabolism, hereditary unconjugated hyperbilirubinemia [Gilbert syndrome]) gene analysis, common variants (eg, *28, *36, *37)
81355	VKORC1 (vitamin K epoxide reductase complex, subunit 1) (eg, warfarin metabolism), gene analysis, common variant(s) (eg, -1639G>A, c.173+1000C>T)
81381	HLA Class I typing, high resolution (ie, alleles or allele groups); one allele or allele group (eg, B*57:01P), each
81404	UGT1A1 (UDP glucuronosyltransferase 1 family, polypeptide A1) (eg, hereditary unconjugated hyperbilirubinemia [Crigler-Najjar syndrome]) full gene sequence

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0034U TPMT (thiopurine S-methyltransferase), NUDT15 (nudix hydroxylase 15) (eg, thiopurine metabolism), gene analysis, common variants (ie, TPMT *2, *3A, *3B, *3C, *4, *5, *6, *8, *12; NUDT15 *3, *4, *5)
(Thiopurine Methyltransferase (TPMT) and Nudix Hydroxylase (NUDT15))

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)
(Mayo CYP2D6)

Considered not medically necessary:

(Proprietary tests that do not meet criteria are considered not medically necessary when submitted with their specific assigned code listed below or any less specific coding.)

81230 CYP3A4 (cytochrome P450 family 3 subfamily A member 4) (eg, drug metabolism), gene analysis, common variant(s) (eg, *2, *22)

81291 MTHFR (5,10-methylenetetrahydrofolate reductase) (eg, hereditary hypercoagulability) gene analysis, common variants (eg, 677T, 1298C)

81328 SLC01B1 (solute carrier organic anion transporter family, member 1B1) (eg, adverse drug reaction), gene analysis, common variant(s) (eg, *5)

81346 TYMS (thymidylate synthetase) (eg, 5-fluorouracil/5-FU drug metabolism), gene analysis, common variant(s) (eg, tandem repeat variant)

0029U Drug metabolism (adverse drug reactions and drug response), targeted sequence analysis (ie, CYP1A2, CYP2C19, CYP2C9, CYP2D6, CYP3A4, CYP3A5, CYP4F2, SLC01B1, VKORC1 and rs12777823)
(Focused Pharmacogenomics Panel)

0031U CYP1A2 (cytochrome P450 family 1, subfamily A, member 2) (eg, drug metabolism) gene analysis, common variants (ie, *1F, *1K, *6, *7)
(Cytochrome P450 1A2 Genotype)

0032U COMT (catechol-O-methyltransferase) (drug metabolism) gene analysis, c.472G>A (rs4680) variant
(Catechol-O-Methyltransferase (COMT) Genotype)

0175U Psychiatry (eg, depression, anxiety), genomic analysis panel, variant analysis of 15 genes
(Genomind® Professional PGx Express™ CORE)

0258U Autoimmune (psoriasis), mRNA, next generation sequencing, gene expression profiling of 50-100 genes, skin-surface collection using adhesive patch, algorithm reported as likelihood of response to psoriasis biologics
(Mind.Px)

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0286U (CNT (CEP72, NUDT15 and TPMT) Genotyping Panel)	CEP72 (centrosomal protein, 72-KDa), NUDT15 (nudix hydrolase 15) and TPMT (thiopurine S-methyltransferase) (eg, drug metabolism) gene analysis, common variants
0289U (MindX Blood Test™ - Memory/Alzheimer's)	Neurology (Alzheimer disease), mRNA, gene expression profiling by RNA sequencing of 24 genes, whole blood, algorithm reported as predictive risk score
0290U (MindX Blood Test™ - Pain)	Pain management, mRNA, gene expression profiling by RNA sequencing of 36 genes, whole blood, algorithm reported as predictive risk score
0291U (MindX Blood Test™ - Mood)	Psychiatry (mood disorders), mRNA, gene expression profiling by RNA sequencing of 144 genes, whole blood, algorithm reported as predictive risk score
0292U (MindX Blood Test™ - Stress)	Psychiatry (stress disorders), mRNA, gene expression profiling by RNA sequencing of 72 genes, whole blood, algorithm reported as predictive risk score
0293U (MindX Blood Test™ - Suicidality)	Psychiatry (suicidal ideation), mRNA, gene expression profiling by RNA sequencing of 54 genes, whole blood, algorithm reported as predictive risk score
0294U (MindX Blood Test™ - Longevity)	Longevity and mortality risk, mRNA, gene expression profiling by RNA sequencing of 18 genes, whole blood, algorithm reported as predictive risk score
ANY	GeneSight®

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Background

Pharmacogenomic Testing

Pharmacogenomic testing is utilized as a tool in the field of precision medicine. Precision medicine can guide optimal health care decisions by identifying individual variability to direct approaches for prevention, diagnosis, and treatment of disease (Collins and Varums 2015). As this approach to clinical practice has grown, so has the availability of pharmacogenomic testing in the clinical realm.

