



CIGNA MEDICAL COVERAGE POLICY

The following Coverage Policy applies to all plans administered by CIGNA Companies including plans administered by Great-West Healthcare, which is now a part of CIGNA.

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Subject Pharmacogenetic Testing

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Hyperlink to Related Coverage Policies

- Drug Metabolizing Enzyme Genotyping Systems (AmpliChip™, Invader®)
- Genetic Testing for Heritable Disorders
- Genotype and Phenotype Testing for HIV Drug Resistance
- Genotyping for Thiopurine Methyltransferase (TPMT) Deficiency in Individuals with Inflammatory Bowel Disease (IBD)
- Monitoring Thiopurine Metabolite Levels in Inflammatory Bowel Disease (IBD)
- Pharmacogenetic Testing for Warfarin Metabolism
- Tumor Markers for Diagnosis and Management of Cancer

INSTRUCTIONS FOR USE

Coverage Policies are intended to provide guidance in interpreting certain **standard** CIGNA HealthCare benefit plans as well as benefit plans formerly administered by Great-West Healthcare. Please note, the terms of a participant's particular benefit plan document [Group Service Agreement (GSA), Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a participant's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a participant's benefit plan document **always supercedes** the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable group benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. Proprietary information of CIGNA. Copyright ©2010 CIGNA

Coverage Policy

Gene biomarkers or gene mutation-specific coverage criteria for pharmacogenetic testing may be described in one of the Related Coverage Policies listed. If a separate Coverage Policy does not otherwise outline coverage criteria for the specific pharmacogenetic testing, the following coverage criteria apply:

CIGNA covers pharmacogenetic testing (e. g., genotyping, mutation analysis) as medically necessary when ALL of the following criteria are met:

- The individual is a candidate for a targeted drug therapy associated with a specific gene biomarker or gene mutation.
- The results of the pharmacogenetic test will directly impact clinical decision-making AND clinical outcome for the individual.

- The testing method is considered to be scientifically valid to identify the specific gene biomarker or gene mutation.
- The testing method has been scientifically proven to show a relationship between a specific gene biomarker or gene mutation and a specific therapeutic drug target.

CIGNA covers pharmacogenetic testing (e.g., genotyping, mutation analysis) for the BCR-ABL T315-I mutation in individuals with chronic myelogenous leukemia (CML) or Philadelphia chromosome positive (Ph⁺) acute lymphoblastic leukemia (ALL) as medically necessary for the detection of resistance to imatinib mesylate (Gleevec[®]), dasatinib (Sprycel[®]) or nilotinib (Tasigna[®]) for ANY of the following indications:

- inadequate initial response to tyrosine kinase inhibitor therapy (i.e., failure to achieve complete hematological response at 3 months, minimal cytogenetic response at 6 months or major cytogenetic response at 12 months)
- loss of response to tyrosine kinase inhibitor therapy (i.e., hematologic relapse, cytogenetic relapse, loss of major molecular response (MMR))
- progression to accelerated or blast phase CML while on tyrosine kinase inhibitor therapy

CIGNA does not cover pharmacogenetic testing (e.g., genotyping, mutation analysis) to detect response to targeted drug therapy for ANY of the following indications because it is experimental, investigational or unproven.

- CYP2C19 or CYP2C9 mutations (e.g., for clopidogrel [Plavix[®]] resistance or inhibition)
- CYP2D6 or CYP2D7 mutations (e.g., for tamoxifen [Nolvadex[®]] resistance or inhibition in individuals with breast cancer)
- other BCR-ABL mutations (e.g., for imatinib [Gleevec[®]], dasatinib [Sprycel[®]], or nilotinib [Tasigna[®]] resistance or inhibition in individuals with CML or ALL)
- other gene biomarkers or gene mutations not otherwise specifically described in this or another CIGNA Coverage Policy

CIGNA does not cover pharmacogenetic screening in the general population because such testing is considered not medically necessary.

General Background

Mapping of the human genome has resulted in the identification and subsequent investigation of inter-individual differences in genetic material, specifically deoxyribonucleic acid (DNA). Slight variations in DNA, called single nucleotide polymorphisms (SNPs), can result in subtle differences in proteins that translate to major differences in how the protein functions. Although polymorphism of drug-metabolizing genes has the greatest impact for inter-individual differences in drug response, genetics is only one of the variables. Other factors include the characteristics of the condition for which the drug is prescribed, co-administration of other drugs, and non-genetic factors, including the individual's diet, weight, and smoking habits.

The study of variations in DNA sequence as related to drug response is referred to as pharmacogenetic testing (Federal Drug Administration [FDA], 2008). Pharmacogenetics encompasses variation in genes encoding drug transporters, drug-metabolizing enzymes and drug targets, as well as specific genes related to the action of drugs. A pharmacogenetic test is a type of genetic test meant to guide treatment strategies, patient evaluations and decisions based on their ability to predict response to treatment in particular clinical contexts (Agency for Healthcare Research and Quality [AHRQ], 2010). Pharmacogenetic testing of tumor or other disease tissue before prescription of a drug may allow the selection of the patients most likely to benefit from treatment (Haga, 2008). When applied in a clinical setting, the information from these tests could potentially identify sources of individual variability in drug response, including both effectiveness and toxicity. The prospective use of DNA typing poses the potential of individualized therapeutic management and advances personalized medicine (National Academy of Clinical Biochemistry [NACB], 2010).

Criteria for Developing Pharmacogenetic Tests: According to the Secretary’s Advisory Committee on Genetic Testing ([SACGT], 1999-2000), the clinical use of a genetic test should be based on analytical (i.e., analytical sensitivity and specificity), and clinical validity (i.e., clinical sensitivity and specificity), and both positive and negative predictive value. Before a genetic test can be generally accepted in clinical practice, data must be collected to demonstrate the benefits and risks that accrue from both positive and negative results (i.e., the test must have clinical utility). Clinical utility refers to the usefulness of the test and the value of the information to the person being tested (SACGT, 1999-2000). Clinical utility determines whether the use of genetic testing to modify management decisions improves patient outcomes. Best evidence is prospective from randomized clinical trials of standard management procedures versus genetic test-directed management. Evidence may also be derived using banked samples from already-completed clinical trials; or by constructing an indirect chain of evidence linking test result to clinical outcome (Blue Cross and Blue Shield Association [BCBSA] Technology Evaluation Center [TEC], 2007).

