Medical Coverage Policy

Effective Date.....11/1/2024
Next Review Date.....2/15/2025
Coverage Policy Number..... 0500

Pharmacogenetic Testing for Non-Cancer Indications

Table of Contents

Related Coverage Resources

Genetics
Inflammatory Bowel Disease - Testing for the Diagnosis and Management
Laboratory Management Guidelines

INSTRUCTIONS FOR USE

The following Coverage Policy applies to health benefit plans administered by Cigna Companies. Certain Cigna Companies and/or lines of business only provide utilization review services to clients and do not make coverage determinations. References to standard benefit plan language and coverage determinations do not apply to those clients. Coverage Policies are intended to provide guidance in interpreting certain standard benefit plans administered by Cigna Companies. Please note, the terms of a customer's particular benefit plan document [Group Service Agreement, Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a customer's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a customer's benefit plan document always supersedes the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Each coverage request should be reviewed on its own merits. Medical directors are expected to exercise clinical judgment where appropriate and have discretion in making individual coverage determinations. Where coverage for care or services does not depend on specific circumstances, reimbursement will only be provided if a requested service(s) is submitted in accordance with the relevant criteria outlined in the applicable Coverage Policy, including covered diagnosis and/or procedure code(s). Reimbursement is not allowed for services when billed for conditions or diagnoses that are not covered under this Coverage Policy (see "Coding Information" below). When billing, providers

must use the most appropriate codes as of the effective date of the submission. Claims submitted for services that are not accompanied by covered code(s) under the applicable Coverage Policy will be denied as not covered. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. In certain markets, delegated vendor guidelines may be used to support medical necessity and other coverage determinations.

Overview

This Coverage Policy addresses pharmacogenetic testing for non-cancer related indications. Pharmacogenetics is the study of gene variations within an individual's deoxyribonucleic acid (DNA) and how these differences influence an individual's response to medications. An individual's unique genetic makeup helps determine how he or she responds to a drug and whether or not side effects or adverse reactions may be experienced. Variations in genes may also cause an individual to metabolize a drug more quickly, more slowly or at the same rate as anticipated, based on dosage.

For additional information regarding pharmacogenetic testing for oncology and hematology-related conditions, please see Medical Coverage Policy 0520 Molecular and Proteomic Diagnostic Testing for Hematology and Oncology Indications.

Coverage Policy

Many benefit plans limit coverage of genetic testing services. Please refer to the applicable benefit plan language to determine benefit availability and terms, conditions and limitations of coverage for the services discussed in this Coverage Policy.

Medically Necessary

Pharmacogenetic testing (e. g., genotyping, pathogenic/likely pathogenic variant analysis) is considered medically necessary when ALL of the following criteria are met (this list may not be all inclusive):

- The individual is a candidate for a targeted drug therapy associated with a specific gene biomarker or gene pathogenic/likely pathogenic variant
- The results of the pharmacogenetic test will directly impact clinical decision-making
- The testing method is considered to be scientifically valid to identify the specific gene biomarker or gene pathogenic/likely pathogenic variant
- EITHER of the following:
  - Identification of the specific gene or biomarker for use with a specific drug target has been demonstrated to improve clinical outcomes for the individual's condition being addressed
  - Identification of the gene biomarker is noted to be clinically necessary prior to initiating therapy with drug target as noted within the U.S. Food and Drug Administration (FDA)-approved prescribing label

Pharmacogenetic screening in the general population is considered not medically necessary.

Gene expression classifiers for pharmacologic response are not covered or reimbursable.

Health Equity Considerations

Health equity is the highest level of health for all people; health inequity is the avoidable difference in health status or distribution of health resources due to the social conditions in which people are born, grow, live, work, and age.

Social determinants of health are the conditions in the environment that affect a wide range of health, functioning, and quality of life outcomes and risks. Examples include safe housing, transportation, and neighborhoods; racism, discrimination and violence; education, job opportunities and income; access to nutritious foods and physical activity opportunities; access to clean air and water; and language and literacy skills.

General Background

Pharmacogenetics encompasses variations in genes that encode drug transporters, drug-metabolizing enzymes and drug targets, as well as specific genes related to the action of drugs. A slight variation in deoxyribonucleic acid (DNA) can result in a subtle change in a protein which translates into major differences in how the protein functions. The study of variations in DNA sequence as related to drug response is referred to as pharmacogenetic testing. A pharmacogenetic test is meant to guide treatment strategies, patient evaluations and decisions based on its ability to predict response to treatment in particular clinical contexts (Terasawa, et al., 2010).

A particular variant is not always phenotype specific in that it may have a different impact depending on the drug in question. Racial and ethnic differences in the frequency and nature of genetic variants are also possible and should be recognized in translating outcomes from one population to another. The relation of a gene or gene biomarker and a drug target must be validated for each therapeutic indication in different racial and ethnic groups, as well as in different treatment and disease contexts (Crews, et al., 2012).

Although genetics has an impact on genes related to inter-individual differences in drug response, it is only one of the many variables affecting these genes. Other factors include the characteristics of the condition for which the drug is prescribed, co-administration of other drugs, and non-genetic factors, including the individual's diet, weight, and smoking habits. Identification of gene variations may be clinically useful in a small number of drugs; however, it may be insufficient in others to explain complex differences in metabolism, efficacy and toxicity. The presence of polymorphisms alone may be a poor predictor of phenotype because of variability (CADTH, 2006).

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; however, laboratories offering such tests as a clinical service must meet the general regulatory standards of the Clinical Laboratory Improvement Act (CLIA) and must be licensed by CLIA for high-complexity testing. Additionally, laboratories in the U.S. should follow the College of American Pathology Guidelines. High complexity techniques used for pharmacogenetic testing include immunohistochemistry (IHC), fluorescent in situ hybridization (FISH), polymerase chain reaction (PCR) and microarray assays. According to the U.S. Food and Drug Administration (FDA) (2007), diagnostic tests that assay the presence of a particular pattern (e.g., single nucleotide polymorphism [SNP] set, haplotype pattern) should ideally be validated in a prospective clinical trial.

An increasing number of multigene genotyping panels with the goals of detecting inter-individual differences in drug metabolism and response to a variety of drug targets are commercially

available. The number of gene biomarkers and gene mutations and associated drug targets which are tested for vary widely between tests; some tests evaluate for a few biomarkers and associated drug targets while others may include hundreds of biomarkers within the test. Some multigene assays assess for the presence or absence of multiple biomarkers and provide lists of potential therapeutic agents, clinical trials and review of published literature associated with the biomarkers that are identified in the patient sample.

Clinical Utility
The clinical use of a genetic test should be based on analytical validity (i.e., analytical sensitivity and specificity), and clinical validity (i.e., clinical sensitivity and specificity), and both positive and negative predictive value. Before a genetic test can be generally accepted in clinical practice, data must be collected to demonstrate the benefits and risks from both positive and negative results (i.e., the test must have clinical utility).

The clinical usefulness or utility of pharmacogenetic testing is the extent to which results of testing will impact clinical decision-making and improve health outcomes. Pharmacogenetic test results are meant to guide patient evaluation and treatment strategy and decisions based on the ability to predict response to treatment in particular clinical contexts, and to allow the clinician to predict an individual's response to specific pharmacotherapy, assist in making treatment choices, individualize drug dosages in order to maintain a consistent drug level in the body and avoid adverse reactions from overdose or suboptimal effects from under medication (Terasawa, et al., 2010; Al-Ghoul and Valdes, 2008). The integration of genomic data in patient treatment requires evidence of consistency and size of measured effects, medication compliance and phenoconversion. The effects of ethnicity must be evaluated, especially in the context of global drug development and extrapolation of clinical trial genomic data from one population to another (Ehmann, et al., 2014).

To definitively show that pharmacogenetic testing has value in clinical practice, it is not enough to demonstrate that drug response varies by genotype. Testing for the genotype and subsequently tailoring the treatment strategy based on genetic information should be more clinically effective and/or cost effective than treating an individual by an established treatment standard (McKinnon, et al., 2007).

When applied in a clinical setting, the information from these tests can potentially identify individual variability in drug response, including both effectiveness and toxicity. The individual for whom testing is proposed should be a candidate for a targeted drug therapy associated with a specific gene biomarker or gene mutation and results of testing must directly impact clinical decision making. The identification of the specific gene or biomarker for use with a specific drug target must also be demonstrated by published, peer-reviewed clinical trial data to improve clinical outcomes for an individual receiving that specific treatment and be considered scientifically valid to identify the biomarker.

Gene Expression Classifiers
The genetic basis for disease is determined by the inheritance of genes containing specific sequences of DNA. The phenotypic expression of these genes, through the synthesis of specific proteins, involves interaction with environmental signals that trigger activation of particular genes. Ribonucleic acid (RNA) is transcribed from a DNA template; messenger RNA (mRNA) is then translated into protein. Transcription and translation underlie gene expression. Three to five percent of genes are active in a particular cell, even though all cells have the same information contained in their DNA. Most of the genome is selectively repressed, a property that is governed by the regulation of gene expression, mostly at the level of transcription (i.e., the production of messenger RNA from the DNA). In response to a cellular perturbation, changes in gene expression take place that result in the expression of hundreds of gene products and the suppression of

others. This molecular heterogeneity can affect when and how a disease presents clinically in an individual with genetic predisposition to a condition and how individuals with a given disease will respond to specific treatments. Analyses of gene expression can be clinically useful for disease classification, diagnosis, prognosis, and tailoring treatment to underlying genetic determinants of pharmacologic response (Steiling and Christenson, 2021). However, there is a lack of evidence to support the use of gene expression classifiers and profiling for pharmacologic response.

U.S. Food and Drug Administration (FDA)
The FDA considers the use of genomic information in drug labels either to require a genetic test for prescribing a drug, to recommend the use of a genetic test prior to drug therapy, or simply to provide information about the current knowledge of genomics that is relevant to drug therapy without the requirement or recommendation of a specific action. While the clinical utility of genotyping prior to treatment is not proven for all medications for which genomic information is included (Slavin, et al., 2015), clinical utility is established when identification of a specific gene biomarker is noted to be clinically necessary prior to initiating therapy with a specific drug target as noted within the section heading "Indications and Usage" of the U.S. Food and Drug Administration (FDA)-approved prescribing label.