The *CYP450* gene superfamily is composed of many isoenzymes that are involved in the metabolism of about 75% of commonly prescribed drugs. Many of the clinically available pharmacogenomic tests include genes related to the *CYP450* superfamily. *CYP2C19*, *CYP2D6* and *CYP2C9* enzymes metabolize

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approximately 15%, 20-25%, and 10% of all currently used drugs, respectively, that are most often prescribed as treatments for oncologic, psychiatric, neurologic, or cardiovascular conditions (Drozda et al. 2014). These genes are highly polymorphic, and certain genotypes have been classified by their effect on metabolism (poor, intermediate, normal or ultrarapid) of specific drugs. While the speed of metabolism can affect optimal dosing strategy for a drug, it is also important to note that genetic variability accounts for only a portion of the individual differences in drug response, and there are many other variables in the pharmacokinetics and pharmacodynamics of medications (Solomon, Cates and Li 2019; Pasternak et al. 2017).

Single Gene Pharmacogenetic Assays

There are many challenges in gathering sufficient evidence to support the clinical utility of pharmacogenetic testing, including the relatively low effect size of individual variants, 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 (Fabbri et al. 2018; Zeier et al. 2018; Jarvis et al. 2019). Other limitations of published studies include conflicts of interest among the researchers and lack of blinding for participants and providers (Zeier et al. 2018; Bousman and Dunlop 2018). 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.

The US Food and Drug Administration (FDA) includes pharmacogenetic testing recommendations with the labeling of many drugs. In some cases, genetic testing is required to determine if the patient will respond to the planned treatment. For example, certain pharmacologic chaperone molecules are only effective against disease caused by specific types of genetic pathogenic variants (e.g., ivacaftor for cystic fibrosis and migalastat for Fabry disease). Genetic testing is also required when there is a well-established risk that the medication will trigger severe complications in individuals with specific genetic variants, such as rasburicase in individuals with G6PD deficiency and abacavir hypersensitivity in individuals with the HLA-B*57:01 allele. Other FDA labels do not provide a strong recommendation for genetic testing, but note that there may be actionable information about optimal dosing, efficacy, or toxicity of the drug in a subset of patients with a specific genotype. This is often the case for drugs known to interact with the *CYP450* genes. In other cases, the FDA will note that a gene is known to be involved in the metabolism or pharmacodynamics of the drug, but there is limited or no evidence of different responses among people with different genotypes, and the clinical utility of testing prior to administration is not clear. The overall number of drugs which 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 (Chin et al. 2017). 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 (Dong et al. 2018; Nurnberger et al. 2018). 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 (Pratt et al. 2018; Pratt et al. 2019).

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

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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 (Caudle et al. 2014).

Multi-Gene Pharmacogenomic Assays

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 a number of 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” (Bousman and Dunlop 2018). While pharmacogenomic tests are a promising candidate to address this need, as evidenced by many retrospective reviews, there is a lack of large and adequately powered randomized controlled studies that address whether the use of pharmacogenomic panels in prescribing medications improves outcomes in various conditions (Drozda et al. 2014; Zeier et al. 2018; Lin and Chun 2019). Another hurdle, as evidenced by the systematic review of available studies by Fabbri et al. (2019), is the lack of best practice guidelines for developing clinical evidence. This deficit ultimately impacts the quality of available studies.

Evidence to support pharmacogenomic-guided antidepressant treatment is generally low strength because randomized controlled trials are few and underpowered, and variability in study designs make direct comparisons difficult (Perterson et al. 2017; Rosenblat and McIntyre 2017; Solomon, Cates and Li 2018). While published results from a recent large patient-blinded randomized controlled trial, the Genomics Used to Improve DEpression Decisions (GUIDED) trial, revealed that patients reached secondary outcomes of improvements in response (26.0% versus 19.9%, $p=0.036$) and remission (15.3% versus 10.1%, $p=0.007$) rates compared to patients with treatment as usual; the study failed to meet the primary outcome of statistically significant symptom improvement (27.2% versus 24.4%, $p=0.107$) in patients with treatment guided by pharmacogenomic testing (Greden et al. 2019). This study adds more data to the literature purporting a promising future for pharmacogenomic-directed treatment, but it also underscores the need for additional evidence to support it beyond paired cytochrome gene testing. In addition, it highlights the conundrum of available market-place genetic tests' rate of evolution outpacing evidence of clinical utility in the newest iteration, i.e., the current pharmacogenomic panel available on the market is larger than the panel studied in the GUIDED trial.

The majority of professional society guidelines related to pharmacogenomic testing address specific drug-gene interactions rather than multi-gene panels (Beckett et al. 2018). Although individual biomarkers may have clinical utility in certain circumstances, clinicians will often choose larger panels due to the increasing availability in the market (Moyer et al. 2017), without sufficient evidence that panel testing of multiple genes has any benefit over single-gene testing or standard trial-and-error methods (Zeier et al. 2018).

Among clinically available pharmacogenomic panel tests, interpretation of results and final medication recommendations vary substantially and even contradict each other, highlighting the need for standardized guidelines before panel-based pharmacogenomic testing becomes a routine part of clinical practice (Bousman and Dunlop 2018; Bousman et al. 2018). In 2018, the FDA issued a consumer warning against the use of many pharmacogenetic tests, indicating that there is limited scientific and clinical evidence to support the claims of clinical utility that are advertised by these

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laboratories (FDA 2018). Subsequently, the FDA issued a statement in 2020 introducing a web-based resource that includes a table of certain gene-drug interactions the FDA feels sufficient evidence is available to support the association between genetic variants and drug metabolism. The FDA does note this table is not complete, and also does not provide references to support the pharmacogenetic associations included in the table (FDA 2020).