To definitively show that pharmacogenetic testing has value in clinical practice, it is not enough to demonstrate that drug response varies by genotype. There must be an alternative treatment strategy, and proof that testing for the genotype and subsequently tailoring the treatment strategy based on genetic information are more clinically effective or cost effective (or both) than merely treating everyone in the usual manner (Arnett, 2007). Use of the test to identify gene variants and affected populations must be more efficient than current practice in preventing serious adverse effects. After taking into account known non-genetic factors that cause variation in response, the remaining variability in patient response can often be managed empirically by changing drugs or dosage. Adverse effects of available drugs are generally preventable with appropriate monitoring, or can be reversed by withdrawal of the drug (BlueCross BlueShield Association [BCBSA] Technology Evaluation Center [TEC], 2007).

A particular variant is not always phenotype specific in that it may have a different impact depending on the drug in question (National Academy of Clinical Biochemistry [NACB], 2010). Racial and ethnic differences in the frequency and nature of genetic variants also must be recognized in attempting to extrapolate research from one population to another. Pharmacogenomic relations must be validated for each therapeutic indication in different racial and ethnic groups, as well as in different treatment and disease contexts (Kager, 2008). Pharmacogenetic testing is not currently recommended for general population screening (NACB, 2010).

The U.S. Food and Drug Administration (FDA) considers the use of genomic information in drug labels either to require a genetic test for prescribing a drug, to recommend the use of a genetic test prior to drug therapy, or simply to provide information about the current knowledge of genomics that is relevant to drug therapy without the requirement or recommendation of a specific action (NACB, 2010). Much of the existing research in the area of pharmacogenetic testing has been limited by study design, including uncontrolled and poorly defined case and control groups, presence of confounding variables, and the use of retrospective and non-blinded study protocols.

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratories offering such tests as a clinical service must meet the general regulatory standards of the Clinical Laboratory Improvement Act (CLIA) and must be licensed by CLIA for high-complexity testing. Additionally, laboratories in the U.S. should follow the College of American Pathology Guidelines (BCBSAT, 2010; NACB, 2010). Techniques include immunohistochemistry (IHC), fluorescent in situ hybridization (FISH), polymerase chain reaction (PCR) and microarray assays. According to the FDA, diagnostic tests that assay the presence of a particular pattern (e.g., single nucleotide polymorphism [SNP] set, haplotype pattern) should ideally be validated in a prospective clinical trial (2007).

Gene Biomarkers: Specific gene biomarkers and associated drug targets that have been identified and are addressed in related Coverage Policies (please see related Coverage Policy section) include, but are not limited to the following:

Gene Biomarker	Drug Target
VKORC1, CYP2C9	Warfarin
CCR5	Miraviroc (Selzentry®)
HLA-B*5701	Abacavir (Ziagen®, Epzicom®, Trizivir®)

Other gene biomarkers and associated drug targets that have been identified but are not otherwise described in a separate Coverage Policy include the following:

Gene Biomarker	Drug Target
CYP2C19	Clopidogrel (Plavix®)
BCR-ABL	Imatinib (Gleevec®), Nilotinib (Tasigna®), Dasatinib (Sprycel®)
CYP2D6	Tamoxifen (Nolvadex®)

Pharmacogenetic Testing for CYP2C19: Cytochrome P450 2C19 (i.e., CYP2C19) is a highly polymorphic liver enzyme of the cytochrome P450 gene superfamily which is involved in the metabolism and elimination of about 5%-10% of many commonly prescribed drugs. Diverse therapeutic agents such as antidepressants, anti-epileptics, and proton pump inhibitors have been identified as substrates.

The variability in CYP2C19 alleles varies significantly between ethnicities and populations. The frequency of individuals who have one or more deficient CYP2C19 alleles is thought to be about 2%-5% in Caucasians, and 13%-23% in individuals of Asian heritage (National Academy of Clinical Biochemistry [NACB], 2010). Four phenotypes have been identified: poor metabolizers, intermediate metabolizers, ultra-rapid metabolizers, and extensive metabolizers. Poor metabolizers have a deficiency in drug metabolism due to a lack of the functional enzyme. They are at increased risk of drug-induced side effects due to diminished drug elimination or lack of therapeutic effect resulting from failure to generate the active form of the drug. Intermediate metabolizers are heterozygous for one deficient allele or carry two alleles that cause reduced enzyme activity. These individuals may require lower than average drug dosages for optimal therapeutic response. Ultra-rapid metabolizers have multiple gene copies, a trait that is dominantly inherited. They have increased metabolic capacity and may require an increased dosage due to higher than normal rates of drug metabolism. Extensive metabolizers have two normal alleles and normal drug metabolism (Ingelman-Sundberg, 2004).

Several gene variants associated with reduced or absent CYP2C19 activity exist, although the CYP2C19*2 allele accounts for more than 90% of cases of poor metabolism. Together the CYP2C19*2 and *3 alleles are responsible for the majority of reduced function alleles in Caucasian (85%) and Asian (99%) poor metabolizers, while the CYP2C19*1 allele corresponds to fully functional metabolism. Other alleles associated with absent or reduced metabolism are less frequent, and include, but are not limited to CYP2C19*4–*8 (Bristol Myers Squibb/Sanofi-Aventis, 2010). CYP2C19*17 has been associated with ultra-rapid enzyme activity.

The mechanisms leading to a poor response to clopidogrel have not yet been fully identified and are most likely caused by many factors. Clinical variables such as obesity, insulin resistance, smoking, and the nature of the coronary event may also contribute to the variability of the clopidogrel response as well as noncompliance (Simon, 2009; Shuldiner, 2009). Variation in platelet function in response to clopidogrel has also been associated with the use of a number of drugs such as lipophilic statins, calcium channel blockers, proton pump inhibitors and St John's wort, although these factors account for only a small fraction of the variation in response.

A number of variant CYP2C19 alleles have been implicated by genome-wide association studies for anti-platelet activity in individuals receiving clopidogrel. Clopidogrel bisulfate (Plavix®), Bristol Meyers Squibb/Sanofi Pharmaceuticals, Bridgewater, NJ) is an anti-platelet drug used to prevent blood clots in individuals with existing cardiovascular disease. Clopidogrel is a prodrug that requires conversion to its active form, and is catalyzed predominantly by cytochrome P450 (CYP) 3A4 and 3A5 with contributions from 2C19, 2C9, and 1A2 enzymes. Carriers of the loss-of-function allele display a reduced pharmacodynamic response to clopidogrel and a higher rate of recurrent cardiovascular events compared with non-carriers (Hulot, 2009).

U.S. Food and Drug Administration (FDA)

In March 2010 (updated in August 2010) the FDA approved a 'Black Box' warning label for clopidogrel noting diminished effectiveness in poor metabolizers. The FDA does not require testing for the gene variant nor does it give recommendations regarding alternative treatment or dosing. The label states "Poor metabolizers treated with Plavix® at recommended doses exhibit higher cardiovascular event rates following acute coronary

syndrome (ACS) or percutaneous coronary intervention (PCI) than patients with normal CYP2C19 function. Tests are available to identify a patient's CYP2C19 genotype and can be used as an aid in determining therapeutic strategy. Consider alternative treatment or treatment strategies in patients identified as CYP2C19 poor metabolizers." In August 2010, warnings were added to the prescribing information which note, "Reduced effectiveness in impaired CYP2C19 function. Avoid concomitant use with drugs that are strong or moderate CYP2C19 inhibitors (e.g., omeprazole)."

