Pharmacogenomic Testing

Policy # 00169
Original Effective Date: 07/15/2005
Current Effective Date: 12/01/2023

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

Note: Genetic Testing for Diagnosis and Management Mental Health Conditions is addressed separately in medical policy 00402.

When Services May Be Eligible for Coverage

Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Based on review of available data, the Company may consider one genotyping for the appropriate biomarker for each of the FDA-approved therapies and associated biomarkers noted in Table 1 in the Policy Guidelines, to be **eligible for coverage.****

Patient Selection Criteria

Coverage eligibility may be considered for one genotyping for the appropriate biomarker for each of the following FDA-approved therapies and associated biomarkers noted in Table 1 in the Policy Guidelines, when **ALL** the following conditions are met:

- The medication for which genotyping is being done is the most appropriate treatment for the individual's underlying condition; **AND**
- The pharmacogenomic test has demonstrated analytical and clinical validity and clinical utility; **AND**
- The biomarker testing is focused on the specific genetic polymorphisms relevant to guiding treatment for the individual's condition and expected treatment.

When Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers genotype testing for individual genetic polymorphisms to determine drug-metabolizer status to be **investigational*** in all other situations, including but not limited to:

- genotyping to determine cytochrome P450 2C9 (CYP2C9), P450 4F2 (CYP4F2), and vitamin K epoxide reductase subunit C1 (VKORC1) genetic variants for the purpose of managing the administration and dosing of warfarin
- testing for genetic variants in dipyrimidine dehydrogenase (DPYD) gene to guide 5-fluorouracil (5-FU) dosing and/or treatment
- My5-FU™‡ testing or other types of assays for determining 5-fluorouracil (5-FU) area under the curve (AUC) in order to adjust 5-FU dose
- testing for genetic variants in thymidylate synthase (TYMS) genes to guide 5-FU dosing and/or treatment choice
- genotyping to determine cytochrome p450 2D6 (CYP2D6) variants for the purpose of managing treatment with tamoxifen
- genetic testing for the presence of variants in the SLCO1B1 gene to identify patients at risk of statin-induced myopathy
- kinesin-like protein 6 (KIF6) genotyping for predicting cardiovascular risk and/or the effectiveness of statin therapy
- genetic testing for pain management, including panels of single-nucleotide variants [SNV] or individual SNV testing such as *5HT2C, 5HT2A, SLC6A4, DRD1, DRD2, DRD4, DAT1, SLC6A3, DBH, COMT, MTHFR, GABA A receptor, OPRM1, OPRK1, UGT2B15 genes* and Cytochrome p450 genes *(CYP2D6, CYP2C19, CYP2C9, CYP3A4, CYP2B6, CYP1A2)*

Based on review of available data, the Company considers the use of panel and multi-gene tests for polymorphisms to determine drug-metabolizer status to be **investigational.***

When Services Are Not Covered

Based on review of available data, the Company considers repeat germline testing to be **not covered**.**.**

Note:
Repeat germline testing that investigates the same genetic information is not reasonable and necessary as it is duplicative and not required for medical treatment decisions. Examples of germline

tests include, but are not limited to, single gene testing, gene panel tests, and whole exome or whole genome sequencing for inherited disorders and pharmacogenomic/cytochrome P450 testing.

Policy Guidelines

Table 1. Therapies and associated biomarkers

Biomarker	Drug	Therapeutic Area/Indication
CYP2C19	clopidogrel	Cardiology/Thrombotic event prevention
CYP2C9	siponimod	Neurology/Multiple sclerosis, relapsing forms
CYP2D6	eliglustat	Metabolic Disorders/Gaucher disease
CYP2D6	tetrabenazine	Neurology/Huntington disease (tetrabenazine dosage > 50 mg/day)
G6PD	rasburicase	Hematology/Chemo-related hyperuricemia
G6PD	tafenoquine, primaquine	Infectious Diseases/Malaria prophylaxis or treatment, PCP
HLA-B*1502	carbamazepine, oxcarbazepine	Neurology/Seizures, Trigeminal neuralgia, bipolar disorder
HLA-B*5701	abacavir	Infectious Diseases/HIV
HLA-B*58:01	allopurinol	Rheumatology/Gout, hyperuricemia, recurrent Ca oxalate calculi
NAGS	carglumic acid	Gastroenterology/Hyperammonemia
POLG	divalproex sodium, valproic acid	Neurology/Seizures, bipolar disorder, migraine prophylaxis

TPMT/T15	mercaptopurine, thioguanine, azathioprine	Hematology, Gastroenterology, Rheumatology/ALL, AML, CD, UC, organ rejection prophylaxis,

