Clinical UM Guideline

Subject:	Genotype Testing for Individual Genetic Polymorphisms to Determine Drug-Metabolizer Status		
Guideline #:	CG-GENE-11	**Publish Date:**	07/06/2022
Status:	Reviewed	**Last Review Date:**	05/12/2022

Description

This document addresses genotype testing for individual polymorphisms which can identify variants of specific genes associated with abnormal and normal drug metabolism. The use of such testing is based on the theory that individuals with certain gene variants may potentially be able to receive higher or lower doses of some drugs, or should avoid some drugs altogether, to improve the likelihood of achieving clinical goals as well as lessening the risk of adverse drug effects.

Note: Testing for thiopurine methyltransferase (TPMT) for individuals receiving treatment with azathioprine or 6-mercaptopurine therapy, and testing for NS3 Q80K for individuals being treated for Hepatitis C virus are **NOT** addressed in this document.

Note: For additional information regarding pharmacogenomics, please see:

- CG-GENE-10 Chromosomal Microarray Analysis (CMA) for Developmental Delay, Autism Spectrum Disorder, Intellectual Disability and Congenital Anomalies
- CG-GENE-13 Genetic Testing for Inherited Diseases
- GENE.00010 Panel and other Multi-Gene Testing for Polymorphisms to Determine Drug-Metabolizer Status

Clinical Indications

Medically Necessary:

Genotype testing for genetic polymorphisms of Human Leukocyte Antigen B*1502 (HLA-B*1502) to determine the drug-metabolizer status of individuals for whom the use of carbamazepine is being proposed is considered **medically necessary** when both of the criteria below have been met:

A. The individual is from a population who is at high risk due to ethnic heritage; **and**
B. There are no other alternatives to the use of carbamazepine.

Genotype testing for identification of the CYP2C19 variant of Cytochrome P450 is considered **medically necessary** to determine the drug-metabolizer status of individuals who meet either of the following criteria:

A. The individual is currently undergoing treatment with clopidogrel and has not been tested: **or**
B. The use of clopidogrel is being proposed.

Federal and State law, as well as contract language including definitions and specific coverage provisions/exclusions, and Medical Policy take precedence over Clinical UM Guidelines and must be considered first in determining eligibility for coverage. The member's contract benefits in effect on the date that services are rendered must be used. Clinical UM Guidelines, which address medical efficacy, should be considered before utilizing medical opinion in adjudication. Medical technology is constantly evolving, and we reserve the right to review and update Clinical UM Guidelines periodically. Clinical UM guidelines are used when the plan performs utilization review for the subject. Due to variances in utilization patterns, each plan may choose whether or not to adopt a particular Clinical UM Guideline. To determine if review is required for this Clinical UM Guideline, please contact the customer service number on the back of the member's card.

No part of this publication may be reproduced, stored in a retrieval system or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from the health plan.

© CPT Only – American Medical Association

Medicaid managed care administered by Amerigroup Corporation, an independent company.

Historical

Genotype testing for Human Leukocyte Antigen B (HLA-B*5701) is considered **medically necessary** before beginning treatment with abacavir for persons infected with HIV-1.

Genotype testing for identification of the CYP2D6 variant of Cytochrome P450 to determine the drug-metabolizer status of individuals being considered for treatment with eliglustat is considered **medically necessary.**

Genotype testing for identification of the CYP2D6 variant of Cytochrome P450 to determine the drug-metabolizer status of individuals with Huntington's disease being considered for treatment with a dosage of tetrabenazine greater than 50 mg per day is considered **medically necessary.**

Genotype testing to determine the presence of the HLA-B*58:01 allele in individuals from a population who are at high risk due to ethnic heritage for whom the use of allopurinol is being considered for treatment is considered **medically necessary.**

Genotype testing to determine the presence of CYP2C9 genotype before administration of siponimod is considered **medically necessary.**

Not Medically Necessary:

Genotype testing for individual genetic polymorphisms for individuals who potentially may receive the drugs listed above is considered **not medically necessary** when the criteria or circumstances detailed above are not met.

Genotype testing for individual genetic polymorphisms to determine drug-metabolizer status is considered **not medically necessary** in all other circumstances.

Coding

The following codes for treatments and procedures applicable to this guideline are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

CYP2C19
When services may be Medically Necessary when criteria are met:

CPT	
81225	*CYP2C19 (cytochrome P450, family 2, subfamily C, polypeptide 19)* (eg, drug metabolism), gene analysis, common variants (eg, *2, *3, *4, *8, *17) [for clopidogrel metabolism]

Federal and State law, as well as contract language including definitions and specific coverage provisions/exclusions, and Medical Policy take precedence over Clinical UM Guidelines and must be considered first in determining eligibility for coverage. The member's contract benefits in effect on the date that services are rendered must be used. Clinical UM Guidelines, which address medical efficacy, should be considered before utilizing medical opinion in adjudication. Medical technology is constantly evolving, and we reserve the right to review and update Clinical UM Guidelines periodically. Clinical UM guidelines are used when the plan performs utilization review for the subject. Due to variances in utilization patterns, each plan may choose whether or not to adopt a particular Clinical UM Guideline. To determine if review is required for this Clinical UM Guideline, please contact the customer service number on the back of the member's card.

No part of this publication may be reproduced, stored in a retrieval system or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from the health plan.

© CPT Only – American Medical Association

Medicaid managed care administered by Amerigroup Corporation, an independent company.

Historical

ICD-10 Diagnosis

All diagnoses

When services are Not Medically Necessary:
For the procedure code listed above when criteria are not met.

HLA-B
When services may be Medically Necessary when criteria are met:

CPT	
81381	HLA Class I typing, high resolution (ie, alleles or allele groups); one allele or allele group (eg, B*57:01P), each [when specified as Human Leukocyte Antigen B*57:01P (HLA-B*5701) for abacavir metabolism, Human Leukocyte Antigen B*58:01 (HLA-B*58:01) for allopurinol metabolism, or Human Leukocyte Antigen B*1502 (HLA-B*1502) for carbamazepine metabolism]
81479	Unlisted molecular pathology procedure [when specified as genotype testing for polymorphisms of Human Leukocyte Antigen B*1502 (HLA-B*1502) for carbamazepine metabolism]

ICD-10 Diagnosis	
B20	Human immunodeficiency virus [HIV] disease
E08.40-E08.49	Diabetes mellitus due to underlying condition with neurological complications
E09.40-E09.49	Drug or chemical induced diabetes mellitus with neurological complications
E10.40-E10.49	Type 1 diabetes mellitus with neurological complications
E11.40-E11.49	Type 2 diabetes mellitus with neurological complications
E13.40-E13.49	Other specified diabetes mellitus with neurological complications
F31.0-F31.9	Bipolar disorder
G40.001-G40.919	Epilepsy and recurrent seizures
G50.0-G59	Nerve, nerve root and plexus disorders
G60.0-G60.9	Hereditary and idiopathic neuropathy
G62.0-G62.9	Other and unspecified polyneuropathies
G63	Polyneuropathy in diseases classified elsewhere
G65.0-G65.2	Sequelae of inflammatory and toxic polyneuropathies
G90.01-G90.09	Idiopathic peripheral autonomic neuropathy
M10.00-M10.9	Gout
M79.2	Neuralgia and neuritis, unspecified
N20.0	Calculus of kidney
T45.1X5A-T45.1X5S	Adverse effect of antineoplastic and immunosuppressive drugs

Historical

Federal and State law, as well as contract language including definitions and specific coverage provisions/exclusions, and Medical Policy take precedence over Clinical UM Guidelines and must be considered first in determining eligibility for coverage. The member's contract benefits in effect on the date that services are rendered must be used. Clinical UM Guidelines, which address medical efficacy, should be considered before utilizing medical opinion in adjudication. Medical technology is constantly evolving, and we reserve the right to review and update Clinical UM Guidelines periodically. Clinical UM guidelines are used when the plan performs utilization review for the subject. Due to variances in utilization patterns, each plan may choose whether or not to adopt a particular Clinical UM Guideline. To determine if review is required for this Clinical UM Guideline, please contact the customer service number on the back of the member's card.

No part of this publication may be reproduced, stored in a retrieval system or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from the health plan.

© CPT Only – American Medical Association

Medicaid managed care administered by Amerigroup Corporation, an independent company.

When services are Not Medically Necessary:
For the procedure and diagnosis codes listed above when criteria are not met or for the following:

CPT	
81381	HLA Class I typing, high resolution (ie, alleles or allele groups); one allele or allele group (eg, B*57:01P), each [when specified as Human Leukocyte Antigen A*3101 (HLA-A*3101) for carbamazepine metabolism]
ICD-10 Diagnosis	
	All diagnoses

CYP2D6
When services may be Medically Necessary when criteria are met:

CPT	
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) [for eliglustat or tetrabenazine metabolism]
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) *CYP2D6* Common Variants and Copy Number, Mayo Clinic, Laboratory Developed Test
0071U	*CYP2D6 (cytochrome P450, family 2, subfamily D, polypeptide 6)* (eg, drug metabolism) gene analysis, full gene sequence *CYP2D6* Full Gene Sequencing, Mayo Clinic, Laboratory Developed Test
0072U	*CYP2D6 (cytochrome P450, family 2, subfamily D, polypeptide 6)* (eg, drug metabolism) gene analysis, targeted sequence analysis (ie, *CYP2D6-2D7* hybrid gene) *CYP2D6-2D7* Hybrid Gene Targeted Sequence Analysis, Mayo Clinic, Laboratory Developed Test
0073U	*CYP2D6 (cytochrome P450, family 2, subfamily D, polypeptide 6)* (eg, drug metabolism) gene analysis, targeted sequence analysis (ie, *CYP2D7-2D6* hybrid gene) *CYP2D7-2D6* Hybrid Gene Targeted Sequence Analysis, Mayo Clinic, Laboratory Developed Test
0074U	*CYP2D6 (cytochrome P450, family 2, subfamily D, polypeptide 6)* (eg, drug metabolism) gene analysis, targeted sequence analysis (ie, non-duplicated gene when duplication/multiplication is trans) *CYP2D6* trans-duplication/multiplication non-duplicated gene targeted sequence analysis, Mayo Clinic, Laboratory Developed Test

Historical

Federal and State law, as well as contract language including definitions and specific coverage provisions/exclusions, and Medical Policy take precedence over Clinical UM Guidelines and must be considered first in determining eligibility for coverage. The member's contract benefits in effect on the date that services are rendered must be used. Clinical UM Guidelines, which address medical efficacy, should be considered before utilizing medical opinion in adjudication. Medical technology is constantly evolving, and we reserve the right to review and update Clinical UM Guidelines periodically. Clinical UM guidelines are used when the plan performs utilization review for the subject. Due to variances in utilization patterns, each plan may choose whether or not to adopt a particular Clinical UM Guideline. To determine if review is required for this Clinical UM Guideline, please contact the customer service number on the back of the member's card.

No part of this publication may be reproduced, stored in a retrieval system or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from the health plan.

© CPT Only – American Medical Association

Medicaid managed care administered by Amerigroup Corporation, an independent company.

0075U	*CYP2D6 (cytochrome P450, family 2, subfamily D, polypeptide 6)* (eg, drug metabolism) gene analysis, targeted sequence analysis (ie, 5' gene duplication/multiplication) *CYP2D6* 5' gene duplication/multiplication targeted sequence analysis, Mayo Clinic, Laboratory Developed Test
0076U	*CYP2D6 (cytochrome P450, family 2, subfamily D, polypeptide 6)* (eg, drug metabolism) gene analysis, targeted sequence analysis (ie, 3' gene duplication/ multiplication) *CYP2D6* 3' gene duplication/multiplication targeted sequence analysis, Mayo Clinic, Laboratory Developed Test

ICD-10 Diagnosis

E75.22	Gaucher disease
G10	Huntington's disease

When services are Not Medically Necessary:
For the procedure and diagnosis codes listed above when criteria are not met or for all other diagnoses not listed.

CYP2C9
When services may be Medically Necessary when criteria are met:

CPT

81227	*CYP2C9 (cytochrome P450, family 2, subfamily C, polypeptide 9)* (eg, drug metabolism), gene analysis, common variants (eg, *2, *3, *5, *6) [for siponimod (Mayzent) metabolism]

ICD-10 Diagnosis

G35	Multiple sclerosis

When services are Not Medically Necessary:
For the procedure and diagnosis codes listed above when criteria are not met or for all other diagnoses not listed.

Other polymorphism genes
When services are Not Medically Necessary:

CPT

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

Historical

Federal and State law, as well as contract language including definitions and specific coverage provisions/exclusions, and Medical Policy take precedence over Clinical UM Guidelines and must be considered first in determining eligibility for coverage. The member's contract benefits in effect on the date that services are rendered must be used. Clinical UM Guidelines, which address medical efficacy, should be considered before utilizing medical opinion in adjudication. Medical technology is constantly evolving, and we reserve the right to review and update Clinical UM Guidelines periodically. Clinical UM guidelines are used when the plan performs utilization review for the subject. Due to variances in utilization patterns, each plan may choose whether or not to adopt a particular Clinical UM Guideline. To determine if review is required for this Clinical UM Guideline, please contact the customer service number on the back of the member's card.

No part of this publication may be reproduced, stored in a retrieval system or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from the health plan.

© CPT Only – American Medical Association

Medicaid managed care administered by Amerigroup Corporation, an independent company.

81231	*CYP3A5 (cytochrome P450 family 3 subfamily A member 5)* (eg, drug metabolism), gene analysis, common variant(s) (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)
81346	*TYMS (thymidylate synthetase)* (eg, 5-fluorouracil/5-FU drug metabolism), gene analysis, common variant(s) (eg, tandem repeat variant)
81350	*UGT1A1 (UDP glucuronosyltransferase 1 family, polypeptide A1)* (eg, drug metabolism, hereditary unconjugated hyperbilirubinemia [Gilbert syndrome]), gene analysis, common variants (eg, *28, *36, *37) [when specified for drug metabolism (irinotecan)]
81355	*VKORC1 (vitamin K epoxide reductase complex, subunit 1)* (eg, warfarin metabolism), gene analysis, common variant(s) (eg, -1639G>A, c.173+1000C>T)
81479	Unlisted molecular pathology procedure [when specified as drug metabolism testing for all other drugs not listed as medically necessary]
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; Mayo Clinic
0032U	*COMT (catechol-O-methyltransferase)* (drug metabolism) gene analysis, c.472G>A (rs4680) variant Catechol-O-methyltransferase *(COMT)* Genotype; Mayo Clinic
0033U	*HTR2A (5-hydroxytryptamine receptor 2A), HTR2C (5-hydroxytryptamine receptor 2C)* (eg, citalopram metabolism) gene analysis, common variants (ie, *HTR2A* rs7997012 [c.614-2211T>C], *HTR2C* rs3813929 [c.-759C>T] and rs1414334 [c.551-3008C>G]) Serotonin Receptor Genotype (*HTR2A* and *HTR2C*); Mayo Clinic

HCPCS

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

ICD-10 Diagnosis

All diagnoses

Discussion/General Information

Identification of genetic factors that influence drug absorption, metabolism, and action at the receptor level has the potential to allow for individualized therapy based on optimal drug effectiveness and a minimized toxicity profile. Drug efficacy and toxicity vary substantially between individuals. Because drugs and doses are typically adjusted to meet individual requirements as needed by using trial and error, clinical consequences may include a prolonged time to optimal therapy and serious adverse events. It has been found that inherited deoxyribonucleic acid (DNA)

Federal and State law, as well as contract language including definitions and specific coverage provisions/exclusions, and Medical Policy take precedence over Clinical UM Guidelines and must be considered first in determining eligibility for coverage. The member's contract benefits in effect on the date that services are rendered must be used. Clinical UM Guidelines, which address medical efficacy, should be considered before utilizing medical opinion in adjudication. Medical technology is constantly evolving, and we reserve the right to review and update Clinical UM Guidelines periodically. Clinical UM guidelines are used when the plan performs utilization review for the subject. Due to variances in utilization patterns, each plan may choose whether or not to adopt a particular Clinical UM Guideline. To determine if review is required for this Clinical UM Guideline, please contact the customer service number on the back of the member's card.

No part of this publication may be reproduced, stored in a retrieval system or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from the health plan.

© CPT Only – American Medical Association

Medicaid managed care administered by Amerigroup Corporation, an independent company.

Historical

sequence variation (polymorphisms) in genes for drug-metabolizing enzymes may have a significant effect on the efficacy or toxicity of a drug. This field of research is referred to as pharmacogenomics.