An FDA Safety Communication (2018) warns against the use of many genetic tests with unapproved claims to predict patient response to specific medications. The Communication's intent was to alert patients and health care providers that for many genetic tests, claims to predict a patient's response to specific medications have not been reviewed by the FDA, and may not have the scientific or clinical evidence to support this use for most medications. Changing drug treatment based on the results from such a genetic test could lead to inappropriate treatment decisions and potentially serious health consequences for the patient. The FDA specifically notes the relationship between DNA variations and the effectiveness of antidepressant medication has never been established. According to the FDA, there are a limited number of cases for which at least some evidence does exist to support a correlation between a genetic variant and drug levels within the body, and this is described in the labeling of FDA cleared or approved genetic tests and FDA approved medications.

Literature Review
Increasingly, published, peer-reviewed scientific evidence regarding the clinical utility of pharmacogenetic testing informs on the ability of such testing to benefit health outcomes. Prospective clinical trials of standard management procedures compared with genetic test-directed management offers the highest level of evidence. Evidence may also be derived using banked samples from already-completed clinical trials; or by constructing an indirect chain of evidence linking test results to clinical outcome. To date, much of the existing research in the area of pharmacogenetic testing has been limited by study design, including uncontrolled and poorly defined case and control groups, presence of confounding variables, and the use of retrospective and non-blinded study protocols.

Although genome-wide association studies report inter-individual variability, high-quality, randomized controlled trial data demonstrating improved clinical outcomes are lacking. Many early phase clinical trials are exploratory, with no formal genomic hypothesis, and have small sample sizes that make it difficult to identify important gene variants influencing pharmacokinetics and pharmacodynamics (Lesko and Schmidt, 2014). However, clinical utility has been established for pharmacogenetic testing for a number of gene biomarkers and their specific drug targets.

Zeier et al. (2018) reviewed the evidence for several combinatorial pharmacogenetic test decision support tools whose potential utility to improve antidepressant treatment response or side effect burden has been evaluated in clinical settings. The authors note available literature suffers from publication bias, because some products garner more investment than do others, and questions

about scientific integrity are inherent in studies conducted by or reports authored by personnel with significant financial interests in the outcome. Although some of the preliminary published data sound promising, particularly with regard to the CYP450 gene variants and side effect burden, we conclude that there is insufficient evidence to support widespread use at this point in time.

Wang et al. (2014) published results of a study evaluating the evidence that supports pharmacogenomic biomarker testing in drug labels and how frequently testing is recommended. Using guidelines published by the Evaluation of Genomic Applications in Practice and Prevention Working Group and FDA databases, the authors reviewed drug labels that described the use of a biomarker for reference to clinical validity and clinical utility. Of 119 notations in drug labels 36.1% provided evidence of clinical validity evidence while 15.1% provided evidence of clinical utility. Sixty-one labels (51.3%) made recommendations regarding clinical management based on the results of a biomarker test. Of these, 30.3% provided clinical utility data. A full description of supporting studies was included in 13 labels (10.9%). The authors noted that it may be premature to include biomarker recommendations in drug labels when data regarding patient outcomes are not available.

Pharmacogenetic testing is not currently recommended for general population screening. Clinical trials regarding the use of pharmacogenetic testing for screening in the general population are lacking in the published, peer-reviewed scientific literature and the role of such testing has not been established.

Professional Societies/Organizations
There is limited published professional society consensus guideline support for pharmacogenetic testing for non-cancer-related conditions.

Medicare Coverage Determinations

	Contractor	Determination Name/Number	Revision Effective Date
NCD	National	Pharmacogenomic Testing for Warfarin Response (90.1)	4/2010
LCD	CGS	MolDX: Pharmacogenomics Testing (L38394)	8/2023
LCD	NGS	Molecular Pathology Procedures (L35000)	8/2023
LCD	Novitas Solutions	Pharmacogenomics Testing (L39063)	12/2021
LCD	First Coast Options	MolDX; Pharmacogenomics Testing (L39073)	12/2021
LCD	Noridian Healthcare Solutions	MolDX: Pharmacogenomics Testing (L38335)	12/2023
LCD	Palmetto GBA	MolDX: Pharmacogenomics Testing (L38294)	8/2023
LCD	Wisconsin Physicians Service Insurance Corporation	MolDX: Pharmacogenomics Testing (L38435)	8/2023

Note: Please review the current Medicare Policy for the most up-to-date information.
(NCD = National Coverage Determination; LCD = Local Coverage Determination)

Coding Information

Notes:

1. This list of codes may not be all-inclusive since the American Medical Association (AMA) and Centers for Medicare & Medicaid Services (CMS) code updates may occur more frequently than policy updates.
2. Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement.

Considered Medically Necessary when criteria in the applicable policy statements listed above are met:

CPT®* Codes	Description
81247	G6PD (glucose-6-phosphate dehydrogenase) (eg, hemolytic anemia, jaundice), gene analysis; common variant(s) (eg, A, A-)
81400	Molecular pathology procedure, Level 1 (eg, identification of single germline variant [eg, SNP] by techniques such as restriction enzyme digestion or melt curve analysis)
81401	Molecular pathology procedure, Level 2 (eg, 2-10 SNPs, 1 methylated variant, or 1 somatic variant [typically using nonsequencing target variant analysis], or detection of a dynamic mutation disorder/triplet repeat)
81405	Molecular pathology procedure, Level 6 (eg, analysis of 6-10 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 11-25 exons, regionally targeted cytogenomic array analysis)

Considered Medically Necessary when criteria in the applicable policy statements listed above are met:

CPT®* Codes	Description
81227	CYP2C9 (cytochrome P450, family 2, subfamily C, polypeptide 9) (eg, drug metabolism), gene analysis, common variants (eg, *2, *3, *5, *6)

ICD-10 CM Codes	Description
G35	Multiple sclerosis

Not Covered or Reimbursable:

ICD-10-CM Diagnosis Codes	Description
	All other diagnosis codes

Not Covered or Reimbursable:

CPT®* Codes	Description
81225	CYP2C19 (cytochrome P450, family 2, subfamily C, polypeptide 19) (eg, drug metabolism), gene analysis, common variants (eg, *2, *3, *4, *8, *17)
81230	CYP3A4 (cytochrome P450 family 3 subfamily A member 4) (eg, drug metabolism), gene analysis, common variant(s) (eg, *2, *22)

CPT®* Codes	Description
81231	CYP3A5 (cytochrome P450 family 3 subfamily A member 5) (eg, drug metabolism), gene analysis, common variants (eg, *2, *3, *4, *5, *6, *7)
81283	IFNL3 (interferon, lambda 3) (eg, drug response), gene analysis, rs12979860 variant
81328	SLCO1B1 (solute carrier organic anion transporter family, member 1B1) (eg, adverse drug reaction), gene analysis, common variant(s) (eg, *5)
81355	VKORC1 (vitamin K epoxide reductase complex, subunit 1) (eg, warfarin metabolism), gene analysis, common variant(s) (eg, -1639G>A, c.173+1000C>T)
81418	Drug metabolism (eg, pharmacogenomics) genomic sequence analysis panel, must include testing of at least 6 genes, including CYP2C19, CYP2D6, and CYP2D6 duplication/deletion analysis
0029U	Drug metabolism (adverse drug reactions and drug response), targeted sequence analysis (ie, CYP1A2, CYP2C19, CYP2C9, CYP2D6, CYP3A4, CYP3A5, CYP4F2, SLCO1B1, VKORC1 and rs12777823)
0030U	Drug metabolism (warfarin drug response), targeted sequence analysis (ie, CYP2C9, CYP4F2, VKORC1, rs12777823)
0031U	CYP1A2 (cytochrome P450 family 1, subfamily A, member 2)(eg, drug metabolism) gene analysis, common variants (ie, *1F, *1K, *6, *7)
0032U	COMT (catechol-O-methyltransferase))(eg, drug metabolism) gene analysis, c.472G>A (rs4680) variant
0033U	HTR2A (5-hydroxytryptamine receptor 2A), HTR2C (5-hydroxytryptamine receptor 2C) (eg, citalopram metabolism) gene analysis, common variants (ie, HTR2A rs7997012 [c.614-2211T>C], HTR2C rs3813929 [c.-759C>T] and rs1414334 [c.551-3008C>G])
0173U	Psychiatry (ie, depression, anxiety), genomic analysis panel, includes variant analysis of 14 genes
0175U	Psychiatry (eg, depression, anxiety), genomic analysis panel, variant analysis of 15 genes
0345U	Psychiatry (eg, depression, anxiety, attention deficit hyperactivity disorder [ADHD]), genomic analysis panel, variant analysis of 15 genes, including deletion/duplication analysis of CYP2D6
0347U	Drug metabolism or processing (multiple conditions), whole blood or buccal specimen, DNA analysis, 16 gene report, with variant analysis and reported phenotypes
0348U	Drug metabolism or processing (multiple conditions), whole blood or buccal specimen, DNA analysis, 25 gene report, with variant analysis and reported phenotypes
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
0350U	Drug metabolism or processing (multiple conditions), whole blood or buccal specimen, DNA analysis, 27 gene report, with variant analysis and reported phenotypes
0380U	Drug metabolism (adverse drug reactions and drug response), targeted sequence analysis, 20 gene variants and CYP2D6 deletion or duplication analysis with reported genotype and phenotype
0392U	Drug metabolism (depression, anxiety, attention deficit hyperactivity disorder [ADHD]), gene-drug interactions, variant analysis of 16 genes, including

