



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.

**Subject Drug Metabolizing Enzyme
Genotyping Systems
(AmpliChip™, Invader®)**

**Effective Date6/15/2009
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Coverage Policy Number0381**

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Monitoring Thiopurine Metabolite Levels in
Inflammatory Bowel Disease (IBD)
Pharmacogenetic Testing for Warfarin
Metabolism

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 ©2009 CIGNA

Coverage Policy

CIGNA does not cover drug metabolizing enzyme genotyping systems (e.g., AmpliChip™ Cytochrome P450 (CYP450) Genotyping Test; Invader® UGT1A1 Molecular Assay) because they are considered experimental, investigational or unproven.

General Background

Drug metabolizing enzyme genotyping systems test deoxyribonucleic acid (DNA) for the presence or absence of human genotypic markers that encode a drug metabolizing enzyme. The aim of these systems is to identify genetic mutations that affect the way the body metabolizes (i.e., too fast, too slow or not at all) certain medications. Test results are intended to allow the clinician to predict the patient's response to pharmacotherapy, assist in making treatment choices, individualize drug dosages in order to maintain a consistent drug level in the body, and avoid adverse reactions from overdose or suboptimal effects from under medication (Al-Goul, et al., 2008; FDA, 2005).

The AmpliChip™ Cytochrome P450 (CYP450) Genotyping Test (Roche Molecular Systems, Inc. Pleasanton, CA) is a drug-metabolizing enzyme genotyping device that uses polymerase chain reaction (PCR) amplification technology to prepare DNA obtained from a blood sample. The test detects genetic variations in CYP450, a family of genes, found primarily in the liver where they break down toxins, drugs and compounds. The blood samples are analyzed on the Affymetrix GeneChip® Microarray Instrumentation System. By using tiny chips

housed in a cartridge, Affymetrix microarrays allow analysis of multiple DNA fragments (i.e., oligonucleotides) at one time. The specific gene enzymes that are analyzed by this test, CYP2D6 and CYP2C19, play a role in the metabolism of antidepressants, antipsychotics, beta-blockers, opiates, and some chemotherapy drugs. There are four CYP2D6 phenotypes in the general population: ultrarapid (UM), extensive (EM), intermediate (IM) and poor (PM) metabolizers. The phenotype is proposed to predict how an individual will metabolize and respond to drug therapy.

The Invader[®] UGT1A1 Molecular Assay (Third Wave Technologies, Madison, WI) is a diagnostic pharmacogenetic test used for the detection and genotyping of the *1 telomere-associated (TA) 6 and *28 (TA7) alleles of the uridine diphosphate (UDP) glucuronosyltransferase 1A1 (UGT1A1) gene in genomic DNA. It is tested from whole peripheral blood as an aid in identifying patients at a greater risk for decreased UDP-UGT1A1 activity. The Invader utilizes Tecan GENios, Tecan GENios FL, or Bio-Tek FLX800 fluorometers and the Call Reporting Software (CRS). This gene is responsible for producing the enzyme which influences an individual's ability to metabolize certain drugs, including irinotecan, a drug used in colorectal cancer treatment. According to Third Wave Technologies, Invader technology is applicable to various fields other than pharmacogenetics, such as chromosomal analysis, genetics, infectious disease, and cardiovascular disease.

U.S. Food and Drug Administration (FDA)

Drug metabolizing enzyme genotyping systems are FDA approved as a Class II, 510(k) device. The Roche AmpliChip CYP450 Test is approved "to identify a patient's CYP2D6 genotype from genomic DNA extracted from a whole blood sample" which may aid clinicians in determining therapeutic strategy and treatment doses for drugs that are metabolized by the CYP2D6 gene product. The FDA also cleared the use of AmpliChip "as an aid to clinicians in determining therapeutic strategy and treatment dose for therapeutics that are metabolized by the CYP2C19 gene product" (FDA, 2009; FDA, 2005).

The Invader[®] UGT1A1 Molecular Assay is FDA approved as "an in vitro diagnostic test for the detection and genotyping of the *1 (TA6) and *28 (TA7) alleles of the UDP glucuronosyltransferase 1A1 (UGT1A1) gene in genomic DNA from whole peripheral blood as an aid in the identification of patients with greater risk for decreased UDP-glucuronosyltransferase activity" (FDA, 2007).

The FDA stresses that these tests should be used in conjunction with patient history and other clinical information. They should not be used alone.