It has been proposed that genotype testing for certain genes to detect polymorphisms will allow physicians to predict side effects to drugs and to tailor a drug regimen based on an individual's genetic make-up. It may be that genotype testing will improve the choice of drug, or the dose of the drug, when the drug in question has a narrow therapeutic dose range, when the consequences of treatment failure are severe, and/or when serious adverse reactions are more likely in individuals with certain polymorphisms.

The role of genotype testing for individual polymorphisms to identify variants of specific genes associated with abnormal metabolism, has been evaluated for a number of drugs.

Carbamazepine (Tegretol®)

There has been study into the role of HLA-B*1502 mutations in the occurrence of toxic epidermal necrolysis (TEN) and Stevens-Johnson syndrome in ethnic Han Chinese individuals receiving treatment with the anticonvulsant drug carbamazepine (CBZ). A molecular study by Hung et al. (2006) identified this genetic variation as a contributor to this reaction. Based on data reviewed by an expert panel, the United States Food and Drug Administration (FDA) decided to place a black-box warning on the label of carbamazepine as follows:

> Serious and sometimes fatal dermatologic reactions, including toxic epidermal necrolysis (TEN) and Stevens-Johnson syndrome (SJS), have been reported during treatment with Tegretol. These reactions are estimated to occur in 1 to 6 per 10,000 new users in countries with mainly Caucasian populations, but the risk in some Asian countries is estimated to be about 10 times higher. Studies in patients of Chinese ancestry have found a strong association between the risk of developing SJS/TEN and the presence of HLA-B*1502, an inherited allelic variant of the HLA-B gene. HLA-B*1502 is found almost exclusively in patients with ancestry across broad areas of Asia. Patients with ancestry in genetically at risk populations should be screened for the presence of HLA-B*1502 prior to initiating treatment with Tegretol. Patients testing positive for the allele should not be treated with Tegretol unless the benefit clearly outweighs the risk.

Chen and colleagues (2001) conducted a study of 4877 carbamazepine-naïve subjects who were genotyped for the HLA-B*1502 allele. B*1502 allele-positive subjects were given an alternative medication while negative subjects were treated with carbamazepine. The authors then compared the incidence of SJS and TEN in the study population to historical controls. Results demonstrated that a mild, transient rash developed in 4.3% of B*1502 positive subjects; more widespread rash developed in 0.1% of subjects, who were hospitalized. SJS/TEN did not develop in any of the HLA-B*1502–negative subjects receiving carbamazepine. In contrast, the estimated historical incidence of carbamazepine-induced SJS/TEN (0.23%) would translate into approximately 10 cases among study subjects ($p<0.001$).

Historical

Federal and State law, as well as contract language including definitions and specific coverage provisions/exclusions, and Medical Policy take precedence over Clinical UM Guidelines and must be considered first in determining eligibility for coverage. The member's contract benefits in effect on the date that services are rendered must be used. Clinical UM Guidelines, which address medical efficacy, should be considered before utilizing medical opinion in adjudication. Medical technology is constantly evolving, and we reserve the right to review and update Clinical UM Guidelines periodically. Clinical UM guidelines are used when the plan performs utilization review for the subject. Due to variances in utilization patterns, each plan may choose whether or not to adopt a particular Clinical UM Guideline. To determine if review is required for this Clinical UM Guideline, please contact the customer service number on the back of the member's card.

No part of this publication may be reproduced, stored in a retrieval system or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from the health plan.

© CPT Only – American Medical Association

Medicaid managed care administered by Amerigroup Corporation, an independent company.

Other genetic mutations have also been studied as having clinical impact on the outcomes of individuals who may undergo treatment with carbamazepine. McCormack and others (2011) described a study looking at the association of the HLA-A*3101 allele and the incidence of carbamazepine-related complications. This study included 65 subjects who had experienced carbamazepine-related complications and 3987 control subjects. An independent genome-wide association study demonstrated a significant association between subjects with the HLA-A*3101 allele and the incidence of carbamazepine-induced hypersensitivity reactions among subjects of Northern European ancestry. Further study is warranted to understand the impact of genetic testing on the rate of occurrence of complications in subjects carrying the HLA-A*3101 allele. He and colleagues (2014) studied the impact of several genes on the development of SJS in a population of 225 ethnic Han Chinese subjects (n=25 with SJS, 200 non-SJS controls) who had been exposed to carbamazepine. They observed statistically significant differences in EPHX1 c.337T>C polymorphisms between SJS group subjects and controls in terms of allelic and genotypic frequencies (p=0.011 and p=0.007, respectively). They stated that the C allele and the C-G diplotype of EPHX1 may play important roles in increasing the risk of CBZ-SJS/TEN development (odds ratio [OR], 0.478; p=0.011; OR, 0.21; p=0.025, respectively). No significant associations were reported between ABCB1, CYP3A4, EPHX1, FAS, SCN1A, MICA or BAG6 genes and carbamazepine dose, or dose-adjusted concentration in carbamazepine-tolerant subjects.

In a 2018 systematic review and meta-analysis by Chouchi and colleagues, the authors evaluated the strength of the associations between reported single-nucleotide polymorphisms in potential genes and adverse drug reactions in participants with epilepsy on carbamazepine therapy. The analysis was limited to participants with epilepsy not using any other types of treatment that might induce adverse drug reactions. A total of nine studies were included for meta-analysis. These studies evaluated the associations between the HLA-B*15:02 polymorphism and serious cutaneous reactions (SCRs) including carbamazepine-induced SJS and carbamazepine-induced SJS/TEN in Asian populations with epilepsy. The authors noted that HLA-B*15:02 polymorphisms were significantly associated with carbamazepine SCR risk (OR: 27.325, 95% confidence interval [CI], 9.933-51.166). In Han Chinese participants, the allele was significantly associated with carbamazepine SCRs (OR: 42.059; 95% CI, 9.587-184.514). The HLAB* 15:02 polymorphism was strongly associated with carbamazepine-induced SJS (OR: 152.089; 95% CI, 34.737-665.901). In the Asian population, the HLA-B*15:02 polymorphism was significantly associated with carbamazepine-induced SJS/TEN (OR: 13.993; 95% CI, 7.291-26.856) and in particular, in the Han Chinese population (OR: 17.886; 95% CI, 8.411-38.034). Limitations include a small group of included studies and small sample sizes which led to publication bias and lack of other ethnicities studied. Even with the small number of included studies, the results show that the HLA-B*15:02 polymorphism can induce SCRs among the Asian population using carbamazepine.

Clopidogrel (Plavix®)

Focus has been placed on the impact of drug metabolizer status testing for individuals prescribed clopidogrel. Several published nonrandomized, controlled studies addressed the use of testing for genetic variants in CYP4502C19, ABCB1, CYP2A5, and P2RY12 (Collet, 2009; Mega, 2009; Simon, 2009). These studies found that mutations in these genes, especially CYP2C19 variants, have significant effects on cardiovascular health outcomes.

Federal and State law, as well as contract language including definitions and specific coverage provisions/exclusions, and Medical Policy take precedence over Clinical UM Guidelines and must be considered first in determining eligibility for coverage. The member's contract benefits in effect on the date that services are rendered must be used. Clinical UM Guidelines, which address medical efficacy, should be considered before utilizing medical opinion in adjudication. Medical technology is constantly evolving, and we reserve the right to review and update Clinical UM Guidelines periodically. Clinical UM guidelines are used when the plan performs utilization review for the subject. Due to variances in utilization patterns, each plan may choose whether or not to adopt a particular Clinical UM Guideline. To determine if review is required for this Clinical UM Guideline, please contact the customer service number on the back of the member's card.

No part of this publication may be reproduced, stored in a retrieval system or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from the health plan.

© CPT Only – American Medical Association

Medicaid managed care administered by Amerigroup Corporation, an independent company.

Historical

Mega and colleagues (2009) conducted a study addressing the impact of CYP-450 gene variants on clinical response to clopidogrel treatment. This study included 162 healthy subjects and 1477 subjects with acute coronary disease being treated with clopidogrel. Carriers of at least one CYP2C19 allele had a 32.4% reduction in the active metabolite of clopidogrel, a 9% decrease in maximal platelet aggregation response, a 300% increase in the risk of stent thrombosis (ST), and relative increase of 53% in the composite primary efficacy outcome of the risk of death from cardiovascular causes, myocardial infarction, or stroke, as compared with non-carriers.

A study by Simon and others (2009) enrolled 2208 subjects with acute myocardial infarction (MI) who were receiving clopidogrel therapy. The authors reported a significantly increased risk of adverse cardiovascular events in individuals with CYP2C19 variants when compared to those with no mutations (21.5% vs. 13.3%). Among the 1535 participants who also underwent percutaneous coronary intervention during hospitalization, the rate of cardiovascular events among individuals with two CYP2C19 loss-of-function (LOF) alleles was 3.58 times the rate among those with none.

The current FDA label for clopidogrel (FDA, 2021) has a black-box warning that addresses the use of pharmacogenetic testing. The warning states:

- Effectiveness of Plavix depends on conversion to an active metabolite by the cytochrome P450 (CYP) system, principally CYP2C19.
- Plavix at recommended doses forms less of the active metabolite and so has a reduced effect on platelet activity in patients who are homozygous for nonfunctional alleles of the CYP2C19 gene, (termed "CYP2C19 poor metabolizers").
- Tests are available to identify patients who are CYP2C19 poor metabolizers.
- Consider use of another platelet $P2Y_{12}$ inhibitor in patients identified as CYP2C19 poor metabolizers.

Mega and colleagues published the findings of a large meta-analysis conducted in 2010. This report included 9685 subjects who were treated with clopidogrel in nine studies. The findings indicated that subjects with one or two LOF CYP2C19 alleles had a significantly increased risk of composite endpoint events (hazard ratio [HR], 1.55; p=0.01; HR, 1.76; p=0.002, respectively). Additionally, these subjects had an increased risk of stent thrombosis when compared to non-carriers of LOF alleles.

A study by Simon and colleagues (2011) involved 2210 subjects being treated for acute MI who were genotyped for CYP2C19 polymorphisms. They reported that the presence of two CYP2C19 LOF alleles was significantly associated with the risk of in-hospital death and major myocardial events at 1 year for individuals with acute MI (adjusted odds ratio 6.67) and those undergoing percutaneous coronary interventions (PCI) (adjusted odds ratio 6.87). They also studied the association of PON1 polymorphism with major myocardial events, but reported that no statistically significant association was found.

Mega and others (2011) conducted a randomized double-blind trial that enrolled 333 subjects with cardiovascular disease who were genotyped for CYP2C19*2 LOF allele status. Non-carriers of the allele received either 75 mg or 150 mg daily dose of clopidogrel in one of two blinded 28-day long blocks. Carriers of the CYP2C19*2 allele

Federal and State law, as well as contract language including definitions and specific coverage provisions/exclusions, and Medical Policy take precedence over Clinical UM Guidelines and must be considered first in determining eligibility for coverage. The member's contract benefits in effect on the date that services are rendered must be used. Clinical UM Guidelines, which address medical efficacy, should be considered before utilizing medical opinion in adjudication. Medical technology is constantly evolving, and we reserve the right to review and update Clinical UM Guidelines periodically. Clinical UM guidelines are used when the plan performs utilization review for the subject. Due to variances in utilization patterns, each plan may choose whether or not to adopt a particular Clinical UM Guideline. To determine if review is required for this Clinical UM Guideline, please contact the customer service number on the back of the member's card.

No part of this publication may be reproduced, stored in a retrieval system or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from the health plan.

© CPT Only – American Medical Association

Medicaid managed care administered by Amerigroup Corporation, an independent company.

Historical

received 75 mg, 150 mg, 225 mg, or 300 mg doses of clopidogrel in a blinded sequence of four 14-day long blocks. For the 75 mg dosage, both CYP2C19*2 hetero- and homozygotes had significantly higher on-treatment platelet reactivity than non-carriers ($p<0.001$ for both groups). Higher doses of clopidogrel in CYP2C19*2 heterozygotes significantly reduced the proportion of non-responders to 10% in both 225 mg (8 of 75 subjects, $p<0.001$) and 300 mg (7 of 73 subjects, $p<0.001$). In CYP2C19*2 homozygotes, higher doses of clopidogrel did not provide similar benefits, with 80% of this group being non-responders at 75 mg and 60% still being non-responders at the 300 mg dosage. The authors reported that in CYP2C19*2 heterozygotes, a dose of 225 mg provided similar platelet reactivity scores to that found with non-carriers receiving a 75 mg dose. In CYP2C19*2 homozygotes, not even the 300 mg dose provided equivalent platelet reactivity to non-carriers. There were no deaths, cerebrovascular events, or Thrombolysis in Myocardial Infarction (TIMI) major or minor events reported in either group at any dose level. This study provides significant evidence to demonstrate that CYP2C19*2 guided dosing of clopidogrel can provide significant benefits in platelet reactivity measures. Further data would be helpful in determining if this also results in significant health outcomes in terms of decreased cardiovascular disease-related deaths and complications.

Sibbing and colleagues (2009) published the results of a case series study of 2485 subjects undergoing coronary stent placement after pre-treatment with 600 mg of clopidogrel. Genotyping of all subjects was conducted and the results found that 805 subjects (73%) were CYP2C19 wild-type homozygotes and 680 subjects (27%) carried at least one *2 allele. The authors reported that cumulative 30-day incidence of stent thrombosis was significantly higher in CYP2C19*2 allele carriers vs. wild-type homozygotes (HR=3.81; $p=0.007$). The risk of stent thrombosis was highest (2.1%) in subjects with the CYP2C19 *2/*2 genotype ($p=0.002$). The authors concluded that CYP2C19*2 carrier status is significantly associated with an increased risk of ST following coronary stent placement.

This group published another study in 2010 (Sibbing, 2010) involving 1524 subjects undergoing percutaneous coronary intervention after pretreatment with 600 mg clopidogrel. Genotyping for CYP2C19*17 allelic variant and adenosine diphosphate (ADP)-induced platelet aggregation were assessed. For both heterozygous (n=546) and homozygous (n=76) *17 allele carriers, significantly lower ADP-induced platelet aggregation values were found vs. wild-type homozygotes (n=902; $p=0.039$ and $p=0.008$, respectively). Furthermore, CYP2C19*17 allele carriage was found to be significantly associated with an increased risk of bleeding, with the highest risk observed for CYP2C19*17 homozygous subjects ($p=0.01$). A multivariate analysis confirmed the independent association of CYP2C19*17 allele carriage with platelet aggregation values ($p<0.001$) and the occurrence of bleeding ($p=0.006$). However, no significant influence of CYP2C19*17 was detected in relation to the incidence of stent thrombosis ($p=0.79$). The authors concluded that CYP2C19*17 carrier status is significantly associated with enhanced response to clopidogrel and an increased risk of bleeding.

The results of two large placebo-controlled, randomized controlled trials (RCTs) were published by Pare et al. (2010). The two studies included a total of 5059 subjects randomized to receive either clopidogrel or placebo and followed for the occurrence of primary and secondary composite outcomes. The authors concluded that "no significant difference in the effect of clopidogrel treatment on clinical outcomes was observed when subjects were

Federal and State law, as well as contract language including definitions and specific coverage provisions/exclusions, and Medical Policy take precedence over Clinical UM Guidelines and must be considered first in determining eligibility for coverage. The member's contract benefits in effect on the date that services are rendered must be used. Clinical UM Guidelines, which address medical efficacy, should be considered before utilizing medical opinion in adjudication. Medical technology is constantly evolving, and we reserve the right to review and update Clinical UM Guidelines periodically. Clinical UM guidelines are used when the plan performs utilization review for the subject. Due to variances in utilization patterns, each plan may choose whether or not to adopt a particular Clinical UM Guideline. To determine if review is required for this Clinical UM Guideline, please contact the customer service number on the back of the member's card.

No part of this publication may be reproduced, stored in a retrieval system or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from the health plan.

© CPT Only – American Medical Association

Medicaid managed care administered by Amerigroup Corporation, an independent company.

Historical

stratified according to metabolizer status." However, some increase in efficacy was seen in subjects with gain-of-function alleles in terms of reduced ischemic events.

