Pharmacogenomic Testing for Drug Toxicity and Response

MOL.CU.118.A
v1.0.2026

Pharmacogenomic testing for drug toxicity and response is addressed by this guideline.

Procedures addressed

The inclusion of any procedure code in this table does not imply that the code is under management or requires prior authorization. Refer to the specific Health Plan's procedure code list for management requirements.

Procedures addressed by this guideline	Procedure codes
5HT2C Serotonin Receptor (HTR2C) Gene Variants	81479
5-Fluorouracil (5-FU) Toxicity and Chemotherapeutic Response	81232 81346
ADRB2 Gene Variants	81479
AvertD	81599
BRACAnalysis CDx Germline Companion Diagnostic Test	81162 81479
Catechol-O-Methyltransferase (COMT) Genotype	0032U
CNT (CEP72, TPMT and NUDT15) genotyping panel	0286U
COMT (Catechol Methyl Transferase) Gene Variants	81479
CYP1A2 Genotyping	81479
CYP2B6 Genotyping	81479
CYP2C9 Genotyping	81227
CYP2C19 Genotyping	81225
CYP2C8 Genotyping	81479

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Procedures addressed by this guideline	Procedure codes
CYP2D6 Genotyping for Drug Response	81226
CYP2D6 Common Variants and Copy Number	0070U
CYP2D6 Full Gene Sequencing	0071U
CYP2D6-2D7 Hybrid Gene Targeted Sequence Analysis	0072U
CYP2D7-2D6 Hybrid Gene Targeted Sequence Analysis	0073U
CYP2D6 trans-duplication/ multiplication nonduplicated gene targeted sequence analysis	0074U
CYP2D6 5’ gene duplication/ multiplication targeted sequence analysis	0075U
CYP2D6 3’ gene duplication/ multiplication targeted sequence analysis	0076U
CYP3A4 Gene Analysis	81230
CYP3A5 Gene Analysis	81231
CYP4F2 Genotyping	81479
Cytochrome P450 1A2 (CYP1A2) Genotype	0031U
DPYD Genotyping	81232
Drug metabolism (eg, pharmacogenomics) genomic sequence analysis panel, must include testing of at least 6 genes, including CYP2C19, CYP2D6, and CYP2D6 duplication/deletion analysis	81418
EffectiveRX Comprehensive Panel	0438U
Focused Pharmacogenomics Panel	0029U
G6PD Common Variants	81247
G6PD Full Gene Sequencing	81249
GeneSight Psychotropic	0345U

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Procedures addressed by this guideline	Procedure codes
Genomind Pharmacogenetics Report - Full	0423U
Genomind Professional PGx Express	0175U
HLA-B*1502 Genotyping	81381
HLA-B*5701 Genotyping	81381
IDgenetix	0411U
IFNL3 (IL28B) rs12979860 Gene Variant	81283
Medication Management Neuropsychiatric Panel (EffectiveRX Neuropsychiatric Panel)	0392U
Mental Health DNA Insight	81225 81226 81479
MTHFR Gene Variants	81291
MyGenVar Pharmacogenomics Test	0516U
NT (NUDT15 and TPMT) Genotyping Panel	0169U
NUDT15 Genotyping	81306
OPRM1 Gene Variants	81479
Pain Medication DNA Insight	81225 81226 81227 81291 81479
Psych HealthPGx Panel	0173U
RightMed Comprehensive Test	0349U
RightMed Comprehensive Test Exclude F2 and F5	0348U
RightMed Gene Report	0350U

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Procedures addressed by this guideline	Procedure codes
RightMed Gene Test Exclude F2 and F5	0434U
RightMed Mental Health Gene Report	0476U
RightMed Mental Health Medication Report	0477U
RightMed Oncology Gene Report	0460U
RightMed Oncology Medication Report	0461U
RightMed PGx16 Test	0347U
Statin Induced Myopathy Genotype (SLCO1B1)	81328
Tempus nP	0419U
Thiopurine Methyltransferase (TPMT) and Nudix Hydrolase (NUDT15) Genotyping	0034U
TPMT Genotyping	81335
TYMS Genotyping	81346
UCSF Pharmacogenomics Panel	0533U
UGT1A1 Targeted Variant Analysis	81350
VEGF Gene Variants	81479
VKORC1 Genotyping	81355
Warfarin Response Genotype	0030U
Warfarin responsiveness testing by genetic technique using any method	G9143
Pharmacogenomic tests that make use of molecular and genomic technologies	81479, 81599, and others

What are pharmacogenomic tests?

For the purposes of this guideline, pharmacogenomic tests are those germline tests performed to predict or assess an individual's response to therapy as well as the risk of toxicity from drug treatment.