Warfarin Administration

While there are numerous challenges to warfarin dosing with its highly variable individual responses and challenges achieving and maintaining levels within a therapeutic range, it has the potential to significantly reduce morbidity and mortality from thromboembolic events (Flockhart et al. 2008). Many current guidelines remain silent on the use of pharmacogenetics to guide warfarin therapy. The American College of Medical Genetics and Genomics (ACMG) guideline (2008) does not recommend routine use of pharmacogenetic testing for warfarin. However, they do carve out practical scenarios where testing may be beneficial (Flockhart et al. 2008). The guideline specifically notes *CYP2C9* and *VKORC1* genotypes can reasonably be used as part of diagnostic efforts to determine the cause of an unusually low maintenance dose of warfarin or an unusually high INR during standard dosing (Flockhart et al. 2008). In doing so, health care providers would be able to spend less time and energy on the issues of drug interactions and diet, both of which can be inordinately time consuming in this setting. Testing should not be performed in patients who have achieved a stable dose of warfarin, only in those having difficulty getting to a stable dose upon initiation of warfarin therapy.

Professional Society Guidelines

American College of Medical Genetics and Genomics (ACMG)

ACMG Policy Statement. Pharmacogenetic Testing of *CYP2C9* and *VKORC1* Alleles for Warfarin.

Flockhart DA, O'Kane D, Williams MS, Watson MS, et al; ACMG Working Group. Genet Med. 2008 Feb;10(2):139-50.

PubMed PMID: 18281922.

ACMG Points to Consider Statement. DNA-Based Screening and Population Health.

Murray M, Giovanni M, Doyle D, et al. Genet Med. 2021 Jun;23(6):989-995. PubMed PMID: 33727704.

Association for Molecular Pathology (AMP)

AMP Recommendations for Clinical *CYP2C19* Genotyping Allele Selection.

Pratt VM, Del Tredici AL, Hachad H, et al. J Mol Diagn 2018. May;20(3):269-276. Epub 2018 Feb 21. PubMed PMID: 29474986.

AMP Recommendations for Clinical Warfarin Genotyping Allele Selection.

Pratt V, Cavallari L, Tredici A., et al. J Mol Diagn. 2020 Jul;22(7):847-859. PMID: 32380173.

Clinical Pharmacogenetics Implementation Consortium (CPIC)

CPIC Guideline. *CYP2C19* Genotype and Clopidogrel Therapy. 2022 Update.

Lee CR, Luzum JA, Sangkuhl K, et al. Clin Pharmacol Ther. 2022 Jan 16. Epub ahead of print. PubMed PMID: 35034351.

CPIC Guideline. *CYP2D6* and *CYP2C19* Genotypes and Dosing of Tricyclic Antidepressants

Hicks JK, Sangkuhl K, Swen JJ, et al. Clin Pharmacol Ther. 2017 Jul 102(1):37-44. PubMed PMID: 27997040.

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CPIC Guideline. CYP2D6 and CYP2C19 Genotypes and Dosing of Selective Serotonin Reuptake Inhibitors.

Hicks JK, Bishop JR, Sangkuhl K, et al. *Clin Pharmacol Ther.* 2015 Aug;98(2):127-34. PubMed PMID: 25974703.

CPIC Guidelines. CYP2C9 and HLA-B Genotype and Phenytoin Dosing. 2020 Update.

Karnes JH, Rettie AE, Somogyi AA, et al. *Clin Pharmacol Ther.* 2020 Aug 11. Epub ahead of print. PMID: 32779747.

CPIC Guideline. CYP2D6 and Tamoxifen Therapy.

Goetz MP, Sangkuhl K, Guchelaar HJ, et al. *Clin Pharmacol Ther.* 2018 May;103(5):770-777. PubMed PMID: 29385237.

CPIC Guideline. CYP2D6 Genotype and Use of Ondansetron and Tropisetron.

Bell GC, Caudle KE, Whirl-Carrillo M, et al. *Clin Pharmacol Ther.* 2017 Aug;102(2):213-18. PubMed PMID: 28002639.

CPIC Guideline. CYP2D6, OPRM1, and COMT Genotype and Select Opioid Therapy.

Crews K, Monte A, Huddart R, et al. *Clin Pharmacol Ther.* 2021 Jan 2. PubMed PMID: 33387367.

CPIC Guideline. Dihydropyrimidine Dehydrogenase Genotype and Fluoropyrimidine Dosing.

Amstutz U, Henricks LM, Offer SM, et al. *Clin Pharmacol Ther.* 2018 Feb;103(2):210-216. PubMed PMID: 29152729.

CPIC Guideline. HLA Genotype and Use of Carbamazepine and Oxcarbazepine.

Phillips EJ, Sukasem C, Whirl-Carrillo M, et al. *Clin Pharmacol Ther.* 2018 Apr;103(4):574-581. PubMed PMID: 29392710.