Literature Review

Several genome-wide association studies have reported inter-individual variability in platelet response to clopidogrel (Sofi, 2010; Collet, 2009; Frere, 2009; Hulot, 2009; Mega, 2009; Shuldiner, 2009; Simon, 2009; Gladding, 2008). Sofi et al. (2010) performed a meta-analysis of seven prospective cohort studies involving a total of 8043 patients followed for a period ranging from one month to 8.3 years. Enrolled individuals had diagnoses including acute coronary syndromes or stable coronary atherosclerotic disease. Loading dose varied among studies; three studies used a loading dose of 600mg of clopidogrel, two studies had a loading dose of 300mg, one study used both doses and the loading dose was not reported in one study. All of the studies reported a maintenance dose of 75mg/day. There was significant statistical heterogeneity across the studies ($p < 0.0001$). Statistical analysis in only four of seven studies was adjusted for confounding variables. In studies with stent thrombosis as the primary outcome ($n=4975$), the presence of the CYP2C19*2 variant allele was associated with an increased risk of stent thrombosis ($p < 0.00001$). Patients carrying the CYP2C19*2 allele had an increased risk of a subsequent cardiovascular event in spite of clopidogrel treatment ($p=0.004$). However, no standard dose regimen or alternative therapy was recommended as a result of the findings. Limitations to the study include study design, including a lack of randomized controls.

Collet et al. (2009) reported outcomes of 259 consecutive registry patients with coronary disease who had survived myocardial infarction, had exposure to 75mg of clopidogrel for at least one month, and underwent genotyping by assay with amplification by polymerase chain reaction for the CYP2C19*2 allele. Subjects were a cohort of patients enrolled in a secondary prevention program. Primary endpoint was a composite of cardiovascular death, non-fatal myocardial infarction, and urgent revascularization. In patients receiving a stent ($n=222$), total or partial thrombosis was also assessed. The allelic frequency of CYP2C19*2 was 15.8%. During clopidogrel exposure, 26 patients had 32 major adverse cardiac events. The CYP2C19*2 variant was significantly associated with an increase in the rate of cardiovascular events. In individuals with the CYP2C19*2 variant who received a stent there was a significant increase in stent thrombosis compared with non-carriers. When stent thrombosis was excluded, the effect of CYP2C19*2 on other ischemic events was not significant. There were no significant differences between carriers and non-carriers for plasma fibrinogen, D-dimers, total cholesterol, or LDL-cholesterol. After Cox regression analysis the CYP2C19*2 variant was the only factor significantly associated with an occurrence of a new cardiovascular event during follow-up. No standard dose regimen or alternative treatment options were recommended as a result of the findings.

Frere et al. (2009) reported the results of a prospective trial assessing 603 patients with non-ST elevation acute coronary syndrome (ACS) for the effect of CYP3A4, CYP3A5, and CYP2C19 polymorphisms on clopidogrel response. Post-treatment platelet reactivity was also assessed. In patients receiving 600-mg loading doses of clopidogrel before percutaneous coronary intervention (PCI), the CYP2C19*2 allele was associated with low platelet response to clopidogrel. Carriers of CYP2C19*2 were more prone to having high post-treatment platelet reactivity; homozygotes had higher platelet function indexes than heterozygotes ($p < 0.03$), showing a gene-dose effect with CYP2C19. Body mass index appeared to be strongly positively associated with all measured platelet indexes: non-responders to clopidogrel had higher body mass indexes than responders ($p < 0.03$) and were more likely to be carriers of the CYP2C19*2 allele ($p < 0.03$). The authors noted that it remains possible that the observed association was due to linkage with another yet unknown polymorphism.

Hulot et al. (2009) performed a meta-analysis of 23 studies involving 48674 patients treated with clopidogrel. Ten studies ($n=11959$) assessed the impact of CYP2C19 and 13 studies assessed the impact of co-administration of proton pump inhibitors (PPI) and ischemic outcomes (i.e., major adverse cardiovascular events [MACE]). Eighteen studies were of observational design from prospective or retrospective registries, and five provided reanalyzed data from randomized clinical trials. Carriers of the CYP2C19*2 allele displayed a 30% increase in the risk for MACE compared with non-carriers ($p < 0.001$) and this variant was also associated with an increase in mortality ($n=6225$, $p=0.019$) and stent thrombosis ($n=4905$, $p < 0.001$). The increased risk was apparent in both heterozygote and homozygotes and was independent of the baseline cardiovascular risk. The impact of PPI use was significantly influenced by baseline cardiovascular risk but only in high-risk patients.

When combining all data, clopidogrel-treated patients who presented with CYP2C19 deficits or drug-drug interaction with proton pump inhibitors (PPIs) had a 42% increase in the risk for occurrence for major adverse cardiovascular events (MACE). Limitations included the use of observational data for analysis.

Mega et al. (2009) tested the association between functional genetic variants in CYP genes, plasma concentrations of active drug metabolite, and platelet inhibition in response to clopidogrel in 162 healthy subjects. Additionally, a subset of 1477 subjects with acute coronary syndrome (ACS) was examined for an association between genetic variants and cardiovascular outcomes. In healthy subjects who were treated with clopidogrel, carriers of at least one CYP2C19 reduced-function allele had a relative reduction of 32.4% in plasma exposure to the active metabolite of clopidogrel, as compared with non-carriers ($P < 0.001$). Carriers also had an absolute reduction in maximal platelet aggregation in response to clopidogrel compared with non-carriers ($p < 0.001$). Among clopidogrel-treated subjects with ACS, carriers had an increase in the composite outcome of the risk of death from cardiovascular causes, myocardial infarction, or stroke, as compared with non-carriers (12.1% versus 8.0%, respectively) and an increase in the risk of stent thrombosis (2.6% versus 0.8%, respectively). No significant associations between any of the other CYP genotypes and the primary efficacy outcome were observed, nor did the rates of non-CABG-related major or minor bleeding differ significantly across any CYP genotype. Limitations of the study include retrospective design for the study examining subjects with ACS.

