PHARMACOGENETIC TESTING

Policy Number: LABORATORY 023.1 T2

Effective Date: November 1, 2017

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INSTRUCTIONS FOR USE

This Clinical Policy provides assistance in interpreting Oxford benefit plans. Unless otherwise stated, Oxford policies do not apply to Medicare Advantage members. Oxford reserves the right, in its sole discretion, to modify its policies as necessary. This Clinical Policy is provided for informational purposes. It does not constitute medical advice. The term Oxford includes Oxford Health Plans, LLC and all of its subsidiaries as appropriate for these policies.

When deciding coverage, the member specific benefit plan document must be referenced. The terms of the member specific benefit plan document [e.g., Certificate of Coverage (COC), Schedule of Benefits (SOB), and/or Summary Plan Description (SPD)] may differ greatly from the standard benefit plan upon which this Clinical Policy is based. In the event of a conflict, the member specific benefit plan document supersedes this Clinical Policy. All reviewers must first identify member eligibility, any federal or state regulatory requirements, and the member specific benefit plan coverage prior to use of this Clinical Policy. Other Policies may apply.

UnitedHealthcare may also use tools developed by third parties, such as the MCG™ Care Guidelines, to assist us in administering health benefits. The MCG™ Care Guidelines are intended to be used in connection with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.

CONDITIONS OF COVERAGE

Applicable Lines of Business/ Products: This policy applies to Oxford Commercial plan membership.

Benefit Type: General Benefits Package

Referral Required (Does not apply to non-gatekeeper products): No

Authorization Required (Precertification always required for inpatient admission): Yes¹

Precertification with Medical Director Review Required: Yes¹

Applicable Site(s) of Service (If site of service is not listed, Medical Director review is required): Laboratory

Special Considerations: ¹Precertification with review by a Medical Director or their designee is required.

BENEFIT CONSIDERATIONS

Before using this policy, please check the member specific benefit plan document and any federal or state mandates, if applicable.
Essential Health Benefits for Individual and Small Group

For plan years beginning on or after January 1, 2014, the Affordable Care Act of 2010 (ACA) requires fully insured non-grandfathered individual and small group plans (inside and outside of Exchanges) to provide coverage for ten categories of Essential Health Benefits (“EHBs”). Large group plans (both self-funded and fully insured), and small group ASO plans, are not subject to the requirement to offer coverage for EHBs. However, if such plans choose to provide coverage for benefits which are deemed EHBs, the ACA requires all dollar limits on those benefits to be removed on all Grandfathered and Non-Grandfathered plans. The determination of which benefits constitute EHBs is made on a state by state basis. As such, when using this policy, it is important to refer to the member specific benefit plan document to determine benefit coverage.

Coverage Rationale

Pharmacogenetic Testing

The use of pharmacogenetic testing panels for genetic polymorphisms is considered unproven and not medically necessary for evaluating drug-metabolizer status.

Examples of these panels include, but are not limited to the following:
- AIBioTech® CardioloGene Genetic Panel
- AIBioTech® Pain Management Panel
- AIBioTech® PsychiaGene Genetic Panel
- AIBioTech® Urologene Panel
- AIBioTech® PersonaGene Panel
- Genecept™ Assay
- GeneSight® Analgesic
- GeneSight® Psychotropic
- GeneSight® ADHD
- Millennium PGT®SM
- Proove® Drug Metabolism test panel
- Proove® Narcotic Risk test panel
- SureGene Test for Antipsychotic and Antidepressant Response (STA²R)

Applicable Codes

The following list(s) of procedure and/or diagnosis codes is provided for reference purposes only and may not be all inclusive. Listing of a code in this policy does not imply that the service described by the code is a covered or non-covered health service. Benefit coverage for health services is determined by the member specific benefit plan document and applicable laws that may require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment. Other Policies may apply.

<table>
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<tr>
<th>CPT Code</th>
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<tr>
<td>81479</td>
<td>Unlisted molecular pathology procedure</td>
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CPT® is a registered trademark of the American Medical Association

Description of Services

Pharmacogenetics encompasses variation in genes that encode drug-metabolizing enzymes, drug transporters, and drug targets, as well as other specific genes related to the action of drugs. A slight variation in the deoxyribonucleic acid (DNA) sequence can result in a subtle change in a protein which translates into major differences in how the protein functions. The study of variations in DNA sequence as related to drug response is referred to as pharmacogenetics, and pharmacogenetic testing involves genotyping to detect relevant variants. Genetic variations can be associated with suboptimal drug response, for example poor efficacy or adverse events.