Excerpted from https://cpicpgx.org/genes-drugs/

Background/Overview

Pharmacogenomic testing refers to genotype testing for polymorphisms to identify variants of specific genes associated with drug pharmacodynamics or metabolism. Such testing is sometimes used to guide the dosing or choice of drugs in an individual with the goal of optimizing the response to therapy and/or minimizing the likelihood of an adverse drug effect. Polymorphisms in the genes encoding the drug target can influence the drug pharmacodynamics. Moreover, genetic determinates of excretion or drug metabolism influence pharmacokinetics. Although about 15% of all prescriptions in the United States have potential influence from pharmacogenetics, evidence is available to support genotype-guided prescribing for a limited number of drugs, and sometimes only for specific subpopulations. In some cases, there are race-based screening recommendations that can be difficult to apply because of wide variability in allele frequencies even within ethnic groups along with difficulty in discerning race ancestry and due to mixed ancestry. At the same time, imperatives to use resources judiciously warrant selective screening to target high prevalence groups when they can be accurately identified.

The Clinical Pharmacogenetics Implementation Consortium (CPIC) was developed in 2009 as a shared project between the Pharmacogenomics Knowledge Base (PharmGKB, http://www.pharmgkb.org) and the National Institutes of Health (NIH). The CPIC is focused on facilitation the translation of research findings into clinical actions for selected gene/drug pairs with sufficient evidence. As noted in the CPIC Guideline Development Process publication, "CPIC guidelines are designed to provide guidance to clinicians as to how available genetic test results should be interpreted to ultimately improve drug therapy, rather than to provide guidance as to whether a genetic test should or should not be ordered. With notable exceptions, pharmacogenomics is best used to assess the risk of general suboptimal response. This type of testing does not override the need for clinical assessment and judgement.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

Pharmacogenomic Testing

Policy # 00169
Original Effective Date: 07/15/2005
Current Effective Date: 12/01/2023

FDA lists potential pharmacogenetic associations in the table Section 1: Pharmacogenetic Associations for which the Data Support Therapeutic Management Recommendations.
It is noted that the fact that the FDA has included a particular gene-drug interaction in the table does not necessarily mean the FDA advocates using a pharmacogenetic test before prescribing the corresponding medication, unless the test is a companion diagnostic. Tests that are essential for the safe and effective use of a therapeutic product, including those that identify patients for which the drug is contraindicated, are companion diagnostics.

This table is not intended to affect current regulatory requirements or policies, including the FDA's policy regarding companion diagnostics: Guidance for Industry and FDA Staff: In Vitro Companion Diagnostic Devices. Nor is the table intended to make an assessment on the safe and effective use of, or regulatory requirements for, tests that detect variants in the referenced genes, or to provide comprehensive information on the described gene-drug interactions.

Specific information regarding therapeutic management is provided for some pharmacogenetic associations listed in the table, but most of the associations listed have not been evaluated in terms of the impact of genetic testing on clinical outcomes, such as improved therapeutic effectiveness or increased risk of specific adverse events. In addition, clinical studies, if available, may only have linked genetic variation to a drug's pharmacokinetics (such as the way in which the drug is metabolized), and differences in drug efficacy or safety across different genotype subgroups may not be known. If no statements related to efficacy or toxicity are provided, the scientific evidence the FDA reviewed was considered insufficient to support such associations.

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

Rationale/Source

This medical policy was developed through consideration of peer-reviewed medical literature generally recognized by the relevant medical community, U.S. Food and Drug Administration approval status, nationally accepted standards of medical practice and accepted standards of medical

practice in this community, technology evaluation centers, reference to federal regulations, other plan medical policies, and accredited national guidelines.

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.

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.

To support clinical utility, data should demonstrate that 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).

While there is considerable enthusiasm for pharmacogenomic testing and tremendous growth in direct-to-consumer marketing, there has also been action taken by the FDA and other groups to warn patients that selecting or changing drug treatment in response to genetic test results can also lead to potentially serious health consequences (see FDA warning letter, April 4, 2019; FDA warning letter November 1, 2018). One area where there has been particular enthusiasm is psychiatry, particularly with the use of pharmacogenetic testing to guide antidepressant therapy. While it is known that genetic variants contribute to the variance in response to drug treatments for depression, rigorously conducted clinical trials have not yet shown the clinical utility of such testing. Meta-analyses and non-industry technical assessments of the existing literature have shown notable risks of bias in existing studies, a high degree of between study heterogeneity, and significant methodological limitations. In particular, the randomized, double-blind, clinical trial evaluating the GeneSight pharmacogenomic intervention did not find a statistically significant difference in response rates or remission rates when those tested were compared to those without testing. Systematic reviews of the available studies in this realm are unequivocal that the evidence of clinical utility is lacking.