CPT®* Codes	Description
	deletion/duplication analysis of CYP2D6, reported as impact of gene-drug interaction for each drug
0411U	Psychiatry (eg, depression, anxiety, attention deficit hyperactivity disorder [ADHD]), genomic analysis panel, variant analysis of 15 genes, including deletion/duplication analysis of CYP2D6
0419U	Neuropsychiatry (eg, depression, anxiety), genomic sequence analysis panel, variant analysis of 13 genes, saliva or buccal swab, report of each gene phenotype
0423U	Psychiatry (eg, depression, anxiety), genomic analysis panel, including variant analysis of 26 genes, buccal swab, report including metabolizer status and risk of drug toxicity by condition (Code effective 01/01/2024)
0434U	Drug metabolism (adverse drug reactions and drug response), genomic analysis panel, variant analysis of 25 genes with reported phenotypes (Code effective 01/01/2024)
0437U	Psychiatry (anxiety disorders), mRNA, gene expression profiling by RNA sequencing of 15 biomarkers, whole blood, algorithm reported as predictive risk score (Code effective 01/01/2024)
0438U	Drug metabolism (adverse drug reactions and drug response), buccal specimen, gene-drug interactions, variant analysis of 33 genes, including deletion/duplication analysis of CYP2D6, including reported phenotypes and impacted gene-drug interactions (Code effective 01/01/2024)
0456U	Autoimmune (rheumatoid arthritis), next-generation sequencing (NGS), gene expression testing of 19 genes, whole blood, with analysis of anticyclic citrullinated peptides (CCP) levels, combined with sex, patient global assessment, and body mass index (BMI), algorithm reported as a score that predicts nonresponse to tumor necrosis factor inhibitor (TNFi) therapy
0460U	Oncology, whole blood or buccal, DNA single-nucleotide polymorphism (SNP) genotyping by real-time PCR of 24 genes, with variant analysis and reported phenotypes
0461U	Oncology, pharmacogenomic analysis of single-nucleotide polymorphism (SNP) genotyping by real-time PCR of 24 genes, whole blood or buccal swab, with variant analysis, including impacted gene-drug interactions and reported phenotypes
0476U	Drug metabolism, psychiatry (eg, major depressive disorder, general anxiety disorder, attention deficit hyperactivity disorder [ADHD], schizophrenia), whole blood, buccal swab, and pharmacogenomic genotyping of 14 genes and CYP2D6 copy number variant analysis and reported phenotypes (Code effective 10/01/2024)
0477U	Drug metabolism, psychiatry (eg, major depressive disorder, general anxiety disorder, attention deficit hyperactivity disorder [ADHD], schizophrenia), whole blood, buccal swab, and pharmacogenomic genotyping of 14 genes and CYP2D6 copy number variant analysis, including impacted gene-drug interactions and reported phenotypes (Code effective 10/01/2024)
0516U	Drug metabolism, whole blood, pharmacogenomic genotyping of 40 genes and CYP2D6 copy number variant analysis, reported as metabolizer status (Code effective 10/01/2024)

HCPCS Codes	Description
G9143	Warfarin responsiveness testing by genetic technique using any method, any number of specimen(s)

References

1. Al-Ghoul M, Valdes R Jr. Fundamentals of pharmacology and applications in pharmacogenetics. Clin Lab Med. 2008 Dec;28(4):485-97.

2. Anderson JL, Horne BD, Stevens SM, Grove AS, Barton S, Nicholas ZP, et al.; Couma-Gen Investigators. Randomized trial of genotype-guided versus standard warfarin dosing in patients initiating oral anticoagulation. Circulation. 2007 Nov 27;116(22):2563-70.

3. Anderson JL, Horne BD, Stevens SM, Woller SC, Samuelson KM, Mansfield JW, et al. A randomized and clinical effectiveness trial comparing two pharmacogenetic algorithms and standard care for individualizing warfarin dosing (CoumaGen-II). Circulation. 2012 Apr 24;125(16):1997-2005. Epub 2012 Mar 19.

4. Andreassen TN, Eftedal I, Klepstad P, Davies A, Bjordal K, Lundström S, Kaasa S, Dale O. Do CYP2D6 genotypes reflect oxycodone requirements for cancer patients treated for cancer pain? A cross-sectional multicentre study. Eur J Clin Pharmacol. 2012 Jan;68(1):55-64.

5. Ansell J, Hirsh J, Hylek E, Jacobson A, Crowther M, Palareti G. Pharmacology and management of the vitamin K antagonists: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Chest. 2008 Jun;133(6 Suppl):160S-198S. doi: 10.1378/chest.08-0670. PMID: 18574265.

6. Aquilante CL, Langaee TY, Lopez LM, Yarandi HN, Tromberg JS, et al. Influence of coagulation factor, vitamin K epoxide reductase complex subunit 1, and cytochrome P450 2C9 gene polymorphisms on warfarin dose requirements. Clin Pharmacol Ther. 2006 Apr;79(4):291-302.

7. Bae JW, Choi CI, Lee HI, Lee YJ, Jang CG, Lee SY. Effects of CYP2C9*1/*3 and *1/*13 on the pharmacokinetics of losartan and its active metabolite E-3174. Int J Clin Pharmacol Ther. 2012 Sep;50(9):683-9.

8. Bakker PR, van Os J, van Harten PN. [The genetics of antipsychotic-related movement disorders]. Tijdschr Psychiatr. 2015;57(2):114-9.

9. Baudhuin LM, Langman LJ, O'Kane DJ. Translation of pharmacogenetics into clinically relevant testing modalities. Clin Pharmacol Ther. 2007 Oct;82(4):373-6.

10. Bauer T, Bouman HJ, van Werkum JW, Ford NF, ten Berg JM, Taubert D. Impact of CYP2C19 variant genotypes on clinical efficacy of antiplatelet treatment with clopidogrel: systematic review and meta-analysis. BMJ. 2011 Aug 4;343:d4588. doi: 10.1136/bmj.d4588.

11. Berm EJ, Hak E, Postma M4, Boshuisen M6 Breuning L, Brouwers JR, Dhondt T, Jansen PA, Kok RM, Maring JG, van Marum R, Mulder H, Voshaar RC, Risselada AJ, Venema H, Vleugel L, Wilffert B. Effects and cost-effectiveness of pharmacogenetic screening for CYP2D6 among older adults starting therapy with nortriptyline or venlafaxine: study protocol for a pragmatic randomized controlled trial (CYSCEtrial). Trials. 2015 Jan 31;16:37. doi: 10.1186/s13063-015-0561-0.

12. Bhatt DL, Pare G, Eikelboom JW, Simonsen KL, Emison ES, Fox, KA, et al. The relationship between CYP2C10 polymorphisms and ischaemic and bleeding outcomes in stable patients: the CHARISMA genetics study. Eur Heart J. 2012 Sep;33(17):2143-50.

13. Bradley P, Shiekh M, Mehra V, Vrbicky K, Layle S, Olson MC, et al. Improved efficacy with targeted pharmacogenetic-guided treatment of patients with depression and anxiety: A randomized clinical trial demonstrating clinical utility. J Psychiatr Res. 2018 Jan;96:100-107.

14. Brandl EJ, Tiwari AK, Zhou X, Deluce J, Kennedy JL, Müller DJ, Richter MA. Influence of CYP2D6 and CYP2C19 gene variants on antidepressant response in obsessive-compulsive disorder. Pharmacogenomics J. 2013 Apr 2.

15. Brown JT1, Bishop JR. Atomoxetine pharmacogenetics: associations with pharmacokinetics, treatment response and tolerability. Pharmacogenomics. 2015 Aug 28.

16. Byeon JY, Kim YH, Na HS, Jang JH, Kim SH, Lee YJ, Bae JW, Kim IS, Jang CG, Chung MW, Lee SY. Effects of the CYP2D6*10 allele on the pharmacokinetics of atomoxetine and its metabolites. Arch Pharm Res. 2015 Aug 9. [Epub ahead of print]

17. Cabaleiro T, Roman M, Ochoa D, Talegon M, Prieto-Perez R, Wojnicz A, Lopez-Rodriguez R, Novalbos J, Abad-Santos F. Evaluation of the relationship between sex, polymorphisms in cyp2c8 and cyp2c9 and pharmacokinetics of angiotensin receptor blockers. Drug Metab Dispos. 2013 Jan;41(1):224-9.

18. Caldwell MD, Berg RL, Zhang KQ, Glurich I, Schmelzer JR, Yale SH, et al. Evaluation of genetic factors for warfarin dose prediction. Clin Med Res. 2007 Mar;5(1):8-16.

19. Candiotti KA, Yang Z, Rodriguez Y, Crescimone A, Sanchez GC, Takacs P, Medina C, Zhang Y, Liu H, Gitlin MC. The impact of CYP2D6 genetic polymorphisms on postoperative morphine consumption. Pain Med. 2009 Jul-Aug;10(5):799-805.

20. Caraco Y, Blotnick S, Muszkat M. CYP2C9 genotype-guided warfarin prescribing enhances the efficacy and safety of anticoagulation: a prospective randomized controlled study. Clin Pharmacol Ther. 2008 Mar;83(3):460-70.

21. Carlquist JF, McKinney JT, Nicholas ZP, Clark JL, Kahn SF, Horne BD, et al. Rapid melting curve analysis for genetic variants that underlie inter-individual variability in stable warfarin dosing. J Thromb Thrombolysis. 2007 Jul 29.

22. Caudle KE, Rettie AE, Whirl-Carrillo M, Smith LH, Mintzer S, Lee MT, Klein TE, Callaghan JT, Clinical Pharmacogenetics Implementation Consortium. Clinical pharmacogenetics implementation consortium guidelines for CYP2C9 and HLA-B genotypes and phenytoin dosing. Clin Pharmacol Ther. 2014 Nov;96(5):542-8.

23. Centers for Disease Control and Prevention (CDC). Genomics and Precision Health. Assessing Pharmacogenetic Variation in the United States to Enhance Health Equity of Pharmacogenetic Testing. Mar 15, 2022. Accessed Jan 11, 2024. Available at UR: address: https://blogs.cdc.gov/genomics/2022/03/15/assessing-pharmacogenetic/

24. Centers for Medicare and Medicaid Services (CMS). Local Coverage Determinations (LCDs) alphabetical index. Accessed Jan 8, 2024. Available at URL address: https://www.cms.gov/medicare-coverage-database/reports/local-coverage-proposed-lcds-alphabetical-report.aspx?proposedStatus=A&sortBy=title

25. Centers for Medicare and Medicaid Services (CMS). National Coverage Determinations (NCDs) alphabetical index. Accessed Jan 8, 2024. Available at URL address: https://www.cms.gov/medicare-coverage-database/reports/national-coverage-ncd-report.aspx?chapter=all&sortBy=title

26. Céspedes-Garro C, Jiménez-Arce G, Naranjo ME, Barrantes R, Llerena A; CEIBA.FP Consortium of the Ibero-American Network of Pharmacogenetics & Pharmacogenomics RIBEF. Ethnic background and CYP2D6 genetic polymorphisms in Costa Ricans. Rev Biol Trop. 2014 Dec;62(4):1659-71

27. Chou W, Yan F, Robbins-Weilert D, Ryder T, Liu W, Parrots C, et al. Comparison of Two CYP2D6 Genotyping Methods and Assessment of Genotype-Phenotype Relationships Clin Chem 2003;49:4:542–51.