A 2019 randomized, open-label trial by Claassens and colleagues reported on individuals who underwent percutaneous coronary intervention to assess whether CYP2C19 genotype-guided strategy for selection of oral $P2Y_{12}$ inhibitors can reduce the risk of bleeding without increasing thrombotic risk. Participants were randomized in a 1:1 fashion to either the genotype-guided group (n=1242) or the standard treatment with either ticagrelor or prasugrel (n=1246). Participants without a CYP2C19 loss-of function allele received clopidogrel while carriers of a loss-of-function CYP2C19 allele received ticagrelor or prasugrel. There were two primary outcomes including adverse clinical events and major or minor bleeding. Follow-up was 12 months. In the genotype-guided group, combined primary outcomes occurred in 63 participants (5.1%) and in 73 participants (5.9%) in the standard-treatment group. There were 122 participants (9.8%) that had primary bleeding in the genotype-guided group and 156 participants (12.5%) in the standard-treatment group. The authors concluded "a CYP2C19 genotype–guided strategy for selection of oral $P2Y_{12}$ inhibitor therapy was noninferior to standard treatment with ticagrelor or prasugrel at 12 months with respect to thrombotic events and resulted in a lower incidence of bleeding."

In 2011, three meta-analyses were published looking at the health-related outcomes of CYP2C19 genotype testing for individuals receiving clopidogrel. One of these reported that CYP2C19*2 carrier status was significantly associated with increased risk of cardiovascular events. The other two found no such benefit.

The first study, by Jin and colleagues, included a total of eight prospective cohort studies including 2345 subjects carrying the CYP2C19*2 LOF allele and 5935 wild-type controls. The authors reported that the summary odds ratio demonstrated a statistically significant association in increased cardiac mortality (p=0.007), myocardial infarction (p=0.002), and stent thrombosis (p=0.0001). However, while these findings point to a major role of the CYP2C19 allele in the incidence of major cardiovascular events, the study itself was comparatively small and did not include any RCT data.

In the second study, Bauer et al. looked at the data collected in 15 studies encompassing 28,368 subjects. They found the random effects summary odds ratio for stent thrombosis in carriers of at least one CYP2C19 LOF allele vs. non-carriers was 1.77 ($p<0.001$). However, the authors note that this finding is subject to significant small study bias and replication diversity. When adjusted for these factors, the significance of this finding was nullified. Furthermore, the odds ratio for major cardiovascular events and stent thrombosis was likewise non-significant. The overall quality of the epidemiological evidence reviewed was graded as low, and the authors' conclusion was that "… at the current state of accumulated information, there is no sufficiently robust and consistent evidence that CYP2C19 represents a strong susceptibility gene modifying the clinical efficacy of clopidogrel."

The third meta-analysis was published by Holmes and others and included 32 studies encompassing 42,016 subjects. Six of the included studies were RCTs. As with the Bauer study previously discussed, this study concluded that "this systematic review and meta-analysis does not demonstrate a clinically important association of genotype with cardiovascular outcomes with the possible exception of stent thrombosis." The report stated that

Federal and State law, as well as contract language including definitions and specific coverage provisions/exclusions, and Medical Policy take precedence over Clinical UM Guidelines and must be considered first in determining eligibility for coverage. The member's contract benefits in effect on the date that services are rendered must be used. Clinical UM Guidelines, which address medical efficacy, should be considered before utilizing medical opinion in adjudication. Medical technology is constantly evolving, and we reserve the right to review and update Clinical UM Guidelines periodically. Clinical UM guidelines are used when the plan performs utilization review for the subject. Due to variances in utilization patterns, each plan may choose whether or not to adopt a particular Clinical UM Guideline. To determine if review is required for this Clinical UM Guideline, please contact the customer service number on the back of the member's card.

No part of this publication may be reproduced, stored in a retrieval system or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from the health plan.

© CPT Only – American Medical Association

Medicaid managed care administered by Amerigroup Corporation, an independent company.

Historical

when statistically significant analyses were re-run with only studies that included greater than 200 subjects, the original statistically significant findings were nullified. The authors concluded that significant small study bias existed in the body of evidence. This is supported by positive results of the Harbord test for small study bias (p=0.001). The authors also state that selective outcome reporting and genotype misclassification errors impair the available evidence.

Mao (2013) reported a meta-analysis of 21 studies involving 23,035 subjects. They reported that compared with non-carriers of the CYP2C19 variant allele, carriers were found to have an increased risk of adverse clinical events (OR=1.50; p=0.0003), myocardial infarction (OR=1.62; p<0.00001), stent thrombosis (OR=2.08; p<0.00001), ischemic stroke (OR=2.14; p=0.001) and repeat revascularization (OR=1.35; p=0.004), but not of mortality (p=0.500) and bleeding events (p=0.930). They concluded that the presence of the CYP2C19 polymorphism is significantly associated with risk of adverse clinical events in clopidogrel-treated subjects.

In 2014, Sorich and others reported the results of a meta-analysis of 24 studies with ≥ 500 participants involving 30,076 subjects, looking at the effects of the CYP2C19 genotype on clopidogrel effectiveness. Data was stratified by the predominant clopidogrel indication (percutaneous coronary intervention [PCI] versus non-PCI) and ethnic population (white versus Asian) of each primary study. The association between carriage of more than one CYP2C19 LOF allele and major cardiovascular outcomes differed significantly (p<0.001) between studies of whites not undergoing PCI (relative risk [RR], 0.99; n=7043), whites undergoing PCI (RR, 1.20; n=19,016), and Asians undergoing PCI (RR, 1.91; n=10,017). Similar differences were identified in secondary analyses of two CYP2C19 LOF alleles, stent thrombosis outcomes, and studies with ≥ 200 participants. The conclusions stated that the reported association between CYP2C19 LOF allele carriage and major cardiovascular outcomes differs based on the ethnic population of the study and, to a lesser extent, the clopidogrel indication. This is potentially of major importance given that over 50% of Asians carry at least one CYP2C19 LOF allele.

In 2015, Osnabrugge published a systematic review and critical assessment of 11 overlapping meta-analyses that involved 30 primary studies that addressed the association between CYP2C19 loss-of-function alleles and clinical efficacy of clopidogrel. Of the 11 meta-analyses, eight reported statistically significant associations, with mean effect size ranging from 1.26 to 1.96. Of those eight studies, five reported associations between the presence of loss-of-function polymorphisms and clinical endpoints, and the other three reported no statistically significant pooled effect or could not pool data to a high degree of heterogeneity. The four studies concluding no association were the most recently published. All 11 studies reported a statistically significant association with CYP2C19 LOF alleles and stent thrombosis with mean effect size 1.77 to 3.85. The authors reported that all included meta-analyses reported significant heterogeneity, which was handled in significantly different manners. Publication bias was assessed in nine of the 11 meta-analyses included; six concluded that some publication bias was present and two did not find evidence of bias. The remaining study provided a funnel plot, but no discussion of the data. The authors concluded that meta-analyses on the association between CYP2C19 loss-of-function alleles and clinical efficacy of clopidogrel differed widely with regard to assessment and interpretation of heterogeneity and publication bias.

Historical

Federal and State law, as well as contract language including definitions and specific coverage provisions/exclusions, and Medical Policy take precedence over Clinical UM Guidelines and must be considered first in determining eligibility for coverage. The member's contract benefits in effect on the date that services are rendered must be used. Clinical UM Guidelines, which address medical efficacy, should be considered before utilizing medical opinion in adjudication. Medical technology is constantly evolving, and we reserve the right to review and update Clinical UM Guidelines periodically. Clinical UM guidelines are used when the plan performs utilization review for the subject. Due to variances in utilization patterns, each plan may choose whether or not to adopt a particular Clinical UM Guideline. To determine if review is required for this Clinical UM Guideline, please contact the customer service number on the back of the member's card.

No part of this publication may be reproduced, stored in a retrieval system or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from the health plan.

© CPT Only – American Medical Association

Medicaid managed care administered by Amerigroup Corporation, an independent company.

Doll and colleagues (2016) reported the results of a study involving 2236 subjects receiving clopidogrel or prasugrel, looking at the association of CYP2C19 metabolizer status (extensive vs. reduced) and their primary endpoints of cardiovascular death, MI, or stroke. They reported finding no association between CYP2C19 metabolizer status and the primary endpoints (HR=0.86). Subjects in either group had similar rates of the primary endpoint whether treated with prasugrel (HR=0.82) or clopidogrel (HR=0.91; p=0.495). After adjusting for clinical and treatment variables, they stated that extensive metabolizers had a lower risk of MI vs. reduced metabolizers (HR=0.80), but the risk of other outcomes were similar. Reduced metabolizers had significantly higher mean P2Y12 reaction units versus extensive metabolizers when treated with clopidogrel (39.93), but not with prasugrel (3.87).

In 2017, Cui and colleagues published a meta-analysis involving 5769 subjects in 15 studies with an aim to evaluate a relation between T744C, G52T, and C34T polymorphisms in the P2Y12 receptor gene in relation to clopidogrel resistance in subjects with cardiovascular disease. The authors reported that a G52T and C34T polymorphism might be associated with clopidogrel resistance as evident from platelet function assay ($p<0.05$), and that there was no significant association found between T744C polymorphism and clopidogrel resistance in various genetic models ($p>0.05$). This study did not demonstrate a link between the testing for these polymorphisms and improved clinical outcomes when treatment is guided by their results.

A systematic review and meta-analysis was performed by Pan and colleagues (2017) and included 15 studies involving of 4762 subjects with stroke or transient ischemic attack (TIA) treated with clopidogrel. It was concluded that, in subjects with ischemic stroke or TIA treated with clopidogrel, carriers of CYP2C19 loss-of-function alleles are at a greater risk of stroke and composite vascular events than non-carriers ($p<0.001$). The authors also found there was no significant difference in bleeding rates between CYP2C19 carriers and non-carriers (p=0.59), and other genetic variants were not associated with clinical outcomes associated with clopidogrel efficacy for acute ischemic stroke or TIA. While these findings may suggest the need for genetic testing when clopidogrel is used as the treatment option for stroke or TIA, the meta-analysis lacked statistical heterogeneity among the included studies, one study accounted for 31% of the subjects in the meta-analysis, and the authors disclosed publication bias for the primary end point.

The results of these large, well-done meta-analyses call into question earlier assessments regarding the efficacy of CYP2C19 genotyping for individuals receiving clopidogrel. Additional data from large-scale, well-done prospective RCTs is needed to further clarify this issue.

Abacavir (Ziagen®)

The role of genetic polymorphisms in the metabolism and tolerance of various drugs used to treat HIV-1 infection has been of major interest. The most widely studied of these interactions is between the histocompatibility complex allele for HLA-B*5701 and the occurrence of abacavir (ABC) hypersensitivity reactions (ABC-HSR). Since shortly after the FDA approval of ABC in 1999, studies began to arise associating the presence HLA-B*5701 with the occurrence of ABC-HSR. A large study addressing the incidence of ABC-HSR was conducted by Hetherington and

Federal and State law, as well as contract language including definitions and specific coverage provisions/exclusions, and Medical Policy take precedence over Clinical UM Guidelines and must be considered first in determining eligibility for coverage. The member's contract benefits in effect on the date that services are rendered must be used. Clinical UM Guidelines, which address medical efficacy, should be considered before utilizing medical opinion in adjudication. Medical technology is constantly evolving, and we reserve the right to review and update Clinical UM Guidelines periodically. Clinical UM guidelines are used when the plan performs utilization review for the subject. Due to variances in utilization patterns, each plan may choose whether or not to adopt a particular Clinical UM Guideline. To determine if review is required for this Clinical UM Guideline, please contact the customer service number on the back of the member's card.

No part of this publication may be reproduced, stored in a retrieval system or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from the health plan.

© CPT Only – American Medical Association

Medicaid managed care administered by Amerigroup Corporation, an independent company.

Historical

colleagues (2001). Using data from approximately 200,000 subjects enrolled in various ABC clinical trials, the authors conducted a retrospective review of pooled adverse events. Of the 31,096 subjects identified as having hypersensitivity reactions, 1302 (4.3%) were identified as having ABC-HSR. Of these, 176 (9.8%) were considered definitive ABC-HSR cases after failing rechallenge with ABC. These findings were supported by a later study by the same authors that found the incidence of ABC-HSR to be approximately 4% in a case control study of 197 subjects from the Glaxo-SmithKlein database (Hetherington, 2002). Mallal and others (2002) were the first to publish the results of a trial demonstrating a positive correlation between ABC-HSR and the presence of HLA-B*5701. This small study of 200 HIV-1 subjects exposed to ABC identified 18 individuals with definitive ABC-HSR (9%). However, the Mallal study went further and typed all subjects for HLA loci. They reported that HLA-B*5701 occurred in only 4% of ABC tolerant subjects and 78% in subjects with ABC-HSR ($p<0.0001$), strongly supporting their hypothesis that the presence of the HLA-B*5701 haplotype was strongly associated with ABC-HSR. They went on to calculate that the presence of HLA-B*5701 had a positive predictive value for ABC-HSR of 100% and a negative predictive value of 97%. These findings were supported by a retrospective study by Rauch and colleagues (2008) that performed genotyping on 131 individuals with suspected ABC-HSR. While these authors did not conduct confirmatory rechallenge to confirm ABC-HSR, they did conduct a blind case review of subjects' medical records, sorting them into likely ABC-HSR (n=27, 21%), unlikely ABC-HSR (n=43, 33%), and uncertain ABC-HSR (n=61, 47%). They found that HLA-B*5701 was present in 31% of likely cases compared to 1% of unlikely cases ($p<0.0001$). A retrospective case control study looked at the sensitivity and specificity of HLA-B*5701 genotyping in subjects receiving ABC enrolled 130 white and 69 black subjects for suspected ABC-HSR (Saag, 2008). Positive skin-patch testing identified 42 (33.2%) white and 5 (7.2%) black subjects with confirmed ABC-HSR. All confirmed ABC-HSR subjects were HLA-B*5701 positive (sensitivity=100%), regardless of race. Among all subjects with clinically suspected ABC-HSR, sensitivity was 44% for white subjects and 14% for black subjects. Specificity for white control subjects was 96% and 99% for black subjects. In the most rigorous study to report on this issue, Mallal and colleagues conducted a prospective randomized, double-blind study involving 1956 subjects with HIV-1 who were ABC naïve (2008). Subjects were randomized to undergo prospective HLA-B*5701 screening, with positive subjects forgoing ABC treatment. The control group received routine care with ABC without HLA-B*5701 screening. Similar to the previous studies, the prevalence of HLA-B*5701 was 5.6%. The authors reported that immunologically confirmed ABC-HSR occurred in 2.7% of subjects in the screening group vs. none in the control group. The calculated negative predictive value reported to be 100% and positive predictive value was 47.9%. The existing data, discussed above, adequately demonstrate that the HLA-B*5701 genotype is strongly associated with ABC-HSR, and that screening for this genotype significantly decreases the occurrence of ABC-HSR in individuals who have been prescribed ABC.

A 2020 study by Quiros-Roldan and colleagues evaluated the relationship between HLA-B*5701 and ABC-HSR. Their focus was on the prevalence of hypersensitivity reaction in non-carriers of the HLA-B*5701 allele. In this retrospective review, there were 3144 HIV-positive individuals with known HLA-B*5701 pattern. A total of 171 individuals were known carriers of HLA-B*5701 and 2973 were non-carriers of HLA-B*5701. In the HLA-B*5701 carrier group, 32 participants were treated with a first abacavir-containing regimen while 1769 in the HLA-B*5701 non-carrier group 1769 participants were treated with a first abacavir-containing regimen. The abacavir-containing regimen was discontinued for toxicity/intolerance in 22 participants who were known carriers of HLA-B*5701 and

Federal and State law, as well as contract language including definitions and specific coverage provisions/exclusions, and Medical Policy take precedence over Clinical UM Guidelines and must be considered first in determining eligibility for coverage. The member's contract benefits in effect on the date that services are rendered must be used. Clinical UM Guidelines, which address medical efficacy, should be considered before utilizing medical opinion in adjudication. Medical technology is constantly evolving, and we reserve the right to review and update Clinical UM Guidelines periodically. Clinical UM guidelines are used when the plan performs utilization review for the subject. Due to variances in utilization patterns, each plan may choose whether or not to adopt a particular Clinical UM Guideline. To determine if review is required for this Clinical UM Guideline, please contact the customer service number on the back of the member's card.

No part of this publication may be reproduced, stored in a retrieval system or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from the health plan.

© CPT Only – American Medical Association

Medicaid managed care administered by Amerigroup Corporation, an independent company.

Historical

all were found to have a certain ABC-HCR. There were 169 participants in the non-carrier group who discontinued the abacavir-containing regimen due to toxicity/intolerance. Certain ABC-HSR was found in 85 participants while 84 participants were found to have adverse events, but not HSR.