One area of controversy in the field of pharmacogenomics is the role of DPYD testing for patients being treated with cytolytic chemotherapy using 5-fluorouracil. 5-fluorouracil (5-FU) and capecitabine are commonly used in solid tumors including colorectal, pancreatic, esophageal, head and neck, and breast cancer, and use of these drugs is associated with infrequent severe, life-threatening toxicities including neutropenia, diarrhea, and mucositis. Fluoropyrimidine toxicity is due in part to inherited polymorphisms in the dihydropyrimidine dehydrogenase enzyme, encoded by DPYD, which is responsible for 5-FU elimination. Approximately 5% of patients carry one of five DPYD polymorphisms that increase toxicity risk. DPYD variant carriers who receive standard fluoropyrimidine doses have ~70% risk of severe toxicity and ~3% risk of fatal toxicity, and these risks are even higher in the ~1/250 patients who carry two DPYD variants. The NCCN and the FDA recognize the increased risk of severe fluoropyrimidine toxicity in known DPYD carriers but do not recommend routine testing. While some countries have mandated preemptive DPYD testing for patients scheduled to receive a fluoropyrimidine, preemptive DPYD testing is rarely conducted for a variety of reasons. In the SWOG cancer research group, a survey was conducted of 59 US-based medical oncologists within the SWOG gastrointestinal and breast committees. Those data indicate that the primary reasons for not testing are the perceived low prevalence of DPYD deficiency, lack

of clinical guidelines recommending testing, and a lack of knowledge around which test to order and what to do with the result. There is also concern among the oncology community related to the potential for dose reduction resulting from this testing, leading ultimately to reduced treatment efficacy.

For individuals who are asymptomatic with risk of cardiovascular disease and undergoing treatment with statin therapy who receive testing for *KIF6* Trp719Arg variant status, the evidence includes secondary analyses of randomized controlled trials, case-control studies, and a quasi-experimental single-arm study. Currently, no prospective randomized controlled trials have evaluated the impact of testing for *KIF6* variants on changes in clinical management (e.g., intensifying the statin treatment in carriers, use of alternative approaches for lipid management in noncarriers) or outcomes. One nonrandomized study has suggested that subjects with *KIF6* genotype results showed greater adherence to statin therapy, but, overall, it is uncertain whether testing for *KIF 6* variants will alter the clinical management decisions. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who are taking statin drugs who receive genetic testing for SLCO1B1 variants, the evidence includes a systematic review and two randomized controlled trials. Two randomized controlled trials were identified that evaluated adherence to medication and/or lipid control in patients whose physicians were informed of the SLCO1B1 haplotype at the beginning or at the end of the study. No significant benefits were identified in adherence to medications or in pain related to myopathy with knowledge of the SLCO1B1 haplotype status. There was a short-term (3-month) decrease in low-density lipoprotein (LDL) in the active treatment group in one trial, but knowledge of SLCO1B1 status did not provide benefit in LDL lowering in the other trial after 12 months. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who are treated with tamoxifen for breast cancer or are at high-risk for breast cancer who receive *CYP2D6* genotype-guided tamoxifen treatment, the evidence includes a single randomized controlled trial (RCT), several meta-analyses and systematic reviews, multiple retrospective and prospective cohort studies, and nonconcurrent prospective studies. The RCT examining genotype-directed dosing found no difference in progression-free survival between a standard dose and increased dose; however, this trial was limited by its proof of concept design. No trials of genotype-directed drug choice that compared health outcomes for patients managed with

and without the test were identified. It is not known whether *CYP2D6* genotype-guided tamoxifen treatment results in the selection of a treatment strategy that would reduce the rate of breast cancer recurrence, improve disease-free survival or OS, or reduce adverse events. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have a need for pharmacologic pain management who receive pharmacogenetic testing to target therapy, the evidence includes a hybrid implementation-effectiveness, open-label, randomized trial, prospective cohort study with historical controls that assessed genotype-guided management of postoperative pain, and a prospective non-randomized pragmatic trial that evaluated chronic pain control when treatment occurred via a cytochrome (CYP) P450 2D6-guided approach to opioid prescribing versus standard management. The randomized trial concluded that preemptive CYP2D6-guided opioid selection is feasible in an elective surgery setting and that this approach may decrease postoperative opioid utilization with similar pain control as compared to usual care; however, these results were only exploratory in nature. The prospective cohort study reported on the use of genetic panel test results to guide the selection of analgesics in a postoperative setting and reported statistically significant improvement in total scores of a composite endpoint that measured analgesia, patient satisfaction, and the impact of drug-associated side effects versus historical controls. However, methodologic limitations precluded assessment of the effects on outcomes. The prospective non-randomized pragmatic trial evaluated a CYP2D6-guided approach finding a statistically significant but modest improvement in chronic pain control in the intermediate and poor metabolizers. The effect of pharmacogenetic testing alone cannot be determined from this trial. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

In general, most published *CYP450* pharmacogenomic studies for highly active antiretroviral agents, immunosuppressants, b-blockers, and antitubercular medications are retrospective evaluations of *CYP450* genotype associations or underpowered RCTs, reporting intermediate outcomes (eg, circulating drug concentrations) or less often, final outcomes (eg, adverse events or efficacy). Many of these studies are small, underpowered, and hypothesis generating. Prospective intervention studies, including RCTs documenting clinical usefulness of *CYP450* genotyping to improve existing clinical decision-making to guide dose or drug selection, which will then translate into improvement in patient outcomes, were not identified.