CPIC Guideline. Pharmacogenetics-Guided Warfarin Dosing.

Johnson JA, Caudle KE, Gong L, et al. *Clin Pharmacol Ther.* 2017 Sep;102(3):397-404. PubMed PMID: 28198005.

CPIC Guideline. Guideline for Thiopurine Dosing Based on TPMT and NUDT15 Genotypes.

Relling MV, Schwab M, Whirl-Carrillo M, et al. *Clin Pharmacol Ther.* 2019 May;105(5):1095-1105. PubMed PMID: 30447069.

Dutch Pharmacogenetics Working Group

DPWG Guideline for The Gene-Drug Interaction Between CYP2C19 and CYP2D6 and SSRIs.

Brouwer J, Nijenhuis M, Soree B, et al. *Eur J Hum Genet.* 2021 Nov 16. Epub ahead of print. PubMed PMID: 34782755.

International Society of Psychiatric Genetics (ISPG)

Review and Consensus on Pharmacogenomic Testing in Psychiatry.

Bousman CA, Bengesser SA, Aitchison KJ, et al. *Pharmacopsychiatry.* 2021 Jan;54(1):5-17. PubMed PMID: 33147643.

Veterans Health Administration

VHA Policy Recommendation. Pharmacogenetic Testing in the Veterans Health Administration.

Vassy JL, Stone A, Callaghan JT, et al.; VHA Clinical Pharmacogenetics Subcommittee. *Genet Med.* 2019 Feb;21(2):382-390. PubMed PMID: 29858578.

Joint Statements

AMP and College of American Pathologists (CAP). Recommendations for Clinical CYP2C9 Genotyping Allele Selection.

Pratt VM, Cavallari LH, Del Tredici AL, et al. *J Mol Diagn.* 2019 May 7. PubMed PMID: 31075510.

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AMP, College of American Pathologists (CAP), Dutch Pharmacogenetics Working Group of the Royal Dutch Pharmacists Association, and European Society for Pharmacogenomics and Personalized Therapy. Recommendations for Clinical CYP2D6 Genotyping Allele Selection.

Pratt VM, Cavallari L, Del Tredici AL, et al. *J Mol Diagn*. 2021 Jun 10: S1525-1578(21)00164-1. PubMed PMID: 34118403.