In 2019, the Department of Health and Human Services (DHHS) Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV recommend the following:

- The Panel recommends screening for HLA-B*5701 before starting patients on an abacavir (ABC)-containing regimen to reduce the risk of hypersensitivity reaction (HSR).
- HLA-B*5701-positive patients should not be prescribed ABC.
- The positive status should be recorded as an ABC allergy in the patient's medical record.
- When HLA-B*5701 screening is not readily available, it remains reasonable to initiate ABC with appropriate clinical counseling and monitoring for any signs of HSR.

Eliglustat (Cerdelga®)

In 2014, the FDA approved eliglustat "for the long-term treatment of adult subjects with Gaucher disease type 1 who are CYP2D6 extensive metabolizers (EMs), intermediate metabolizers (IMs), or poor metabolizers (PMs) as detected by an FDA-cleared test."

The evidence addressing the use of CYP2D6 genotyping for individuals who may be prescribed eliglustat for the treatment of Gaucher disease was presented in the FDA's Clinical Pharmacology and Biopharmaceuticals Review of Eliglustat from June 24, 2014. This document describes data addressing CYP2D6 testing for individuals prescribed eliglustat from several sources. The first is a series of three unpublished Phase I and II safety and effectiveness studies involving 151 subjects. All subjects were genotyped and followed for drug response and subject pools were stratified into poor metabolizers (PM), intermediate metabolizers (IM), and ultra-rapid metabolizers (URM). The data demonstrates that there is significant variation in eliglustat metabolism based on CYP2D6 status. Another source of data presented in the FDA Review document is data derived from computer simulations of metabolic response derived from computer modeling using the SimCYP® software package. Again, this data demonstrated that there was significant metabolic response to eliglustat dependent upon CYP2D6 status.

Additionally, two peer-reviewed published articles have addressed the use of CYP2D6 genotyping in populations given eliglustat. The first, by Lukina (2010), was an open-label case series study involving 26 subjects with Gaucher disease. In the results section, the authors briefly comment that, "Lower exposure was associated with lower administered dose, greater body weight, and higher CYP2D6 metabolic activity." No further data or comments are provided, including any outcomes data related to CYP2D6 genotype. The other study was a small Phase I dose-finding RCT involving healthy volunteers evaluating the safety, tolerability, and pharmacokinetics in escalating doses of eliglustat in 36 subjects. The authors commented in the discussion section, "As expected, because Genz-99067 is predominantly metabolized by CYP2D6, participants with genotypes corresponding to slower CYP2D6 metabolism exhibited higher exposure."

Federal and State law, as well as contract language including definitions and specific coverage provisions/exclusions, and Medical Policy take precedence over Clinical UM Guidelines and must be considered first in determining eligibility for coverage. The member's contract benefits in effect on the date that services are rendered must be used. Clinical UM Guidelines, which address medical efficacy, should be considered before utilizing medical opinion in adjudication. Medical technology is constantly evolving, and we reserve the right to review and update Clinical UM Guidelines periodically. Clinical UM guidelines are used when the plan performs utilization review for the subject. Due to variances in utilization patterns, each plan may choose whether or not to adopt a particular Clinical UM Guideline. To determine if review is required for this Clinical UM Guideline, please contact the customer service number on the back of the member's card.

No part of this publication may be reproduced, stored in a retrieval system or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from the health plan.

© CPT Only – American Medical Association

Medicaid managed care administered by Amerigroup Corporation, an independent company.

Historical

Tetrabenazine (Xexazine®)

There is very little available data addressing the possible benefits of such genotype testing for individuals who may receive treatment with tetrabenazine. The only available peer-reviewed published study to report the issue was published by Mehanna and colleagues in 2013. This study involved 127 subjects with Huntington disease (chorea) who were genotyped for CYP2D6. Of this population, 100 were identified as EMs, 14 were IMs, 11 as PMs, and 2 as URMs. The authors noted that the URM subjects required a significantly longer titration period compared to other metabolizer groups (8 vs 3.3, 4.4, and 3 weeks, respectively; $p<0.01$) to achieve optimal benefit. This group also required a higher average daily dose than the other subjects, but this difference did not reach statistical significance. The treatment response was less robust in the IM group when compared with the EM subjects ($p=0.013$), but there were no statistically significant differences between the various groups with regard to adverse effects. They concluded that, aside from the need for a longer titration in the URMs, there are no distinguishing features of individuals with various CYP2D6 genotypes, and, "therefore the current recommendation to systematically genotype all patients prescribed more than 50 mg/day of tetrabenazine should be reconsidered."

However, the FDA-approved label for tetrabenazine (FDA, 2019)states the following:

> Patients requiring doses above 50 mg per day should be genotyped for the drug metabolizing enzyme CYP2D6 to determine if the patient is a poor metabolizer (PM) or an extensive metabolizer (EM).

Despite the low level of evidence supporting the use of genotyping for individuals who may receive tetrabenazine, at this time the use of such testing for individuals who may receive a dose greater than 50 mg/day is supported by the practicing community based on a preponderance of caution.

Allopurinol (Zyloprim®)

Allopurinol reduces serum and urinary uric acid concentrations. It is used as an antihyperuricemic agent for primary or secondary gout, for individuals with leukemia, lymphoma and malignancies who are receiving cancer therapy which causes elevations of serum and urinary uric acid levels, and for individuals with recurrent calcium oxalate calculi. Allopurinol has been known to cause a variety of cutaneous adverse drug reactions ranging from a mild form to drug-induced hypersensitivity syndrome, Stevens-Johnson syndrome, and toxic epidermal necrolysis. Severe cutaneous adverse reactions constitute a set of life-threatening conditions which include drug rash with eosinophilia and systemic symptoms. The HLA-B*58:01 allele has been identified as a strong genetic marker for allopurinol-induced cutaneous adverse drug reactions in individuals of Asian descent.

In a 2015 study by Ko and colleagues, the authors used genotype testing to screen 2910 Taiwanese participants who had an indication for allopurinol for the HLA-B*58:01 allele. A total of 571 participants tested positive for the HLA-B*58:01 allele and were referred for an alternate drug treatment or counselled about severe cutaneous adverse drug reactions. There were 2339 participants who tested negative for the HLA-B*58:01 allele and were given

Federal and State law, as well as contract language including definitions and specific coverage provisions/exclusions, and Medical Policy take precedence over Clinical UM Guidelines and must be considered first in determining eligibility for coverage. The member's contract benefits in effect on the date that services are rendered must be used. Clinical UM Guidelines, which address medical efficacy, should be considered before utilizing medical opinion in adjudication. Medical technology is constantly evolving, and we reserve the right to review and update Clinical UM Guidelines periodically. Clinical UM guidelines are used when the plan performs utilization review for the subject. Due to variances in utilization patterns, each plan may choose whether or not to adopt a particular Clinical UM Guideline. To determine if review is required for this Clinical UM Guideline, please contact the customer service number on the back of the member's card.

No part of this publication may be reproduced, stored in a retrieval system or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from the health plan.

© CPT Only – American Medical Association

Medicaid managed care administered by Amerigroup Corporation, an independent company.

Historical

allopurinol. Of those who tested negative, 155 participants did not take allopurinol and 11 participants were lost during follow-up. The remaining 2173 participants were monitored during treatment for 2 months with a weekly telephone interview. A mild and transient rash and itching occurred in 97 participants who received allopurinol. Three of the participants who had previously tested positive for HLA-B*58:01 showed symptoms of rash and itching after taking an alternative medicine (benzbromarone), not allopurinol. None of the participants who were receiving allopurinol and screened negative for HLA-B*58:01 developed severe cutaneous adverse drug reactions.

A 2016 meta-analysis by Wu and colleagues, reported on 21 pharmacogenetic studies, including 551 participants with allopurinol-induced cutaneous adverse drug reactions. There were 2370 allopurinol-tolerant controls from 16 matched studies. Most of the studies were conducted among East Asian populations. When considering only the severe form of cutaneous adverse drug reactions, the odds ratio of allopurinol-induced severe cutaneous adverse drug reactions for carrier of the HLA-B*58:01 allele was 92.06 (95% CI, 59.54-142.32, p<10-5) compared to 108.39 (95% CI, 73.73-159.36, p<10-5) for matched and population-based studies. Overall, the HLA-B*58:01 allele showed an odds ratio of 82.77 (95% CI, 41.63-164.58, p<10-5) with the risk of allopurinol-induced cutaneous adverse drug reactions compared to 100.87 (95% CI, 63.91-159.21, p<10-5) in population-based studies.

In a 2020 study by Low and colleagues, the authors reported on the association between HLA-B*58:01 and the risk of allopurinol-induced severe cutaneous reactions across different populations. There were 55 individuals with allopurinol-induced severe cutaneous reactions and 42 allopurinol-tolerant controls. The HLA-B*58:01 allele was found in 89.1% of participants with allopurinol-induced severe cutaneous reactions and 14.3% of participants in the allopurinol-tolerant control group. Analysis by ethnicity showed the Chinese population with HLA-B*58:01 allele had an increased risk of developing allopurinol-induced severe cutaneous reactions (OR,137.5, p< 0.0001) followed by the Malaysian population (OR,35.2, p< 0.0001). The Indian population included in the study was too small for meaningful analysis.

The 2020 American College of Rheumatology guideline for the management of gout conditionally recommends testing for the HLA-B*58:01 allele prior to the initiation of allopurinol in select populations including Southeast Asian descent and African Americans.

Siponimod (Mayzent®)

In March 2019, the FDA approved siponimod for the treatment of relapsing forms of multiple sclerosis in adults. This approval was based on a double-blind, randomised, phase 3 study (Kappos, 2018). The CYP2C9 genotype has an impact on the metabolism of siponimod. As part of the FDA approval, CYP2C9 genotype determination should be assessed prior to administration. Dosing regimen is dependent on genotype CYP2C9, specifically *1/*3 or *2/*3 genotype. The current label (FDA, 2021) states the drug is “contraindicated in patients with a CYP2C9*3/*3 genotype.”

A 2019 pharmacokinentics study by Gardin and colleagues found approximately two to fourfold greater mean area under the curve siponimod plasma concentrations in subjects with CYP2C9*2/*3 and CYP2C9*3/*3 (poor

Federal and State law, as well as contract language including definitions and specific coverage provisions/exclusions, and Medical Policy take precedence over Clinical UM Guidelines and must be considered first in determining eligibility for coverage. The member's contract benefits in effect on the date that services are rendered must be used. Clinical UM Guidelines, which address medical efficacy, should be considered before utilizing medical opinion in adjudication. Medical technology is constantly evolving, and we reserve the right to review and update Clinical UM Guidelines periodically. Clinical UM guidelines are used when the plan performs utilization review for the subject. Due to variances in utilization patterns, each plan may choose whether or not to adopt a particular Clinical UM Guideline. To determine if review is required for this Clinical UM Guideline, please contact the customer service number on the back of the member's card.

No part of this publication may be reproduced, stored in a retrieval system or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from the health plan.

© CPT Only – American Medical Association

Medicaid managed care administered by Amerigroup Corporation, an independent company.

Historical

metabolizers) versus CYP2C9*1/*1 genotype (extensive metabolizers), confirming the relevance of CYP2C9 activity on siponimod metabolism.

Warfarin

Perhaps the most studied area regarding the use of genotype polymorphism testing involves genetic variations in enzymes key to the metabolism and operation of the drug warfarin. A significant amount of evidence has shown that the enzymes cytochrome P450 2C9 (CYP2C9) and vitamin K epoxide reductase enzyme subunit C1 (VKORC1) have the most significant role in warfarin metabolic variability (Higashi, 2002; Kirchheiner, 2005; Osman, 2006; Sconce, 2005.) Some reports attribute approximately 55% of warfarin dose variability to these two variants (Sconce, 2005; Wadelius, 2005).

A report published by McClain and colleagues, conducted for the American College of Medical Genetics (ACMG, 2007), evaluated the use of CYP4502C9 (CYP2C9) and VKORC1 testing of individuals receiving warfarin due to increased risk of thrombotic events. The authors concluded the following:

- Analytic validity: Nearly all available data for analytic validity refer to two variants in the CYP2C9 gene; fewer data are available for the variants in the VKORC1 gene. Based on these data, analytic sensitivity and specificity are likely near 100%. Depending on methodology, 1% to 10% of samples may experience repeated assay failures resulting in inconclusive test results.
- Clinical validity: CYP2C9 and VKORC1 genotypes contribute significant and independent information to the stable warfarin dose and compared to the most common combination, some individuals with other genotype combinations will need more than the usual dose, while others would require less. Time to steady state warfarin levels varies by CYP2C9 genotype (3 to 5 days vs. 5 to 8 vs. 12 to 15 for the 3 most common genotypes). CYP2C9 positive predictive value (PPV) for serious bleeding events is estimated to be 7%; the negative predictive value (NPV) is 96%. Similar information for VKORC1 was not available.
- Clinical utility: The purpose of genetic testing in this clinical scenario is to predict an individual's likely stable warfarin dose by incorporating demographic, clinical, and genotype data (CYP2C9 and VKORC1), and initiating warfarin at that predicted dose as a way to limit high INR (International Normalized Ratio) values (over-anticoagulation) leading to an increased risk of serious bleeding events. No large study has yet confirmed such utility, although several randomized trials are currently underway.

Caraco and colleagues (2007) describe a randomized, controlled trial evaluating CYP2C9-guided warfarin therapy. This study included 191 participants (n=96 controls, n=95 in the treatment groups) prescribed warfarin therapy. While this study did find significant benefits in some secondary outcomes, such as time to stable dosing, more time spent in therapeutic range, and lower rates of minor bleeding, the small study population did not permit assessment of significant differences in serious bleeding, thrombotic events, major morbidity or mortality. The authors state that further research is warranted.

Federal and State law, as well as contract language including definitions and specific coverage provisions/exclusions, and Medical Policy take precedence over Clinical UM Guidelines and must be considered first in determining eligibility for coverage. The member's contract benefits in effect on the date that services are rendered must be used. Clinical UM Guidelines, which address medical efficacy, should be considered before utilizing medical opinion in adjudication. Medical technology is constantly evolving, and we reserve the right to review and update Clinical UM Guidelines periodically. Clinical UM guidelines are used when the plan performs utilization review for the subject. Due to variances in utilization patterns, each plan may choose whether or not to adopt a particular Clinical UM Guideline. To determine if review is required for this Clinical UM Guideline, please contact the customer service number on the back of the member's card.

No part of this publication may be reproduced, stored in a retrieval system or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from the health plan.

© CPT Only – American Medical Association

Medicaid managed care administered by Amerigroup Corporation, an independent company.

Historical

A study by Anderson and colleagues (2007) indicates some promise for the use of genetic polymorphism testing for individuals receiving warfarin therapy. In their randomized, blinded study of 206 participants, the authors compared pharmacogenetic-guided therapy vs. standard dosing methodology. While the results indicated that the pharmacogenetic-guided therapy more closely approximated stable doses resulting in significantly smaller and fewer dosing changes, the primary endpoint of reducing out-of-range INRs was not significantly different. However, in a post-hoc subset analysis, the authors reported that in wild-type individuals and those with multiple variant carriers, the differences were significant between groups. These authors also indicate that additional research is warranted based upon their findings.

In February 2009, the International Warfarin Pharmacogenetics Consortium published a study that describes the development and modeling of two warfarin therapy algorithms that aid in the prediction of the ideal therapeutic dose. The first algorithm uses both clinical and pharmacogenetic information from a retrospective cohort of 4043 individuals (2009). The second algorithm uses the same population and methodology, excluding the pharmacogenetic data. Using data from a separate retrospective cohort of 1009 individuals, the consortium created a model testing the use of these two algorithms against a standard fixed treatment approach of 5 mg warfarin/day. While this study is of interest, it is only a model and does not provide real-world clinical results. As has been discussed earlier, clinical validity data is needed for the proper evaluation of the clinical role of pharmacogenetic testing methods. This report does not provide data on adverse events such as thromboembolic events or bleeding. The next step is to see how this algorithm functions in a clinical setting with outcomes data reported.

In early 2008, based upon the information provided above, the ACMG published a position statement regarding the use of CYP2C9 and VKORC1 testing, which concluded:

> The group determined that the analytical validity of these tests has been met, and there is strong evidence to support association between these genetic variants and therapeutic dose of warfarin. However, there is insufficient evidence, at this time, to recommend for or against routine *CYP2C9* and *VKORC1* testing in warfarin-naive patients. Prospective clinical trials are needed that provide direct evidence of the benefits, disadvantages, and costs associated with this testing in the setting of initial warfarin dosing… Although the routine use of warfarin genotyping is not endorsed by this work group at this time, in certain situations, CYP2C9 and VKORC1 testing may be useful, and warranted, in determining the cause of unusual therapeutic responses to warfarin therapy.