Shuldiner et al. (2009) reported the results of a genome-wide association study in 429 healthy Amish subjects who received clopidogrel for seven days. Subjects were genotyped for the cytochrome P450 (CYP) 2C19*2 variant. Platelet response to clopidogrel was highly heritable; 13 single-nucleotide polymorphisms on chromosome 10q24 within the CYP2C18–CYP2C19–CYP2C9–CYP2C8 cluster were associated with diminished clopidogrel response. The CYP2C19*2 variant accounted for 12% of the platelet aggregation to adenosine diphosphate (ADP). In a separate study, 227 patients with coronary disease who underwent percutaneous coronary intervention (PCI) were examined for the relation of CYP2C19*2 to platelet function and cardiovascular outcomes. The relation between CYP2C19*2 genotype and platelet aggregation was replicated in clopidogrel-treated patients undergoing PCI ($P = .02$). Patients with the CYP2C19*2 variant were also more likely to have a cardiovascular ischemic event or death during one year of follow-up.

Simon et al. (2009) analyzed registry data of 2208 consecutively enrolled patients for the relation of allelic variants of genes modulating clopidogrel absorption (ABCB1), metabolic activation (CYP3A5 and CYP2C19), and biologic activity (P2RY12 and ITGB3) to the risk of death from any cause, nonfatal stroke, or myocardial infarction during one year of follow-up. Genotyping for known variants of CYP2C19 and ITGB3 with functional importance — CYP2C19*4, CYP2C19*5, CYP2C19*17, and ITGB3 — was also performed. Patients with two variant alleles of ABCB1 had a higher rate of cardiovascular events at one year than those with the ABCB1 wild-type (i.e., normal) genotype (15.5% vs. 0.7%). Patients carrying any two CYP2C19 loss-of-function alleles (i.e., *2, *3, *4, or *5), had a higher event rate than patients with no loss of function alleles (21.5% versus 13.3%, respectively). Among the 1535 patients who underwent PCI during hospitalization, the rate of cardiovascular events among patients with two CYP2C19 loss-of-function alleles was 3.58 times the rate among those with none.

As compared with patients who did not have an outcome event, the 294 patients who had an event (13% of the study cohort) were older; more frequently had a history of hypertension, diabetes, myocardial infarction, PCI, stroke, or heart failure; and less frequently underwent reperfusion therapy consisting of PCI or intravenous fibrinolysis. Patients who had an outcome event were less likely to receive statins, beta-blockers, angiotensin-converting-enzyme inhibitors, glycoprotein IIb/IIIa inhibitors, and heparin. No significant interaction was found between either the ABCB1 variant allele or the CYP2C19 loss-of-function variant alleles and clinical outcome ($p = 0.99$). The presence of both two CYP2C19 loss-of-function alleles and either one or two ABCB1 variant alleles was associated with the highest risk of events ($p = 0.009$). Patients with an outcome event had a worse risk profile at admission for acute myocardial infarction than did those without an event. However, there was no significant difference in the risk profile or hospital care received between patients with allelic variants for clopidogrel target genes and those without such variants.

Using a cohort of subjects from a randomized, placebo controlled trial (i.e., Plavix Response in Coronary Intervention [PTINC]), Gladding et al. (2008) evaluated 60 patients for the impact of gene variants on response to clopidogrel therapy. The study compared the anti-platelet effect of varying doses of clopidogrel in the presence of the CYP2C19, CYP2C9, CYP3A4, CYP3A5, ABCB1, P2Y12, and CES genes as measured by

polymerase chain reaction (PCR)-based genotyping. Patients undergoing elective percutaneous coronary intervention (PCI) in the randomized trial had platelet function measured after a 600-mg or split 1,200-mg loading dose, and after a 75- or 150-mg daily maintenance dosage of clopidogrel. Lack of platelet inhibition at two hours predicted clopidogrel resistance at seven hours ($p=0.02$). There were fewer non-responders in the 1,200-mg group than in the 600-mg group. Platelet inhibition of less than 2% at two hours was the best predictor of non-response in all patients at seven hours, regardless of dose (sensitivity 100%, specificity 88%).

Platelet inhibition varied between different alleles and was greater two hours after a 600-mg dose in CYP2C19*1 carrier but did not differ significantly in these carriers after a 1,200- and 600-mg loading dose at four hours or seven hours, or after a 150- and 75-mg daily maintenance dosage. CYP2C19*2 or *4 carriers had greater platelet inhibition with the higher 1,200-mg loading dose than with 600 mg at four hours and showed a similar trend at seven hours. Similarly, platelet inhibition was significantly greater with the 150-mg dose than the 75-mg daily maintenance dosage regimen. The authors noted that individuals with the poor-response genotype may specifically benefit from a higher dose of clopidogrel; however, the numbers in this study are small and this finding requires confirmation in a dose escalation study with larger patient numbers. A major limitation of this study is the population size, which particularly affects assessment of the influence of the less common genotypes. Larger clinical trials are also needed to confirm the merits of a genotype-focused dosing approach over individualized treatment based on either laboratory or point-of-care platelet function analysis.

Summary for CYP2C19

Several prospective and retrospective studies have evaluated the association between the presence of CYP2C19 variants and response to clopidogrel; however, there is not yet a consensus regarding the “gold standard” test, or the definition of non-response (Cuissett, 2009). Data are also limited regarding alternative treatment options if variants are identified; clinical trials with alternative therapies are ongoing. Data are limited regarding standard dosing recommendations, and an appropriate dose regimen for this patient population has not been established in clinical outcome trials. Although an association between CYP2C19 and response to various drugs, including clopidogrel is suggested, at this time the clinical utility of pharmacogenetic testing for CYP2C19 gene variants has not been established.

Pharmacogenetic Testing for CYP2D6: Cytochrome P450 2D6 (CYP2D6) is also a part of the P450 gene superfamily and exhibits a high degree of polymorphism. More than 90 allelic variants have been identified. Twenty to 25% of available drugs are subject to metabolism by the CYP2D6 gene. Examples of CYP2D6 substrates include antidepressants, antipsychotics, beta-blockers, and anticancer agents. The impact on therapy is related to the resulting metabolizer status that the polymorphism(s) cause in the individual receiving therapy, and whether the parent drug is active, or requires CYP2D6 to metabolize it into an active metabolite (Pharmacogenomics Knowledge Base [PharmGKB], 2001-2010).

Alleles vary by ethnicity. The most prevalent alleles are CYP2D6 *1 and *2, which produce an enzyme with normal activity. Among reduced function variants, *17, *10, and *8 are the most important in African-Americans, Asians, and Caucasians, respectively (Blue Cross and Blue Shield Association [BCBSA] Technology Evaluation Center [TEC], 2008). Phenotypes that have been identified and associated with CYP2D6 include poor, intermediate, extensive, and ultra-rapid metabolizers. Frequency of the poor metabolizer phenotype is 7%–10% in Caucasians, 1.9%–7.3% in African Americans, and $\leq 1\%$ in most Asian populations studied (National Academy of Clinical Biochemistry [NACB], 2010; Blue Cross and Blue Shield Association [BCBSA] Technology Evaluation Center [TEC], 2008). The extensive metabolizer phenotype is the most common in Caucasian populations, and accounts for 50% of the population (NACB, 2010).