For individuals with conditions requiring warfarin treatment who receive genotype-guided warfarin dosing, the evidence includes multiple randomized controlled trials (RCTs) and systematic reviews of RCTs. Meta-analyses of RCTs found no difference between genotype-guided dosing and clinical dosing for mortality, and only 1 found reduction in TEEs, but genotype-guided dosing was associated with a lower risk of major bleeding. Very few trials enrolled sufficient numbers of subpopulations except White participants. In the Clarification of Optimal Anticoagulation through Genetics study, which included 27% African American participants, African Americans fared better in the clinically-guided group than in the genotype-guided group. One trial of elderly Chinese patients with atrial fibrillation experienced improved time with INR in the therapeutic range and a reduced risk of ischemic stroke, but no difference in bleeding events. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

The clinical utility of pharmacogenomic testing is not established for most instances of its use, and thus it is considered investigational unless otherwise specified. There are some instances where the FDA is explicit in recommending genotyping ahead of prescribing.

Supplemental Information

Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

***DPYD* genotyping**

National Comprehensive Cancer Network Guidelines

National Comprehensive Cancer Network (NCCN) guidelines do not recommend use of area under the curve guidance for 5-fluorouracil dosing or genetic testing for *DPYD* and/or *TYMS* variants in patients with colon, rectal, breast, gastric, pancreatic, or head and neck cancers.

The colon cancer guideline discusses the use of genetic testing for *DPYD* and the risk of severe toxicity after a standard dose of a fluoropyrimidine. Although the guideline discusses evidence for

genetic testing for *DPYD*, it states: "However, because fluoropyrimidines are a pillar of therapy in colorectal cancer (CRC) and it is not known with certainty that given *DYPD* variants are necessarily associated with this risk, universal pretreatment *DPYD* genotyping remains controversial and the NCCN Panel does not support it at this time."

National Institute for Health and Care Excellence
In 2014, the NICE published evidence-based diagnostics guidance on the My5-FU assay for 5-fluorouracil chemotherapy dose adjustment. The evidence for the guidance was reviewed in February 2018. The guidance stated: “The My5-FU assay is only recommended for use in research for guiding dose adjustment in people having fluorouracil chemotherapy by continuous infusion. The My5-FU assay shows promise and the development of robust evidence is recommended to demonstrate its utility in clinical practice.”

***KIF6* genotyping**
In 2019, the American College of Cardiology and American Heart Association issued a joint guideline on use of risk assessment tools to guide decision-making in the primary prevention of atherosclerotic cardiovascular disease, which made no reference to *KIF6* genotyping.

***SLCO1B* genotyping**

Clinical Pharmacogenetics and Pharmacogenomics Implementation Consortium
In 2012, the Clinical Pharmacogenetics and Pharmacogenomics Implementation Consortium issued guidelines for *SLCO1B* genotypes and simvastatin-induced myopathy, which were updated in 2014. These guidelines on patient management for various *SLCO1B* genotypes recommended prescribing a lower dose or considering an alternative statin and considering routine creatinine kinase surveillance in patients with *SLCO1B* genotypes consistent with intermediate or low statin metabolism.

The 2022 update noted that recommendations for the minimum duration of statin therapy for continued safe use long-term are primarily based on expert opinion and the onset of statin-associated musculoskeletal symptoms (SAMS) observed for simvastatin in different *SLCO1B* genotypes in a single prospective clinical trial. One potential benefit of preemptive *SLCO1B1*, *ABCG2*, and *CYP2C9* testing may be a reduction in the incidence of SAMS. It was also noted that prospective data showing that prescribing based on genetic testing results alter SAMS incidence are lacking and

emerging data demonstrate an improvement in patients' perception of statins, appropriate prescribing, neutral data on adherence, and mixed data on reducing LDL-cholesterol levels. A possible risk could be an error in genotyping with decrease in statin dose that was not necessary, inappropriate avoidance of statin therapy, higher LDL-cholesterol and increased cardiovascular risk.