However, selection criteria or specific algorithms were not described based upon clinical study evidence.

The Agency for Healthcare Research and Quality (AHRQ) published a technology assessment addressing the use of pharmacogenetic testing for warfarin and statin therapy (2008). In this assessment, it evaluated the available evidence regarding the clinical impact and outcomes related to the use of pharmacogenetic testing for variants of CYP2C9, VKORC1, and MTHFR. The report concludes:

Historical

Federal and State law, as well as contract language including definitions and specific coverage provisions/exclusions, and Medical Policy take precedence over Clinical UM Guidelines and must be considered first in determining eligibility for coverage. The member's contract benefits in effect on the date that services are rendered must be used. Clinical UM Guidelines, which address medical efficacy, should be considered before utilizing medical opinion in adjudication. Medical technology is constantly evolving, and we reserve the right to review and update Clinical UM Guidelines periodically. Clinical UM guidelines are used when the plan performs utilization review for the subject. Due to variances in utilization patterns, each plan may choose whether or not to adopt a particular Clinical UM Guideline. To determine if review is required for this Clinical UM Guideline, please contact the customer service number on the back of the member's card.

No part of this publication may be reproduced, stored in a retrieval system or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from the health plan.

© CPT Only – American Medical Association

Medicaid managed care administered by Amerigroup Corporation, an independent company.

> Overall, studies evaluating associations between the pharmacogenetic test results and the patient's response to therapy for non-cancer and cancer conditions showed considerable variation in study designs, study populations, medication dosages, and the type of medications. This variation warrants caution when interpreting our results. Data on the relationships among pharmacogenetic test results and patient- and disease-related factors and on the patient's response to therapy are limited. We found no data on the benefits, harms, or adverse effects from subsequent therapeutic management after pharmacogenetic testing. Detailed patient-level analyses are needed to adjust estimates for the effects of modifiers, such as age or tumor stage.

In 2011, Burmester and others conducted a double-blind RCT with 203 subjects randomized to receive warfarin therapy guided by either standard algorithm (n=112) or by genotype-guided algorithm (n=113). Only 184 subjects (80%) completed the 60-day trial period. The results indicated that the genotype-based algorithm was almost more than twice as accurate at predicting final effective dose compared to the standard model ($p<0.0001$). However, no difference was noted between groups for time spent in the therapeutic range, time to stable therapeutic dose, time to INR > 4, or adverse events. The authors concluded that their data was not able to demonstrate that genotype-based initial warfarin dosing is superior to clinical-based dosing with respect to time in therapeutic range through the first 14 days of therapy. However, the impact of this benefit on the incidence of adverse events remains to be evaluated in a large well-designed study.

A large double-blind RCT conducted by Kimmel (2013) involved 1015 subjects initiating warfarin treatment who were randomized to receive treatment guided by a protocol which included genotype data for CYP2C9 and VKORC1 variants plus clinical variables (n=514) or a protocol that included clinical variables only (n=501). Subjects had their initial dose and dose adjustments for the first 4-5 days of therapy guided by the assigned protocols. Subsequent adjustments were per standard protocol for the next 4 weeks. All subjects were followed for 6 months. The results show no significant differences between groups with regard to mean percentage of time within therapeutic range during the first 4 weeks ($p=0.91$). Overall, there were no significant between-group differences in the mean percentage of time above or below the therapeutic range (INR, < 2 or > 3). The time to determination of the maintenance dose did not differ significantly between the two groups overall or according to race or total number of genetic variants. The authors did note a significant difference between groups when a pre-specified sub-analysis was conducted for race. For black subjects, the mean time in the therapeutic range in the first 4 weeks was less in the genotype-guided group ($p=0.01$), and overall, black subjects in the genotype-guided group took longer on average to reach the first therapeutic INR than did those in the clinically-guided group. Black subjects in the genotype-guided group also took longer on average to reach the first therapeutic INR than did those in the control group. No differences between groups were reported with regard to time of INR ≤ 4, major bleeding, or thromboembolism. The authors concluded that the genotype-guided algorithms performed better at predicting maintenance dose among non-black subjects. However, there was no overall benefit of genotype-guided dosing with respect to percentage of time in the therapeutic INR range. The authors end their report by stating, "Our results emphasize the importance of performing randomized trials for pharmacogenetics, particularly for complex regimens such as warfarin."

Federal and State law, as well as contract language including definitions and specific coverage provisions/exclusions, and Medical Policy take precedence over Clinical UM Guidelines and must be considered first in determining eligibility for coverage. The member's contract benefits in effect on the date that services are rendered must be used. Clinical UM Guidelines, which address medical efficacy, should be considered before utilizing medical opinion in adjudication. Medical technology is constantly evolving, and we reserve the right to review and update Clinical UM Guidelines periodically. Clinical UM guidelines are used when the plan performs utilization review for the subject. Due to variances in utilization patterns, each plan may choose whether or not to adopt a particular Clinical UM Guideline. To determine if review is required for this Clinical UM Guideline, please contact the customer service number on the back of the member's card.

No part of this publication may be reproduced, stored in a retrieval system or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from the health plan.

© CPT Only – American Medical Association

Medicaid managed care administered by Amerigroup Corporation, an independent company.

Historical

An unblinded RCT published in 2013 by the EU-PACT study group (Pirmohamed, 2013) reported contradictory findings to those by Kimmel. The study used point-of-care genotype-guided dosing in 455 subjects with either atrial fibrillation (72.1%) or venous thromboembolism (27.9%) receiving initial treatment with warfarin. Subjects were randomized to receive management with either a genotype-guided algorithm which included data for CYP2C9 and VKORC1 variants plus clinical variables (n=227) or management with an algorithm which included clinical variables only (n=228). Similar to the Kimmel study, subjects had their initial dose and dose adjustments for the first 4-5 days of therapy guided by the assigned protocols. Subsequent adjustments were per local clinical practice standards. All subjects were followed for 3 months. The presented analysis included only those subjects with at least 13 days of INR data (genotype-guided group, n=211 vs. control group, n=216). The percentage of time with an INR of 2.0 to 3.0 was 67.4% in the genotype-guided group vs. 60.3% in the control group when adjusted for center and indication ($p<0.001$). In the per-protocol analysis, values in the genotype-guided group (n=166) and control group (n=184) were 68.9% and 62.3% ($p=0.001$). The difference between the two groups with regard to mean percentage of time in the therapeutic range was significantly different at weeks 1-4 ($p<0.001$) and 5-8 ($p<0.001$), but not for weeks 9-12 ($p<0.6$). Subjects in the genotype-guided group were less likely to have an INR of 4.0 or higher vs. the control group ($p<0.03$). A total of 173 subjects (82.0%) in the genotype-guided group reached a stable dose by 3 months vs. 52 subjects (70.4%) in the control group ($p\leq0.003$). Fewer dose adjustments were required in the genotype-guided group ($p=0.02$). No significant differences in bleeding or other adverse events were reported. The authors concluded that genotype-based dosing at the initiation of warfarin therapy increased the time in the therapeutic range by 7% and reduced the incidence of excessive anticoagulation, the time required to reach a therapeutic INR, the time required to reach a stable dose, and the number of adjustments in the dose of warfarin.

In 2015, Mega and colleagues published the results of a large randomized double-blind clinical trial involving 14,348 subjects. Subjects were assigned in a 1:1:1 ratio to warfarin (n=4833) or lower dose edoxaban (30 mg) or higher dose edoxaban (60 mg) (n not provided for either group). Subjects receiving warfarin were genotyped for CYP2C9 and VKORC1 polymorphisms: 2982 (61.7%) were classified as normal responders, 1711 (35.4%) as sensitive responders, and 140 (2.9%) as highly sensitive responders. Compared with normal responders, sensitive and highly sensitive responders spent greater proportions of time over-anticoagulated in the first 90 days of treatment ($p_{trend}<0.0001$) and had increased risks of bleeding with warfarin (sensitive responders HR=1.31; $p=0.0179$; highly sensitive responders HR=2.66; $p<0.0001$). The authors stated that genotype added independent information beyond clinical risk scoring. Looking at intergroup comparisons, it was reported that during the first 90 days of treatment, when compared with warfarin, treatment with edoxaban reduced bleeding more so in sensitive and highly sensitive responders than in normal responders (higher-dose edoxaban $p_{interaction}=0.0066$; lower-dose edoxaban $p_{interaction}=0.0036$). However, after 90 days this reduction in bleeding risk with edoxaban versus warfarin was similarly beneficial across genotypes. The authors concluded that the identification of CYP2C9 and VKORC1 genotypes helps identify individuals who are more likely to experience early bleeding with warfarin and who may derive a greater early safety benefit from initial use of edoxaban vs. warfarin.

In 2017, two RCTs were completed with the aim of evaluating genotype-guided dosing versus clinically-guided dosing for warfarin in two different populations. Gage and colleagues focused on 1650 randomized subjects

Federal and State law, as well as contract language including definitions and specific coverage provisions/exclusions, and Medical Policy take precedence over Clinical UM Guidelines and must be considered first in determining eligibility for coverage. The member's contract benefits in effect on the date that services are rendered must be used. Clinical UM Guidelines, which address medical efficacy, should be considered before utilizing medical opinion in adjudication. Medical technology is constantly evolving, and we reserve the right to review and update Clinical UM Guidelines periodically. Clinical UM guidelines are used when the plan performs utilization review for the subject. Due to variances in utilization patterns, each plan may choose whether or not to adopt a particular Clinical UM Guideline. To determine if review is required for this Clinical UM Guideline, please contact the customer service number on the back of the member's card.

No part of this publication may be reproduced, stored in a retrieval system or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from the health plan.

© CPT Only – American Medical Association

Medicaid managed care administered by Amerigroup Corporation, an independent company.

Historical

undergoing hip or knee arthroplasty; 1597 subjects (96.8%) completed the study. While study personnel and subjects were blinded to genotype and study groups, warfarin dosing was open label. Using the primary end point of the combined risk of major bleeding, INR of 4 or greater, venous thromboembolism, or death, the authors found that 87 subjects (10.8%) in the genotype-guided group met at least one of the end point components (p=0.02). In another study, Wen and colleagues studied 318 subjects of Han-Chinese descent. In this single blind (subjects) study, three different dosing algorithms were used. One was clinically-guided and two were genotype-guided to aid in identifying any difference in the outcomes found from each algorithm. The authors reported that genotype-guided dosing did not significantly improve percentage of time in the therapeutic INR range by 10 to 12 weeks (p=0.84).

Also in 2017, two systematic reviews and meta-analyses on polymorphism and warfarin were published. One study assessed CYP2C9 polymorphism while the other focused on VKORC1 polymorphism. Zhang and colleagues (2017a) studied CYP2C9 polymorphism on pediatric warfarin maintenance dosage requirements in eight articles with a total of 507 subjects. They found that CYP2C9 *1/*2, CYP2C9 *1/*3, and CYP2C9 variant genotypes in this population were significantly associated with lower warfarin maintenance dose requirements (p<0.05). Limitations to this study included small sample size and lack of ethnic diversity in subjects. Tang and colleagues assessed VKORC1 polymorphism and warfarin maintenance dosing in relation to age and ethnicity. From the 53 studies with a total of 9578 subjects, the authors reported that Caucasian carriers of VKORC1 polymorphisms required a higher mean daily warfarin dose compared with Asian carriers (p<0.05), and that warfarin dosing requirements varied in both Asian and Caucasians aged greater than 60 years and less than 60 years (p<0.05). The authors concluded that VKORC1 polymorphism testing is needed for optimal therapeutic warfarin dosing.

In a 2018 study by Syn and colleagues, the authors reported on 269 Asian participants receiving warfarin. In this open-label, non-inferiority, randomized trial conducted in three large tertiary hospitals in South East Asia, all participants were started on low-molecular weight heparins at the point of randomization. The study intervention period consisted of a dose initiation period (first 3 days) and a dose adjustment period (remainder of study). Those in the genotype-guided dosing strategy group received their tailored dose for 3 consecutive days. This dosing was calculated using an algorithm which takes into account the presence of the CYP2C9*3 allele, VKORC1 381 genotype, age, and weight. The participants randomized to the traditional dosing approach were initiated using a standardized loading dose regimen used by the National University Hospital Anticoagulation Clinic. The primary outcome was the number of dose titrations performed up to end of week 2 (day 14). Only the participants who received warfarin for at least 14 days were included in the primary analysis. This included 133 (83.6%) participants in the genotype-guided group and 136 (83.4%) participants in the traditional dosing group. Median duration of warfarin therapy was comparable between the two groups. The average number of dose titrations performed up to the 14th day was 1.77 (95% CI, 1.55 to 2.00) in the genotype-guided group and 2.93 (95% CI, 2.63 to 3.24) in the traditional dosing group. Secondary outcomes were the median time to stable INR, percentage of time spent within the therapeutic range, incidence of dose adjustments and INR monitoring during follow-up, and the proportions of participants who had a bleeding episode. A total of 103 (77.4%) participants in the genotype-guided group achieved stable INR versus 108 (79.4%) participants in the traditional dosing group. During the follow-up period there was no evidence of difference in the percentage of time in the therapeutic range. During the follow-up period, the

Federal and State law, as well as contract language including definitions and specific coverage provisions/exclusions, and Medical Policy take precedence over Clinical UM Guidelines and must be considered first in determining eligibility for coverage. The member's contract benefits in effect on the date that services are rendered must be used. Clinical UM Guidelines, which address medical efficacy, should be considered before utilizing medical opinion in adjudication. Medical technology is constantly evolving, and we reserve the right to review and update Clinical UM Guidelines periodically. Clinical UM guidelines are used when the plan performs utilization review for the subject. Due to variances in utilization patterns, each plan may choose whether or not to adopt a particular Clinical UM Guideline. To determine if review is required for this Clinical UM Guideline, please contact the customer service number on the back of the member's card.

No part of this publication may be reproduced, stored in a retrieval system or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from the health plan.

© CPT Only – American Medical Association

Medicaid managed care administered by Amerigroup Corporation, an independent company.

Historical

frequency of INR measurements did not differ significantly between the genotype-guided group versus the traditional dosing group (8.63 ± 4.26 vs. 9.48 ± 4.05, IRR 0.91; 95% CI, 0.82 to 1.01, p=0.076) respectively. There were no significant differences in bleeding detected between the genotype-guided and traditional dosing groups. This study has several limitations including the open-label design which potentially introduces ascertainment bias, approximately 16% of participants were excluded because they did not continue warfarin for 14 days, and generalizability of the results are limited due to 86.7% of participants being enrolled at a single tertiary care center despite that the study was designed as a multicenter clinical trial.

Acenocoumarol and Phenprocoumon

A second EU-PACT study (Verhoef, 2013) described the results of a single-blind RCT of genotype-guided dosing of acenocoumarol (n=381) and phenprocoumon (n=127). Subjects were randomized to receive management with either a genotype-guided algorithm which included data for CYP2C9 and VKORC1 variants plus clinical variables (n=273) or management with an algorithm which included clinical variables alone (n=275). The percentage of time in the therapeutic range during the first 4 weeks after the initiation of treatment was 52.8% in the genotype-guided group vs. 47.5% in the control group (p=0.02). However, this difference did not persist through the 3 month follow-up period with the percentage of time in the therapeutic INR range being 61.6% for genotype-guided group vs. 60.2% in the control group (p=0.52). No significant differences between the two groups were reported for several secondary outcomes, including number of subjects with INR ≥ 4, percentage of time with INR ≥ 4, percentage of time with INR < 2, time to reach therapeutic INR and number of subjects with stable dose within 12 weeks. Additionally, no significant differences were reported with regard to the incidence of bleeding or thromboembolic events. The authors concluded that genotype-guided dosing of acenocoumarol or phenprocoumon did not improve the percentage of time in the therapeutic INR range during the 12 weeks after the initiation of therapy.

Irinotecan

The Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group published its recommendations regarding the use of UGT1A1 testing for individuals undergoing treatment with irinotecan (2009). This paper concluded:

> The evidence is currently insufficient to recommend for or against the routine use of UGT1A1 genotyping in patients with metastatic colorectal cancer who are to be treated with irinotecan, with the intent of modifying the dose as a way to avoid adverse drug reactions (severe neutropenia).

