Pharmacogenetic Testing

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Lomatipide Mesylate, Mipomersen Sodium
PCSK9 Inhibitors
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INSTRUCTIONS FOR USE

INSTRUCTIONS FOR USE
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Coverage Policy

Many benefit plans limit coverage of genetic testing and genetic counseling services. Please refer to the applicable benefit plan language to determine benefit availability and terms, conditions and limitations of coverage for the services discussed in this Coverage Policy.

For additional information regarding coverage for specific genetic tests please refer to the Genetic Testing Collateral File.

General Coverage Principles

Medically Necessary

Pharmacogenetic testing (e. g., genotyping, mutation analysis) is considered medically necessary when EITHER of the following criteria is met (this list may not be all inclusive):

1.
2.
3.
• All of the following:
  
  ➢ 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
  ➢ The testing method is considered to be scientifically valid to identify the specific gene biomarker or gene mutation
  ➢ EITHER of the following:
    ➢ Identification of the specific gene or biomarker for use with a specific drug target has been demonstrated to improve clinical outcomes for the individual’s condition being addressed
    ➢ Therapy with the targeted drug for the specific condition has been validated by a National Comprehensive Cancer Network (NCCN) category 1, 2A or 2B recommendation

• Identification of the gene biomarker is noted to be clinically necessary prior to initiating therapy with drug target as noted within the section heading “Indications and Usage” of the U.S. Food and Drug Administration (FDA)-approved prescribing label.

Not Medically Necessary

Pharmacogenetic screening in the general population is considered not medically necessary.

Overview

This Coverage Policy addresses pharmacogenetic testing. Pharmacogenetics is the study of gene variations within an individual’s deoxyribonucleic acid (DNA) and how these differences influence an individual’s response to medications. An individual’s unique genetic makeup helps determine how he or she responds to a drug and whether or not side effects or adverse reactions may be experienced. Variations in genes may also cause an individual to metabolize a drug more quickly, more slowly or at the same rate as anticipated, based on dosage.

General Background

General Coverage Principles

Pharmacogenetics encompasses variation in genes that encode drug transporters, drug-metabolizing enzymes and drug targets, as well as specific genes related to the action of drugs. A slight variation in deoxyribonucleic acid (DNA) 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 pharmacogenetic testing. 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 (Agency for Healthcare Research and Quality [AHRQ], 2010).

A particular variant is not always phenotype specific in that it may have a different impact depending on the drug in question. 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. The relation of a gene or gene biomarker 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 (Kager and Evans, 2012).

Although genetics has an impact on genes related to inter-individual differences in drug response, it is only one of the many variables affecting these genes. 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. Identification of gene variations may be clinically useful in a small number of drugs;
however, it may be insufficient in others to explain complex differences in metabolism, efficacy, and toxicity. The presence of polymorphisms alone may be a poor predictor of phenotype because of variability (Canadian Agency for Drugs and Technology in Health [CADTH], 2006).

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; however, 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. High complexity techniques used for pharmacogenetic testing include immunohistochemistry (IHC), fluorescent in situ hybridization (FISH), polymerase chain reaction (PCR) and microarray assays. According to the U.S. Food and Drug Administration (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).

An increasing number of multigene genotyping panels with the goals of detecting inter-individual differences in drug metabolism and response to a variety of drug targets are commercially available. The number of gene biomarkers and gene mutations and associated drug targets which are tested for vary widely between tests; some tests evaluate for a few biomarkers and associated drug targets while others may include hundreds of biomarkers within the test. Some multigene assays assess for the presence or absence of multiple biomarkers and provide lists of potential therapeutic agents, clinical trials and review of published literature associated with the biomarkers that are identified in the patient sample.

**Clinical Utility**

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 validity (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 from both positive and negative results (i.e., the test must have clinical utility).

The clinical usefulness or utility of pharmacogenetic testing is the extent to which results of testing will impact clinical decision-making and improve health outcomes. Pharmacogenetic test results are meant to guide patient evaluation and treatment strategy and decisions based on the ability to predict response to treatment in particular clinical contexts, and to allow the clinician to predict an individual’s response to specific 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 (Agency for Healthcare Research and Quality [AHRQ], 2010; Al-Goul, et al., 2008). The integration of genomic data in patient treatment requires evidence of consistency and size of measured effects, medication compliance and phenoconversion. The effects of ethnicity must be evaluated, especially in the context of global drug development and extrapolation of clinical trial genomic data from one population to another (Ehmann et al. 2014).