Selected References

- 1 Aka I, Bernal CJ, Carroll R, et al. Clinical Pharmacogenetics of Cytochrome P450-Associated Drugs in Children. *J Pers Med*. 2017 Nov 2;7(4). PubMed PMID: 29099060.
- 2 Bean LJH, Funke B, Carlston CM, Gannon JL, Kantarci S, Krock BL, Zhang S, Bayrak-Toydemir P, on behalf of the ACMG Laboratory Quality Assurance Committee. Diagnostic gene sequencing panels: from design to report- a technical standard of the American College of Medical Genetics and Genomics (ACMG). *Genet Med*. 2019 Nov 16. PubMed PMID: 31732716.
- 3 Beckett RD, Kisor DF, Smith T, Vonada B. Systematic evaluation of clinical practice guidelines for pharmacogenomics. *Pharmacogenomics*. 2018 Jun 1;19(8):693-700. Epub 2018 May 23. PubMed PMID: 29790417.
- 4 Berin E and Levy A. Recent developments and future directions for the use of pharmacogenomics in cardiovascular disease treatments. *Expert Opin Drug Metab Toxicol*. 2017 Sep;13(9):973-983. Epub 2017 Aug 20. PubMed PMID: 28792790.
- 5 Bousman CA, Dunlop BW. Genotype, phenotype, and medication recommendation agreement among commercial pharmacogenetic-based decision support tools. *Pharmacogenomics J*. 2018 Sep;18(5):613-622. Epub 2018 May 25. PubMed PMID: 29795409.
- 6 Bousman C, Maruf AA, Müller DJ. Towards the integration of pharmacogenetics in psychiatry: a minimum, evidence-based genetic testing panel. *Curr Opin Psychiatry*. 2019 Jan;32(1):7-15. PubMed PMID: 30299306.
- 7 Bousman CA, Reynolds CF, Ng C, et al. Antidepressant prescribing in the precision medicine era: a prescriber's primer on pharmacogenetic tools. *BMC psychiatry*. 2017 Dec;17(1):60. PubMed PMID: 28178974.
- 8 Brandl EJ, Tiwari AK, Zhou X, et al. Influence of CYP2D6 and CYP2C19 gene variants on antidepressant response in obsessive-compulsive disorder. *Pharmacogenomics J*. 2014 Apr;14(2):176-81. Epub 2013 Apr 2. PubMed PMID: 23545896.
- 9 Campbell JM, Bateman E, Peters MDJ, et al. Fluoropyrimidine and platinum toxicity pharmacogenetics: an umbrella review of systematic reviews and meta-analyses. *Pharmacogenomics*. 2016 Mar;17(4):435-51. Epub 2016 Feb 19. PubMed PMID: 26894782.
- 10 Caudle KE, Klein TE, Hoffman JM, et al. Incorporation of pharmacogenomics into routine clinical practice: The Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline development process. *Curr Drug Metab*. 2014 Feb;15(2):209-17. PubMed PMID: 24479687.
- 11 Chin L, Devine B, Baradaran S, et al. Characterizing the strength of evidence in FDA labels for pharmacogenomic biomarker-guided medication use. *AMIA Jt Summits Transl Sci Proc*. 2017 Jul 26; 2017:30-39. PubMed PMID: 28815101.
- 12 Collins FS, Varmus H. A new initiative on precision medicine. *N Engl J Med*. 2015 Feb 26;372(9): 793-795. PubMed PMID: 25635347.
- 13 Dean L. Warfarin Therapy and VKORC1 and CYP Genotype. 2012 Mar 8 [Updated 2018 Jun 11]. In: Pratt V, McLeod H, Rubinstein W, et al., editors. *Medical Genetics Summaries* [Internet]. Bethesda (MD): National Center for Biotechnology Information (US); 2012-. Available from: <https://www.ncbi.nlm.nih.gov.proxy.lib.mcw.edu/books/NBK84174/>
- 14 Dong AN, Tan BH, Pan Y, Ong CE. Cytochrome P450 genotype-guided drug therapies: An update on current states. *Clin Exp Pharmacol Physiol*. 2018 Oct;45(10):991-1001. Epub 2018 Jul 2. PubMed PMID: 29858511.
- 15 Dong OM, Li A, Suzuki O, et al. Projected impact of a multigene pharmacogenetic test to optimize medication prescribing in cardiovascular patients. *Pharmacogenomics*. 2018 Jun 1;19(9):771-782. PubMed PMID: 29793377.
- 16 Drozda K, Müller DJ, Bishop JR. Pharmacogenomic testing for neuropsychiatric drugs: current status of drug labeling, guidelines for using genetic information, and test options. *Pharmacotherapy*. 2014 Feb;34(2):166-84. PubMed PMID: 24523097.
- 17 Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group. Recommendations from the EGAPP Working Group: testing for cytochrome P450 polymorphisms in adults with nonpsychotic depression treated with selective serotonin reuptake inhibitors. *Genet Med*. 2007 Dec;9(12):819-25. PubMed PMID: 18091431.
- 18 Fabbri C, Zohar J, Serretti A. Pharmacogenetic tests to guide drug treatment in depression: Comparison of the available testing kits and clinical trials. *Prog Neuropsychopharmacol Biol Psychiatry*. 2018 Aug 30; 86:36-44. PMID: 29777729.
- 19 Faruque F, Noh H, Hussain A, et al. Economic value of pharmacogenetic testing for cancer drugs with clinically relevant drug-gene associations: A systematic literature review. *J Manag Care Spec Pharm*. 2019 Feb;25(2):260-271. PubMed PMID: 30698084.
- 20 Gaedigk A, Dinh JC, Jeong H, et al. Ten years' experience with the CYP2D6 activity score: A perspective on future investigations to improve clinical predictions for precision therapeutics. *J Pers Med*. 2018 Apr 17;8(2). PubMed PMID: 29673183.
- 21 Gage BF, Bass AR, Lin H, et al. Effect of Genotype-Guided Warfarin Dosing on Clinical Events and Anticoagulation Control Among Patients Undergoing Hip or Knee Arthroplasty: The GIFT Randomized Clinical Trial. *JAMA*. 2017 Sep 26;318(12):1115-1124. PubMed PMID: 28973620.
- 22 Gong L, Thorn CF, Bertagnolli MM, et al. Celecoxib pathways: pharmacokinetics and pharmacodynamics. *Pharmacogenet Genomics*. 2012 Apr;22(4):310-8. PubMed PMID: 22336956.