28. Claudio-Campos K, Duconge J, Cadilla CL, Ruano G. Pharmacogenetics of drug-metabolizing enzymes in US Hispanics. Drug Metabol Personal Ther. 2015 Jun;30(2):87-105.

29. Collet JP, Hulot JS, Pena A, Villard E, Esteve JB, Silvain J, et al. Cytochrome P450 2C19 polymorphism in young patients treated with clopidogrel after myocardial infarction: a cohort study. Lancet. 2009 Jan 24;373(9660):309-17.

30. Cooper GM, Johnson JA, Langaee TY, Feng H, Stanaway IB, Schwarz UI, et al. A genome-wide scan for common genetic variants with a large influence on warfarin maintenance dose. Blood. 2008 Aug 15;112(4):1022-7.

31. Cresci S, Depta JP, Lenzini PA et al. Cytochrome p450 gene variants, race, and mortality among clopidogrel-treated patients after acute myocardial infarction. Circ Cardiovasc Genet. 2014 Jun;7(3):277-86. Epub 2014 Apr 24.

32. Crews KR, Gaedigk A, Dunnenberger HM, Leeder JS, Klein TE, Caudle KE, Haidar CE, Shen DD, Callaghan JT, Sadhasivam S, Prows CA, Kharasch ED, Skaar TC. Clinical Pharmacogenetics Implementation Consortium Guidelines for Cytochrome P450 2D6 Genotype and Codeine Therapy: 2014 Update. Clin Pharmacol Ther. 2014 Jan 23.

33. Crews KR, Hicks JK, Pui CH, Relling MV, Evans WE. Pharmacogenomics and individualized medicine: translating science into practice. Clin Pharmacol Ther. 2012;92(4):467-475. doi:10.1038/clpt.2012.120

34. Cuisset T, Frere C, Poyet R, Quilici J, Gaborit B, Bali L, et al. Clopidogrel response: Head-to-head comparison of different platelet assays to identify clopidogrel non-responder patients after coronary stenting. Arch Cardiovasc Dis. 2010 Jan;101(1):39-45.

35. D'Empaire I, Guico-Pabia CJ, Preskorn SH. Antidepressant treatment and altered CYP2D6 activity: are pharmacokinetic variations clinically relevant? J Psychiatr Pract. 2011 Sep;17(5): 330-9.

36. Dahabreh IJ, Moorthy D, Lamont JL, Chen ML, Kent DM, Lau J. Testing of CYP2C19 Variants and Platelet Reactivity for Guiding Antiplatelet Treatment [Internet]. Rockville (MD): Agency for Healthcare Research and Quality (US); 2013 Sep.

37. Daly AK, Cascorbi I. Opportunities and limitations: the value of pharmacogenetics in clinical practice. Br J Clin Pharmacol. 2014 Apr;77(4):583-6.

38. de Leon J, et al. The CYP2D6 poor metabolizer phenotype may be associated with risperidone adverse drug reactions and discontinuation. J Clin Psychiatry. 2005 Jan;66(1):15-27.

39. Dickinson GL, Lennard MS, Tucker GT, Rostami-Hodjegan A. The use of mechanistic DM-PK-PD modeling to assess the power of pharmacogenetic studies -CYP2C9 and warfarin as an example. Br J Clin Pharmacol. 2007 Jul;64(1):14-26.

40. Dubovsky SL. The usefulness of genotyping cytochrome P450 enzymes in the treatment of depression. Expert Opin Drug Metab Toxicol. 2015 Mar;11(3):369-79. doi: 10.1517/17425255.2015.998996. Epub 2015 Jan 2.

41. Dunbar L, Miles W, Wheeler A, Sheridan J, Pulford J, Butler R. The CYP2D6 metaboliser status of patients prescribed risperidone for the treatment of psychosis. N Z Med J. 2009 Jun 5;122(1296):29-34.

42. Ehmann F, Caneva L, Papluca M. European Medicines Agency initiatives and perspectives on pharmacogenomics. Br J Clin Pharmacol. 2014 Apr; 77(4): 612–617.

43. Epstein RS, Moyer TP, Aubert RE, O'Kane DJ, Xia F, Verbrugge RR, et al. Warfarin Genotyping Reduces Hospitalization Rates Results From the MM-WES (Medco-Mayo Warfarin Effectiveness Study). J Am Coll Cardiol. 2010 Apr 7.

44. Evrard A, Mbatchi L. Genetic polymorphisms of drug metabolizing enzymes and transporters: the long way from bench to bedside. Curr Top Med Chem. 2012;12(15):1720-9.

45. Fargher EA, Eddy C, Newman W, Qasim F, Tricker K, Elliot RA, et al. Patients' and healthcare professionals' views on pharmacogenetic testing and its future delivery in the NHS. Pharmacogenomics. 2007 Nov;8(11):1511-9.

46. Ferder NS, Eby CS, Deych E, Harris JK, Ridker PM, Milligan PE, et al. Ability of VKORC1 and CYP2C9 to predict therapeutic warfarin dose during the initial weeks of therapy. J Thromb Haemost. 2010;8(1):95-100.

47. Ferreira PG, Costa S, Dias N, Ferreira AJ, Franco F. Simultaneous interstitial pneumonitis and cardiomyopathy induced by venlafaxine. J Bras Pneumol. 2014 May-Jun;40(3):313-8.

48. Flockhart DA, O'Kane D, Williams MS, Watson MS, Gage B, Gandolfi R, et al.; ACMG Working Group on Pharmacogenetic Testing of CYP2C9, VKORC1 Alleles for Warfarin Use. Pharmacogenetic testing of CYP2C9 and VKORC1 alleles for warfarin. Genet Med. 2008 Feb;10(2):139-50.

49. Fohner A, Muzquiz LI, Austin MA, Gaedigk A, Gordon A, Thornton T, Rieder MJ, Pershouse MA, Putnam EA, Howlett K, Beatty P, Thummel KE, Woodahl EL. Pharmacogenetics in American Indian populations: analysis of CYP2D6, CYP3A4, CYP3A5, and CYP2C9 in the Confederated Salish and Kootenai Tribes. Pharmacogenet Genomics. 2013 Aug;23(8):403-14.

50. Franchini M, Mengoli C, Cruciani M, Bonfanti C, Mannucci PM. Effects on bleeding complications of pharmacogenetic testing for initial dosing of vitamin K antagonists: a systematic review and meta-analysis. J Thromb Haemost. 2014 Sep;12(9):1480-7.

51. Franco V, Perucca E. CYP2C9 polymorphisms and phenytoin metabolism: implications for adverse effects. Expert Opin Drug Metab Toxicol. 2015 Aug; 11(8):1269-79.

52. Frere C, Cuisset T, Morange PE, Quicili J, Camion-Jau L, Suat N, et al. Effect of cytochrome p450 polymorphisms on platelet reactivity after treatment with clopidogrel in acute coronary syndrome. Am J Cardiol. 2008 Apr 15;101(8):1088-93.

53. Gaikwad T, Ghosh K, Shetty S. VKORC1 and CYP2C9 genotype distribution in Asian countries. Thromb Res. 2014 Sep;134(3):537-44.

54. Gage BF, Lesko LJ. Pharmacogenetics of warfarin: regulatory, scientific, and clinical issues. J Thromb Thrombolysis. 2007 Oct 1; [Epub ahead of print]

55. Gardiner SH, Begg EJ. Pharmacogenetics, drug-metabolizing enzymes, and clinical practice. Pharmacol Rev. 2006 Sep;58(3):521-90.

56. Ginsburg GS, Konstance RP, Allsbrook JS, Schulman KA. Implications of pharmacogenomics for drug development and clinical practice. Arch Intern Med. 2005 Nov 14;165(20):2331-6.

57. Gladding P, Webster M, Zeng I, Farrell H, Stewart J, Ruygrok P, et al. The pharmacogenetics and pharmacodynamics of clopidogrel response: an analysis of the PRINC (Plavix Response in Coronary Intervention) trial. JACC Cardiovasc Interv. 2008 Dec;1(6):620-7.

58. Glowacki F, Lionet A, Buob D, Labalette M, Allorge D, Provôt F, et al. CYP3A5 and ABCB1 polymorphisms in donor and recipient: impact on Tacrolimus dose requirements and clinical outcome after renal transplantation. Nephrol Dial Transplant. 2011 Sep;26(9):3046-50.

59. Goetz MP, Rae JM, Suman VJ, Safgren SL, Ames MM, Visscher DW, et al. Pharmacogenetics of tamoxifen biotransformation is associated with clinical outcomes of efficacy and hot flashes. J Clin Oncol. 2005 Dec 20;23(36):9312-28.

60. Goetz MP, Sangkuhl K, Guchelaar H-J, et al. Clinical Pharmacogenomics Implementation Consortium (CPIC) guideline for CYP2D6 and tamoxifen therapy. Clin Pharmacol Ther. 2018. doi: 10.1002/cpt.1007. [Epub ahead of print].

61. Greden JF, Parikh SV, Rothschild AJ, Thase ME, Dunlop BW, DeBaptista C, et al. 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;111-59-67.

62. Guilherme SK and Botton MR. Pharmacogenomics of warfarin in populations of African descent. Br J Clin Pharmacol. 2013 Feb;75(2);334-346.

63. Guisti B, Gori AM, Marcucci R, Saracini C, Sestini I, Paniccia R, et al. Relation of cytochrome P450 2C19 loss-of-function polymorphism to occurrence of drug-eluting coronary stent thrombosis. Am J Cardiol. 2009 Mar 15;103(6):806-11.

64. Gulseth MP, Grice GR, Dager WE. Pharmacogenomics of warfarin: uncovering a piece of the warfarin mystery. Am J Health Syst Pharm. 2009 Jan 15;66(2):123-33.