To definitively show that pharmacogenetic testing has value in clinical practice, it is not enough to demonstrate that drug response varies by genotype. Testing for the genotype and subsequently tailoring the treatment strategy based on genetic information should be more clinically effective and/or cost effective than treating an individual by an established treatment standard (Arnett, 2007).

When applied in a clinical setting, the information from these tests can potentially identify individual variability in drug response, including both effectiveness and toxicity. The individual for whom testing is proposed should be a candidate for a targeted drug therapy associated with a specific gene biomarker or gene mutation and results of testing must directly impact clinical decision making. The identification of the specific gene or biomarker for use with a specific drug target must also be demonstrated by published, peer-reviewed clinical trial data to improve clinical outcomes for an individual receiving that specific treatment and be considered scientifically valid to identify the biomarker.

For cancer-related conditions, clinical utility is established if there is a Category 1, 2A or 2B National Comprehensive Cancer Network™ [NCCN Guideline™] recommendation specific for the gene biomarker and associated drug target. Notation in the US Food and Drug Administration ‘Indications and Usage’ section of the
US Food and Drug Administration (FDA) prescribing label that identification of the gene biomarker is clinically necessary prior to prescribing of the drug target also establishes clinical utility for pharmacogenetic testing.

The National Comprehensive Cancer Network™ evidence grading system describes the level of evidence and the degree to which there is consensus for various treatment recommendations:

<table>
<thead>
<tr>
<th>NCCN Category</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.</td>
</tr>
<tr>
<td>2A</td>
<td>Based upon lower level of evidence, there is uniform NCCN consensus that the intervention is appropriate.</td>
</tr>
<tr>
<td>2B</td>
<td>Based upon lower-level of evidence, there is NCCN consensus that the intervention is appropriate.</td>
</tr>
</tbody>
</table>

US Food and Drug Administration (FDA)
The 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. While the clinical utility of genotyping prior to treatment is not proven for all medications for which genomic information is included (Slavin, 2015), clinical utility is established when identification of a specific gene biomarker is noted to be clinically necessary prior to initiating therapy with a specific drug target as noted within the section heading “Indications and Usage” of the U.S. Food and Drug Administration (FDA)-approved prescribing label.

An FDA Safety Communication (2017) warns against the use of many genetic tests with unapproved claims to predict patient response to specific medications. The Communication’s intent was to alert patients and health care providers that for many genetic tests, claims to predict a patient’s response to specific medications have not been reviewed by the FDA, and may not have the scientific or clinical evidence to support this use for most medications. Changing drug treatment based on the results from such a genetic test could lead to inappropriate treatment decisions and potentially serious health consequences for the patient. The FDA specifically notes the relationship between DNA variations and the effectiveness of antidepressant medication has never been established. According to the FDA, there are a limited number of cases for which at least some evidence does exist to support a correlation between a genetic variant and drug levels within the body, and this is described in the labeling of FDA cleared or approved genetic tests and FDA approved medications.

Literature Review
Increasingly, published, peer-reviewed scientific evidence regarding the clinical utility of pharmacogenetic testing informs on the ability of such testing to benefit health outcomes. Prospective clinical trials of standard management procedures compared with genetic test-directed management offers the highest level of evidence. Evidence may also be derived using banked samples from already-completed clinical trials; or by constructing an indirect chain of evidence linking test results to clinical outcome. To date, 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.

Although genome-wide association studies report inter-individual variability, high-quality, randomized controlled trial data demonstrating improved clinical outcomes are lacking. Many early phase clinical trials are exploratory, with no formal genomic hypothesis, and have small sample sizes that make it difficult to identify important gene variants influencing pharmacokinetics and pharmacodynamics (Lesko and Schmidt, 2014). However, clinical utility has been established for pharmacogenetic testing for a number of gene biomarkers and their specific drug targets.

