

PHARMACOGENETIC TESTING

Policy Number: 2018T0587C

Effective Date: November 1, 2018

[Instructions for Use](#) ⓘ

Table of Contents	Page
COVERAGE RATIONALE	1
APPLICABLE CODES	1
DESCRIPTION OF SERVICES	2
CLINICAL EVIDENCE	2
U.S. FOOD AND DRUG ADMINISTRATION	3
CENTERS FOR MEDICARE AND MEDICAID SERVICES	3
REFERENCES	4
POLICY HISTORY/REVISION INFORMATION	4
INSTRUCTIONS FOR USE	4

Related Commercial Policies
<ul style="list-style-type: none"> • Cardiovascular Disease Risk Tests • Chemosensitivity and Chemoresistance Assays in Cancer

Community Plan Policy
<ul style="list-style-type: none"> • Pharmacogenetic Testing

Medicare Advantage Coverage Summaries
<ul style="list-style-type: none"> • Genetic Testing • Laboratory Tests and Services

COVERAGE RATIONALE

Pharmacogenetic Testing

The use of pharmacogenetic multigene testing panels for genetic polymorphisms is 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 PGTSM
- 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 and Coverage Determination Guidelines may apply.

CPT Code	Description
0029U	Drug metabolism (adverse drug reactions and drug response), targeted sequence analysis (i.e., CYP1A2, CYP2C19, CYP2C9, CYP2D6, CYP3A4, CYP3A5, CYP4F2, SLCO1B1, VKORC1 and rs12777823)
81479	Unlisted molecular pathology procedure

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

Borobia et al. (2018) reported on the implementation of a pharmacogenetic testing program in 2014 at La Paz University Hospital (LPUH) in Madrid. LPUH is a 1,308-bed tertiary-care teaching hospital of the Spanish NHS serving a population of ~600,000 people. The goal of the study was to implement pharmacogenetics into clinical practice and evolve from an *ad hoc* strategy linked to a prescription to a proactive practice, where genetic information would be obtained prior to a prescription in at risk populations. The targeted populations were at risk for inflammatory bowel disease, psoriasis, transplant patients, high cardiovascular disease risk, leukemia, and colorectal cancer. The authors utilized a 180 single nucleotide polymorphism (SNP) panel (PharmArray) for testing. Ordering providers would submit a recommendation and request for testing to a centralized Pharmacogenetic Testing Unit who would evaluate the request based on patient demographics, if the requested marker fell into one of three categories. Category A was for pre-emptive screening of an actionable marker, such as HLA-B5701 for abacavir response. Category B was for drugs with a well-defined protocol for treating certain diseases, such as TPMT for thiopurine response for treatment of inflammatory bowel disease. Category C was for drugs without a well-defined protocol. In this situation, the pharmacogenetics unit would evaluate the therapeutic issue and determine if a pharmacogenetic test would be clinically useful. From January 2014 through December 2016, the Pharmacogenetic Testing Unit received 2,539 consultation requests. The most common tests were TPMT and MTHFR. There were 1,939 requests for treatment selection that had well defined protocols, and 711 for drugs with pharmacogenetic treatment recommendations for certain diseases, or had poorly defined recommendations. Of these, 600 were found appropriate and approved, and 32% had a molecular profile that impacted the drug. In this sub-group, 58% (107) had a dose adjustment as a result. The total cost of the program was estimated at 216 € (\$254) per patient, and 91% of physicians surveyed said they would now use pharmacogenetics regularly.

O'Donnell et al. (2014, 2017) implemented a pharmacogenomic testing program, The 1200 Patients Project, at the University of Chicago to adult patients who were regularly taking at least one prescription drug, but not more than six. Patients could be referred by a care provider or self-referred to the program. After participating in an informed consent process, patients were tested for pharmacogenetics variants using a commercially available multi-gene pharmacogenetic testing panel (Sequenom ADME). Overall, 868 patients that completed pharmacogenetic testing had 2279 patient encounters that were reviewed. Four medical specialties and seventeen providers represented all clinic visits; executive health, nephrology, hepatology, and pulmonology. The most prevalent medications included aspirin, atorvastatin, hydrochlorothiazide, lisinopril, and amlodipine. Of all medications on active patient drug lists, 34% had associated alerts that included green (21%), cautionary yellow (13%) and high risk red (0.5%). The remaining medications had no actionable pharmacogenetic information. There were a total of 2869 alerts provided. Green alerts were viewed 40% of the time, and 4% had medication changes documented. Yellow alerts were viewed 66% of the time, and 5% had medication changes documented. Red alerts were viewed 89% of the time, and 24% had medication changes documented. Nearly half of all medication changes were for omeprazole and atorvastatin. Simvastatin and rabeprazole had the highest overall percentage of changes influenced by the pharmacogenetic test results. Changes made in these prescriptions reduced the pharmacogenetic risk to the patient. The authors note that limitations to this study include the small number of providers involved and the modest response to actionable alerts, which narrowed down to 60 prescription changes out of 405 possibly actionable red and yellow alerts. In addition, the providers included in the study were also co-investigators which may highlight a bias toward pharmacogenetics, and they knew their behavior would be examined, which may have altered their choices from what they would have done if they had not known their choices were being monitored.

