Pharmacogenetic Testing for Drug Metabolism

Description of Procedure or Service
Drug efficacy and toxicity vary substantially across individuals. Because drugs and doses are typically adjusted, if needed, by trial and error, clinical consequences may include a prolonged time to optimal therapy. In some cases, serious adverse events may result.

Various factors may influence the variability of drug effects, including age, liver function, concomitant diseases, nutrition, smoking, and drug-drug interactions. Inherited (germline) DNA sequence variation (polymorphisms) in genes coding for drug metabolizing enzymes, drug receptors, drug transporters, and molecules involved in signal transduction pathways also may have major effects on the activity of those molecules and thus on the efficacy or toxicity of a drug.

Pharmacogenomics is the study of how an individual's genetic inheritance affects the body's response to drugs. It may be possible to predict therapeutic failures or severe adverse drug reactions in individual patients by testing for important DNA variants (genotyping) in genes related to the metabolic pathway (pharmacokinetics) or signal transduction pathway (pharmacodynamics) of the drug. Potentially, test results could be used to optimize drug choice and/or dose for more effective therapy, avoid serious adverse effects, and decrease medical costs.

The cytochrome P450 family is a major subset of all drug-metabolizing enzymes; several CYP450 enzymes are involved in the metabolism of a significant portion of currently administered drugs. CYP2D6 metabolizes approximately 25% of all clinically used medications (eg, dextromethorphan, beta blockers, antiarrhythmics, antidepressants, and morphine derivatives), including many of the most prescribed drugs. CYP2C19 metabolizes several important drugs, including proton pump inhibitors, diazepam, propranolol, imipramine, and amitriptyline.

Some CYP450 enzyme genes are highly polymorphic, resulting in some enzyme variants that have variable metabolic capacities among individuals, and some with little to no impact on activity. Thus, CYP450 enzyme variants constitute 1 important group of drug-gene interactions influencing the variability of effect of some CYP450 metabolized drugs.

Individuals with 2 copies (alleles) of the most common (wild-type) DNA sequence of a particular CYP450 enzyme gene resulting in an active molecule are termed extensive metabolizers (EMs; normal). Poor metabolizers (PMs) lack active enzyme gene alleles, and intermediate metabolizers (IMs), who have 1 active and 1 inactive enzyme gene allele, may experience to a lesser degree some of the consequences of PMs. Ultrarapid metabolizers (UMs) are individuals with more than 2 alleles of an active enzyme gene. There is pronounced ethnic variability in the population distribution of metabolizer types for a given CYP enzyme.

UMs that have administered an active drug may not reach therapeutic concentrations at usual recommended doses of active drugs, while PMs may suffer more adverse events at usual doses
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due to reduced metabolism and increased concentrations. Conversely, for administered prodrugs that must be converted by CYP450 enzymes into active metabolites, UMs may suffer adverse effects and PMs may not respond.

Many drugs are metabolized to varying degrees by more than one enzyme, either within or outside of the CYP450 superfamily. In addition, interaction between different metabolizing genes, interaction of genes and environment, and interactions among different non-genetic factors also influence gene metabolizing functions. Thus, identification of a variant in a single gene in the metabolic pathway may be insufficient in all but a small proportion of drugs to explain inter-individual differences in metabolism and consequent efficacy or toxicity.

The cytochrome P450 (CYP450) metabolic enzyme CYP2D6 has a major role in tamoxifen metabolism. The CYP2D6 gene is polymorphic; variant DNA gene sequences resulting in proteins with reduced or absent enzyme function may be associated with lower plasma levels of active tamoxifen metabolites, which could have an impact on tamoxifen treatment efficacy.

Testing of the cytochrome P450 (CYP450) metabolic enzyme CYP2C9 combined with vitamin K epoxide reductase subunit 1 (VKORC1) may predict a warfarin starting dose that approximates the individual patient’s likely maintenance dose and may benefit patients by decreasing the risk of serious bleeding events and the time to stable INR.

Genetic factors may also contribute to a range of aspects of mental health as well, pain and pain control. The currently available genetic tests relevant to pain management and mental health treatments assess single nucleotide polymorphisms (SNPs) in single genes potentially relevant to pharmacokinetic or pharmacodynamics processes.