Literature Review - AmpliChip CYP450 Genotyping Test

Using AmpliChip, Ramon et al. (2009) conducted a retrospective chart review of 91 subject to "evaluate the impact of CYP2D6 genotyping in predicting disease-free survival and toxicity in breast cancer patients treated with adjuvant tamoxifen". The patients, all estrogen-receptor positive, were divided into group 1 (*4/*4, *4/*41, *1/*5 and *2/*5) and group 2 (the remaining genotypes). The patients had been treated with radiotherapy and either adjuvant monotherapy-tamoxifen or an adjuvant tamoxifen and concomitant chemotherapy. Follow-up ranged from 91–133 months. Following patient selection, blood samples were taken for analysis. There was a significant difference in the disease-free survival (DFS) rate between the groups (p=0.016), a mean 95 months for group 1 compared to a mean 119 months for group 2. There were no significant differences in toxicity based upon the CYP2D6 genotype (p=0.02), but mild and severe toxicities were seen in the poor metabolizers. Author-noted limitations of the study included: retrospective bias of patient selection, small patient population and the infrequency of the CYP2D6 variants in the European population.

Rebsamen et al. (2009) conducted a study to evaluate the performance of AmpliChip in CYP2D6 prediction. DNA samples from 165 individuals. The AmpliChip results were confirmed by 100 samples tested for *3, *4, *5, *6 using real-time polymerase chain reaction (PCR). Genotype sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) for AmpliChip testing were all 100%. The phenotype predictive ability of AmpliChip was determined by assessing the metabolic ratio (MR) between dextromethorphan (DEM), an antitussive drug, and its metabolite dextrorphan in urine specimens collected eight hours after ingestion of 25 milligrams of DEM. The frequency of the phenotypes was 10% ultra rapid (UM), 69% extensive (EM), 12% intermediate (IM) and 9% poor metabolizers (PM). The phenotypes were compared to the genotypes. With the exception of UM, an overall good AmpliChip phenotype prediction was observed and reported as follows: EM sensitivity 95%; specificity 47%; PPV 80%; NPV, 80%; UM sensitivity 6%; specificity 99%, PPV 50%, NPV 90%; IM sensitivity 42%, specificity 97%, PPV 61%, NPV 93%; PM sensitivity, specificity, PPV and NPV were each 100%.

de Leon et al. (2005) tested patients on risperidone therapy to determine if CYP2D6 poor metabolizer (PM) phenotype was associated with risperidone acute drug reactions (ADRs) (n=325) and discontinuation of risperidone due to ADRs (n=205). A total of 73 patients had moderate-to-severe ADRs while on risperidone and 12 (16%) were poor metabolizers. Of the 81 patients who had risperidone discontinued due to ADRs, seven (9%) were PMs. The CYP2D6 PM metabolizer significantly increased the odds of having moderate ADRs by 3.1 (CI=1.4–7.0; p=0.004) and increased the odds of discontinuation due to ADRs by 3.0 (CI=0.085–10.6; p=0.07). Although the PM seems to be associated with ADRs and discontinuation due to ADRs to risperidone, the authors stated that further studies in larger populations were indicated.

Chou et al. (2003) conducted a comparative study of the outcomes of CYP450 GeneChip microarray assay compared to standard methods of genetic testing. Blood samples were drawn from 236 volunteers who then ingested 60 mg of dextromethorphan followed by urine testing. CYP2D6 alleles 2–*4 and *6–*11 were tested by the Affymetrix CYP450 GeneChip and multiple CYP2D6 alleles including *3–*7, *9, *17, and *41 were tested by allele-specific polymerase chain reaction. Based on the number and purported activities of the CYP2D6 alleles, the 229 subjects were divided into the four genotype subgroups, PM, IM, EM and UM. The mean dextromethorphan metabolic ratio for each group was significantly different compared to that of all other groups with the exception of the differences between the UM and EM groups which was not significant. The overall difference in the group mean dextromethorphan metabolic ratio values was significant (P<0.001). The results showed a greater than 99% concordance between GeneChip and standard gene testing.

Technology Assessments - AmpliChip CYP450 Genotyping Test

The Agency for Healthcare Research and Quality (AHRQ) published an evidence report/technology assessment on CYP450 genetic testing in adult patients beginning treatment for non-psychotic depression with selective serotonin reuptake inhibitors (SSRIs). The review revealed a paucity of high-quality clinical studies. Based upon 37 articles that met inclusion criteria, the report concluded that “there is a paucity of good-quality data addressing the questions of whether testing for CYP450 polymorphisms in adults entering SSRI treatment for non-psychotic depression leads to improvement in outcomes, or whether testing results are useful in medical, personal, or public health decision making”. AHRQ stated that there were no guidelines regarding how the results of AmpliChip can be incorporated into clinical practice and there is little information regarding benefits from the use of AmpliChip (Matchar, et al., 2007).

The Blue Cross and Blue Shield Association (BCBSA), Technology Evaluation Center (TEC) (2007) evaluated the “evidence for CYP2D6 genotyping [AmpliChip], compared to no testing, to direct treatment regimen choices for patients at high risk for primary breast cancer or breast cancer recurrence, and improve survival outcomes”. The report concluded that “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” and “no direct evidence of clinical utility”.