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 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 pharmacogenetic (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 of monogenic, oligogenic, and complex pharmacogenetics traits. Monogenic (Mendelian) traits represent inherited disorders and some severe (idiosyncratic) adverse drug reactions (ADRs) typically influenced by single rare coding variants. One such example includes statin induced myopathy. Predominantly oligogenic traits represent variation largely influenced by a small number of genes, such as the interaction between the VKORC1 gene and CYP2C9. Finally, complex PGx traits resemble most multifactorial quantitative traits, where a phenotype is influenced by numerous small-effect variants, together with epigenetic effects and environmental factors, and represent the largest category of PGx possibilities. The low density lipoprotein (LDL) response to statins is an example of this, where the response is influenced by small effects of SORT1/CELSR2/PSRC1, SLCO1B1, APOE, and LPA. At this time, data is promising for a wide array of genes and drugs, and it is predicted that every person carries at least one actionable PGx variant. However, demonstration of clinical utility has been limited to a small number of genes that have a large effect on drug response. No health benefit of multigene or genome wide PGx testing has been established, and due to the complex interactions between genes, epigenetics, and the environment, it is unlikely to be attained in the foreseeable future. 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. 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 and Zineh, 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:

<https://www.fda.gov/medicaldevices/deviceregulationandguidance/ivdregulatoryassistance/ucm124105.htm>.

(Accessed April 22, 2018)

CENTERS FOR MEDICARE AND MEDICAID SERVICES (CMS)

Medicare does not have a National Coverage Determination (NCD) that specifically addresses the use of pharmacogenetic multigene testing panels for genetic polymorphisms. Local Coverage Determinations (LCDs) exist; refer to the LCDs for [MoIDX: GeneSight® Assay for Refractory Depression](#), [MoIDX: CYP2C19, CYP2D6, CYP2C9, and VKORC1 Genetic Testing](#), [CYP2C19, CYP2D6, CYP2C9, and VKORC1 Genetic Testing](#) and [MoIDX: Genetic Testing for CYP2C19, CYP2D6, CYP2C9, and VKORC1](#).

(Accessed May 30, 2018)

REFERENCES

- Borobia AM, Dapia I, Tong HY, et al. Clinical implementation of pharmacogenetic testing in a hospital of the Spanish National Health System: Strategy and experience over 3 years. *Clin Transl Sci*. 2018 Mar;11(2):189-199.
- Crews KR, Hicks JK, Pui CH, et al. Pharmacogenomics and individualized medicine: translating science into practice. *Clin Pharmacol Ther*. 2012 Oct; 92(4):467-75.
- Jung J, Tawa EA, Muench C, et al. Genome-wide association study of treatment response to venlafaxine XR in generalized anxiety disorder. *Psychiatry Res*. 2017 Aug; 254:8-11.
- Lesko LJ. Personalized medicine: elusive dream or imminent reality? *ClinPharmacol Ther*. 2007 Jun; 81(6):807-16.
- Lesko LJ, Zineh I. DNA, drugs and chariots: on a decade of pharmacogenomics at the US FDA. *Pharmacogenomics*. 2010; 11(4):507-512.
- National Academy for Clinical Biochemistry, (the academy of the American Association for Clinical Chemistry) Laboratory Medicine Practice Guidelines: Laboratory Analysis and Application of Pharmacogenetics to Clinical Practice 2010. Available at: <https://www.aacc.org/science-and-practice/practice-guidelines/pharmacogenetics>. Accessed May 25, 2018.
- O'Donnell PH, Danahey K, Jacobs M, et al. Adoption of a clinical pharmacogenomics implementation program during outpatient care—initial results of The University of Chicago “1200 Patients Project.” *American Journal of Medical Genetics Part C, Seminars in Medical Genetics*. 2014;166(1):68-75.
- Scott SA. Personalizing medicine with clinical pharmacogenetics. *Genet Med*. 2011 Dec; 13(12):987-95.
- Zhang G, Nebert DW. Personalized medicine: Genetic risk prediction of drug response. *Pharmacol Ther*. 2017 Jul; 175:75-90.

POLICY HISTORY/REVISION INFORMATION

Date	Action/Description
11/01/2018	<ul style="list-style-type: none">• Reorganized policy template:<ul style="list-style-type: none">○ Simplified and relocated <i>Instructions for Use</i>○ Removed <i>Benefit Considerations</i> section• Updated coverage rationale; modified language to clarify the listed service is unproven and not medically necessary• Archived previous policy version 2018T0587B

INSTRUCTIONS FOR USE

This Medical Policy provides assistance in interpreting UnitedHealthcare standard benefit plans. When deciding coverage, the member specific benefit plan document must be referenced as the terms of the member specific benefit plan may differ from the standard plan. In the event of a conflict, the member specific benefit plan document governs. Before using this policy, please check the member specific benefit plan document and any applicable federal or state mandates. UnitedHealthcare reserves the right to modify its Policies and Guidelines as necessary. This Medical Policy is provided for informational purposes. It does not constitute medical advice.

UnitedHealthcare may also use tools developed by third parties, such as the MCG™ Care Guidelines, to assist us in administering health benefits. UnitedHealthcare Medical Policies 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.