Pharmacogenetic tests consist of panels of SNPs including, but not limited to the following:

- ANK3 (ankyrin)
- CACNA1C (gated calcium channel)
- 5HT2C (serotonin receptor gene)
- 5HT2A (serotonin receptor gene)
- SLC6A4 (serotonin transporter gene)
- DRD1 (dopamine receptor gene)
- DRD2 (dopamine receptor gene)
- DRD4 (dopamine receptor gene)
- DAT1 or SLC6A3 (dopamine transporter gene)
- DBH (dopamine beta-hydroxylase gene)
- COMT (catechol O-methyltransferase gene)
- MTHFR (methylene-tetrahydrofolate reductase gene)
- γ-aminobutyric acid (GABA) A receptor gene
- OPRM1 (µ-opioid receptor gene)
- OPRK1 (κ-opioid receptor gene)
- SULT4A1 (sulfotransferase Family 4A)
- UGT2B15 (uridine diphosphate glycosyltransferase 2 family, member 15)
- Cytochrome p450 genes: CYP2D6, CYP2C19, CYP2C9, CYP3A4, CYP3A5, CYP2B6, CYP1A2

A number of commercially available tests and test panels are detailed below. This is not an all-inclusive list:

The Genecept™ Assay (Genomind, Chalfont, PA) is a genetic panel test that includes a range of genetic mutations and/or polymorphisms that have been associated with psychiatric disorders and/or response to psychotropic medication.
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The STA2R (SureGene Test for Antipsychotic and Antidepressant Response, SureGene, Louisville, KY) is another genetic panel that provides information about medication response, adverse event likelihood, and drug metabolism.

The Proove Narcotic Risk panel (Proove Biosciences, Irvine, CA) is a panel to evaluate genes involved in the development of substance abuse or dependence and in response to medical therapy for substance abuse or dependence.

The Proove® Opioid Risk Panel (Proove Biosciences, Irvine, CA) is a panel of 11 genes that is intended to predict opioid abuse and failure of opioid therapy. Genetic testing results are provided with an overall “Dependence Risk Index.”

The Proove® Pain Perception panel, is a panel test for SNPs in several genes related to pain perception, including COMT and at least 3 other genes. Results are provided with a report which stratifies patients’ pain sensitivity based on COMT haplotype.

GeneSight® Analgesic (Assurex Health, Mason, OH) is a genetic panel test that is intended to analyze how patients’ genes can affect their metabolism and possible response to FDA-approved opioids, NSAIDs and muscle relaxants commonly used to treat chronic pain.

GeneSight® Psychotropic (Assurex Health, Mason, OH) is a genetic panel that provides information about genes that may affect a patient’s response to antidepressant and antipsychotic pharmacotherapy.

Mental Health DNA Insight™ panel (Pathway Genomic, San Diego, CA) is a test intended to analyze DNA to genetic variants in relation to response to psychiatric medications.

Pain Medication DNA Insight™ (Pathway Genomics, San Diego, CA) is a panel test intended to identify genetic variants that affect how an individual will respond to the analgesic effects of certain types of pain medications.

Millennium PGT (Pain Management) (Millennium Health, San Diego, CA) is a genetic panel test intended to help physicians select pain medication. The panel includes analysis of 11 genes related to pain management; results are provided with a proprietary “Millennium Analysis of Patient Phenotype” report that provides decision support for medications that may be affected by the patient’s genotype.

The AmpliChip® (Roche Molecular Systems, Inc.) is the only FDA-cleared test for CYP450 genotyping. The AmpliChip® is a microarray consisting of many DNA sequences complementary to 2 CYP450 genes and applied in microscopic quantities at ordered locations on a solid surface (chip).

Related Policies
General Approach to Genetic Testing
General Approach to Evaluating the Utility of Genetic Panels

***Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.

Policy

Pharmacogenetic testing for drug metabolism is considered investigational. BCBSNC does not provide coverage for investigational services.
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Benefits Application

This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this medical policy.

When Pharmacogenetic Testing is covered

Not applicable.