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- 23 Greden JF, Parikh SV, Rothschild AJ, Thase ME, Dunlop BW, De Battista C, Conway CR, Forester BP, Mondimore FM, Shelton RC, Macaluso M, Li J, Brown K, Gilbert A, Burns L, Jablonski MR, Dechairo B. Impact of pharmacogenomics on clinical outcomes in major depressive disorder in the GUIDED trial: A large, patient-and rater-blinded, randomized, controlled study. *J Psychiatr Res.* 2019 Apr; 111:59-67. PMID: 30677646.
- 24 Jarvis JP, Peter AP, Shaman JA. Consequences of CYP2D6 copy-number variation for pharmacogenomics in psychiatry. *Front Psychiatry.* 2019 Jun 20; 10:432. PubMed PMID 31281270.
- 25 Ji Y, Skierka JM, Blommel JH, et al. Preemptive pharmacogenomic testing for precision medicine: a comprehensive analysis of five actionable pharmacogenomic genes using next-generation DNA sequencing and a customized CYP2D6 genotyping cascade. *J Mol Diagn.* 2016 May;18(3):438-45. Epub 2016 Mar 3. PubMed PMID: 26947514.
- 26 Jürgens G, Rasmussen HB, Werge T, et al. Does the medication pattern reflect the CYP2D6 genotype in patients with diagnoses within the schizophrenic spectrum? *J Clin Psychopharmacol.* 2012 Feb;32(1):100-5. PubMed PMID: 22198443.
- 27 Koutsilieri S, Caudle KE, Alzghari SK, Monte AA, Relling MV, Patrinos GP. Optimizing thiopurine dosing based on TPMT and NUDT15 genotypes: It takes two to tango. *Am J Hematol.* 2019 Apr 3. PubMed PMID: 30945335.
- 28 Landau R, Smiley R. Pharmacogenetics in obstetric anesthesia. *Best Pract Res Clin Anaesthesiol.* 2017 Mar;31(1):23-34. Epub 2017 Feb 6. PubMed PMID: 28625302.
- 29 Li X, Li D, Wu JC, Liu ZQ, Zhou HH, Yin JY. Precision dosing of warfarin: open questions and strategies. *Pharmacogenomics J.* 2019 Jun;19(3):219-229. PMID: 30745565.
- 30 Lieberman JA, Stroup TS, McEvoy JP, et al. Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. *N Engl J Med.* 2005 Sep 22;353(12):1209-23. Epub 2005 Sep 19. PubMed PMID: 16172203.
- 31 Lin B, Chung WK. Cases in precision medicine: The role of pharmacogenetics in precision prescribing. *Ann Intern Med.* 2019 May 21. [Epub ahead of print] PubMed PMID: 31108507.
- 32 Matchar DB, Thakur ME, Grossman I, et al. Testing for cytochrome P450 polymorphisms in adults with non-psychotic depression treated with selective serotonin reuptake inhibitors (SSRIs). *Evid Rep Technol Assess (Full Rep).* 2007 Jan;(146):1-77. PubMed PMID: 17764209.
- 33 McClain MR, Palomaki GE, Piper M, Haddow JE. A rapid-ACCE review of CYP2C9 and VKORC1 alleles testing to inform warfarin dosing in adults at elevated risk for thrombotic events to avoid serious bleeding. *Genet Med.* 2008 Feb;10(2):89-98. PubMed PMID: 18281915.
- 34 Moyer AM, Rohrer Vitek CR, Giri J, et al. Challenges in ordering and interpreting pharmacogenomic tests in clinical practice. *Am J Med.* 2017 Dec; 130(12): 1342-1344. PubMed PMID: 28757317.
- 35 Murphy GM Jr, Hollander SB, Rodrigues HE. Effects of the serotonin transporter gene promoter polymorphism on mirtazapine and paroxetine efficacy and adverse events in geriatric major depression. *Arch Gen Psychiatry.* 2004 Nov;61(11):1163-9. PubMed PMID: 15520364.
- 36 Murphy GM Jr, Kremer C, Rodrigues HE, et al. Pharmacogenetics of antidepressants medication intolerance. *Am J Psychiatry* 2003 Oct;160(10):1830-35. PubMed PMID: 14514498.
- 37 Niitsu T, Fabbri C, Bentini F, et al. Pharmacogenetics in major depression: a comprehensive meta-analysis. *Prog Neuropsychopharmacol Biol Psychiatry.* 2013 Aug 1; 45:183-94. Epub 2013 Jun 1. PubMed PMID: 23733030.
- 38 Nurnberger JI Jr, Austin J, Berrettini WH, et al. What should a psychiatrist know about genetics? Review and recommendations from the residency education committee of the International Society of Psychiatric Genetics. *J Clin Psychiatry.* 2018 Nov 27;80(1). PubMed PMID: 30549495.
- 39 Offer SM, Fossum CC, Wegner NJ, et al. Comparative functional analysis of DPYD variants of potential clinical relevance to dihydropyrimidine dehydrogenase activity. *Cancer Res.* 2014 May 1;74(9):2545-54. Epub 2014 Mar 19. PubMed PMID: 2468345.
- 40 Pasternak AL, Ward KM, Luzum JA, et al. Germline genetic variants with implications for disease risk and therapeutic outcomes. *Physiol Genomics.* 2017 Oct 1;49(10):567-581. PubMed PMID: 28887371.
- 41 Perez V, Salavert A, Espadaler J, et al. Efficacy of prospective pharmacogenetic testing in the treatment of major depressive disorder: results of a randomized, double-blind clinical trial. *BMC psychiatry.* 2017; 17(1), 250. PubMed PMID: 28705252.
- 42 Peterson K, Dieperink E, Anderson J, et al. Rapid evidence review of the comparative effectiveness, harms, and cost-effectiveness of pharmacogenomics-guided antidepressant treatment versus usual care for major depressive disorder. *Psychopharmacology.* 2017 Jun;234(11):1649-1661. Epub 2017 Apr 29. PubMed PMID: 28456840.
- 43 Poland RE, Lesser IM, Wan YJ, et al. Response to citalopram is not associated with SLC6A4 genotype in African Americans and Caucasians with major depression. *Life Sci.* 2013 May 30;92(20-21):967-70. Epub 2013 Apr 3. PubMed PMID: 23562852.
- 44 Pratt VM, Cavallari LH, Del Tredici AL, Hachad H, Ji Y, Moyer AM, Scott SA, Whirl-Carrillo M, Weck KE. Recommendations for Clinical CYP2C9 Genotyping Allele Selection: A Joint Recommendation of the Association for Molecular Pathology and College of American Pathologists. *J Mol Diagn.* 2019 Sep;21(5):746-755. PubMed PMID: 31075510.
- 45 Reynolds GP, Zhang ZJ, Zhang XB. Polymorphism of the promoter region of the serotonin 5-HT2C receptor gene and clozapine-induced weight gain. *Am J Psychiatry* 2003 Apr;160(4):677-9. PubMed PMID: 12668355.
- 46 Rosenblat JD, Lee Y, McIntyre RS. Does Pharmacogenomic Testing Improve Clinical Outcomes for Major Depressive Disorder? A Systematic Review of Clinical Trials and Cost-Effectiveness Studies. *J Clin Psychiatry.* 2017 Jun;78(6):720-729. PubMed PMID: 28068459.
- 47 Samer CF, Lorenzini KI, Rollason V, et al. Applications of CYP450 testing in the clinical setting. *Mol Diagn Ther.* 2013 Jun; 17(3):165-184. PubMed PMID: 23588782.
- 48 Samwald M, Xu H, Blagec K, et al. Incidence of exposure of patients in the United States to multiple drugs for which pharmacogenomic guidelines are available. *PLoS One.* 2016 Oct 20;11(10): e0164972. PubMed PMID: 27764192.
- 49 Serretti A, Calati R, Massat I, et al. Cytochrome P450 CYP1A2, CYP2C9, CYP2C19 and CYP2D6 genes are not associated with response and remission in a sample of depressive patients. *Int Clin Psychopharmacol.* 2009;24(5):250-6. PubMed PMID: 19593158.