A pharmacogenetic test is meant to guide treatment strategies, patient evaluations and decisions based on its ability to predict response to treatment in particular clinical contexts. An overview of many aspects of pharmacogenetics and its application in specific clinical settings is provided by the National Academy of Clinical Biochemistry (NACB) Laboratory Medicine Practice Guidelines (2010).

Clinical Evidence

Jung et al. (2017) conducted a genome-wide association study (GWAS) in Generalized Anxiety Disorder (GAD) to identify potential predictors of venlafaxine XR treatment outcome. Ninety-eight European American patients participated in a venlafaxine XR clinical trial for GAD, with Hamilton Anxiety Scale (HAM-A) response/remission at 24
weeks as the primary outcome measure. All participants were genotyped with the Illumina PsychChip, and 266,820 common single nucleotide polymorphisms (SNPs) were analyzed. Although no SNPs reached genome-wide significance, 8 SNPs were marginally associated with treatment response/remission and HAM-A reduction at week 12 and 24 (p<0.00001). The authors concluded that several identified genes may indicate markers crossing neuropsychiatric diagnostic categories. The authors acknowledged that the limitations of this study include small sample size, and the and lack of statistical power for a genome-wide association study. Areas for future research include the replication of results with larger samples sizes to increase statistical power and further elucidate the treatment effects of antidepressant venlafaxine XR on GAD.

In a review of the literature, Zhang et al. (2017) outlined results of recent genome-wide PGx studies, and their insight into genetic basis of variability in drug response. Drug responses are highly variable because innumerable factors contribute to ultimate phenotypic outcomes. These can be grouped into three categories. [a] Monogenic (Mendelian) traits include early examples mostly of inherited disorders, and some severe (idiosyncratic) ADRs typically influenced by single rare coding variants. Predominantly oligogenic traits represent variation largely influenced by a small number of major pharmacokinetic or pharmacodynamic genes. Complex PGx traits resemble most multifactorial quantitative traits -- influenced by numerous small-effect variants, together with epigenetic effects and environmental factors. Prediction of monogenic drug responses is relatively simple, involving detection of underlying mutations; due to rarity of these events and incomplete penetrance, however, prospective tests based on genotype will have high false-positive rates, plus pharmacoeconomics will require justification. Prediction of predominantly oligogenic traits is slowly improving. Although a substantial fraction of variation can be explained by limited numbers of large-effect genetic variants, uncertainty in successful predictions and overall cost-benefit ratios will make such tests elusive for everyday clinical use. Prediction of complex PGx traits is almost impossible in the foreseeable future. Genome-wide association studies of large cohorts will continue to discover relevant genetic variants; however, these small-effect variants, combined, explain only a small fraction of phenotypic variance -- thus having limited predictive power and clinical utility.

Known genetic variability can be a significant contributor to inter-individual variation in drug response in addition to clinical and environmental factors including drug-drug interactions. There are numerous examples of gene variants with well characterized effects on the pharmacokinetics or pharmacodynamics of certain drugs. However, some gene variants have been identified that are not always phenotype-specific, i.e., having a different impact depending on the drug in question (NACB). Racial and ethnic differences in the frequency and nature of genetic variants are also possible and should be recognized in translating outcomes from one population to another. It has been suggested that the relation of a gene variant and a drug target must be validated for each therapeutic indication in different racial and ethnic groups, as well as in different treatment and disease contexts. (Crews et al., 2012; Lesko, 2007)

Evidence standards to validate genotype-phenotype associations for the purpose of identifying optimal drug dose are undergoing discussion. (Lesko, 2010) The randomized clinical trial is the common benchmark for interventional evidence in medicine, yet they are often resource-prohibitive for testing pharmacogenetic hypotheses. (Scott 2011) Some unsolved questions are whether prospective, randomized controlled trials are necessary to qualify or validate a predictive genetic test to inform dosing in clinical practice, to what extent prospective and retrospective observational studies support genotype-phenotype associations for determining optimal dose using genetic testing, and what clinical endpoints are appropriate. (Lesko, 2007)

Professional Societies

National Academy for Clinical Biochemistry (NACB)

According to the NACB (2010), pharmacogenetic testing is not currently recommended for general population screening.

U.S. FOOD AND DRUG ADMINISTRATION (FDA)

Laboratories that perform genetic tests are regulated under the Clinical Laboratory Improvement Amendments (CLIA) Act of 1988. More information is available at:
(Accessed June 28, 2017)

REFERENCES

The foregoing Oxford policy has been adapted from an existing UnitedHealthcare national policy that was researched, developed and approved by UnitedHealthcare Medical Technology Assessment Committee. [2017T0587A]


**POLICY HISTORY/REVISION INFORMATION**

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<td>11/01/2017</td>
<td>• New policy</td>
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