Therapy with CYP2D6 substrates can be complex, not only due to genetic variation, but also due to drug-drug interactions. For example, an extensive metabolizer can appear to be an intermediate or poor metabolizer because most of the available enzyme is being inhibited by a confounding drug. Additionally, a related phenotype can occur with chronic dosing of a CYP2D6 drug (i.e., autophenocopying), in which a CYP2D6 substrate can inhibit its own metabolism over time as the concentration of the drug approaches steady state (PharmGKB, 2001-2010).

CYP2D6 is a key enzyme in the metabolism of tamoxifen, a selective estrogen receptor modulator which is important for the treatment and prevention of breast cancer. Tamoxifen is a pro-drug and is extensively metabolized by the cytochrome P450 system to several primary and secondary metabolites, including tamoxifen 4-hydroxylation and endoxifen. Because the CYP2D6 enzyme has known inter-individual variability, it has been

hypothesized that breast cancer patients with poor and intermediate metabolizer genotypes who are treated with tamoxifen may have worse clinical outcomes compared to patients with extensive metabolizer genotypes (Agency for Healthcare Research and Quality [AHRQ], 2010; Dezentje, 2009; Blue Cross and Blue Shield Association [BCBSA] Technology Evaluation Center [TEC], 20087). A substantial portion of the variability in metabolite concentrations is not explained by the CYP2D6 genotype, however. Additional polymorphic enzymes play a role in the metabolism of tamoxifen including CYP2C9, CYP2C19, CYP3A, SULT1A1 and UGT2B15. Polymorphisms in the genes for these enzymes may also have an effect on overall tamoxifen efficacy. Additionally, a number of drugs known to inhibit CYP2D6 and reduce tamoxifen metabolite concentrations are often prescribed with this population. These include selective-serotonin reuptake inhibitors and statins.

U.S. Food and Drug Administration (FDA)

There are no labeling recommendations from the FDA regarding CYP2D6 genotyping for use with tamoxifen citrate (Nolvadex[®], AstraZeneca, Wilmington, DE) or its generic versions.

Literature Review

Several studies focus on the association of CYP2D6 genetic variants and tamoxifen. The Agency for Healthcare Research and Quality (AHRQ, 2010) performed a systematic review of the published literature and reported the results of 16 studies. No consistent associations were found between CYP2D6 polymorphisms and tamoxifen treated women with breast cancer across these studies. The AHRQ noted limitations in the study designs; ten studies were retrospective, and the studies included in the review were generally small in size, followed poor analytic practices, and differed both in the direction and in the formal statistical significance of their results. There was complete or extensive overlap in patient populations of six studies. AHRQ documented extensive heterogeneity in the definitions of CYP2D6-derived metabolizer categories across eligible studies; different studies classified the same genotypes into different categories of predicted enzymatic activity. Seven studies reported analyses on overall survival outcomes. The majority of studies (n=9) assessed the ability of CYP2D6 testing to predict outcomes only in women who received tamoxifen. None of the included studies performed analyses for interaction to predict response to therapy. No study demonstrated a statistically significant relationship between CYP2D6-defined metabolizer status and overall survival or mortality in either adjusted or unadjusted analyses. No study explicitly reported details on changes in treatment plans before and after testing as a result of genotyping.

AHRQ (2010) noted "It is unclear whether pharmacogenetic testing of germline (heritable) mutations in CYP2D6 can predict differential response to adjuvant tamoxifen in women with non-metastatic breast cancer. Further, evidence is severely limited for tamoxifen-treated women with metastatic disease." They further noted "We found no evidence on whether patient or disease relevant factors affect the association between CYP2D6-derived metabolizer status and outcomes in tamoxifen treated women. Several studies performed simple adjustments for patient level factors. This is not only noninformative, but also questionable from an analytic standpoint." "Most studies were relatively small and thus underpowered to detect what would be a plausible effect size for the modification of response to tamoxifen by a single polymorphism."

A technology assessment by the Blue Cross and Blue Shield Association [BCBSA] Technology Evaluation Center [TEC], 2008) evaluated the evidence for CYP2D6 genotyping, compared to no testing, to direct treatment regimen choices and improve survival outcomes for patients at high risk for primary breast cancer or breast cancer recurrence. The study reviewed full-length, peer-reviewed papers reporting studies of postmenopausal women undergoing endocrine therapy whose treatment regimen selection was based on CYP2D6 genotyping versus usual selection methods and studies of the association of CYP2D6 genotype with intermediate (e.g., tamoxifen active metabolite levels) or final outcomes (e.g., time to recurrence, survival).

The assessment noted "There is no direct evidence of clinical utility. Two indirect evidence chains can be constructed. One depends on demonstrating a significant association between endoxifen and clinical outcomes; this evidence does not exist. The other depends on the association of genotype with clinical outcomes; there are several limitations to this evidence, and, as a result, it is judged insufficient to support clinical utility. There was no direct evidence of clinical utility." The assessment further noted "There is insufficient evidence to permit conclusions regarding the use of CYP2D6 genotyping for directing endocrine therapy regimen selection for women at high risk for or with breast cancer." "Whether or not the use of CYP2D6 genotyping for directing endocrine therapy regimen selection for women at high risk for or with breast cancer improves health outcomes has not been demonstrated in the investigational setting."

Goetz et al. (2007) performed a retrospective review of the combined effect of CYP2D6 and HOXB13/IL17BR in the outcomes of disease-free survival (DFS) and overall survival (OS) in a cohort of 160 women with lymph node–negative breast cancer treated with adjuvant tamoxifen monotherapy. In 110 of 160 women the HOXB13/IL17BR gene expression data and a comprehensive assessment of CYP2D6*4 genotype and medication history were known. The combined CYP2D6:HOXB13/IL17BR risk factor was significantly associated with DFS ($p = 0.004$) and OS ($p = 0.009$). Relative to women with extensive CYP2D6 metabolism and low HOXB13/IL17BR, those with either decreased metabolism or a high HOXB13/IL17BR ratio had significantly worse OS ($p = 0.031$), whereas women with both decreased metabolism and high HOXB13/IL17BR ratio had the shortest survival ($p = 0.024$). The authors suggest that a combined index of inherited CYP26 and tumor HOXB13/IL17BR variation may identify individuals with varying degrees of tamoxifen resistance.