65. Haas DW, Ribaudo HJ, Kim RB, Tierney C, Wilkinson GR, Gulick RM, et al. Pharmacogenetics of efavirenz and central nervous system side effects: an Adult AIDS Clinical Trials Group study. AIDS. 2004 Dec 3;18(18):2391-400.

66. Hall-Flavin DK, Winner JG, Allen JD, Carhart JM, Proctor B, Snyder KA, Drews MS, Eisterhold LL, Geske J, Mrazek DA. Utility of integrated pharmacogenomics testing to support the treatment of major depressive disorder in a psychiatric outpatient setting. Pharmacogenet Genomics. 2013 Oct;23(10):535-48.

67. Hall-Flavin DK, Winner JG, Allen JD, Jordan JJ, Nesheim RS, Snyder KA, Drews MS, Eisterhold LL, Biernacka JM, Mrazek DA. Using a pharmacogenomic algorithm to guide the treatment of depression. Transl Psychiatry. 2012 Oct 16;2:e172.

68. Haufroid V, Hantson P. CYP2D6 genetic polymorphisms and their relevance for poisoning due to amfetamines, opioid analgesics and antidepressants. Clin Toxicol (Phila). 2015 Jul;53(6):501-10

69. Heller T, Kirchheiner J, Armstrong VW, Luthe H, Tzvetkov M, Brockmöller J, Oellerich M. AmpliChip CYP450 GeneChip: a new gene chip that allows rapid and accurate CYP2D6 genotyping. Ther Drug Monit. 2006 Oct;28(5):673-7.

70. Hicks JK, Swen JJ, Thorn CF, Sangkuhl K, Kharasch ED, Ellingrod VL, et al. Clinical Pharmacogenetics Implementation Consortium guideline for CYP2D6 and CYP2C19 genotypes and dosing of tricyclic antidepressants. Clinical pharmacology and therapeutics. 2013;93(5):402-8. Epub 2013/03/15. doi: 10.1038/clpt.2013.2

71. Higashi MK, Veenstra DL, Kondo LM, Wittkowsky AK, Srinouanprachanh SL, Farin FM, Rettie AE. Association between CYP2C9 genetic variants and anticoagulation-related outcomes during warfarin therapy. JAMA. 2002 Apr 3;287(13):1690-8.

72. Hillman MA, Wilke RA, Yale SH, Vidaillet HJ, Caldwell MD, Glurich I, et al. A prospective, randomized pilot trial of model-based warfarin dose initiation using CYP2C9 genotype and clinical data. Clin Med Res. 2005 Aug;3(3):137-45.

73. Hirsh J, Fuster V, Ansell J, Halperin J. American Heart Association/American College of Cardiology Foundation Guide to Warfarin Therapy. Circulation. 2003;107:1692-711.

74. Holmes MV, Perel P, Shah T, Hingorani AD, Casas JP. CYP2C19 genotype, clopidogrel metabolism, platelet function, and cardiovascular events: a systematic review and meta-analysis. JAMA. 2011 Dec 28;306(24):2704-14.

75. Horne BD, Lenzini PA, Wadelius M, Jorgensen AL, Kimmel SE, Ridker PM, et al. Pharmacogenetic warfarin dose refinements remain significantly influenced by genetic factors after one week of therapy. Thromb Haemost. 2012 Feb;107(2):232-40. Epub 2011 Dec 21.

76. Huang SW, Chen HS, Wang XQ, Huang L, Xu DL, Hu XJ, et al. Validation of VKORC1 and CYP2C9 genotypes on interindividual warfarin maintenance dose: a prospective study in Chinese patients. Pharmacogenet Genomics. 2009 Mar;19(3):226-34.

77. Hulot JS, Cullot JP, Cayla G, Silvain J, Allanic F, Bellemain-Appaix A, et al. CYP2C19 but not PON1 genetic variants influence clopidogrel pharmacokinetics, pharmacodynamics, and clinical efficacy in post-myocardial infarction patients. Circ Cardiovasc Interv. 2011 Oct 1;4(5):422-8.

78. Hulot JS, Cullot JP, Silvain J, Pena A, Bellemain-Appaix A, Barthelemy O, et al. Cardiovascular risk in clopidogrel-treated patients according to cytochrome P450 2C19*2 loss-of-function allele or proton pump inhibitor coadministration: a systematic meta-analysis. J Am Coll Cardiol. 2010 Jul 6;56(2):134-43.

79. Ingelman-Sundberg, Rodriguez-Antona C. Pharmacogenetics of drug-metabolizing enzymes: implications for a safer and more effective drug therapy. Philos Trans R Soc Lond B Biol Sci. 2005 Aug 29;360(1460):1563-70.

80. Ingelman-Sundberg M. Pharmacogenetic biomarkers as tools for improved drug therapy; emphasis on the cytochrome P450 system. Biochem Biophy Res Commun. 2010 May 21;396(1):90-4.

81. Ingelman-Sundberg M. Pharmacogenetics of cytochrome P450 and its applications in drug therapy: the past, present and future. Trends Pharmacol Sci.2004 Apr;25(4):193-200.

82. International Warfarin Pharmacogenetics Consortium, Klein TE, Altman RB, Eriksson N, Gage BF, Kimmel SE, Lee MT, et al. Estimation of the warfarin dose with clinical and pharmacogenetic data. N Engl J Med. 2009 Feb 19;360(8):753-64.

83. Joffe HV, Xu R, Johnson FB, Longtine J, Kucher N, Goldhaber SZ. Warfarin dosing and cytochrome P450 2C9 polymorphisms. Thromb Haemost. 2004 Jun;91(6):1123-8.

84. Johnson JA, Cavallari LH, Beitelshees AL, Lewis JP, Shuldiner AR, Roden DM. Pharmacogeneomics: application to the management of cardiovascular disease. Clin Pharmacol Ther. 2011 Oct;90(4):519-31.

85. Johnson JA, Caudle KE, Gong L, et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for pharmacogenetics-guided warfarin dosing: 2017 update. Clin Pharmacol Ther. 2017;102(3): 397-404.

86. Johnson JA, Gong L, Whirl-Carillo M, Gage BF, Scott SA, Stein CM, et al. Clinical Pharmacogenetics implementation consortium guidelines for CYP2C9 and VKORC1 genotypes and warfarin dosing. Clin Pharmacol Ther. 2011 Oct;90(4):625-9.

87. Jurgens G, Rasmussen HB, Werge T, Dalhoff K, Nordentoft M, Andersen SE. 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.

88. Kamali F. Genetic influences on the response to warfarin. Curr Opin Hematol. 2006 Sep;13(5):357-61.

89. Kamali F, Pirmohamed M. The future prospects of pharmacogenetics in oral anticoagulation therapy. Br J Clin Pharmacol. 2006 Jun;61(6):746-51.

90. Kangelaris KN, Bent S, Nussbaum RL, Garcia DA, Tice JA. Genetic testing before anticoagulation? A systematic review of pharmacogenetic dosing of warfarin. J Gen Intern Med. 2009 May;24(5):656-64.

91. Khoury MJ. Dealing with the evidence dilemma in genomics and personalized medicine. Clin Pharmacol Ther. 2010 Jun;87(6):635-8.

92. Khoury MJ, Rich EC, RandhawaG, Teutsch SM, Niederhuber J. Comparative effectiveness research and genomic medicine: an evolving partnership for 21st century medicine. Genet Med. 2009 Oct;11(10):707-11.

93. King CR, Porche-Sorbet RM, Gage BF, Ridker PM, Renaud Y, Phillips MS, Eby C. Performance of commercial platforms for rapid genotyping of polymorphisms affecting warfarin dose. Am J Clin Pathol. 2008 Jun;129(6):876-83.

94. Kitzmiller JP, Groen DK, Phelps MA, Sadee W. Pharmacogenomic testing: relevance in medical practice: why drugs work in some patients but not in others. Cleve Clin J Med. 2011 Apr;78(4):243-57.

95. Kringen MK, Haug KB, Grimholt RM, Stormo C, Narum S, Opdal MS, et al. Genetic variation of VKORC1 and CYP4F2 genes related to warfarin maintenance dose in patients with myocardial infarction. J Biomed Biotechnol. 2011;2011:739-751.

96. Krishna V, Diamond GA, Kaul S. The role of platelet reactivity and genotype testing in the prevention of atherothrombotic cardiovascular events remains unproven. Circulation. 2012 Mar 13;125(10):1288-303.

97. Krynetskiy E, McDonnell P. Building individualized medicine: prevention of adverse reactions to warfarin therapy. J Pharmacol Exp Ther. 2007 Aug;322(2):427-34.

98. Lamba JK, Lin YS, Schuetz EG, Thummel KE. Genetic contribution to variable human CYP3A-mediated metabolism. Adv Drug Deliv Rev. 2002 Nov 18;54(10):1271-94.

99. Langley MR, Booker JK, Evans JP, McLeod HL, Weck KE. Validation of clinical testing for warfarin sensitivity: comparison of CYP2C9-VKORC1 genotyping assays and warfarin-dosing algorithms. J Mol Diagn. 2009 May;11(3):216-25.

100. Lassen D, Damkier P, Brøsen K. The Pharmacogenetics of Tramadol. Clin Pharmacokinet. 2015 Aug;54(8):825-36. doi: 10.1007/s40262-015-0268-0.

101. Lee JM, Park S, Shinn DJ, Choi D, Shim CY, Yo YG, et al. Relation of genetic polymorphisms in the cytochrome P450 gene with clopidogrel resistance after drug-eluting stent implantations in Koreans. Am J Cardiol. 2009 Jul 1;104(1):46-51.

102. Lefevre F, Goodman SN, Piper MA. Pharmacogenetic testing for warfarin dosing still awaits validation. J Am Coll Cardiol. 2011 Feb 8;57(6):756

103. Lenzini P, Wadelius M, Kimmel S, Anderson JL, Jorgenson AL, Pirohamed M, et al. Integration of genetic, clinical and INR data to refine warfarin dosing. Clin Pharmacol Ther. 2010 May;87(5):572-8.

104. Lesko LJ, Schmidt S. Clinical implementation of genetic testing in medicine: a US regulatory science perspective. Br J Clin Pharmacol. 2014 Apr; 77(4): 606–611.