A systematic review and meta-analysis consisting of 746 wild genotype cases and 394 variant genotype cases in 12 studies was published in 2017 by Zhang and colleagues (2017b). The study was designed to assess if UGT1A1*6 polymorphisms and irinotecan-related severe neutropenia in cancer patients have an association. Findings from the meta-analysis suggest the UGT1A1*6 polymorphisms correlated with an increased risk of IRI-induced neutropenia in cancer patients. The authors also concluded that increased cases of severe neutropenia could be associated with diverse regions, cancer type, low dose of IRI, and the duration of treatment.

Federal and State law, as well as contract language including definitions and specific coverage provisions/exclusions, and Medical Policy take precedence over Clinical UM Guidelines and must be considered first in determining eligibility for coverage. The member's contract benefits in effect on the date that services are rendered must be used. Clinical UM Guidelines, which address medical efficacy, should be considered before utilizing medical opinion in adjudication. Medical technology is constantly evolving, and we reserve the right to review and update Clinical UM Guidelines periodically. Clinical UM guidelines are used when the plan performs utilization review for the subject. Due to variances in utilization patterns, each plan may choose whether or not to adopt a particular Clinical UM Guideline. To determine if review is required for this Clinical UM Guideline, please contact the customer service number on the back of the member's card.

No part of this publication may be reproduced, stored in a retrieval system or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from the health plan.

© CPT Only – American Medical Association

Medicaid managed care administered by Amerigroup Corporation, an independent company.

Historical

Also in 2017, Chen and colleagues performed a meta-analysis to determine if UGT1A1*6 and UGT1A1*28 are effective predictor biomarkers of IRI-induced neutropenia, diarrhea, and IRI-based chemotherapy tumor response in Asians with lung cancer. The analysis included 577 subjects in 9 studies. The results suggest that UGT1A1*6 polymorphism is significantly associated with an increased risk of IRI-induced neutropenia and diarrhea, and UGT1A1*28 polymorphism is not an effective predictor biomarker of IRI-induced neutropenia and diarrhea. In addition, the results show that UGT1A1*6 and UGT1A1*28 polymorphisms may not affect IRI-based chemotherapy tumor response.

The two meta-analyses published in 2017 suggest UGT1A1*6 polymorphisms correlate with an increased risk of IRI-induced neutropenia in cancer patients; however, there are limitations to this finding. Both studies have relatively low sample sizes compared to other meta-analyses. Also, many of the studies included are lower quality including retrospective and nonrandomized designs and are not considered effective. Higher quality studies are needed to substantiate this finding.

In a 2020 retrospective review by Chen and colleagues, the authors reported on the correlation of UGT1A1 gene polymorphism in a population of Guangxi Zhuang individuals with metastatic colorectal cancer who were receiving irinotecan-based chemotherapy. With a total of 86 individuals enrolled, the authors noted that the distribution of UGT1A1*28 and UGT1A1*6 gene polymorphisms in this population differed from what has been reported in the European and Chinese Han populations. The authors noted no significant association between UGT1A1 gene polymorphism and the therapeutic efficacy of irinotecan.

Dihydropyrimidine Dehydrogenase (DPYD)

Deenen and others conducted a retrospective nested case control study of 45 subjects with colorectal cancer (CRC) who had capecitabine-related toxicity and 100 randomly selected controls (2011). All subjects were selected from a sample of 568 individuals with previously untreated CRC enrolled in the CAIRO2 trial and were tested for DPYD genetic variants. From this data, genotype frequencies of polymorphisms were calculated. The authors reported that four variant alleles (IVS14+1G>A, 1236G>A, 2846G>A, and 2194G>A) were significantly associated with severe diarrhea when carriers were treated with capecitabine-based chemotherapy. Furthermore, heterozygous carriers of IVS14+1G>A were significantly at risk for developing grade 3 to 4 toxicity. No association with overall survival was noted for any specific allele. While this study did identify a role of several alleles in capecitabine-related toxicity, no data regarding outcomes benefit of screening for DPYD genotypes was provided. Further research is warranted with high level/high quality recommendations for use.

Phenytoin

Phenytoin is a commonly prescribed antiepileptic drug for generalized tonic clonic and partial seizures. With its narrow therapeutic range, there are numerous challenges in clinical practice. The main enzymes responsible for metabolic elimination of phenytoin are CYP2C9 and CYP2C19. In a 2018 systematic review and meta-analysis,

Historical

Federal and State law, as well as contract language including definitions and specific coverage provisions/exclusions, and Medical Policy take precedence over Clinical UM Guidelines and must be considered first in determining eligibility for coverage. The member's contract benefits in effect on the date that services are rendered must be used. Clinical UM Guidelines, which address medical efficacy, should be considered before utilizing medical opinion in adjudication. Medical technology is constantly evolving, and we reserve the right to review and update Clinical UM Guidelines periodically. Clinical UM guidelines are used when the plan performs utilization review for the subject. Due to variances in utilization patterns, each plan may choose whether or not to adopt a particular Clinical UM Guideline. To determine if review is required for this Clinical UM Guideline, please contact the customer service number on the back of the member's card.

No part of this publication may be reproduced, stored in a retrieval system or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from the health plan.

© CPT Only – American Medical Association

Medicaid managed care administered by Amerigroup Corporation, an independent company.

Liao and colleagues quantitatively estimated the effect of different CYP2C9/2C19 genotypes on the maintenance dose of phenytoin. A total of six studies with 993 participants were included. The studies consisted of an Asian population with data from researchers in Japan, Korea, Taiwan, and Southern India. Due to lack of heterogeneity in the studies, random-effects model was applied. Meta-analysis showed that no significant phenytoin dose adjustments were required for participants bearing the CYP2C9EM/CYP2C19IM genotype. The CYP2C9EM/CYP2C19PM genotype required an 11% (p=0.02; 95% CI, –0.20 to –0.02) lower maintenance dose of phenytoin than the CYP2C9EM/CYP2C19EM genotype. Due to lack of heterogeneity across the studies and a small number of studies in the meta-analysis, the tests are considered not clinically appropriate with a lack of high-quality studies.

Tamoxifen

The use of CYP2D6 genotyping testing to determine drug metabolizer status and predict breast cancer-related outcomes in individuals with breast cancer treated with tamoxifen has been a topic of significant debate for the past few years. Several large scale RCTs have been published addressing this issue. Abraham and colleagues reported the results of their study, which used data from the Studies of Epidemiology and Risk Factors in Cancer Heredity (SEARCH) study (2010). This study included 6640 subjects with invasive breast cancer, with 3155 subjects receiving tamoxifen therapy and genotyped for CYP2D6. Along with genetic data, survival data was used to calculate breast cancer specific survival (BCSS) in this population. The authors concluded that there was weak, if any, effect of CYP2D6 on BCSS in tamoxifen-treated subjects. These findings were corroborated in two separate large scale double-blind RCTs published in 2012. The first was a study using subjects enrolled in the Arimidex, Tamoxifen, Alone or in Combination (ATAC) study, which involved 1203 women genotyped for CYP2D6 and 1209 genotyped for UGT2B7 (Rae, 2012). No statistically significant associations were observed between CYP2D6 and disease recurrence. Additionally, a near-null association was noted between UGT2B7 and recurrence in tamoxifen treated subjects. The second study, by Regan et al. included subjects enrolled in the Breast International Group (BIG) 1-98 study, which involved 1243 subjects with breast cancer treated with tamoxifen (2012). As with the previously mentioned studies, the BIG study authors found no association between CYP2D6 metabolism phenotype and breast cancer-free interval.

The results of these trials have been somewhat controversial, with several editorials pointing out significant methodological flaws. Kelly and Pritchard commented that the power of these studies was insufficient to show a positive association between CYP2D6 and outcomes in subjects taking tamoxifen (2012). Pharoah and others pointed out that both the Rae and Regan studies were not properly randomized to control for the exposure of interest (2012). Both these studies were randomized for treatment regimen, not CYP2D6 genotype. They continue, criticizing both studies for the use of tumor samples to determine genotype, and the Regan study in particular for failure to report consistency of genotype quality and Hardy-Weinberg equilibrium (HWE) data. The Rae article did not provide data on power calculation, and Pharoah indicates that the study was probably underpowered. Nakamura and colleagues also point out the inadequacies in the Regan study in relation to HWE issues, and insufficient data provided with regard to genotype data quality (2012). Finally, as Pharoah pointed out, the use of tumor samples to determine genotype is flawed. They comment that CYP2D6 is frequently deleted in some common cancers, leading

Historical

Federal and State law, as well as contract language including definitions and specific coverage provisions/exclusions, and Medical Policy take precedence over Clinical UM Guidelines and must be considered first in determining eligibility for coverage. The member's contract benefits in effect on the date that services are rendered must be used. Clinical UM Guidelines, which address medical efficacy, should be considered before utilizing medical opinion in adjudication. Medical technology is constantly evolving, and we reserve the right to review and update Clinical UM Guidelines periodically. Clinical UM guidelines are used when the plan performs utilization review for the subject. Due to variances in utilization patterns, each plan may choose whether or not to adopt a particular Clinical UM Guideline. To determine if review is required for this Clinical UM Guideline, please contact the customer service number on the back of the member's card.

No part of this publication may be reproduced, stored in a retrieval system or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from the health plan.

© CPT Only – American Medical Association

Medicaid managed care administered by Amerigroup Corporation, an independent company.

to misclassification of the subject's actual phenotype, as the unaffected cells in their body may contain a different genotype than their cancer cells.

The results of these studies indicate that the use of CYP2D6 genotyping does not provide data that significantly affects breast cancer-related health outcomes. However, as the editorials accompanying these studies indicate, there are many flaws in these trials that leave important questions unanswered. There is a lack of sufficient high level recommendations in fully assessing the use of genotyping in this population of individuals.

Other Tests

Testing for genetic polymorphisms has also been proposed for a wide array of other drugs, involving many different conditions and enzymes. At this time, the available literature addressing such testing does not support use in accordance with generally accepted standards of clinical practice. Outcomes that require further attention include major adverse events, utilization of health resources, and time to clinically significant changes in condition using appropriate and validated measures.

Summary

While the potential of pharmacogenomics is intriguing for many clinical applications, it is imperative to establish evidence-based guidelines for healthcare professionals delineating the most effective courses of action based on such genotype testing results. Critical elements of assessing the effectiveness of such genetic tests include: (1) analytic (diagnostic) validity; (2) clinical validity; and (3) clinical utility. Analytic validity measures the technical performance of the test, in terms of accurately identifying the genetic markers to be measured. Clinical validity measures the strength of association between genetic test results and clinical parameters such as dose, therapeutic efficacy, or adverse events. Clinical utility, the ultimate goal of genetic testing, measures the ability of the test to improve clinical outcomes, such as whether prescribing or dosing based on information from genetic testing improves therapeutic efficacy or adverse event rate as compared with treatment without genetic testing.

Therefore, when considering whether or not a test to determine drug metabolizer status is appropriate in the treatment of individuals prescribed certain medications, specific issues need to be evaluated, including:

- A specific mutation, or set of mutations, has been established in the scientific literature to be reliably associated with drug metabolism status; AND
- A biochemical or other non-genetic test is identified but the results are indeterminate, or the genetic status cannot be identified through such biochemical or other non-genetic testing; AND
- The results of the genetic test could impact the medical management of the individual with a resulting improvement in health outcomes.

Federal and State law, as well as contract language including definitions and specific coverage provisions/exclusions, and Medical Policy take precedence over Clinical UM Guidelines and must be considered first in determining eligibility for coverage. The member's contract benefits in effect on the date that services are rendered must be used. Clinical UM Guidelines, which address medical efficacy, should be considered before utilizing medical opinion in adjudication. Medical technology is constantly evolving, and we reserve the right to review and update Clinical UM Guidelines periodically. Clinical UM guidelines are used when the plan performs utilization review for the subject. Due to variances in utilization patterns, each plan may choose whether or not to adopt a particular Clinical UM Guideline. To determine if review is required for this Clinical UM Guideline, please contact the customer service number on the back of the member's card.

No part of this publication may be reproduced, stored in a retrieval system or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from the health plan.

© CPT Only – American Medical Association

Medicaid managed care administered by Amerigroup Corporation, an independent company.

The FDA has added language to the labels of many approved drugs to include pharmacogenomic information; however, evidence supporting pharmacogenomic biomarker testing varies widely. Wang and colleagues (2014) published a study evaluating evidence supporting pharmacogenomic biomarker testing in FDA drug labels. The study found that only a minority of labels cited evidence of clinical utility.

While current evidence regarding the use of genotyping tests for the determination of drug metabolizer status indicates that available testing methods may accurately identify genetic variations in an individual, in many cases such testing is not considered in accordance with generally accepted standards of medical practice. To support clinical utility, data should demonstrate that such testing, and the clinical decisions made based on the testing, result in a significant impact on health outcomes (including enhanced clinical effectiveness or in decreased short-term or long-term serious adverse events as compared to no testing).

Definitions

Cytochrome P450: Refers to a family of 60 different enzymes involved in drug and toxin metabolism.

Genotype testing: Determining the DNA sequence in genes.

Metabolize: Refers to breaking down a drug so that it is no longer clinically active.

Polymorphisms: Refers to genetic variation between individuals resulting in differences in gene expression, in this case differing activity of various enzymes.

Uridine diphosphate glucuronosyltransferase 1A1 (UGT1A1): An enzyme that is involved in drug metabolism.

Vitamin K epoxide reductase subunit C1 (VKORC1): An enzyme involved with the metabolism of vitamin K; its C1 subunit (VKORC1) is the target of the anticoagulant warfarin.

Warfarin: A commonly prescribed anticoagulant (that is, blood thinner).

References

Peer Reviewed Publications:

1. Abraham JE, Maranian MJ, Driver KE, et al. CYP2D6 gene variants: association with breast cancer specific survival in a cohort of breast cancer patients from the United Kingdom treated with adjuvant tamoxifen. Breast Cancer Res. 2010; 12(4):R64.
2. Aithal GP, Day CP, Kesteven PJ, Daly AK. Association of polymorphisms in the cytochrome P450 CYP2C9 with warfarin dose requirement and risk of bleeding complications. Lancet. 1999; 353(9154):717-719.

Federal and State law, as well as contract language including definitions and specific coverage provisions/exclusions, and Medical Policy take precedence over Clinical UM Guidelines and must be considered first in determining eligibility for coverage. The member's contract benefits in effect on the date that services are rendered must be used. Clinical UM Guidelines, which address medical efficacy, should be considered before utilizing medical opinion in adjudication. Medical technology is constantly evolving, and we reserve the right to review and update Clinical UM Guidelines periodically. Clinical UM guidelines are used when the plan performs utilization review for the subject. Due to variances in utilization patterns, each plan may choose whether or not to adopt a particular Clinical UM Guideline. To determine if review is required for this Clinical UM Guideline, please contact the customer service number on the back of the member's card.

No part of this publication may be reproduced, stored in a retrieval system or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from the health plan.

© CPT Only – American Medical Association

Medicaid managed care administered by Amerigroup Corporation, an independent company.