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- 50 Shah RR. Genotype-guided warfarin therapy: Still of only questionable value two decades on. *J Clin Pharm Ther.* 2020 Mar 13. PubMed PMID 32168383.
- 51 Sluiter RL, van Marrewijk C, de Jong D, Scheffer H, Guchelaar HJ, Derijks L, Wong DR, Hooymans P, Vermeulen SH, Verbeek ALM, Franke B, van der Wilt GJ, Kievit W, Coenen MJH. Genotype-guided thiopurine dosing does not lead to additional costs in patients with inflammatory bowel disease. *J Crohns Colitis.* 2019 Jul 25; 13(7):838-845. PubMed PMID: 30698675.
- 52 Smits KM, Smits LJ, Schouten JS, et al. Influence of SERTPR and STin2 in the serotonin transporter gene on the effect of selective serotonin reuptake inhibitors in depression: a systematic review. *Mol Psychiatry.* 2004 May;9(5):433-41. PubMed PMID: 15037864.
- 53 Solomon HV, Cates KW, Li KJ. Does obtaining CP2D6 and CYP2C19 pharmacogenetic testing predict antidepressant response or adverse drug reactions? *Psychiatry Res.* 2019 Jan; 271:604-613. PubMed PMID: 30554109.
- 54 Somogyi AA, Collier JK, Barratt DT. Pharmacogenetics of opioid response. *Clin Pharmacol Ther.* 2015 Feb;97(2):125-7. Epub 2014 Dec 9. PubMed PMID: 25670515.
- 55 Syn NL, Wong AL-A, Lee S-C, et al. Genotype-guided versus traditional clinical dosing of warfarin in patients of Asian ancestry: a randomized controlled trial. *BMC Medicine.* 2018; 16:104. PubMed PMID: 29986700.
- 56 Tse G, Gong M, Li G, Wong SH; International Health Informatics Study (IHIS) Network. Genotype-guided warfarin dosing vs. conventional dosing strategies: a systematic review and meta-analysis of randomized controlled trials. *Br J Clin Pharmacol.* 2018 Sep;84(9):1868-1882. PubMed PMID: 29704269.
- 57 U.S. Food & Drug Administration. The FDA Warns Against the Use of Many Genetic Tests with Unapproved Claims to Predict Patient Response to Specific Medications: FDA Safety Communication. October 31, 2018. Available at: <https://www.fda.gov/medical-devices/safety-communications/fda-warns-against-use-many-genetic-tests-unapproved-claims-predict-patient-response-specific>.
- 58 U.S. Food & Drug Administration. FDA Announces Collaborative Review of Scientific Evidence to Support Associations Between Genetic Information and Specific Medications: FDA Statement. February 20, 2020. Available at: <https://www.fda.gov/news-events/press-announcements/fda-announces-collaborative-review-scientific-evidence-support-associations-between-genetic>.
- 59 Verbelen M, Weale ME, Lewis CM. Cost-effectiveness of pharmacogenetic-guided treatment: are we there yet? *Pharmacogenomics J.* 2017 Oct;17(5):395-402. Epub 2017 Jun 13. PubMed PMID: 28607506.
- 60 Voora D, Eby C, Linder MW, Milligan PE, Bukaveckas BL, McLeod HL, Maloney W, Clohisy J, Burnett RS, Grosso L, Gatchel SK, Gage BF. Prospective dosing of warfarin based on cytochrome P-450 2C9 genotype. *Thromb Haemost.* 2005 Apr;93(4):700-5. PubMed PMID: 15841315.
- 61 Wang B, Canestaro WJ, Choudhry NK. Clinical evidence supporting pharmacogenomic biomarker testing provided in US Food and Drug Administration drug labels. *JAMA Intern Med.* 2014 Dec;174(12):1938-44. PubMed PMID: 25317785.
- 62 Whirl-Carrillo M, McDonagh EM, Hebert JM, et al. Pharmacogenomics knowledge for personalized medicine. *Clin Pharmacol Ther.* 2012 Oct;92(4):414-7. PubMed PMID: 22992668.
- 63 Yu YW, Tsai SJ, Chen TJ, et al. Association study of the serotonin transporter promoter polymorphism and symptomatology and antidepressant response in major depressive disorders. *Mol Psychiatry.* 2002;7(10):1115-9. PubMed PMID: 12476327.
- 64 Zeier Z, Carpenter LL, Kalin NH, Rodriguez CI, McDonald WM, Widge AS, Nemeroff CB. Clinical implementation of pharmacogenetic decision support tools for antidepressant drug prescribing. *Am J Psychiatry.* 2018 ASep 1;175(9): 873-886. PubMed PMID: 29690793.
- 65 Zhao XQ, Cao WJ, Yang HP, et al. DPYD gene polymorphisms are associated with risk and chemotherapy prognosis in pediatric patients with acute lymphoblastic leukemia. *Tumour Biol.* 2016 Aug;37(8):10393-402. Epub 2016 Feb 4. PubMed PMID: 26846104.