When Pharmacogenetic Testing is not covered

Pharmacogenetic testing for the purpose of aiding in the choice of drug or dose to increase efficacy and/or avoid toxicity for all other drugs is considered investigational, aside from determinations in the separate policies noted above. This includes, but is not limited to, pharmacogenetic testing for the following applications:

- selection or dose of selective serotonin reuptake inhibitor (SSRI)
- selection and dosing of selective norepinephrine reuptake inhibitors (SNRIs)
- selection and dosing of tricyclic antidepressants
- selection or dose of antipsychotic drugs
- selection or dosing of codeine
- dosing of efavirenz and other antiretroviral therapies for HIV (common component of highly active antiretroviral therapy for HIV) infection.
- dosing of immunosuppressant for organ transplantation
- selection or dose of beta blockers (e.g., metoprolol)
- managing treatment with tamoxifen for individuals at high risk for or with breast cancer
- dosing and management of anti-tuberculosis medications
- managing treatment for mental health disorders and medications
- dosing and management for warfarin dose
- managing treatment for pain control
- selection or dosing for clopidogrel

The use of genetic testing panels that include multiple CYP450 mutations and/or single nucleotide polymorphisms is considered investigational.

Policy Guidelines

Because the clinical utility of genetic testing for individual CYP450 polymorphisms has not been demonstrated, the use of genetic panel testing for CYP450 polymorphisms is considered investigational.

The published data on the association between CYP2D6 genotype and tamoxifen treatment outcome have yielded inconsistent results. Some of the inconsistencies in the literature may be due to differences across studies in the types of additional therapies patients were receiving, how many and which CYP2D6 alleles were tested, tissue type examined (tumor or germline DNA), and coadministration of CYP2D6 inhibitors. The largest, most well-designed studies do not support a significant association. The impact of testing on net health outcome is not known.

For gene assays associated with drug dosing or selection, management changes that occur as a result of these assays are ill-defined, with uncertain impact on clinical outcomes. In addition, it is not well
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understood how unexpected results or unknown variants are handled, and whether these type of results have an impact on diagnostic work-up, treatment decisions, and health outcomes.

Billing/Coding/Physician Documentation Information

This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at www.bcbsnc.com. They are listed in the Category Search on the Medical Policy search page.

*Applicable codes: 81225, 81226, 81227, 81401, 81402, 81404, 81405, 81291, 81355, G9143, 0015U

BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

Scientific Background and Reference Sources

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Specialty Matched Consultant Advisory Panel review 8/2015
Medical Director review 8/2015
Medical Director review 7/2016
Specialty Matched Consultant Advisory Panel review 7/2017
Medical Director review 7/2017

Policy Implementation/Update Information

10/1/15  New policy developed as a comprehensive policy addressing Pharmacogenetic Testing for Drug Metabolism. The following policies have now been combined: Cytochrome p450 Genotyping, Genetic Testing for Mental Health Conditions, Pharmacogenetic Testing for Pain Management, Pharmacogenetic Testing for Warfarin Dose. Pharmacogenetic testing for the purpose of aiding in the choice of drug or dose to increase efficacy and/or avoid toxicity for all other drugs is considered investigational. The use of genetic testing panels that include multiple CYP450 mutations and/or single nucleotide polymorphisms is considered investigational. Specialty Matched Consultant Advisory Panel review 8/26/2015. Medical Director review 8/2015. Policy noticed 10/1/15 for effective date 11/30/15. (td)

4/29/16  Description section updated. References updated. (td)

8/30/16  Specialty Matched Consultant Advisory Panel review 7/2016. Medical Director review. (jd)

12/30/16 Minor revisions to policy. No change to policy statement/intent. Code G9143 added to Billing/Coding section. (jd)
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Medical policy is not an authorization, certification, explanation of benefits or a contract. Benefits and eligibility are determined before medical guidelines and payment guidelines are applied. Benefits are determined by the group contract and subscriber certificate that is in effect at the time services are rendered. This document is solely provided for informational purposes only and is based on research of current medical literature and review of common medical practices in the treatment and diagnosis of disease. Medical practices and knowledge are constantly changing and BCBSNC reserves the right to review and revise its medical policies periodically.