105. Li KX, Loshak H. Pharmacogenomic Testing in Depression: A Review of Clinical Effectiveness, Cost-Effectiveness, and Guidelines. Ottawa (ON): Canadian Agency for Drugs and Technologies in Health; January 31, 2020. Accessed Jan 8, 2024. Available at URL address: https://www.cadth.ca/pharmacogenomic-testing-depression-review-clinical-effectiveness-cost-effectiveness-and-guidelines

106. Limdi NA, McGwin G, Goldstein JA, Beasley TM, Arnett DK, Adler BK, et al. Influence of CYP2C9 and VKORC1 1173C/T Genotype on the Risk of Hemorrhagic Complications in African-American and European-American Patients on Warfarin. Clin Pharmacol Ther. 2007 Jul 25.

107. Limdi NA, Veenstra DL. Warfarin pharmacogenetics. Pharmacotherapy. 2008 Sep;28(9):1084-97.

108. Lindh JD, Lundgren S, Holm L, Alfredsson L, Rane A. Several-fold increase in risk of overanticoagulation by CYP2C9 mutations. Clin Pharmacol Ther. 2005 Nov;78(5):540-50.

109. Linares OA, Daly D, Linares AD, Stefanovski D, Boston RC. Personalized oxycodone dosing: using pharmacogenetic testing and clinical pharmacokinetics to reduce toxicity risk and increase effectiveness. Pain Med. 2014 May;15(5):791-806.

110. Lorenzini K, Calmy A, Ambrosioni J, Assouline B, Daali Y, Fathi M, Rebsamen M, Desmeules J, Samer CF. Serotonin syndrome following drug-drug interactions and CYP2D6 and CYP2C19 genetic polymorphisms in an HIV-infected patient. AIDS. 2012 Nov 28;26(18):2417-8.

111. Ma JD, Lee KC, Kuo GM. Clinical application of pharmacogenomics. J Pharm Pract. 2012 Aug;25(4):417-27

112. MacPhee IA, Holt DW. A pharmacogenetic strategy for immunosuppression based on the CYP3A5 genotype. Transplantation. 2008 Jan 27;85(2):163-5.

113. Magavern EF, Gurdasani D, Ng FL, Lee SS. Health equality, race and pharmacogenomics. Br J Clin Pharmacol. 2022 Jan;88(1):27-33. doi: 10.1111/bcp.14983. Epub 2021 Aug 4. PMID: 34251046; PMCID: PMC8752640.

114. Maruthur NM, Gribble MO, Bennett WL, Bolen S, Wilson LM, Balakrishnan P, Sahu A, Bass E, Kao WH Clark JM. The pharmacogenetics of type 2 diabetes: a systematic review. Diabetes Care. 2014;37(3):876-86.

115. McClain MR, Palomaki GE, Piper M, Haddow JE; Commissioned by ACMG. A Rapid ACCE Review of CYP2C9 and VKORC1 Allele Testing to Inform Warfarin Dosing in Adults at Elevated Risk for Thrombotic Events to Avoid Serious Bleeding. Feb 2008. Accessed Jan 8, 2024. Available at URL address: https://www.acmg.net/docs/Resources/Warfarin_CYP_VKOR_ACCE_review_8.21.07.pdf?hkey=6e8df859-fbf5-4bea-b5e4-dc482181e558

116. McKinnon RA, Ward MB, Sorich MJ. A critical analysis of barriers to the clinical implementation of pharmacogenomics. Ther Clin Risk Manag. 2007 Oct;3(5):751-59.

117. McMillin GA, Melis R, Wilson A, Strong MB, Wanner NA, Vinik RG, et al. Gene-based warfarin dosing compared with standard of care practices in an orthopedic surgery population: a prospective, parallel cohort study. Ther Drug Monit. 2010 Jun;32(3):338-45.

118. Mega JL, Close SL, Wiviott SD, Shen L, Hockett RD, Brandt JT, et al. Cytochrome P450 genetic polymorphisms and the response to prasurgrel: relationship to pharmacokinetic, pharmacodynamic and clinical outcomes. Circulation. 2009 May 19;119(19):2553-60.

119. Mega JL, Close SL, Wiviott SD, Shen L, Hockett RD, Brandt JT, et al. Cytochrome p-450 polymorphisms and response to clopidogrel. N Engl J Med. 2009 Jan 22;360(4):354-62.

120. Mega JL, Hochholzer W, Frelinger AL 3rd, Kluk MJ, Angiolillo DJ, Kereiakes DJ, et al. Dosing clopidogrel based on CYP2C19 genotype and the effect on platelet reactivity in patients with stable cardiovascular disease. JAMA. 2011 Nov 23;306(20):2221-8.

121. Mega JL, Simon T, Collet JP, Anderson JL, Antman EM, Bliden K, et al. reduced-function CYP2C19 genotype and risk of adverse clinical outcomes among patients treated with clopidogrel predominantly for PCI-a meta-analysis. JAMA. 2010 Oct 27;304(16):1821-30.

122. Mega JL, Walker JR, Ruff CT, Vandell AG, Nordio F, Deenadayalu N, Murphy SA, Lee J, Mercuri MF, Giugliano RP, Antman EM, Braunwald E, Sabatine MS. Genetics and the clinical response to warfarin and edoxaban: findings from the randomised, double-blind ENGAGE AF-TIMI 48 trial. Lancet. 2015 Jun;385(9984):2280-7.

123. Mehta R, Kelleher D, Preece A, Hughes S, Crater G, et al. Effect of verapamil on systemic exposure and safety of umeclidinium and vilanterol: a randomized and open-label study. Int J Chron Obstruct Pulmon Dis. 2013;8:159-67. Epub 2013 Mar 27.

124. Millican EA, Lenzina PA, Milligan PE, Grosso L, Eby C, Devch E, et al. Genetic-based dosing in orthopedic patients beginning warfarin therapy. Blood. 2007 Sep 1;110(5):1511-5.

125. Monte AA, Heard KJ, Campbell J, Hamamura D, Weinshilboum RM, Vasiliou V. The effect of CYP2D6 drug-drug interactions on hydrocodone effectiveness. Acad Emerg Med. 2014 Aug;21(8):879-85

126. Moyer TP, O'Kane DJ, Baudhuin LM, Wiley CL, Fortini A, Fisher PK, et al. Warfarin sensitivity genotyping: a review of the literature and summary of patient experience. Mayo Clin Proc. 2009 Dec;84(12):1079-94.

127. Musunuru K, Hickey KT, Al-Khatib SM, et al. Basic Concepts and Potential Applications of Genetics and Genomics for Cardiovascular and Stroke Clinicians: A Scientific Statement from the American Heart Association. Circ Cardiovas Genet. 2015;8:216-242.

128. Nakamura A, Mihara K, Nemoto K, Nagai G, Kagawa S, Suzuki T, Kondo T. Lack of correlation between the steady-state plasma concentrations of aripiprazole and haloperidol in Japanese patients with schizophrenia. Ther Drug Monit. 2014 Dec;36(6):815-8.

129. National Center for Biotechnology Information (NCBI). U.S. National Library of Medicine. Genetic Testing Registry. Accessed Jan 8, 2024. Available at URL address: http://www.ncbi.nlm.nih.gov/gtr/genes/

130. National Institute for Health Research (NIHR). The clinical effectiveness and cost-effectiveness of testing for cytochrome P450 polymorphisms in patients with schizophrenia treated with antipsychotics: a systematic review and economic evaluation. Health Technol Assess. 2010 Jan;14(3):1-157, iii. Accessed Jan 8, 2024. Available at URL address: https://www.journalslibrary.nihr.ac.uk/hta/hta14030/#/abstract

131. National Institute for Health Research (NIHR). [UK] The clinical effectiveness and cost-effectiveness of genotyping for CYP2D6 for the management of women with breast cancer treated with tamoxifen: a systematic review. Health Technol Assess 2011;15(33):1–102. Accessed Jan 8, 2024. Available at URL address: https://www.journalslibrary.nihr.ac.uk/search/#/?search=CYP2D6&sitekit=true&indexname=full-index&task=search&selected_facets=

132. National Institutes of Health (NIH). MedlinePlus. U.S. National Library of Medicine. Accessed Nov 28, 2022. Available at URL address: https://medlineplus.gov/genetics/

133. Ngedwa S. Pharmacogenomics and warfarin therapy [Issues in emerging health technologies issue 104]. Ottawa: Canadian Agency for Drugs and Technology in Health; 2007.

134. Oake N, Fergusson DA, Forster AJ, van Walraven C. Frequency of adverse events in patients with poor anticoagulation: a meta-analysis. CMAJ. 2007 May 22;176(11):1589-94.

135. Ong FS, Deignan JL, Kuo JZ, Bernstein KE, Rotter JI, Grody WW, et al. Clinical utility of pharmacogenetic biomarkers in cardiovascular therapeutics: a challenge for clinical implementation. Pharmacogenomics. 2012 Mar;13(4):465-75.

136. Palomaki GE, Bradley LA, Douglas MP, Kolor K, Dotson WD, Can UGT1A1 genotyping reduce morbidity and mortality in patients with metastatic colorectal cancer treated with irinotecan? An evidence-based review. Genet Med. 2009 Jan;11(1):21-34.

137. Papanastasopoulos P and Stebbing J. Molecular Basis of 5-Fluorouracil-related Toxicity: Lessons from Clinical Practice. Anticancer ResearchApril 2014 vol. 34 no. 41531-1535

138. Pare G, Meta SR, Yusuf S, Anand SS, Connolly SJ, Hirsh J, et al. Effects of CYP2C19 genotype on outcomes of clopidogrel treatment. N Engl J Med. 2010 Oct 28;363918):1704-14.

139. Pena A, Collet JP, Hullot JS, Silvain J, Barthelemy O, Beygui F, et al. Can we override clopidogrel resistance? Circulation. 2009 Jun 2;119(21):2854-7.

140. Peyvandi F, Spreafico M, Siboni SM, Moia M, Mannucci PM. CYP2C9 genotypes and dose requirements during the induction phase of oral anticoagulant therapy. Clin Pharmacol Ther. 2004 Mar;75(3):198-203.