Pharmacogenetic testing for pain management

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

Clinical Pharmacogenomics Implementation Consortium
The Clinical Pharmacogenomics Implementation Consortium (2020) published a guideline for cytochrome P450 (CYP) 2C9 and nonsteroidal anti-inflammatory drugs (NSAIDs), which was developed to provide interpretation of CYP2C9 genotype tests so that the results could potentially guide dosing and/or appropriate NSAID use. The guideline notes that CYP2C9 genotyping information may provide an opportunity "to prescribe NSAIDs for acute or chronic pain conditions at genetically-informed doses to limit long-term drug exposure and secondary adverse events for patients who may be at increased risk." However, the authors also acknowledge that "while traditional pharmacogenetic studies have provided evidence associating common CYP2C9 genetic variation with NSAID pharmacokinetics, there is sparse prospective evidence showing that genetically-guided NSAID prescribing improves clinical outcomes."

In 2021, the Consortium published an updated guideline for CYP2D6, μ-opioid receptor gene 1 (OPRM1), and catechol O-methyl-transferase (COMT) genotypes and select opioid therapy. These recommendations state that codeine and tramadol should be avoided in CYP2D6 poor metabolizers due to diminished efficacy and in ultra-rapid metabolizers due to toxicity potential. In both situations, if opioid use is warranted, a non-codeine opioid should be considered. Regarding hydrocodone, there is insufficient evidence and confidence to provide a recommendation to guide clinical practice for CYP2D6 ultra-rapid metabolizers. For CYP2D6 poor metabolizers, the use of hydrocodone label age- or weight-specific dosing is recommended; however, if no response is

observed and opioid use is warranted, a non-codeine and non-tramadol opioid option is warranted. There is insufficient evidence and confidence to provide a recommendation to guide clinical practice at this time for oxycodone or methadone based on CYP2D6 genotype. Additionally, there are no therapeutic recommendations for dosing opioids based on either OPRM1 or COMT genotype.

National Comprehensive Cancer Network
NCCN guidelines for adult cancer pain (v 2.2023) note that pharmacogenomic testing may be considered prior to initiation or during analgesic treatment when concerns of toxicity or lack of response are demonstrated or suspected. Many commonly prescribed analgesics are metabolized via P450 (CYP) such as *CYP2D6, CYP2C19, or CYP2C9*. Opioid-mediated analgesia can be influenced by the Catechol-O-methyltransferase (*COMT*) gene and the μ-opioid receptor (*OPRM2) A118G* single-nucleotide polymorphism; however, the clinical importance of these are unclear.

Tamoxifen and *CYP2D6* genotyping

Clinical Pharmacogenetics Implementation Consortium
In 2018, the Clinical Pharmacogenetics Implementation Consortium issued therapeutic recommendations for tamoxifen prescribing based on *CYP2D6* genotype/metabolic phenotype. For the clinical endpoints of recurrence and event-free survival, the evidence was graded as moderate for the statements that CYP2D6 poor metabolizers have a higher risk of breast cancer recurrence or worse event-free survival. However, for the comparison of other metabolizer groups and other clinical endpoints, the evidence was considered weak regarding an association between CYP2D6 metabolizer groups and clinical outcomes.

National Comprehensive Cancer Network
Regarding the use of *CYP2D6* genotyping before prescribing tamoxifen, the National Comprehensive Cancer Network breast cancer guidelines (v.3.-2022) state: "CYP2D6 genotype testing is not recommended for patients considering tamoxifen."

American Society of Clinical Oncology
In 2016, the guidelines published by the American Society of Clinical Oncology (ASCO) on the use of biomarkers to guide decisions on adjuvant systemic therapy for women with early-stage invasive breast cancer stated the following for *CYP2D6* variants to guide adjuvant endocrine therapy selection:

- "The clinician should not use CYP2D6 polymorphisms to guide adjuvant endocrine therapy selection (Type: evidence based; Evidence quality: intermediate; Strength of recommendation: moderate).
- The ability of polymorphisms in CYP2D6 to predict tamoxifen benefit has been extensively studied. The results of these pharmacogenomics studies have been controversial, with more recent studies being negative. At this point, data do not support the use of this marker to select patients who may or may not benefit from tamoxifen therapy."

Warfarin and *CYP2C9* and *VKORC1* genotyping

American College of Medical Genetics
In 2008, the American College of Medical Genetics policy statement on pharmacogenetic testing concluded: "There is insufficient evidence, at this time, to recommend for or against routine *CYP2C9* and *VKORC1* testing in warfarin-naive patients."

American College of Chest Physicians
In 2012, the ninth edition of the American College of Chest Physicians' evidence-based clinical practice guidelines on antithrombotic therapy and prevention of thrombosis stated: "For patients initiating VKA [vitamin K antagonist] therapy, we recommend against the routine use of pharmacogenetic testing for guiding doses of VKA (Grade 1B)." The updated 2021 guidelines make no mention of genotype-guided warfarin dosing.