Historical

3. Anderson JL, Horne BD, Stevens SM, et al.; Couma-Gen Investigators. Randomized trial of genotype-guided versus standard warfarin dosing in patients initiating oral anticoagulation. Circulation. 2007; 116(22):2563-2570.
4. Artigalás O, Vanni T, Hutz MH, et al. Influence of CYP19A1 polymorphisms on the treatment of breast cancer with aromatase inhibitors: a systematic review and meta-analysis. BMC Med. 2015; 13:139.
5. Bauer T, Bouman HJ, van Werkum JW, et al. Impact of CYP2C19 variant genotypes on clinical efficacy of antiplatelet treatment with clopidogrel: systematic review and meta-analysis. BMJ. 2011; 343:d4588.
6. 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; 14(2):176-181.
7. Burmester JK, Berg RL, Yale SH, et al. A randomized controlled trial of genotype-based Coumadin initiation. Genet Med. 2011; 13(6):509-518.
8. Caldwell MD, Berg RL, Zhang KQ, et al. Evaluation of genetic factors for warfarin dose prediction. Clin Med Res. 2007; 5(1):8-16.
9. 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; 83(3):460-470.
10. Carlquist JF, Horne BD, Muhlestein JB, et al. Genotypes of the cytochrome p450 isoform, CYP2C9, and the vitamin K epoxide reductase complex subunit 1 conjointly determine stable warfarin dose: a prospective study. J Thromb Thrombolysis. 2006; 22(3):191-197.
11. Chen P, Lin JJ, Lu CS, et al. Carbamazepine-induced toxic effects and HLA-B*1502 screening in Taiwan. N Engl J Med. 2011; 364(12):1126-1133.
12. Chen S, Hua L, Feng C, et al. Correlation between UGT1A1 gene polymorphism and irinotecan chemotherapy in metastatic colorectal cancer: a study from Guangxi Zhuang. BMC Gastroenterol. 2020; 20(1):96.
13. Chen X, Liu L, Guo Z, et al. UGT1A1 polymorphisms with irinotecan-induced toxicities and treatment outcome in Asians with lung cancer: a meta-analysis. Cancer Chemother Pharmacol. 2017; 79(6):1109-1117.
14. Chouchi M, Kaabachi W, Tizaoui K, et al. The HLA-B*15:02 polymorphism and Tegretol®-induced serious cutaneous reactions in epilepsy: An updated systematic review and meta-analysis. Rev Neurol (Paris). 2018; 174(5):278-291.
15. Claassens DMF, Vos GJA, Bergmeijer TO, et al. A genotype-guided strategy for oral $P2Y_{12}$ inhibitors in primary PCI. N Engl J Med. 2019; 381(17):1621-1631.
16. Collet JP, Hulot JS, Pena A, et al. Cytochrome P450 2C19 polymorphism in young patients treated with clopidogrel after myocardial infarction: a cohort study. Lancet. 2009; 373(9660):309-317.
17. Cui G, Zhang S, Zou J, et al. P2Y12 receptor gene polymorphism and the risk of resistance to clopidogrel: a meta-analysis and review of the literature. Adv Clin Exp Med. 2017; 26(2):343-349.
18. Doll JA, Neely ML, Roe MT, et al. TRILOGY ACS Investigators. Impact of CYP2C19 metabolizer status on patients with ACS treated with prasugrel versus clopidogrel. J Am Coll Cardiol. 2016; 67(8):936-947.
19. 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. JAMA. 2017; 318(12):1115-1124.
20. Gage BF, Eby C, Milligan PE, et al. Use of pharmacogenomics and clinical factors to predict the maintenance of dose of warfarin. Thromb Haemost. 2004; 91(1):86-94.

Federal and State law, as well as contract language including definitions and specific coverage provisions/exclusions, and Medical Policy take precedence over Clinical UM Guidelines and must be considered first in determining eligibility for coverage. The member's contract benefits in effect on the date that services are rendered must be used. Clinical UM Guidelines, which address medical efficacy, should be considered before utilizing medical opinion in adjudication. Medical technology is constantly evolving, and we reserve the right to review and update Clinical UM Guidelines periodically. Clinical UM guidelines are used when the plan performs utilization review for the subject. Due to variances in utilization patterns, each plan may choose whether or not to adopt a particular Clinical UM Guideline. To determine if review is required for this Clinical UM Guideline, please contact the customer service number on the back of the member's card.

No part of this publication may be reproduced, stored in a retrieval system or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from the health plan.

© CPT Only – American Medical Association

Medicaid managed care administered by Amerigroup Corporation, an independent company.

Historical

21. Gardin A, Ufer M, Legangneux E, et al. Effect of fluconazole coadministration and CYP2C9 genetic polymorphism on siponimod pharmacokinetics in healthy subjects. Clin Pharmacokinet. 2019; 58(3):349-361.
22. Goetz MP, Rae JM, Suman VJ, et al. Pharmacogenetics of tamoxifen biotransformation is associated with clinical outcomes of efficacy and hot flashes. J Clin Oncol. 2005; 23(36):9312-9318.
23. Han JY, Lim HS, Shin ES, et al. Comprehensive analysis of UGT1A polymorphisms predictive for pharmacokinetics and treatment outcome in patients with non-small-cell lung cancer treated with irinotecan and cisplatin. J Clin Oncol. 2006; 24(15):2237-2244.
24. He XJ, Jian LY, He XL, et al. Association of ABCB1, CYP3A4, EPHX1, FAS, SCN1A, MICA, and BAG6 polymorphisms with the risk of carbamazepine-induced Stevens-Johnson syndrome/toxic epidermal necrolysis in Chinese Han patients with epilepsy. Epilepsia. 2014; 55(8):1301-1306.
25. Herman D, Peternel P, Stegnar M, et al. The influence of sequence variations in factor VII, gamma-glutamyl carboxylase and vitamin K epoxide reductase complex genes on warfarin dose requirement. Thromb Haemost. 2006; 95(5):782-787.
26. Hetherington S, Hughes AR, Mosteller M, et al. Genetic variations in HLA-B region and hypersensitivity reactions to abacavir. Lancet. 2002; 359(9312):1121-1122.
27. Hetherington S, McGuirk S, Powell G, et al. Hypersensitivity reactions during therapy with the nucleoside reverse transcriptase inhibitor abacavir. Clin Ther. 2001; 23(10):1603-1614.
28. Higashi MK, Veenstra DL, Kondo LM, et al. Association between CYP2C9 genetic variants and anticoagulation-related outcomes during warfarin therapy. JAMA. 2002; 287(13):1690-1698.
29. Higgins MJ, Rae JM, Flockhart DA, et al. Pharmacogenetics of tamoxifen: who should undergo CYP2D6 genetic testing? J Natl Compr Canc Netw. 2009; 7(2):203-213.
30. Holmes MV, Perel P, Shah T, et al. CYP2C19 genotype clopidogrel metabolism, platelet function, and cardiovascular events: a systematic review and meta-analysis. JAMA. 2011; 206 (24):2704-2714.
31. Hou Q, Li S, Li L, et al. Association between SLCO1B1 gene T521C polymorphism and statin-related myopathy risk: a meta-analysis of case-control studies. Medicine (Baltimore). 2015; 94(37):e1268.
32. Hung SI, Chung WH, Jee SH, et al. Genetic susceptibility to carbamazepine-induced cutaneous adverse drug reactions. Pharmacogenet Genomics. 2006; 16(4):297-306.
33. Ingelman-Sundberg M. Genetic polymorphisms of cytochrome P450 2D6 (CYP2D6): clinical consequences, evolutionary aspects and functional diversity. Pharmacogenomics J. 2005; 5(1):6-13.
34. Innocenti F, Undevia SD, Iyer L, et al. Genetic variants in the UDP-glucuronosyltransferase 1A1 gene predict the risk of severe neutropenia of irinotecan. J Clin Oncol. 2004; 22(8):1382-1388.
35. International Warfarin Pharmocogenetics Consortium. Estimation of the warfarin dose with clinical and pharmacogenetic data. N Engl J Med. 2009; 360(8):753-764.
36. Ismail R, Teh LK. The relevance of CYP2D6 genetic polymorphism on chronic metoprolol therapy in cardiovascular patients. J Clin Pharm Ther. 2006; 31(1):99-109.
37. Jin B, Ni HC, Shen W, et al. Cytochrome P450 2C19 polymorphism is associated with poor clinical outcomes in coronary artery disease patients treated with clopidogrel. Mol Biol Rep. 2011; 38(3):1697-1702.
38. Joffe HV, Xu R, Johnson FB, et al. Warfarin dosing and cytochrome P450 2C9 polymorphisms. Thromb Haemost. 2004; 91(6):1123-1128.

Federal and State law, as well as contract language including definitions and specific coverage provisions/exclusions, and Medical Policy take precedence over Clinical UM Guidelines and must be considered first in determining eligibility for coverage. The member's contract benefits in effect on the date that services are rendered must be used. Clinical UM Guidelines, which address medical efficacy, should be considered before utilizing medical opinion in adjudication. Medical technology is constantly evolving, and we reserve the right to review and update Clinical UM Guidelines periodically. Clinical UM guidelines are used when the plan performs utilization review for the subject. Due to variances in utilization patterns, each plan may choose whether or not to adopt a particular Clinical UM Guideline. To determine if review is required for this Clinical UM Guideline, please contact the customer service number on the back of the member's card.

No part of this publication may be reproduced, stored in a retrieval system or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from the health plan.

© CPT Only – American Medical Association

Medicaid managed care administered by Amerigroup Corporation, an independent company.

Historical

39. Kappos L, Bar-Or A, Cree BAC, et al. Siponimod versus placebo in secondary progressive multiple sclerosis (EXPAND): a double-blind, randomised, phase 3 study. Lancet. 2018; 391(10127):1263-1273.
40. Ke CH, Chung WH, Tain YL, et al. Utility of human leukocyte antigen-B*58: 01 genotyping and patient outcomes. Pharmacogenet Genomics. 2019; 29(1):1-8.
41. Kelly CM, Pritchard KI. CYP2D6 genotype as a marker for benefit of adjuvant tamoxifen in postmenopausal women: lessons learned. J Natl Cancer Inst. 2012; 104(6):427-428.
42. Kimmel SE, French B, Kasner SE, et al.; COAG Investigators. A pharmacogenetic versus a clinical algorithm for warfarin dosing. N Engl J Med. 2013; 369(24):2283-2293.
43. Kirchheiner J, Brockmoller J. Clinical consequences of cytochrome P450 2C9 polymorphisms. Clin Pharmacol Ther. 2005; 77(1):1-16.
44. Ko TM, Tsai CY, Chen SY, et al. Use of HLA-B*58:01 genotyping to prevent allopurinol induced severe cutaneous adverse reactions in Taiwan: national prospective cohort study. BMJ. 2015; 351:h4848.
45. Lenz O, Vijgen L, Berke JM, et al. Virologic response and characterisation of HCV genotype 2-6 in patients receiving TMC435 monotherapy (study TMC435-C202). J Hepatol. 2013; 58(3):445-451.
46. Liao K, Liu Y, Ai CZ, et al. The association between CYP2C9/2C19 polymorphisms and phenytoin maintenance doses in Asian epileptic patients: a systematic review and meta-analysis. Int J Clin Pharmacol Ther. 2018; 56(7):337-346.
47. Low DE, Nurul-Aain AF, Tan WC, et al. HLA-B*58: 01 association in allopurinol-induced severe cutaneous adverse reactions: the implication of ethnicity and clinical phenotypes in multiethnic Malaysia. Pharmacogenet Genomics. 2020; 30(7):153-160.
48. Lukina E, Watman N, Arreguin EA, et al. A phase 2 study of eliglustat tartrate (Genz-112638), an oral substrate reduction therapy for Gaucher disease type 1. Blood. 2010; 116(6):893-899.
49. Mallal S, Nolan D, Witt C, et al. Association between presence of HLA-B*5701, HLA-DR7, and HLA-DQ3 and hypersensitivity to HIV-1 reverse-transcriptase inhibitor abacavir. Lancet. 2002; 359(9308):727-732.
50. Mallal S, Phillips E, Carosi G, et al.; PREDICT-1 Study Team. HLA-B*5701 screening for hypersensitivity to abacavir. N Engl J Med. 2008; 358(6):568-579.
51. Mao L, Jian C, Changzhi L, et al. Cytochrome CYP2C19 polymorphism and risk of adverse clinical events in clopidogrel-treated patients: a meta-analysis based on 23,035 subjects. Arch Cardiovasc Dis. 2013; 106(10):517-527.
52. Margaglione M, Colaizzo D, D'Andrea G, et al. Genetic modulation of oral anticoagulation with warfarin. Thromb Haemost. 2000; 84(5):775-778.
53. McCormack M, Alfirevic A, Bourgeois S, et al. HLA-A*3101 and carbamazepine-induced hypersensitivity reactions in Europeans. N Engl J Med. 2011; 364(12):1134-1143.
54. Mega JL, Close SL, Wiviott SD, et al. Cytochrome P-450 polymorphisms and response to clopidogrel. N Engl J Med. 2009; 360(4):354-362.
55. Mega JL, Hochholzer W, Frelinger AL 3rd, et al. Dosing clopidogrel based on CYP2C19 genotype and the effect on platelet reactivity in patients with stable cardiovascular disease. JAMA. 2011; 306(20):2221-2228.
56. Mega JL, Simon T, Collet JP, 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; 304(16):1821-1830.

Federal and State law, as well as contract language including definitions and specific coverage provisions/exclusions, and Medical Policy take precedence over Clinical UM Guidelines and must be considered first in determining eligibility for coverage. The member's contract benefits in effect on the date that services are rendered must be used. Clinical UM Guidelines, which address medical efficacy, should be considered before utilizing medical opinion in adjudication. Medical technology is constantly evolving, and we reserve the right to review and update Clinical UM Guidelines periodically. Clinical UM guidelines are used when the plan performs utilization review for the subject. Due to variances in utilization patterns, each plan may choose whether or not to adopt a particular Clinical UM Guideline. To determine if review is required for this Clinical UM Guideline, please contact the customer service number on the back of the member's card.

No part of this publication may be reproduced, stored in a retrieval system or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from the health plan.

© CPT Only – American Medical Association

Medicaid managed care administered by Amerigroup Corporation, an independent company.

Historical

57. Mega JL, Walker JR, Ruff CT, et al. Genetics and the clinical response to warfarin and edoxaban: findings from the randomised, double-blind ENGAGE AF-TIMI 48 trial. Lancet. 2015; 385(9984):2280-2287.
58. Mehanna R, Hunter C, Davidson A, et al. Analysis of CYP2D6 genotype and response to tetrabenazine. Mov Disord. 2013; 28(2):210-215.
59. Millican EA, Lenzini PA, Milligan PE, et al. Genetic-based dosing in orthopedic patients beginning warfarin therapy. Blood. 2007; 110(5):1511-1515.
60. Muszkat M, Blotnik S, Elami A, et al. Warfarin metabolism and anticoagulant effect: a prospective, observational study of the impact of CYP2C9 genetic polymorphism in the presence of drug-disease and drug-drug interactions. Clin Ther. 2007; 29(3):427-437.
61. Nakamura Y, Ratain MJ, Cox NJ, et al. Re: 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; 104(16):1264.
62. Osman A, Enström C, Arbring K, et al. Main haplotypes and mutational analysis of vitamin K epoxide reductase (VKORC1) in a Swedish population: a retrospective analysis of case records. J Thromb Haemost. 2006; 4(8):1723-1729.
63. Palanisamy N, Danielsson A, Kokkula C, et al. Implications of baseline polymorphisms for potential resistance to NS3 protease inhibitors in Hepatitis C virus genotypes 1a, 2b and 3a. Antiviral Res. 2013; 99(1):12-17.
64. Pan Y, Chen W, Xu Y, et al. Genetic polymorphisms and clopidogrel efficacy for acute ischemic stroke or transient ischemic attack: a systematic review and meta-analysis. Circulation. 2017; 135(1):21-33.
65. Paré G, Mehta SR, Yusuf S, et al. Effects of CYP2C19 genotype on outcomes of clopidogrel treatment. N Engl J Med. 2010; 363(18):1704-1714.
66. Peterschmitt MJ, Burke A, Blankstein L, et al. Safety, tolerability, and pharmacokinetics of eliglustat tartrate (Genz-112638) after single doses, multiple doses, and food in healthy volunteers. J Clin Pharmacol. 2011; 51(5):695-705.
67. Pharoah PD, Abraham J, Caldas C. Re: CYP2D6 genotype and tamoxifen response in postmenopausal women with endocrine-responsive breast cancer: the Breast International Group 1-98 trial and Re: CYP2D6 and UGT2B7 genotype and risk of recurrence in tamoxifen-treated breast cancer patients. J Natl Cancer Inst. 2012; 104(16):1263-1264.
68. Pirmohamed M, Burnside G, Eriksson N, et al.; EU-PACT Group. A randomized trial of genotype-guided dosing of warfarin. N Engl J Med. 2013; 369(24):2294-2303.
69. Quiros-Roldan E, Gardini G, Properzi M, et al. Abacavir adverse reactions related with HLA-B*57: 01 haplotype in a large cohort of patients infected with HIV. Pharmacogenet Genomics. 2020; 30(8):167-174.
70. Rae JM, Drury S, Hayes DF, et al.; ATAC trialists. CYP2D6 and UGT2B7 genotype and risk of recurrence in tamoxifen-treated breast cancer patients. J Natl Cancer Inst. 2012; 104(6):452-460.
71. Rauch A, Nolan D, Thurnheer C, et al.; Swiss HIV Cohort Study. Refining abacavir hypersensitivity diagnoses using a structured clinical assessment and genetic testing in the Swiss HIV Cohort Study. Antivir Ther. 2008; 13(8):1019-1028.
72. Regan MM, Leyland-Jones B, Bouzyk M, et al.; Breast International Group (BIG) 1-98 Collaborative Group. 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; 104(6):441-451.