The Canadian Agency for Drugs and Technologies in Health (CADTH) (2006) reports that studies have shown that AmpliChip does accurately identify CYP2D6 and CYP2C19, but have not linked its use to an improvement in patient outcomes or shown that outcomes can be predicted or altered by knowledge of drug metabolizing enzyme status.

Literature Review Invader UGT1A1 Molecular Assay

Baudhuin et al. (2007) analyzed 119 DNA samples to evaluate and compare the Invader with an automated fluorescent sequencing assay and a capillary electrophoresis allelic size-based method (fragment analysis) for genotyping the UGT1A1 TATA box. The majority of the (TA)_n were *6/*6 and *6/*7. There was 100% concordance in the sequencing and size-based analysis. The Invader was also concordant if genotypes *6/*6, *6/*7, or *7/*7 were present. Compared to the other two methods, the 88 samples of *6/*6, *6/*7, or *7/*7 genotypes analyzed by Invader were in 100% concordance. As it relates to failures, six samples failed using the sequencing assay, two failed using the size-based analysis, and nine failed using the Invader. Turn-around time was five hours for the Invader, seven hours for sequencing assays and three hours for size-based assays. The Invader method required more concentrated DNA for analysis and had a limited genotyping spectrum (i.e., *6/*6, *6/*7, or *7/*7). The authors concluded that all three methods were valuable, but the Invader had the most drawbacks.

Hoskins et al. (2007) conducted a meta-analysis of nine studies (n=821) that assessed the association of irinotecan dose with the risk of irinotecan-related hematologic toxicities (grade III-IV) for patients with a

UGT1A1*28/*28 genotype. According to the authors, those patients with the UGT1A1*28/*28 genotype had a higher risk of toxicity than those patients with the UGT1A1*1/*1 or UGT1A1*1/*28 genotypes at both high doses (200-350 mg/m² every 21 days) (p=0.005) and medium doses (180 mg/m² every two weeks) (p=0.008). At low doses (80-125 mg/m² weekly), the risk was similar for all genotypes. The authors stated initial studies found UGT1A1*28 genotype to be associated with the risk of toxicity, subsequent studies have been inconsistent. They also indicated that analysis of the studies was limited by the many sources of heterogeneity among the studies. This data suggested that there may be an association between the UGT1A1*28 genotype and irinotecan-induced toxicity at higher irinotecan doses. Further, well-designed studies are warranted to address many unanswered questions including those regarding dosing strategies based on the UGT1A1*28 genotype.

Professional Societies/Organizations

The Evaluation of Genomic Applications in Practice and Prevention Project (EGAPP), a project developed by the National Office of Public Health Genomics at the Centers for Disease Control and Prevention, made the following statement regarding CYP450 genetic testing in adult patients beginning SSRI treatment: "The EGAPP Working Group found insufficient evidence to support a recommendation for or against use of CYP450 testing in adults beginning SSRI treatment for non-psychotic depression. In the absence of supporting evidence, and with consideration of other contextual issues, EGAPP discourages use of CYP450 testing for patients beginning SSRI treatment until further clinical trials are completed" (EGAPP, 2007).

Summary

Further studies are needed to determine how drug metabolizing enzyme genotyping systems such as the AmpliChip[®] Cytochrome P450 (CYP450) genotyping test and the Invader[®] UGT1A1 Molecular Assay might be utilized to improve health outcomes. There is insufficient evidence in the peer-reviewed scientific literature to determine the clinical significance of these systems at the present time.

Coding/Billing Information

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

Experimental, investigational or unproven and not covered when used to report drug metabolizing enzyme genotyping systems:

CPT* Codes	Description
83891	Molecular diagnostics; isolation or extraction of highly purified nucleic acid, each nucleic acid type (ie, DNA or RNA)
83892	Molecular diagnostics; enzymatic digestion, each enzyme treatment
83894	Molecular diagnostics; separation by gel electrophoresis (eg, agarose, polyacrylamide), each nucleic acid preparation
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
83901	Molecular diagnostics; amplification, target, multiplex, each additional nucleic acid sequence beyond 2 (List separately in addition to code for primary procedure)
83903	Molecular diagnostics; mutation scanning, by physical properties (eg, single strand conformational polymorphisms [SSCP], heteroduplex, denaturing gradient gel electrophoresis [DGGE], RNA'ase A), single segment, each
83909	Molecular diagnostics; separation and identification by high resolution technique (eg, capillary electrophoresis), each nucleic acid preparation
83912	Molecular diagnostics; interpretation and report
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])
88384	Array-based evaluation of multiple molecular probes; 11 through 50 probes
88385	Array-based evaluation of multiple molecular probes; 51 through 250 probes
88386	Array-based evaluation of multiple molecular probes; 251 through 500 probes

ICD-9-CM Diagnosis Codes	Description
	All codes

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Policy History

Pre-Merger Organizations	Last Review Date	Policy Number	Title
CIGNA HealthCare	6/15/2008	0381	Drug Metabolizing Enzyme Genotyping Systems (AmpliChip, Invader)

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