In an earlier retrospective study, Goetz et al. (2005) evaluated the tumor specimens of a cohort of 223 women with resected estrogen receptor (ER)-positive breast cancer, who had participated in a tamoxifen-only arm of a randomized phase III clinical trial. The buccal swabs of 17 living women with the disease were also evaluated for CYP2D6 (*4 and *6) and CYP3A5 (*3). The concordance rate between the tumor and buccal types was 100%. Women with the CYP2D6*4/*4 genotype had a worse relapse-free time ($p=0.23$) and DFS ($p=0.12$) but not OS ($p=0.169$). In multivariate analysis individuals with the CYP2D6*4 genotype had worse relapse-free survival (RFS, $p=0.176$) and DFS ($p=0.089$). The CYP3A5 variant was not associated with any of these clinical outcomes.

Wegman et al. (2007) retrospectively evaluated 677 tamoxifen-treated postmenopausal patients with breast cancer who were genotyped for CYP3A5, CYP2D6, SULT1a1, or UGT2B15. Two hundred thirty-eight patients had been randomized to either three or five years of tamoxifen. Significantly better DFS was noted in individuals homozygous for CYP2D6*4. No prognostic significance was noted for SULT1A1 or UGT2B15. No reliable differences were noted between treatment duration and the genotypes of CYP2D6. Significantly improved relapse-free survival (RFS) was noted in individuals with CYP3A5 who received prolonged tamoxifen therapy. No differences were noted for individuals with CYP2D6, SULT1A1, or UGT2b15.

Nowell et al. (2005) performed a retrospective review of 162 women with primary invasive breast cancer who received tamoxifen and 175 women who did not receive hormonal therapy. Paraffin-embedded archived tissues were used for DNA analysis. Tissue was genotyped for CYP2D6*3, CYP2D6*4, and CYP2D6*6 polymorphisms and UGT2B15 and SULT1A1 alleles. After adjusting for age, race, stage of disease at diagnosis, and hormone receptor status, no significant association was found between CYP2D6 genotype and overall survival in either group of breast cancer patients. Tamoxifen treated patients with UGT2B15 high activity genotypes had increased risk of recurrence and poorer survival. When UGT2B15 and SULT1A1 'at-risk' alleles were combined, women with two variant alleles had significantly greater risk of recurrence and poorer survival than those with common alleles.

Summary for CYP2D6

The metabolism of tamoxifen is complex and the mechanisms responsible for the resistance are unlikely to be explained by a single polymorphism; instead it is a combination of several mechanisms (Wegman, 2007). Data are limited regarding alternative dosing recommendations, and an appropriate dose regimen for this patient population has not been established in clinical outcome trials. Data are also limited regarding alternative treatment options if variants are identified. At this time there are insufficient data regarding the clinical utility of pharmacogenetic testing for CYP2D6 as related to the effectiveness of tamoxifen therapy in individuals with breast cancer.

Pharmacogenetic Testing for BCR-ABL: The breakpoint cluster region (BCR)-Abelson (ABL) fusion gene is a cancer-causing gene (i.e., oncogene) generated when a part of the ABL gene on chromosome 9 and a part of chromosome 22 break off and swap places (i.e., balanced translocation). The ABL gene relocates to the BCR gene on chromosome 22; the resulting chromosome is known as the Philadelphia chromosome (Ph, t(9;22)). This chromosome is found in about 95% of individuals with chronic myelogenous leukemia (CML), and 30% of adults with acute lymphoblastic leukemia (ALL) and is important both in terms of diagnosis and for monitoring response to treatment (Agency for Healthcare Research and Quality [AHRQ], 2010; National Cancer Institute [NCI], 2010; Najfeld, 2008; National Institute for Clinical Excellence [NICE], 2002). In CML, the standard method for monitoring response to therapy is conventional cytogenetic analysis of metaphase chromosomes obtained from marrow aspirate (Najfeld, 2008; NICE, 2002). The test can also identify additional chromosome abnormalities which may be important indicators of prognosis; however, because of the relatively small numbers

of cells examined the sensitivity is approximately 5% if 20 metaphases are examined (National Institute for Clinical Excellence [NICE], 2002).

Other laboratory techniques may include hyperphase and interphase fluorescence in situ hybridization (FISH), and real-time quantitative polymerase chain reaction (RQ-PCR). These molecular assays improve the ability to measure residual disease and to estimate risk of relapse (Nashed, 2003). Real-time quantitative PCR (RQ-PCR) is by far the most sensitive method. It provides an accurate measure of the total leukemia cell mass and the degree to which breakpoint cluster region-Abelson (BCR-ABL) transcripts are reduced by therapy, and correlates with progression-free survival. Current international recommendations for optimal molecular monitoring of patients receiving imatinib treatment include an RQ-PCR assay expressing the BCR-ABL transcript levels, which is predictive of prognosis (Bhatia, 2008; Najfeld, 2008). Molecular responses at 12 and 18 months are also predictive of long-term outcome (Bhatia, 2008). In acute lymphocytic leukemia (ALL), because many patients have a different fusion protein from the one found in chronic myelogenous leukemia (CML), the BCR-ABL gene may be detectable only by pulsed-field gel electrophoresis or reverse-transcriptase polymerase chain reaction (RT-PCR). These tests should be performed whenever possible in patients with ALL, especially those with B-cell lineage disease (NCI, 2010a).

The BCR-ABL gene encodes an enzyme called tyrosine kinase. BCR-ABL tyrosine kinase is not controlled by normal cellular mechanisms and its presence leads to enhanced cell proliferation, resistance to apoptosis (i.e., programmed cell death) and altered adhesion (NICE, 2002). Unregulated tyrosine kinase activity is important to the development of several disorders including CML, and some types of ALL. Other disorders in which unregulated tyrosine activity is implicated include gastrointestinal stromal tumors (GIST), dermatofibrosarcoma protuberans, myelodysplastic syndromes, and mast cell disease. With these disorders other gene biomarkers and variants have been identified. For the purpose of this Coverage Policy, discussion is limited to the BCR-ABL fusion gene in individuals with CML and ALL.

Several drugs have been approved by the Federal Drug Administration (FDA) for use in selected individuals with CML and ALL, including Imatinib mesylate (Gleevec®, Novartis, East Hanover, NJ), dasatinib (Sprycel®, Bristol Myers Squibb Company, Princeton, NJ), and nilotinib hydrochloride monohydrate (Tasigna®, Novartis, East Hanover, NJ). These drugs are tyrosine kinase inhibitors (TKI), that is, drugs that bind to the tyrosine kinase enzyme and inhibit its activity (AHRQ, 2010). The goal of therapy is to achieve a molecular response as measured by the reduction or elimination of BCR-ABL transcripts. Increasing the dose schedule of TKIs can often overcome the resistance due to gene amplification. Those individuals who cannot tolerate or are resistant to imatinib may benefit from the second generation of TKIs, such dasatinib and nilotinib. Because their mechanism of action is different from imatinib they retain activity against nearly all imatinib resistant mutations (Najfeld, 2008).