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

U.S. Preventive Services Task Force Recommendations
Not applicable.

Medicare National Coverage
Warfarin
The Centers for Medicare & Medicaid Services (2009) published a national coverage determination on pharmacogenomic testing for warfarin response. The Centers for Medicare & Medicaid Services stated that "the available evidence does not demonstrate that pharmacogenomic testing of *CYP2C9* or *VKORC1* alleles to predict warfarin responsiveness improves health outcomes in Medicare beneficiaries outside the context of CED [coverage with evidence development], and is therefore not reasonable and necessary…."

However, the Centers also "believes that the available evidence supports that coverage with evidence development (CED) … is appropriate for pharmacogenomic testing of CYP2C9 or VKORC1 alleles to predict warfarin responsiveness by any method, and is therefore covered only when provided to Medicare beneficiaries who are candidates for anticoagulation therapy with warfarin who:

1. Have not been previously tested for *CYP2C9* or *VKORC1* alleles; and
2. Have received fewer than 5 days of warfarin in the anticoagulation regimen for which the testing is ordered; and
3. Are enrolled in a prospective, randomized, controlled clinical study when that study meets [described] standards."

References

1. Carelon Medical Benefits Management, Clinical Appropriateness Guidelines: Genetic Testing, "Pharmacogenomic Testing", February 12, 2023.
2. Lin B, Chung WK. Cases in Precision Medicine: The Role of Pharmacogenetics in Precision Prescribing. Ann Intern Med. 2019;170(11):796-804. Epub 2019 May 21. PMID: 31108507
3. Goodman CW, Brett AS. Race and Pharmacogenomics-Personalized Medicine or Misguided Practice? JAMA. 2021;325(7):625-6. Epub 2021 Jan 26. PMID: 33492362
4. Relling MV and Klein TE. The Clinical Pharmacogenetics Implementation Consortium of the Pharmacogenomics Research Network. Clin Pharmacol Ther. 2011; 89(3):464-467. Epub 2011 Jan 26. PMID: 21270786
5. Relling MV, Klein TE, Gammal RS, et al. The Clinical Pharmacogenetics Implementation Consortium: 10 Years Later. Clin Pharmacol Ther. 2020;107(1):171-5. Epub 2019 Sep 29. PMID: 31562822
6. Food & Drug Administration (FDA). Table of Pharmacogenetic Associations.

https://www.fda.gov/medical-devices/precision-medicine/table-pharmacogenetic-associations#about

7. Food & Drug Administration (FDA). Table of Pharmacogenetic Associations, Section 1: Pharmacogenetic Associations for which the Data Support Therapeutic Management Recommendations https://www.fda.gov/medical-devices/precision-medicine/table-pharmacogenetic-associations#section1
8. Wake DT, Ilbawi N, Dunnenberger HM, et al. Pharmacogenomics: Prescribing Precisely. Med Clin North Am. 2019;103(6):977-90. Epub 2019 Oct 5. PMID: 31582008
9. Winner JG, Carhart JM, Altar CA, et al. A prospective, randomized, double-blind study assessing the clinical impact of integrated pharmacogenomic testing for major depressive disorder. Discov Med. 2013;16(89):219-27. Epub 2013 Nov 16. PMID: 24229738
10. Rosenblat JD, Lee Y, McIntyre RS. Does Pharmacogenomic Testing Improve Clinical Outcomes for Major Depressive Disorder? A Systematic Review of Clinical Trials and Cost-Effectiveness Studies. J Clin Psychiatry. 2017;78(6):720-9. Epub 2017 Jan 10. PMID: 28068459
11. Health Quality Ontario. Pharmacogenomic Testing for Psychotropic Medication Selection: A Systematic Review of the Assurex GeneSight Psychotropic Test. Ont Health Technol Assess Ser. 2017;17(4):1-39. PMID: 28515818
12. Meulendijks D, Henricks LM, Sonke GS, et al. Clinical relevance of DPYD variants c.1679T>G, c.1236G>A/HapB3, and c.1601G>A as predictors of severe fluoropyrimidine-associated toxicity: a systematic review and meta-analysis of individual patient data. Lancet Oncol. 2015;16(16):1639-50. Epub 2015 Nov 26. PMID: 26603945
13. Lee AM, Shi Q, Pavey E, et al. DPYD variants as predictors of 5-fluorouracil toxicity in adjuvant colon cancer treatment (NCCTG N0147). J Natl Cancer Inst. 2014;106(12). Epub 2014 Nov 9. PMID: 25381393
14. Ciccolini J. DPD deficiency in patients treated with fluorouracil. Lancet Oncol. 2015;16(16):1574-6. Epub 2015 Nov 26. PMID: 26603944
15. Cooper-DeHoff, R M, Nicimi, M, Ramsey, LB, et al. The Clinical Pharmacogenetics Implementation Consortium Guideline for SLCO1B1, ABCG2, and CYP2C9 genotypes and Statin-Associated Musculoskeletal Symptoms. Clin Pharmacol Ther. 2022 111(5): 1007=21. https://files.cpicpgx.org/data/guideline/publication/statins/2022/publication.pdf
16. CPIC levels to genes/drugs. (2023). https://cpicpgx.org/genes-drugs/
17. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Colon Cancer. Version 2.2023.

18. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Breast Cancer. Version 3.2022.
19. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Adult Cancer Pain. Version 2.2023.
20. Link E, Parish S, Armitage J, et al. SLCO1B1 variants and statin-induced myopathy--a genomewide study. N Engl J Med. Aug 21 2008; 359(8): 789-99. PMID 18650507
21. 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.
22. Centers for Medicare & Medicaid Services. National Coverage Determination (NCD) for Pharmacogenomic Testing for Warfarin Response (90.1). 2009; https://www.cms.gov/medicarecoverage-database/details/ncddetails.aspx?NCDId=333&ncdver=1&bc=AgAAQAAAAAAAAA%3d%3d&.
23. National Institute for Health and Care Excellence (NICE). Fluorouracil chemotherapy: The My5-FU assay for guiding dose adjustment. December, 2014. https://www.nice.org.uk/guidance/dg16/resources/fluorouracil-chemotherapy-the-my5fu-assay-for-guiding-dose-adjustment-pdf-1053633149125
24. American Society of Clinical Oncology (ASCO). Use of Biomarkers to Guide Decisions on Adjuvant Systemic Therapy for Women With Early-Stage Invasive Breast Cancer. 2016. https://old-prod.asco.org/sites/new-www.asco.org/files/content-files/practice-and-guidelines/documents/2016-Adj-Biomarkers-Summary-of-Recs-Table.pdf
26. CHEST 2012; 141(2)(Suppl):7S–47S. Executive Summary (chestnet.org).
27. Clinical Pharmacogenetics Implementation Consortium (CPIC) Guidelines for Pharmacogenetics-guided Warfarin Dosing: 2017 Update (March 2017). CPIC® Guideline for Pharmacogenetics-Guided Warfarin Dosing – CPIC (cpicpgx.org)
28. Arnett D, Blumenthal R, Albert M, et al. 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease: Executive Summary. J Am Coll Cardiol. 2019 Sep, 74 (10) 1376–1414. https://doi.org/10.1016/j.jacc.2019.03.009
29. Frankin G, et al. 2014 American Academy of Neurology. 2014; 83:1277-1284. https://n.neurology.org/content/neurology/83/14/1277.full.pdf

Pharmacogenomic Testing

Policy # 00169
Original Effective Date: 07/15/2005
Current Effective Date: 12/01/2023

Policy History

Original Effective Date: 07/15/2005
Current Effective Date: 12/01/2023

06/07/2005	Medical Director Review
06/21/2005	Medical Policy Committee review
07/15/2005	Managed Care Advisory Council approval
07/07/2006	Medical Policy Committee approval. Format revision including addition of FDA and or other governmental regulatory approval and rationale/source. Coverage eligibility unchanged.
05/02/2007	Medical Director Review
05/23/2007	Medical Policy Committee approval. Rationale/source. Coverage eligibility unchanged.
05/07/2009	Medical Director Review
05/20/2009	Medical Policy Committee approval. Added a statement with seven bulleted applications for clarification of CYP450 genotyping to, "Services Are Considered Investigational" section. Coverage eligibility unchanged.
06/03/2010	Medical Policy Committee review
06/16/2010	Medical Policy Implementation Committee approval. Policy statement regarding cytochrome p450 genetic testing to guide selection or dose of beta blockers added as investigational criteria.
05/05/2011	Medical Policy Committee review
05/18/2011	Medical Policy Implementation Committee approval. Changed the use of CYP450 genotyping with clopidogrel (Plavix) from investigational to eligible for coverage.
05/03/2012	Medical Policy Committee review
05/16/2012	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
05/02/2013	Medical Policy Committee review
05/22/2013	Medical Policy Implementation Committee approval.
05/01/2014	Medical Policy Committee review
05/21/2014	Medical Policy Implementation Committee approval. Added "dosing and management of antituberculosis medications" to the investigational applications.
05/07/2015	Medical Policy Committee review