Federal and State law, as well as contract language including definitions and specific coverage provisions/exclusions, and Medical Policy take precedence over Clinical UM Guidelines and must be considered first in determining eligibility for coverage. The member's contract benefits in effect on the date that services are rendered must be used. Clinical UM Guidelines, which address medical efficacy, should be considered before utilizing medical opinion in adjudication. Medical technology is constantly evolving, and we reserve the right to review and update Clinical UM Guidelines periodically. Clinical UM guidelines are used when the plan performs utilization review for the subject. Due to variances in utilization patterns, each plan may choose whether or not to adopt a particular Clinical UM Guideline. To determine if review is required for this Clinical UM Guideline, please contact the customer service number on the back of the member's card.

No part of this publication may be reproduced, stored in a retrieval system or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from the health plan.

© CPT Only – American Medical Association

Medicaid managed care administered by Amerigroup Corporation, an independent company.

Historical

73. Rojas L, Neumann I, Herrero MJ, et al. Effect of CYP3A5*3 on kidney transplant recipients treated with tacrolimus: a systematic review and meta-analysis of observational studies. Pharmacogenomics J. 2015; 15(1):38-48.
74. Saag M, Balu R, Phillips E, et al.; Study of hypersensitivity to abacavir and pharmacogenetic evaluation study team. High sensitivity of human leukocyte antigen-b*5701 as a marker for immunologically confirmed abacavir hypersensitivity in white and black patients. Clin Infect Dis. 2008; 46(7):1111-1118.
75. 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; 7(2):97-104.
76. Schelleman H, Chen Z, Kealey C, et al. Warfarin response and vitamin K epoxide reductase complex 1 in African Americans and Caucasians. Clin Pharmacol Ther. 2007; 81(5):742-747.
77. Schroth W, Goetz MP, Hamann U, et al. Association between CYP2D6 polymorphisms and outcomes among women with early stage breast cancer treated with tamoxifen. JAMA. 2009; 302(13):1429-1436.
78. Sconce EA, Khan TI, Wynne HA, 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; 106(7):2329-2333.
79. Shams ME, Arneth B, Hiemke C, et al. CYP2D6 polymorphism and clinical effect of the antidepressant venlafaxine. J Clin Pharm Ther. 2006; 31(5):493-502.
80. Sibbing D, Koch W, Gebhard D, et al. Cytochrome 2C19*17 allelic variant, platelet aggregation, bleeding events, and stent thrombosis in clopidogrel-treated patients with coronary stent placement. Circulation. 2010; 121(4):512-518.
81. Sibbing D, Stegherr J, Latz W, et al. Cytochrome P450 2C19 loss-of-function polymorphism and stent thrombosis following percutaneous coronary intervention. Eur Heart J. 2009; 30(8):916-922.
82. Simon T, Steg PG, Becquemont L, et al. Effect of paraoxonase-1 polymorphism on clinical outcomes in patients treated with clopidogrel after an acute myocardial infarction. Clin Pharmacol Ther. 2011; 90(4):561-567.
83. Simon T, Verstuyft C, Mary-Krause M, et al.; French Registry of Acute ST-Elevation and Non-ST-Elevation Myocardial Infarction (FAST-MI) Investigators. Genetic determinants of response to clopidogrel and cardiovascular events. N Engl J Med. 2009; 360(4):363-375.
84. Sorich MJ, Rowland A, McKinnon RA, Wiese MD. CYP2C19 genotype has a greater effect on adverse cardiovascular outcomes following percutaneous coronary intervention and in Asian populations treated with clopidogrel: a meta-analysis. Circ Cardiovasc Genet. 2014; 7(6):895-902.
85. Swaisland HC, Cantarini MV, Fuhr R, Holt A. Exploring the relationship between expression of cytochrome P450 enzymes and gefitinib pharmacokinetics. Clin Pharmacokinet. 2006; 45(6):633-644.
86. Syn NL, Wong AL, Lee SC, et al. Genotype-guided versus traditional clinical dosing of warfarin in patients of Asian ancestry: a randomized controlled trial. BMC Med. 2018; 16(1):104.
87. Tan SH, Lee SC, Goh BC, Wong J. Pharmacogenetics in breast cancer therapy. Clin Cancer Res. 2008; 14(24):8027-8041.
88. Tang W, Shi QP, Ding F, et al. Impact of VKORC1 gene polymorphisms on warfarin maintenance dosage: A novel systematic review and meta-analysis of 53 studies. Int J Clin Pharmacol Ther. 2017; 55(4):304-321.

Federal and State law, as well as contract language including definitions and specific coverage provisions/exclusions, and Medical Policy take precedence over Clinical UM Guidelines and must be considered first in determining eligibility for coverage. The member's contract benefits in effect on the date that services are rendered must be used. Clinical UM Guidelines, which address medical efficacy, should be considered before utilizing medical opinion in adjudication. Medical technology is constantly evolving, and we reserve the right to review and update Clinical UM Guidelines periodically. Clinical UM guidelines are used when the plan performs utilization review for the subject. Due to variances in utilization patterns, each plan may choose whether or not to adopt a particular Clinical UM Guideline. To determine if review is required for this Clinical UM Guideline, please contact the customer service number on the back of the member's card.

No part of this publication may be reproduced, stored in a retrieval system or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from the health plan.

© CPT Only – American Medical Association

Medicaid managed care administered by Amerigroup Corporation, an independent company.

Historical

89. Tran A, Jullien V, Alexandre J, et al. Pharmacokinetics and toxicity of docetaxel: role of CYP3A, MDR1, and GST polymorphisms. Clin Pharmacol Ther. 2006; 79(6):570-580.
90. Veal GJ, Cole M, Chinnaswamy G, et al. Cyclophosphamide pharmacokinetics and pharmacogenetics in children with B-cell non-Hodgkin's lymphoma. Eur J Cancer. 2016; 55:56-64.
91. Verhoef TI, Ragia G, de Boer A, et al.; EU-PACT Group. A randomized trial of genotype-guided dosing of acenocoumarol and phenprocoumon. N Engl J Med. 2013; 369(24):2304-2312.
92. Wadelius M, Chen LY, Downes K, et al. Common VKORC1 and GGCX polymorphisms associated with warfarin dose. Pharmacogenomics J. 2005; 5(4):262-270.
93. 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; 174(12):1938-1944.
94. Wen MS, Chang KC, Lee TH, et al. Pharmacogenetic dosing of warfarin in the Han-Chinese population: a randomized trial. Pharmacogenomics. 2017; 18(3):245-253.
95. Wilkinson GR. Drug metabolism and variability among patients in drug response. N Engl J Med. 2005; 352 (21):2211-2221.
96. Wu R, Cheng YJ, Zhu LL, et al. Impact of HLA-B*58:01 allele and allopurinol-induced cutaneous adverse drug reactions: evidence from 21 pharmacogenetic studies. Oncotarget. 2016; 7(49):81870-81879.
97. Zhang J, Tian L, Huang J, et al. Cytochrome P450 2C9 gene polymorphism and warfarin maintenance dosage in pediatric patients: A systematic review and meta-analysis. Cardiovasc Ther. 2017a; 35(1):26-32.
98. Zhang X, Yin JF, Zhang J, et al. UGT1A1*6 polymorphisms are correlated with irinotecan-induced neutropenia: a systematic review and meta-analysis. Cancer Chemother Pharmacol. 2017b; 80(1):135-149.
99. Zhu Y, Shennan M, Reynolds KK, et al. Estimation of warfarin maintenance dose based on VKORC1 (-1639 G>A) and CYP2C9 genotypes. Clin Chem. 2007; 53(7):1199-1205.

Government Agency, Medical Society, and Other Authoritative Publications:

1. Agency for Healthcare Research and Quality. Technology Assessment: Reviews of selected pharmacogenetic tests for non-cancer and cancer conditions. November 12, 2008. Available at: http://www.cms.gov/medicare-coverage-database/details/technology-assessments-details.aspx?TAId=61&bc=BAAgAAAAAAAA&. Accessed on February 18, 2022.
2. American College of Rheumatology. Guidelines for the management of gout. 2020. Available at: https://www.rheumatology.org/Portals/0/Files/Gout-Guideline-Final-2020.pdf. Accessed on February 18, 2022.
3. Centers for Medicare and Medicaid Services National Coverage Determination for Pharmacogenomic Testing for Warfarin Response. NCD #90.1. Effective August 3, 2009.
4. Cerdelga® [Product Information], Waterford, Ireland. Genzyme Corporation. August 2018. Available at: http://www.cerdelga.com/pdf/cerdelga_prescribing_information.pdf. Accessed on February 18, 2022.
5. Department of Health and Human Services. Guidelines for the use of antiretroviral agents in adults and adolescents with HIV. December 2019. Available at: https://clinicalinfo.hiv.gov/sites/default/files/guidelines/documents/AdultandAdolescentGL.pdf. Accessed on February 18, 2022.

Historical

Federal and State law, as well as contract language including definitions and specific coverage provisions/exclusions, and Medical Policy take precedence over Clinical UM Guidelines and must be considered first in determining eligibility for coverage. The member's contract benefits in effect on the date that services are rendered must be used. Clinical UM Guidelines, which address medical efficacy, should be considered before utilizing medical opinion in adjudication. Medical technology is constantly evolving, and we reserve the right to review and update Clinical UM Guidelines periodically. Clinical UM guidelines are used when the plan performs utilization review for the subject. Due to variances in utilization patterns, each plan may choose whether or not to adopt a particular Clinical UM Guideline. To determine if review is required for this Clinical UM Guideline, please contact the customer service number on the back of the member's card.

No part of this publication may be reproduced, stored in a retrieval system or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from the health plan.

© CPT Only – American Medical Association

Medicaid managed care administered by Amerigroup Corporation, an independent company.

6. Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group. Recommendations from the EGAPP Working Group: can UGT1A1 genotyping reduce morbidity and mortality in patients with metastatic colorectal cancer treated with irinotecan? Genet Med. 2009; 11(1):15-20.
7. Flockhart DA, O'Kane D, Williams MS, 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; 10(2):139-150.
8. Mayzent® [Product Information], East Hanover, NJ. Novartis Pharmaceuticals Corp. August 2021. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/209884Orig1s006Lbledt.pdf. Accessed on February 18, 2022.
9. McClain MR, Palomaki GE, Piper M, et al. A rapid ACCE1 review of CYP2C9 and VKORC1 allele testing to inform warfarin dosing in adults at elevated risk for thrombotic events to avoid serious bleeding. February 2008. Available at: https://www.acmg.net/docs/Warfarin_Dosing.pdf. Accessed on February 18, 2022.
10. National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology™ (NCCN)© 2022 National Comprehensive Cancer Network, Inc. For additional information visit the NCCN website at: http://www.nccn.org/index.asp. Accessed on February 18, 2022.
    - Breast Cancer (V2.2022). Revised December 20, 2021.
11. Plavix® [Prescribing Information], Bridgewater, NJ. Sanofi Aventis. March 2021. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/020839s074lbl.pdf. Accessed on February 18, 2022.
12. Tegretol® [Product Information], East Hanover, NJ. Novartis Pharmaceuticals Corp. March 2018. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/016608s115_018281_s058_018927s055_020234_s047.pdf. Accessed on February 18, 2022.
13. U.S. Food and Drug Administration (FDA). Clinical Pharmacology and Biopharmaceuticals Review. June 25, 2014. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2014/205494Orig1s000ClinPharmR.pdf. Accessed on February 18, 2022.
14. Xenazine® [Product Information], Washington, DC. Prestwick Pharmaceuticals. November 2019. Available at: http://www.lundbeck.com/upload/us/files/pdf/Products/Xenazine_PI_US_EN.pdf. Accessed on February 18, 2022.
15. Ziagen® [Product Information], Research Triangle Park, NC. GlaxoSmithKlein. November 2020. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/020977s035,020978s038lbl.pdf. Accessed on February 18, 2022.
16. Zyloprim® [Product Information], East Brunswick, NJ. Casper Pharma LLC. December 2018. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/016084s044lbl.pdf. Accessed on February 18, 2022.

Index

Federal and State law, as well as contract language including definitions and specific coverage provisions/exclusions, and Medical Policy take precedence over Clinical UM Guidelines and must be considered first in determining eligibility for coverage. The member's contract benefits in effect on the date that services are rendered must be used. Clinical UM Guidelines, which address medical efficacy, should be considered before utilizing medical opinion in adjudication. Medical technology is constantly evolving, and we reserve the right to review and update Clinical UM Guidelines periodically. Clinical UM guidelines are used when the plan performs utilization review for the subject. Due to variances in utilization patterns, each plan may choose whether or not to adopt a particular Clinical UM Guideline. To determine if review is required for this Clinical UM Guideline, please contact the customer service number on the back of the member's card.

No part of this publication may be reproduced, stored in a retrieval system or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from the health plan.

© CPT Only – American Medical Association

Medicaid managed care administered by Amerigroup Corporation, an independent company.

Historical

Adrucil®
Allopurinol
AmpliChip™ Cytochrome P450 (CYP450) Genotype Test
Camptosar®
Carac®
Carbatrol®
Coumadin®
Cytochrome P450 (CYP450)
Cytochrome P450 2C9 (CYP2C9)
Dilantin®
Efudex®
Equetro®
Fluoroplex®
Invader®
Jantoven®
Mayzent
Nolvadex®
Plavix®
Polymorphisms, Drug Testing
Tegretol®Verigene® Warfarin Metabolism Nucleic Acid Test
Vitamin K Epoxide Reductase
Vitamin K Epoxide Reductase Subunit C1 (VKORC1)
VKORC1
Warfarin DoseAdvise™
Ziagen

The use of specific product names is illustrative only. It is not intended to be a recommendation of one product over another, and is not intended to represent a complete listing of all products available.

History

Status	Date	Action
Reviewed	05/12/2022	Medical Policy & Technology Assessment Committee (MPTAC) review. Updated References section.
Revised	05/13/2021	MPTAC review. Revised MN statement for carbamazepine and allopurinol from "Asian descent" to "high risk due to ethnic heritage." Revised MN statements to remove drug trade names. Revised NMN statements to remove bullet points below statements. Updated Discussion/General Information and References sections. Reformatted Coding section.

Federal and State law, as well as contract language including definitions and specific coverage provisions/exclusions, and Medical Policy take precedence over Clinical UM Guidelines and must be considered first in determining eligibility for coverage. The member's contract benefits in effect on the date that services are rendered must be used. Clinical UM Guidelines, which address medical efficacy, should be considered before utilizing medical opinion in adjudication. Medical technology is constantly evolving, and we reserve the right to review and update Clinical UM Guidelines periodically. Clinical UM guidelines are used when the plan performs utilization review for the subject. Due to variances in utilization patterns, each plan may choose whether or not to adopt a particular Clinical UM Guideline. To determine if review is required for this Clinical UM Guideline, please contact the customer service number on the back of the member's card.

No part of this publication may be reproduced, stored in a retrieval system or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from the health plan.

© CPT Only – American Medical Association

Medicaid managed care administered by Amerigroup Corporation, an independent company.

Historical

Reviewed	05/14/2020	MPTAC review. Updated Discussion/General Information and References sections.
	02/18/2020	Updated Coding section with correct descriptor for 81227.
	12/31/2019	Updated Coding section with 01/01/2020 CPT changes; revised descriptor for 81350.
New	06/06/2019	MPTAC review. Initial document development. Genotype testing for individual polymorphisms of metabolizing enzymes for specific drugs removed from GENE.00010 and moved into this new clinical utilization management guideline. New indication to MN statement regarding CYP2C9 and siponimod.

Historical

Federal and State law, as well as contract language including definitions and specific coverage provisions/exclusions, and Medical Policy take precedence over Clinical UM Guidelines and must be considered first in determining eligibility for coverage. The member's contract benefits in effect on the date that services are rendered must be used. Clinical UM Guidelines, which address medical efficacy, should be considered before utilizing medical opinion in adjudication. Medical technology is constantly evolving, and we reserve the right to review and update Clinical UM Guidelines periodically. Clinical UM guidelines are used when the plan performs utilization review for the subject. Due to variances in utilization patterns, each plan may choose whether or not to adopt a particular Clinical UM Guideline. To determine if review is required for this Clinical UM Guideline, please contact the customer service number on the back of the member's card.

No part of this publication may be reproduced, stored in a retrieval system or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from the health plan.

© CPT Only – American Medical Association

Medicaid managed care administered by Amerigroup Corporation, an independent company.