Zeier et al., (2018) reviewed the evidence for several combinatorial pharmacogenetic test decision support tools whose potential utility to improve antidepressant treatment response or side effect burden has been evaluated in clinical settings. The authors note available literature suffers from publication bias, because some products garner more investment than do others, and questions about scientific integrity are inherent in studies conducted...
by or reports authored by personnel with significant financial interests in the outcome. Although some of the preliminary published data sound promising, particularly with regard to the CYP450 gene variants and side effect burden, we conclude that there is insufficient evidence to support widespread use at this point in time.

Wang et al. (2014) published results of a study evaluating the evidence that supports pharmacogenomic biomarker testing in drug labels and how frequently testing is recommended. Using guidelines published by the Evaluation of Genomic Applications in Practice and Prevention Working Group and FDA databases, the authors reviewed drug labels that described the use of a biomarker for reference to clinical validity and clinical utility. Of 119 notations in drug labels 36.1% provided evidence of clinical validity evidence while 15.1% provided evidence of clinical utility. Sixty-one labels (51.3%) made recommendations regarding clinical management based on the results of a biomarker test. Of these, 30.3% provided clinical utility data. A full description of supporting studies was included in 13 labels (10.9%). The authors noted that it may be premature to include biomarker recommendations in drug labels when data regarding patient outcomes are not available.

Pharmacogenetic testing is not currently recommended for general population screening. Clinical trials regarding the use of pharmacogenetic testing for screening in the general population are lacking in the published, peer-reviewed scientific literature and the role of such testing has not been established.

Professional Societies/ Organizations
While the NCCN has established recommendations for pharmacogenetic testing for a number of specific gene biomarkers and drug targets for cancer-related indications, there is limited published professional society consensus guideline support for pharmacogenetic testing for non-cancer-related conditions.

American Board of Internal Medicine Choosing Wisely
A statement by the American Society of Clinical Oncology recommends the following:
- Don’t use cancer-directed therapy for solid tumor patients with the following characteristics: low performance status (3 or 4), no benefit from prior evidence-based interventions, not eligible for a clinical trial, and no strong evidence supporting the clinical value of further anti-cancer treatment.

The statement further notes cancer directed treatments are likely to be ineffective for solid tumor patients who meet the above stated criteria. Exceptions include patients with functional limitations due to other conditions resulting in a low performance status or those with disease characteristics (e.g., mutations) that suggest a high likelihood of response to therapy. Implementation of this approach should be accompanied with appropriate palliative and supportive care.

Centers for Medicare & Medicaid Services (CMS):
- National Coverage Determinations (NCDs): Pharmacogenomic Testing for Warfarin Response (90.1), last revised 8/3/2009. The Coverage Policy is broader in scope than the NCD. Refer to the CMS NCD table of contents link in the reference section.
- Local Coverage Determinations (LCDs): No Local Coverage Determinations found.

Use Outside of the US
No relevant statements.

Coding/Billing Information

Note: 1) This list of codes may not be all-inclusive.
2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement

Considered Medically Necessary when criteria in the applicable policy statements listed above are met:

<table>
<thead>
<tr>
<th>CPT® Codes</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>81210</td>
<td>BRAF (B-Raf proto-oncogene, serine/threonine kinase) (eg, colon cancer, melanoma), gene analysis, V600 variant(s)</td>
</tr>
</tbody>
</table>

DPYD (dihydropyrimidine dehydrogenase) (eg, 5-fluorouracil/5-FU and capecitabine drug metabolism), gene analysis, common variant(s) (eg, *2A, *4, *5, *6)

EGFR (epidermal growth factor receptor) (eg, non-small cell lung cancer) gene analysis, common variants (eg, exon 19 LREA deletion, L858R, T790M, G719A, G719S, L861Q)

G6PD (glucose-6-phosphate dehydrogenase) (eg, hemolytic anemia, jaundice), gene analysis; common variant(s) (eg, A, A-)

KRAS (Kirsten rat sarcoma viral oncogene homolog) (eg, carcinoma) gene analysis; variants in exon 2 (eg, codons 12 and 13)

KRAS (Kirsten rat sarcoma viral oncogene homolog) (eg, carcinoma) gene analysis; additional variant(s) (eg, codon 61, codon 146)