141. Potkin SG, Preskorn S, Hochfeld M, Meng X. A thorough QTc study of 3 doses of iloperidone including metabolic inhibition via CYP2D6 and/or CYP3A4 and a comparison to quetiapine and ziprasidone. J Clin Psychopharmacol. 2013 Feb;33(1):3-10.

142. Province MA, Goetz MP, Brauch H, Flockhart DA, Hebert JM, Whaley R, et al. CYP2D6 genotype and adjuvant tamoxifen: meta-analysis of heterogeneous study populations. Clin Pharmacol Ther. 2014Feb;95(2):216-27.

143. Prows CA, Zhang X, Huth MM, Zhang K, Saldaña SN, Daraiseh NM, Esslinger HR, Freeman E, Greinwald JH, Martin LJ, Sadhasivam S. Codeine-related adverse drug reactions in children following tonsillectomy: a prospective study. Laryngoscope. 2014 May;124(5):1242-50. doi: 10.1002/lary.24455. Epub 2013 Nov 13.

144. Qasim A, Seery J, Buckley M, Morain CO. TPMT in the treatment of inflammatory bowel disease with azathioprine. Gut. 2003;52(5):767.

145. Rebsamen MC, Desmeules J, Daali Y, Chiappe A, Diemand A, Rey C, et al. The AmpliChip CYP450 test: cytochrome P450 2D6 genotype assessment and phenotype prediction. Pharmacogenomics J. 2009 Feb;9(1):34-41.

146. Regan MM, Leyland-Jones B, Bouzyk M, Pagani O, Tang W, Kammler R, et al. CYP2D6 genotype and tamoxifen response in postmenopausal women with endocrine-responsive breast cancer: the breast international group 1-98 trial. J Natl Cancer Inst. 2012 Mar 21;104(6):441-51.

147. Rettie AE, Tai G. The pharmocogenomics of warfarin: closing in on personalized medicine. Mol Interv. 2006 Aug;6(4):223-7.

148. Rieder MJ, Reiner AP, Gage BF, Nickerson DA, Eby CS, McLeod HL, et al. Effect of VKORC1 haplotypes on transcriptional regulation and warfarin dose. N Engl J Med. 2005 Jun 2;352(22):2285-93.

149. Rietveld L, van der Hoek T, van Beek MH, Schellekens AF. Familial liability for metoprolol-induced psychosis. Gen Hosp Psychiatry. 2015 Jun 25. pii: S0163-8343(15)00153-X

150. Robarge J, Fletcher R, Nguyen, A, Thorn CF. Pharmacogenomics Knowledge Base. ©2001-2023 PharmGKB. Accessed Jan 8, 2024. Available at URL address: https://www.pharmgkb.org

151. Rochat B. Role of cytochrome P450 activity in the fate of anticancer agents and in drug resistance: focus on tamoxifen, paclitaxel, and imatinib metabolism. Clin Pharmacokinet. 2005;44(4):349-66.

152. Roses AD. Pharmacogenetics. Hum Mol Genet. 2001 Oct 1;10(20):2261-7.

153. Sanderson S, Emery J, Higgins J. CYP2C9 gene variants, drug dose, and bleeding risk in warfarin-treated patients: a HuGEnet systematic review and meta-analysis. Genet Med. 2005 Feb;7(2):97-104.

154. Samer CF, Daali Y, Wagner M, Hopfgartner G, Eap CB, Rebsamen MC, et al. Genetic polymorphisms and drug interactions modulating CYP2D6 and CYP3A activities have a major effect on oxycodone analgesic efficacy and safety. Br J Pharmacol. 2010 Jun;160(4):919-30.

155. Schwarz UI, Ritchie MD, Bradford Y, Li C, Dudek SM, Frye-Anderson A, Kim RB, et al. Genetic determinants of response to warfarin during initial anticoagulation. N Engl J Med. 2008 Mar 6;358(10):999-1008.

156. Sconce EA, Khan TI, Wynne HA, Avery P, Monkhouse L, King BP, et al. The impact of CYP2C9 and VKORC1 genetic polymorphism and patient characteristics upon warfarin dose requirements: proposal for a new dosing regimen. Blood. 2005 Oct 1;106(7):2329-33. Epub 2005 Jun 9.

157. Scordo MG, Pengo V, Spina E, Dahl ML, Gusella M, Padrini R. Influence of CYP2C9 and CYP2C19 genetic polymorphisms on warfarin maintenance dose and metabolic clearance. Clin Pharmacol Ther. 2002 Dec;72(6):702-10.

158. Scott SA, Sangkuhl K, Stein CM, Hulot J-S, Mega JL, Roden DM, Klein TE, Sabatine MS, Johnson JA, Shuldiner AR. Clinical Pharmacogenetics Implementation Consortium Guidelines for CYP2C19 Genotype and Clopidogrel Therapy: 2013 Update. Clin Pharmacol Ther. 2013 Sep;94(3):317-23. Epub 2013 May 22.

159. Secretary's Advisory Committee on Genetics, Health, and Society (SACGHS). Federal Register. Department of Health and Human Services. Rockville (MD). Accessed Jan 8, 2024. Available at URL address: https://www.federalregister.gov/documents/2008/04/17/E8-8216/secretarys-advisory-committee-on-genetics-health-and-society

160. Serretti A, Calati R, Massat I, Linotte S, Kasper S, Lecrubier Y, Sens-Espel R, Bollen J, Zohar J, Berlo J, Lienard P, De Ronchi D, Mendlewicz J, Souery D. 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 Sep;24(5):250-6.

161. Shah RR. Genotype-guided warfarin therapy: Still of only questionable value two decades on. J Clin Pharm Ther. 2020;45(3):547-560. doi:10.1111/jcpt.13127

162. Shuldiner AR, O'Connell JR, Bliden KP, Gandhi A, Ryan K, Horenstein RB, et al. Association of cytochrome P450 2CY19 genotype with the antiplatelet effect and clinical efficacy of clopidogel therapy. JAMA. 2009 Aug 26;302(8):849-57.

163. Sibbing D, Koch W, Gebhard D, Schuster T, Braun S, Stegherr J, et al. Cytochrome P450 2C19*17 allelic variant, platelet aggregation, bleeding events, and stent thrombosis in clopidogrel-treated patients with coronary stent placement. Circulation. 2010 Feb 2;121(4):512-8.

164. Sibbing D, Stegherr J, Latz W, Koch W, Mehilli J, Dorrler K, et al. Cytochrome P450 2C19 loss-of-function polymorphism and stent thrombosis following percutaneous coronary intervention. Eur Heart J. 2009 Apr;30(8):916-22.

165. Siller-Matula JM, Delle-Karth G, Lang IM, Neunteufl T, Kozinski M, Kubica J, et al. Phenotyping vs genotyping for prediction of clopidogrel efficacy and safety: the PEGASUS-PCI study. J Thromb Haemost. 2012 Apr;10(4):529-42.

166. Simon T, Verstuyft C, Mary-Krause M, Quteineh L, Drouet E, Meneveneau N, et al. Genetic determinants of response to clopidogrel and cardiovascular events. N Engl J Med. 2009 Jan 22;36(4):363-75.

167. Singer DE, Albers GW, Dalen JE, Go AS, Halperin JL, Manning WJ. Antithrombotic therapy in atrial fibrillation: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. Chest 2004 Sep;126(3 Suppl):429S-56S.

168. Singh A. Pharmacogenomics--the potential of genetically guided prescribing. Aust Fam Physician. 2007 Oct;36(10):820-4.

169. Singh M, Thapa B, Arora R. Clopidogrel pharmacogenetics and its clinical implications. Am J Ther. 2010 May-Jun;17(3):e66-73.

170. Slavin TP, Niell-Swiller M, Solomon I, Nehoray B, Rybak C, Blazer KR, Weitzel JN. Clinical Application of Multigene Panels: Challenges of Next-Generation Counseling and Cancer Risk Management. Front Oncol. 2015 Sep 29;5:208.

171. Society for Cardiovascular Angiography and Interventions; Society of Thoracic Surgeons; Writing Committee Members, Holmes DR, Jr., Dehmer GJ, Kaul S, et al. ACCF/AHA clopidogrel clinical alert: approaches to the FDA "boxed warning" : a report of the American College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents and the American Heart Association. Circulation. 2010 Aug 3;122(5):537-57. Epub 2010 Jun 28.

172. Sofi F, Giusti B, Marcucci R, Gori AM, Abbate R, Gensini GF. Cytochrome p450 2C19(*)2 polymorphism and cardiovascular recurrences in patients taking clopidogrel: a meta-analysis. Pharmacogenomics J. 2010 Mar 30.

173. Spina E, de Leon J. Clinical applications of CYP genotyping in psychiatry. J Neural Transm. 2015 Jan;122(1):5-28. doi: 10.1007/s00702-014-1300-5. Epub 2014 Sep 9.

174. Staatz CE, Goodman LK, Tett SE. Effect of CYP3A and ABCB1 single nucleotide polymorphisms on the pharmacokinetics and pharmacodynamics of calcineurin inhibitors: Part I. Clin Pharmacokinet. 2010 Mar;49(3):141-75.

175. Steiling K, Christenson S. Tools for genetics and genomics: Gene expression profiling. In: UpToDate, Raby B (Ed), UpToDate, Waltham, MA. Literature review current through: Oct 2022. Topic last updated: Aug 2, 2021.

176. Stergiopoulos K, Brown DL. Genotype-guided vs clinical dosing of warfarin and its analogues: meta-analysis of randomized clinical trials. JAMA Intern Med. 2014;174(8):1330-1338.

177. Sun F, Bruening W, Uhl S, Ballard R, Tipton K, Schoelles K. Quality, regulation and clinical utility of laboratory developed molecular tests. Technology assessment report. LABC0707. Original date 2010 May 19. Correction date 2010 October 6. Accessed Jan 8, 2024. Available at URL address: http://www.cms.gov/determinationprocess/downloads/id72TA.pdf

178. Swen JJ, Huizinga TW, Gelderblom H, de Vries EG, Assendelft WJ, Kirchheiner J, et al. Translating pharmacogenomics: challenges on the road to the clinic. PLoS Med. 2007 Aug 14;4(8):e209.