05/20/2015	Medical Policy Implementation Committee approval. Added INV statement for the use of genetic testing panels that include multiple CYP450 mutations. Updated existing INV bullet "dosing of codeine" and "dose of efavirenz and other antiretroviral therapies".
02/04/2016	Medical Policy Committee review
02/17/2016	Medical Policy Implementation Committee approval. Policy statements for CYP2B6 genotyping added. CYP450 genotyping in choosing or dosing clopidogrel changed to INV. Serotonin-norepinephrine reuptake inhibitors added to existing INV indication for CYP450 genotyping.
01/01/2017	Coding update: Removing ICD-9 Diagnosis Codes
02/02/2017	Medical Policy Committee review
02/15/2017	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
01/01/2018	Coding update
02/01/2018	Medical Policy Committee review
02/21/2018	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
04/01/2018	Coding update
08/09/2018	Medical Policy Committee review
08/15/2018	Medical Policy Implementation Committee approval. Policy title changed from "Cytochrome P450 Genotyping" to "Cytochrome P450 Genotype-Guided Treatment Strategy". Four criteria removed from the third investigational statement; the intent of statements otherwise unchanged. Information on pharmacologic treatments used to treat mental health disorders were removed from this policy and added to policy 00402.
08/30/2018	Coding update
08/01/2019	Medical Policy Committee review
08/14/2019	Medical Policy Implementation Committee approval. Coverage changes, coverage eligibility statement added to Patient Selection Criteria for CYP2C9 genotyping to determine drug metabolizer status will be met for patients with Multiple Sclerosis being considered for treatment with Siponimod. Addition to FDA labeling section to include label guidelines for siponimod (Mayzent) for patients with CYP2C9 genotypes.
08/06/2020	Medical Policy Committee review

Pharmacogenomic Testing

Policy # 00169
Original Effective Date: 07/15/2005
Current Effective Date: 12/01/2023

08/12/2020	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
08/05/2021	Medical Policy Committee review
08/11/2021	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
04/05/2022	Coding update
08/04/2022	Medical Policy Committee review
08/10/2022	Medical Policy Implementation Committee approval. Revised the criteria language for CYP2C9 genotyping. Coverage intent unchanged.
09/20/2022	Coding update
12/07/2022	Coding update
03/19/2023	Coding update
09/05/2023	Medical Policy Committee review
09/11/2023	Medical Policy Implementation Committee approval. Title changed from "Cytochrome p450 Genotype-Guided Treatment Strategy" to "Pharmacogenomic Testing". The entire policy has been revised. The policy intent has been expanded for comprehensive pharmacogenomic testing. CPIC resource table added for reference.

Next Scheduled Review Date: 09/2024

Coding

The five character codes included in the Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®)‡, copyright 2022 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.

The responsibility for the content of Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines is with Blue Cross and Blue Shield of Louisiana and no endorsement by the AMA is intended or should be implied. The AMA disclaims responsibility for any consequences or liability attributable or related to any use, nonuse or interpretation of information contained in Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines. Fee schedules, relative value units, conversion factors and/or related components are not assigned by the AMA, are not part of CPT,

and the AMA is not recommending their use. The AMA does not directly or indirectly practice medicine or dispense medical services. The AMA assumes no liability for data contained or not contained herein. Any use of CPT outside of Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines should refer to the most current Current Procedural Terminology which contains the complete and most current listing of CPT codes and descriptive terms. Applicable FARS/DFARS apply.

Codes used to identify services associated with this policy may include (but may not be limited to) the following:

Code Type	Code
CPT	0029U, 0031U, 0070U, 0071U, 0072U, 0073U, 0074U, 0075U, 0076U, 0347U, 0348U, 0349U, 0350U, 0380U, 81225, 81226, 81227, 81230, 81231, 81418 Add codes effective 12/01/2023: 0030U, 0032U, 0034U, 0169U, 0286U, 81232, 81247, 81248, 81249, 81250, 81283, 81306, 81328, 81335, 81346, 81350, 81355, 81381, 81400, 81479 Delete codes effective 12/01/2023: 81401, 81402, 81404, 81405
HCPCS	Add code effective 12/01/2023: G9143
ICD-10 Diagnosis	E75.22, G10, All related Diagnoses

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or

diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:

1. Consultation with technology evaluation center(s);
2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
3. Reference to federal regulations.

**Medically Necessary (or "Medical Necessity") - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

A. In accordance with nationally accepted standards of medical practice;
B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, "nationally accepted standards of medical practice" means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

‡ Indicated trademarks are the registered trademarks of their respective owners.

NOTICE: Federal and State law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage.

NOTICE: If the Patient's health insurance contract contains language that differs from the BCBSLA Medical Policy definition noted above, the definition in the health insurance contract will be relied upon for specific coverage determinations.

Pharmacogenomic Testing

Policy # 00169
Original Effective Date: 07/15/2005
Current Effective Date: 12/01/2023

NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.