PML/RARalpha, (t(15;17)), (promyelocytic leukemia/retinoic acid receptor alpha) (eg, promyelocytic leukemia) translocation analysis; common breakpoints (eg, intron 3 and intron 6), qualitative or quantitative

PML/RARalpha, (t(15;17)), (promyelocytic leukemia/retinoic acid receptor alpha) (eg, promyelocytic leukemia) translocation analysis; single breakpoint (eg, intron 3, intron 6 or exon 6), qualitative or quantitative

TPMT (thiopurine S-methyltransferase) (eg, drug metabolism), gene analysis, common variants (eg, *2, *3)

TYMS (thymidylate synthetase) (eg, 5-fluorouracil/5-FU drug metabolism), gene analysis, common variant(s) (eg, tandem repeat variant)

Molecular pathology procedure, Level 1 (eg, identification of single germline variant [eg, SNP] by techniques such as restriction enzyme digestion or melt curve analysis)

Molecular pathology procedure, Level 2 (eg, 2–10 SNPs, 1 methylated variant, or 1 somatic variant [typically using nonsequencing target variant analysis], or detection of a dynamic mutation disorder/triplet repeat)

Molecular pathology procedure, Level 6 (eg, analysis of 6–10 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 11–25 exons, regionally targeted cytogenomic array analysis)


Targeted genomic sequence analysis, solid organ neoplasm, DNA analysis of 324 genes, interrogation for sequence variants, gene copy number amplifications, gene rearrangements, microsatellite instability and tumor mutational burden


Considered Medically Necessary when criteria in the applicable policy statements listed above are met:

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<thead>
<tr>
<th>CPT® Codes</th>
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<tr>
<th>ICD-10 CM Codes</th>
<th>Description</th>
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<tbody>
<tr>
<td>G35</td>
<td>Multiple sclerosis</td>
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Considered Not Medically Necessary:
<table>
<thead>
<tr>
<th>CPT® Codes</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>81230</td>
<td>CYP3A4 (cytochrome P450 family 3 subfamily A member 4) (eg, drug metabolism), gene analysis, common variant(s) (eg, *2, *22)</td>
</tr>
<tr>
<td>81283</td>
<td>IFNL3 (interferon, lambda 3) (eg, drug response), gene analysis, rs12979860 variant</td>
</tr>
<tr>
<td>81328</td>
<td>SLCO1B1 (solute carrier organic anion transporter family, member 1B1) (eg, adverse drug reaction), gene analysis, common variant(s) (eg, *5)</td>
</tr>
<tr>
<td>81350</td>
<td>UGT1A1 (UDP glucuronosyltransferase 1 family, polypeptide A1) (eg, irinotecan metabolism), gene analysis, common variant(s) (eg, *28, *36, *37)</td>
</tr>
<tr>
<td>81355</td>
<td>VKORC1 (vitamin K epoxide reductase complex, subunit 1) (eg, warfarin metabolism), gene analysis, common variant(s) (eg, -1639G&gt;A, c.173+1000C&gt;T)</td>
</tr>
<tr>
<td>81479†</td>
<td>Unlisted molecular pathology procedure</td>
</tr>
<tr>
<td>0028U</td>
<td>CYP2D6 (cytochrome P450, family 2, subfamily D, polypeptide 6) (eg, drug metabolism) gene analysis, copy number variants, common variants with reflex to targeted sequence analysis</td>
</tr>
<tr>
<td>0029U</td>
<td>Drug metabolism (adverse drug reactions and drug response), targeted sequence analysis (ie, CYP1A2, CYP2C19, CYP2C9, CYP2D6, CYP3A4, CYP3A5, CYP4F2, SLCO1B1, VKORC1 and rs12777823)</td>
</tr>
<tr>
<td>0030U</td>
<td>Drug metabolism (warfarin drug response), targeted sequence analysis (ie, CYP2C9, CYP4F2, VKORC1, rs12777823)</td>
</tr>
<tr>
<td>0031U</td>
<td>CYP1A2 (cytochrome P450 family 1, subfamily A, member 2) (eg, drug metabolism) gene analysis, common variants (ie, *1F, *1K, *6, *7)</td>
</tr>
<tr>
<td>0032U</td>
<td>COMT (catechol-O-methyltransferase) (eg, drug metabolism) gene analysis, c.472G&gt;A (rs4680) variant</td>
</tr>
<tr>
<td>0033U</td>
<td>HTR2A (5-hydroxytryptamine receptor 2A), HTR2C (5-hydroxytryptamine receptor 2C) (eg, citalopram metabolism) gene analysis, common variants (ie, HTR2A rs7997012 [c.614-221T&gt;C], HTR2C rs3813929 [c.-759C&gt;T] and rs1414334 [c.551-3008C&gt;G])</td>
</tr>
<tr>
<td>0071U†</td>
<td>CYP2D6 (cytochrome P450, family 2, subfamily D, polypeptide 6) (eg, drug metabolism) gene analysis, full gene sequence (List separately in addition to code for primary procedure)</td>
</tr>
<tr>
<td>0072U</td>
<td>CYP2D6 (cytochrome P450, family 2, subfamily D, polypeptide 6) (eg, drug metabolism) gene analysis, targeted sequence analysis (ie, CYP2D6-2D7 hybrid gene) (List separately in addition to code for primary procedure)</td>
</tr>
<tr>
<td>0073U</td>
<td>CYP2D6 (cytochrome P450, family 2, subfamily D, polypeptide 6) (eg, drug metabolism) gene analysis, targeted sequence analysis (ie, CYP2D7-2D6 hybrid gene) (List separately in addition to code for primary procedure)</td>
</tr>
<tr>
<td>0074U</td>
<td>CYP2D6 (cytochrome P450, family 2, subfamily D, polypeptide 6) (eg, drug metabolism) gene analysis, targeted sequence analysis (ie, non-duplicated gene when duplication/multiplication is trans) (List separately in addition to code for primary procedure)</td>
</tr>
<tr>
<td>0075U</td>
<td>CYP2D6 (cytochrome P450, family 2, subfamily D, polypeptide 6) (eg, drug metabolism) gene analysis, targeted sequence analysis (ie, 5’ gene duplication/multiplication) (List separately in addition to code for primary procedure)</td>
</tr>
<tr>
<td>0076U</td>
<td>CYP2D6 (cytochrome P450, family 2, subfamily D, polypeptide 6) (eg, drug metabolism) gene analysis, targeted sequence analysis (ie, 3’ gene duplication/multiplication) (List separately in addition to code for primary procedure)</td>
</tr>
<tr>
<td>0078U</td>
<td>Pain management (opioid-use disorder) genotyping panel, 16 common variants (ie, ABCB1, COMT, DAT1, DBH, DOR, DRD1, DRD2, DRD4, GABA, GAL, HTR2A, HTTLPR, MTHFR, MUOR, OPRK1, OPRM1), buccal swab or other germline tissue sample, algorithm reported as positive or negative risk of opioid-use disorder</td>
</tr>
</tbody>
</table>

†Note: Considered Not Medically Necessary when used to report any non-covered genetic test for pharmacogenetics testing that does not have an assigned CPT/HCPCS code
Considered Experimental/Investigational/Unproven:

<table>
<thead>
<tr>
<th>HCPCS Codes</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>G9143</td>
<td>Warfarin responsiveness testing by genetic technique using any method, any number of specimen(s)</td>
</tr>
</tbody>
</table>


References


49. Epstein RS, Moyer TP, Aubert RE, O’Kane DJ, Xia F, Verbrugge RR, et al. Warfarin Genotyping Reduces Hospitalization Rates Results From the MM-WES (Medco-Mayo Warfarin Effectiveness Study). J Am Coll Cardiol. 2010 Apr 7. [Epub ahead of print]


158. Papanastasopoulos P and Stebbing J. Molecular Basis of 5-Fluorouracil-related Toxicity: Lessons from Clinical Practice. Anticancer Research April 2014 vol. 34 no. 41531-1535


243. Zeir Z, Carpenter LL, Kalin, NH, McDonald WM, Widge AS, Nemeroff BB. Clinical implementation of pharmacogenetic decision support tools for antidepressant drug prescribing. Am J Psychiatry. 2018 Sep 1;175(9):873-886