179. Takahashi H, Wilkinson GR, Nutescu EA, Morita T, Ritchie MD, Scordo MG, et al. Different contributions of polymorphisms in VKORC1 and CYP2C9 to intra- and inter-population

differences in maintenance dose of warfarin in Japanese, Caucasians and African-Americans. Pharmacogenet Genomics. 2006 Feb;16(2):101-10.

180. Tansey KE, Guipponi M, Perroud N, Bondolfi G, Domenici E, Evans D, et al. Genetic predictors of response to serotonergic and noradrenergic antidepressants in major depressive disorder: a genome-wide analysis of individual-level data and a meta-analysis. PLoS Med. 2012;9(10):e1001326. doi: 10.1371/journal.pmed.1001326. Epub 2012 Oct 16.

181. Terasawa T, Dahabreh I, Castaldi PJ, et al. Systematic Reviews on Selected Pharmacogenetic Tests for Cancer Treatment: CYP2D6 for Tamoxifen in Breast Cancer, KRAS for anti-EGFR antibodies in Colorectal Cancer, and BCR-ABL1 for Tyrosine Kinase Inhibitors in Chronic Myeloid Leukemia [Internet]. Rockville (MD): Agency for Healthcare Research and Quality (US); 2010 Jun 7.

182. Terrazzino S, Quaglia M, Stratta P, Canonico PL, Genazzani AA. The effect of CYP3A5 6986A>G and ABCB1 3435C>T on tacrolimus dose-adjusted trough levels and acute rejection rates in renal transplant patients: a systematic review and meta-analysis. Pharmacogenet Genomics. 2012 Aug;22 (8):642-5.

183. Thakur M, Grossman I, McCrory DC, Orlando LA, Steffens DC, Cline KE, et al. Review of evidence for genetic testing for CYP450 polymorphisms in management of patients with nonpsychotic depression with selective serotonin reuptake inhibitors. Genet Med. 2007 Dec;9(12):826-35.

184. Tham LS, Goh BC, Nafziger A, Guo JY, Wang LZ, Soong R, Lee SC. A warfarin-dosing model in Asians that uses single-nucleotide polymorphisms in vitamin K epoxide reductase complex and cytochrome P450 2C9. Clin Pharmacol Ther. 2006 Oct;80(4):346-55.

185. Trenck D, Hochholzer W, Fromm MF, Chialda LE, Pahl A, Valina CM, et al. Cytochrome P450 2C19 681G>A polymorphism and high-on clopidogrel platelet reactivity associated with adverse 1-yr clinical outcome of percutaneous coronary intervention with drug-eluting or bare-metal stents. J Am Coll Cardiol. 2008 May 20;51(20):1925-34.

186. Ulvestad M, Skottheim IB, Jakobsen GS, Bremer S, Molden E, Asberg A, et al. Impact of OATP1B1, MDR1, and CYP3A4 expression in liver and intestine on interpatient pharmacokinetic variability of atorvastatin in obese subjects. Clin Pharmacol Ther. 2013 Mar;93(3):275-82. Epub 2012 Dec 27.

187. U.S. Food and Drug Administration (FDA). Drugs@FDA. Accessed Jan 8, 2024. Available at URL address: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm

188. U.S. Food and Drug Administration (FDA). Guidance Document. Drug Metabolizing Enzyme Genotyping System - Class II Special Controls Guidance for Industry and FDA Staff document. Mar 10, 2005. Accessed Jan 28, 2024. Available at URL address: http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm077933.htm

189. U.S. Food and Drug Administration (FDA). Guidance Document. Pharmacogenetic Tests and Genetic Tests for Heritable Markers. Guidance for Industry and FDA Staff. 2007 June 19. Accessed Jan 8, 2024. Available at URL address: http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm071075.pdf

190. U.S. Food and Drug Administration (FDA). Guidance Document. Clinical Pharmacogenomics: Premarket Evaluation in Early-Phase Clinical Studies and Recommendations for Labeling. 2020 7 May. Accessed Jan 8, 2024. Available at URL address: https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM337169.pdf

191. U.S. Food and Drug Administration (FDA). Table of Pharmacogenomic Biomarkers in Drug Labeling. Updated Aug 10, 2023. Accessed Jan 8, 2024. Available at URL address: http://www.fda.gov/Drugs/ScienceResearch/ResearchAreas/Pharmacogenetics/ucm083378.htm

192. U. S. Food and Drug Administration (FDA). 510(k) Premarket Notification. Drug metabolizing enzyme genotyping systems. Roche AmpliChip Cytochrome P450 P450 2C19-K043576. Jan 10, 2005. Accessed Jan 8, 2024. Available at URL address: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmn.cfm?ID=K043576

193. Vandenberghe F1, Guidi M, Choong E, von Gunten A, Conus P, Csajka C, Eap CB Genetics-Based Population Pharmacokinetics and Pharmacodynamics of Risperidone in a Psychiatric Cohort. Clin Pharmacokinet. 2015 Jul 1.

194. Veenstra DL, You JH, Rieder MJ, Farin FM, Wilkerson HW, Blough DK, et al. Association of Vitamin K epoxide reductase complex 1 (VKORC1) variants with warfarin dose in a Hong Kong Chinese patient population. Pharmacogenet Genomics. 2005 Oct;15(10):687-91.

195. Vermiere S, Van Assche G, Rutgeerts P. Role of genetics in prediction of disease course and response to therapy. World J Gastroenterol. 2010 Jun 7;16(21):2609-15.

196. Visscher H, Amstutz U, Sistonen J, Ross CJ, Hayden MR, Carleton BC. Pharmacogenomics of cardiovascular drugs and adverse effects in pediatrics. J Cardiovasc Pharmacol. 2011 Sep;58(3):228-39.

197. Wadelius M, Chen LY, Eriksson N, Bumpstead S, Ghori J, Wadelius C, et al. Association of warfarin dose with genes involved in its action and metabolism. Hum Genet. 2007 Mar;121(1):23-34

198. Wadelius M, Chen LY, Downes K, Ghori J, Hunt S, Eriksson N, et al. Common VKORC1 and GGCX polymorphisms associated with warfarin dose. Pharmacogenomics J. 2005;5(4):262-70.

199. Wadelius M, Chen LY, Lindh JD, Eriksson N, Ghori MJ, Bumpstead S, et al. The largest prospective warfarin-treated cohort supports genetic forecasting. Blood. 2008 Jun 23.

200. 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.

201. Wang D, Guo Y, Wrighton SA, Cooke GE, Sadee W. Intronic polymorphism in CYP3A4 affects hepatic expression and response to statin drugs. Pharmacogenomics J. 2011 Aug;11(4):274-86.

202. Wegman P, Elingarami S, Cartensen J, Stal O, Nordenskjold B, Wingren S. Genetic variants of CYP3A5, CYP2D6, SULT1A1, UGT2B15, and tamoxifen response in postmenopausal patients with breast cancer. Breast Cancer Res. 2007;9(1):R7.

203. Winner JG, Carhart JM, Altar CA, Allen JD, Dechairo BM. A prospective, randomized, double-blind study assessing the clinical impact of integrated pharmacogenomic testing for major depressive disorder. Discov Med. 2013 Nov;16(89):219-27. Accessed Jan 8, 2024. Available at URL address: http://www.discoverymedicine.com/Joel-G-Winner/2013/11/08/a-prospective-randomized-double-blind-study-assessing-the-clinical-impact-of-integrated-pharmacogenomic-testing-for-major-depressive-disorder/

204. Xi B, Wang C, Liu L, Zeng T, Liang Y, Li J, Mi J. Association of the CYP3A5 polymorphism (6986G>A) with blood pressure and hypertension. Hypertens Res. 2011 Nov;34(11):1216-20.

205. Xu Y, Sun Y, Yao L, Shi L, Wu Y, Ouyang T, et al. Association between CYP2D6 *10 genotype and survival of breast cancer patients receiving tamoxifen treatment. Ann Oncol. 2008 Apr 11.

206. Zabalza M, Subirana I, Sala J, Lluis-Ganella C, Lucas G, Tomás M, Masiá R, Marrugat J, Brugada R, Elosua R. Meta-analyses of the association between cytochrome CYP2C19 loss- and gain-of-function polymorphisms and cardiovascular outcomes in patients with coronary artery disease treated with clopidogrel. Heart. 2012 Jan;98(2):100-8.

207. Zeier Z, Carpenter LL, Kalin NH, et al. Clinical Implementation of Pharmacogenetic Decision Support Tools for Antidepressant Drug Prescribing. Am J Psychiatry. 2018;175(9):873-886. doi:10.1176/appi.ajp.2018.17111282

208. Zhao W, Elie V, Roussey G, Brochard K, Niaudet P, Leroy V, et al. Population pharmacokinetics and pharmacogenetics of tacrolimus in de novo pediatric kidney transplant recipients. Clin Pharmacol Ther. 2009 Dec;86(6):609-18.

209. Zhao F, Wang J, Yang Y, Wang X, Shi R, Xu Z, Huang Z, Zhang G. Effect of CYP2C19 genetic polymorphisms on the efficacy of proton pump inhibitor-based triple therapy for Helicobacter pylori eradication: a meta-analysis. Helicobacter. 2008 Dec;13(6):532-41.

210. Zhou SF. Polymorphism of human cytochrome P450 2D6 and its clinical significance: part I. Clin Pharmacokinet. 2009;48(11):689-723.

211. Zhou SF. Polymorphism of human cytochrome P450 2D6 and its clinical significance: part II. Clin Pharmacokinet. 2009;48(12):761-804.

212. Zhu Y, Shennan M, Reynolds KK, Johnson NA, Herrnberger MR, Valdes R Jr, Linder MW. Estimation of warfarin maintenance dose based on VKORC1 (-1639 G>A) and CYP2C9 genotypes. Clin Chem. 2007 Jul;53(7):1199-205.

213. Zubenko GS, Sommer BR, Cohen BM. On the marketing and use of pharmacogenetics tests for psychiatric treatment. JAMA Psychiatry. 2018 Aug 1:75(8):769-770.

Revision Details

Type of Revision	Summary of Changes	Date

Focused review	• No clinical policy statement changes.	11/1/2024
Annual review	• Revised policy statement for biomarker genotyping/mutation analysis.	2/15/2024