The two major obstacles to successful TKI-based therapies are the persistence of BCR-ABL fusion-positive cells and relapse of the disease due to emergence of resistance (Najfeld, 2008; AHRQ, 2010). Acquired resistance to imatinib treatment is manifested in two ways: amplification of BCR-ABL fusion product and mutations in the ABL kinase domain. Specific mutations in BCR-ABL have been shown to confer resistance to imatinib both in vitro and in vivo, by affecting the binding of the drug to the tyrosine kinase enzyme (AHRQ, 2010). Currently 40 different ABL kinase domain mutations have been described. Of interest is the T315I mutation which is thought to be resistant to all current TKI therapy. The mutation frequency in imatinib resistant patients with CML ranges between 2% and 20%, with variability related to detection methods as well as patient cohort characteristics and treatment. T315I mutation frequency appears to be greater in patients with Philadelphia chromosome-positive (Ph⁺) ALL and likely increases with the continuation of TKI treatment (Nicolini, 2009). The detection of mutations of the BCR-ABL gene has been proposed as a pharmacogenetic test with potential impact on management decisions (AHRQ, 2010).

Literature Review

Several studies have reported associations between variations of BCR-ABL and response to drug therapy. AHRQ (2010) performed a systematic review of the published literature regarding variations of the BCR-ABL1 fusion gene and response to imatinib, dasatinib, and nilotinib in CML. Thirty-one studies were analyzed for outcomes of interest including overall survival and cancer specific survival; progression-free or event-free survival (as defined by each study); and treatment failure. Typically, treatment failure is defined as absence of hematologic, cytogenetic, or molecular response to treatment, according to various criteria. Data was analyzed for first-, second-, and third- line TKI therapy. Second-line TKI therapy studies (four publications) demonstrated

sensitivity and specificity ranges of 0.35 to 0.83 and from 0.58 to 1.00, respectively, for high-dose imatinib and imatinib-based combination. These studies were small, the calculated sensitivity and specificity values have wide confidence intervals, and a range of different mutations was identified in each of them. No robust conclusions could be made. Eight studies (9 publications) pertained to dasatinib; some had overlapping populations. Sensitivities and specificities ranged from 0.27 to 0.90 and from 0.14 to 0.87, respectively. A lack of predictive ability is suggested. For nilotinib, three studies had relevant data. Sensitivity ranged from 0.56 to 0.71 and specificity ranged from 0.42 to 0.56 for all identified mutations. Only one included study reviewed overall survival (OS). No statistically significant differences in the time-to-death among patients with, versus without mutations were found. When any breakpoint cluster region- Abelson (BCR-ABL1) mutation was considered, almost all studies reported sensitivity and specificity values that are not suggestive of strong predictive ability. The Agency for Healthcare Research and Quality (AHRQ) notes that no study explicitly reported details on changes in treatment plans before or after testing.

AHRQ determined “The presence of any BCR-ABL mutation does not appear to differentiate response to tyrosine kinase inhibitor (TKI) treatment (i.e., imatinib, dasatinib, nilotinib).” AHRQ also notes “the majority of evidence pertains to the short term surrogate outcomes of hematologic, cytogenetic or molecular response. Data on overall or progression-free survival are sparse. “ “There is consistent evidence that presence of the relatively rare T315-I mutation can predict TKI treatment failure, mainly in terms of hematologic and cytogenetic response.”

Jabbour et al. (2009) studied 169 patients with chronic myelogenous leukemia (CML) after imatinib failure. The goals of the study were to investigate whether in vitro sensitivity of kinase domain mutations could be used to predict the response to therapy as well as the long-term outcome of patients receiving second-generation TKIs after imatinib failure. Treatment failure was defined as loss of a cytogenetic, or complete hematologic response (CHP), or failure to achieve a CHR or any hematologic response (for patients in accelerated phase or blast phase after 3 months of therapy, or persistence of 100% Philadelphia chromosome (Ph)⁺-positive metaphases after 6 months of therapy, or more than or equal to 35% after 12 months). Fifty-seven patients (66%) had received prior therapy with interferon-alpha before the start of imatinib; 29 (34%) had received imatinib as their first-line therapy for CML. Mutations were detected by cDNA sequencing for mutations in the kinase domain of BCR-ABL before a change to dasatinib or nilotinib in 86 patients. Ninety-four mutations were identified in 86 patients with imatinib failure. Seven patients harbored more than 1 mutation. There was no difference in patient characteristics between those with mutations at the time of imatinib failure versus those with no mutations. Forty-one patients received dasatinib and 45 received nilotinib after developing failure to imatinib therapy. Hematologic and cytogenetic response rates were similar for patients without or with KD mutations. After a median follow-up of 23 months, 48 (58%) of patients without baseline mutations were alive compared with 52 (60%) with any mutation.

Nicolini et al. (2009) reported the results of a retrospective observational study of 222 patients with CML in chronic-phase, accelerated-phase, or blastic-phase and Philadelphia chromosome-positive (Ph⁺) ALL patients with the BCR-ABL T315I mutation. After T315I mutation detection, second-generation TKIs were used in 56% of cases, hydroxyurea in 39%, imatinib in 35%, cytarabine in 26%, MK-0457 in 11%, stem cell transplantation in 17%, and interferon-alpha in 6% of cases. Median overall survival from T315I mutation detection was 22.4, 28.4, 4.0, and 4.9 months, and median progression-free survival was 11.5, 22.2, 1.8, and 2.5 months, respectively, for chronic phase, accelerated phase, blastic phase, and Ph(+) ALL patients. These results suggest that survival of patients harboring a T315I mutation is dependent on disease phase at the time of mutation detection.

In a study by Jabbour et al. (2006) 171 patients were screened for mutations after failing TKI therapy with a median follow-up of 38 months from start of therapy. Sixty-six mutations impacting 23 amino acids in the BCR-ABL oncogene were identified in 62 (36%) patients. Factors associated with the development of mutations were older age, previous interferon therapy and accelerated or blast phase at the start of TKI therapy. By multivariate analysis, factors associated with a worse survival were development of clonal evolution and a higher percentage of peripheral blood basophils. The presence of a BCR-ABL kinase domain mutation had no impact on survival. When survival was measured from the time therapy started, non-P-loop mutations were associated with a shorter survival than P-loop mutations. The authors concluded that BCR-ABL P-loop mutations were not associated with a worse outcome. This study suggests that outcomes of individuals who fail TKI therapy may be influenced by multiple factors.