Revision History

Medical Advisory Board Review:

v2.2022 03/17/2022: Approved

v1.2022 09/20/2021: Approved

v2.2021 03/12/2021: Approved

v1.2021 11/13/2020: Approved

v2.2020 05/08/2020: Reviewed

v1.2020 11/04/2019: Reviewed

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v2.2019 05/23/2019: No Criteria Changes

v1.2019 11/07/2018: Reviewed

v1.2018 03/31/2018: Reviewed

Clinical Steering Committee Review:

v2.2022 02/14/2022: Approved

v1.2022 08/23/2021: Approved

v2.2021 02/22/2021: Approved

v1.2021 10/13/2020: Approved

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v1.2020 10/11/2019: Approved

v2.2019 04/03/2019: Approved

v1.2019 10/03/2018: Approved

v1.2018 02/28/2018: Approved

v1.2017 01/25/2017: Approved

Revisions:

Version	Date	Editor	Description
v2.2022 GEN06-0922.2	02/02/2022	Carrie Langbo, MS, CGC	Semi-annual review. The Scope and appropriate use criteria were updated. CPT codes, professional society guidelines, background and references were updated.
v1.2022 GEN06-0322.1	08/16/2021	Carrie Langbo, MS, CGC	Semi-annual review. Genetic testing for Thrombophilia criteria, CPT codes, professional society guidelines and references were moved to the Genetic Testing Guideline for Single Gene and Multifactorial Conditions. The

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			Background and Professional Society Guidelines were updated.
v2.2021 GEN06-0921.1	02/15/2021	Carrie Langbo, MS, CGC	Semi-annual review. No criteria changes. Professional society guidelines were updated.
v1.2021	9/11/2020	Carrie Langbo, MS, CGC	Semi-annual review. Background, professional society guidelines and references were updated.
v2.2020	03/13/2020	Ann Schmidt, MS, CGC	Semi-annual review. Criteria was expanded to cover testing for CYP2C9 and VKORC1. CPT codes, background and references were updated.
v1.2020	09/11/2019	Carrie Langbo, MS, CGC	Semi-annual review. Criteria was expanded to allow thrombophilia testing in pregnant women with a history of any type of VTE. Revised terminology for pharmacogenomic and pharmacogenetic testing. Updated professional society guidelines, background and references.
v2.2019	04/03/2019	Ann Schmidt, MS, CGC	Semi-annual review. No criteria changes. Updated professional society guidelines and references.
v1.2019	10/03/2018	Kate Charyk, MS, CGC	Semi-annual review. Professional society guidelines and references updated. Renumbered to 2019. Reformatted CPT code list. PMID added.
v1.2018	03/31/2018	Heather Dorsey, MS, CGC	Semi-annual review. Expanded F2/F5 criteria to allow additional management changes for unprovoked VTE and estrogen changes with significant family history. Disclaimer sentence added to scope. Professional society guidelines

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			and references updated. Renumbered to 2018.
v1.2017	11/1/2017	Gwen Fraley, MS, CGC	Quarterly review. No criteria changes. Updated references.
v1.2017	09/15/2017	Megan Czarniecki, MS, CGC	Formatted references to NLM style. Moved methodological considerations to appropriate use criteria and background. Updated associated CPT codes. Approved by Policy Lead.
v1.2017	07/03/2017	Heather Dorsey, MS, CGC	Quarterly review. No criteria changes. Updated references.
v1.2017	04/18/2017	Megan Czarniecki, MS, CGC	Quarterly review. No criteria changes. Updated references.
v1.2017	01/23/2017	Cheryl Thomas, MS, CGC	Quarterly review. No criteria changes. Updated references. Renumbered for 2017.
v1.2016	10/05/2016	Gwen Fraley, MS, CGC	Combined Thrombophilias and Pharmacogenetic testing into same guidelines. Updated references.
v1.2015	10/08/2015	Marie Schuetzle, MS, CGC	Original version

Original Effective Date: 10/08/2015

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