Nicolini and colleagues (2006) retrospectively analyzed the predictive impact of 94 breakpoint cluster region (BCR)- Abelson (ABL) kinase domain mutations found in 89 protein tyrosine kinase inhibitor (TKI) resistant chronic myelogenous leukemia (CML) individuals. With a median follow-up of 39 months, overall survival was worse for P-loop and another point mutation (T315-I), but not for other BCR-ABL mutations. For individuals in chronic phase only, analysis demonstrated a worse overall survival for P-loop and worse progression free survival for T315-I mutations.

U.S. Food and Drug Administration (FDA)

There are no labeling recommendations from the FDA regarding BCR-ABL genotyping for use with imatinib mesylate (Gleevec[®], Novartis, East Hanover, NJ), dasatinib (Sprycel[®], Bristol Myers Squibb Company, Princeton, NJ), or nilotinib hydrochloride monohydrate (Tasigna[®], Novartis, East Hanover, NJ).

Summary for BCR-ABL

Although certain BCR-ABL mutations may be associated with TKI therapy resistance, sensitivity and specificity values in outcome studies are not suggestive of strong predictive ability, with the exception of the T315-I mutation. Early identification of this mutation may allow for alternative treatment regimens including increased dose scheduling and drug selection. Data in the published peer-reviewed scientific literature supports the clinical utility of testing for the presence of the T315-I mutation as evidence of TKI resistance. At this time the clinical utility of testing for other mutations to determine TKI resistance has not been established.

Professional Societies/Organizations

American College of Cardiology Foundation/American Heart Association (ACCF/AHA): Regarding clopidogrel and the FDA's "boxed warning", the ACCF/AHA recommendations for practice include the following:

- "Adherence to existing ACCF/AHA guidelines for the use of antiplatelet therapy should remain the foundation for therapy.
- Clinicians must be aware that genetic variability in CYP enzymes alter clopidogrel metabolism, which in turn can affect its inhibition of platelet function.
- The specific impact of the individual genetic polymorphisms on clinical outcomes remains to be determined (e.g., the importance of CYP2C19*2 versus *3 or *4 for a specific patient), and the frequency differs among ethnic groups.
- Information regarding the predictive value of pharmacogenomic testing is very limited at this time.
- The evidence base is insufficient to recommend either routine genetic or platelet function testing at the present time."

American Society of Clinical Oncology (ASCO): In the Guideline titled "Update on the Use of Pharmacologic Interventions Including Tamoxifen, Raloxifene, and Aromatase Inhibition for Breast Cancer Risk Reduction", ASCO (2009) notes "The guideline does not recommend testing for variants in the risk reduction setting at the present time."

National Comprehensive Cancer Network[™] (NCCN[™]): Regarding kinase domain mutation testing, the NCCN notes "Kinase domain mutation analysis is recommended in chronic phase CML if there is inadequate initial response (failure to achieve complete hematological response at 3 months, minimal cytogenetic response at 6 months or major cytogenetic response at 12 months or any sign of loss of response (defined as hematologic relapse, cytogenetic relapse or 1 log increase in BCR-ABL transcript ratio and loss of MMR)." The NCCN also recommends that "KD mutation testing be performed for progression to accelerated or blast phase CML (2010)."

Canadian Agency for Drugs and Technologies in Health (CADTH): CADTH (2007) notes "Prospective studies are needed to determine whether pharmacogenomic testing improves patient outcomes, identify which subgroups of patients may benefit, and clarify the risks and costs associated with the use of these tests."

National Cancer Institute (NCI): Regarding BCR-ABL mutation analysis in individuals with chronic myelogenous leukemia (CML), the NCI notes "Mutations in the tyrosine kinase domain can confer resistance to imatinib mesylate; alternative inhibitors such as dasatinib or nilotinib, higher doses of imatinib mesylate, and allogeneic stem cell transplantation (SCT) are being studied, as evidenced in the UCLA-0501047-01 trial, for example, in this setting. Clinical trial participation should help establish the optimal sequence of these options (2010)."

Summary

Pharmacogenetic testing of specific gene biomarkers or mutations may be appropriate if an individual is a candidate for a targeted drug therapy associated with a specific gene biomarker or mutation and the results will directly impact clinical decision making and/or clinical outcomes. The testing method should be proven by scientifically valid methods to identify the specific gene biomarker or gene mutation and results should be reproducible and subject to peer review. The evidence in the peer-reviewed scientific literature supports the clinical utility of pharmacogenetic testing for the T315-I mutation. The clinical utility of pharmacogenetic testing for all other indications has not been established at this time.

Coding/Billing Information

Note: This list of codes may not be all-inclusive.

Covered when medically necessary when used to report pharmacogenetic testing for the BCR-ABL T315-I mutation:

CPT®* Codes	Description
83891	Molecular diagnostics; isolation or extraction of highly purified nucleic acid; each nucleic acid type (ie, DNA or RNA)
83896	Molecular diagnostics; nucleic acid probe, each
83898	Molecular diagnostics; amplification, target, each nucleic acid sequence
83900	Molecular diagnostics; amplification, target, multiplex, first 2 nucleic acid sequences
83902	Molecular diagnostics; reverse transcription
83912	Molecular diagnostics; interpretation and report
84999	Unlisted chemical procedure

ICD-9-CM Diagnosis Codes	Description
204.00-204.02	Acute lymphoid leukemia
205.10-205.12	Chronic myeloid leukemia

Experimental/Investigational/Unproven/Not Covered when used to report pharmacogenetic testing for any other indication listed as experimental/investigation/unproven or not medically necessary in this policy:

CPT* Codes	Description
83892	Molecular diagnostics; enzymatic digestion, each enzyme treatment
83901	Molecular diagnostics; amplification, target, multiplex, each additional nucleic acid sequence beyond 2 (List separately in addition to code for primary procedure)
83914	Mutation identification by enzymatic ligation or primer extension, single segment, each segment (eg, oligonucleotide ligation assay [OLA], single base chain extension [SBCE], or allele-specific primer extension [ASPE])
	Multiple/varied

***Current Procedural Terminology (CPT®) © 2010 American Medical Association: Chicago, IL.**

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Policy History

Pre-Merger Organizations	Last Review Date	Policy Number	Title
CIGNA HealthCare	N/A	N/A	N/A
Great-West Healthcare	N/A	N/A	N/A

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Connecticut General Life Insurance Company has acquired the business of Great-West Healthcare from Great-West Life & Annuity Insurance Company (GWLA). Certain products continue to be provided by GWLA (Life, Accident and Disability, and Excess Loss). GWLA is not licensed to do business in New York. In New York, these products are sold by GWLA’s subsidiary, First Great-West Life & Annuity Insurance Company, White Plains, N.Y.