Testing may be performed prior to treatment in order to determine if the individual has genetic variants that could affect drug response and/or increase the risk for adverse

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drug reactions. Testing may also be performed during treatment to assess whether an individual is having an adequate response or investigate the cause of an unexpected or adverse reaction.

Companion Diagnostics

Companion diagnostics are assays that help determine whether a drug may be safe or effective for a particular individual. Companion assays are evaluated as part of the Food & Drug Administration's (FDA's) development and approval process for the new drug. According to the FDA, "A companion diagnostic is a medical device, often an in vitro device, which provides information that is essential for the safe and effective use of a corresponding drug or biological product. The test helps a health care professional determine whether a particular therapeutic product's benefits to patients will outweigh any potential serious side effects or risks." [1] Although specific companion diagnostic tests may be identified in the FDA label for a new drug approval, similar laboratory-developed tests (LDTs) performed by a CLIA-certified laboratory are generally accepted as alternatives that can typically provide the required information.

Complementary Diagnostics

Complementary diagnostics are assays that were developed and in use prior to the FDA's approval of a new drug. They are not evaluated through the FDA's development and approval process for new drugs. Complementary diagnostics are used to help provide additional information about how a drug might be used, or whether someone should receive a certain class of drugs. These tests are not specifically required for the safe and effective use of a drug, which is part of what differentiates them from companion diagnostics. As with companion diagnostics, LDTs that are similar to the defined complementary diagnostic, when performed by a CLIA-certified laboratory, are able to provide the same information.[2]

The FDA website includes a table of drugs that have information about gene variants and other biomarkers on their labels (may not be all-inclusive): **https://www.fda.gov/drugs/science-and-research-drugs/table-pharmacogenomic-biomarkers-drug-labeling** . While some drug labels provide specific actions to take based on the results of genetic testing, other labels merely describe a gene's role in the drug's metabolism (i.e. pharmacokinetics).

An international consortium called the Clinical Pharmacogenetics Implementation Consortium (CPIC) also develops and maintains detailed gene/drug practice guidelines to assist healthcare providers in the interpretation of pharmacogenomic test results when they are available; however, the consortium does not make specific recommendations about whether these tests should be performed.[3]

Note: This benefit/harm statement only applies to those jurisdictions that do not have Medicare guidance. Based upon the guidelines and evidence provided in the clinical

policy, following EviCore's criteria for pharmacogenomic testing for drug toxicity and response will ensure that testing will be available to those members most likely to benefit from the information provided by the assays. For those not meeting criteria, it ensures alternate management/diagnostic strategies are considered. However, it is possible that some members who would benefit from the testing, but do not meet clinical criteria, will not receive an immediate approval for testing.

Test information

Introduction

Pharmacogenomic testing involves testing single nucleotide polymorphisms (SNPs) within genes that affect an individual's metabolism and response to certain medications.

Test Methods

For pharmacogenomic testing, one of the following testing strategies is typically employed:

- **Targeted testing:** assesses SNPs in a single gene or narrow subset of genes focused on response to one particular medication that is currently prescribed or under consideration for an individual.
- **Multi-gene panels:** assess SNPs in multiple genes to determine general drug response or response to a broad category of medications (e.g., psychotherapeutic, cardiovascular, etc.). Some laboratories apply a proprietary algorithm in order to classify the suitability of various medications based on the results. In contrast to targeted testing, multi-gene panels do not require that a particular medication be prescribed or under consideration, and the test may identify variants in many genes with no current impact on the individual's clinical care.

Criteria

Criteria: General Coverage Guidance

Pharmacogenomic tests are considered medically necessary when ALL of the following conditions are met:

- The individual is currently taking or considering treatment with a drug potentially affected by a known mutation that can be detected by a corresponding test.
- Technical and clinical validity: The test must be accurate, sensitive, and specific, based on sufficient, quality scientific evidence to support the claims of the test.
- Clinical utility: Healthcare providers can use the test results to guide changes in drug therapy management that will improve patient outcomes.

- Reasonable use: The usefulness of the test is not significantly offset by negative factors, such as expense, clinical risk, or social, or ethical challenges.

Criteria: Targeted Pharmacogenomic Tests

Testing of variants in a single gene or narrow subset of genes (e.g., a targeted panel consisting solely of TPMT and NUDT15) associated with response to a specific medication will be considered medically necessary when the following criteria are met:

- Requested testing is performed in a CLIA-certified laboratory, AND
- Testing of the requested gene(s) has not been previously performed, AND
- Healthcare providers can use the test results to directly impact medical care for the individual, AND
- At least one of the following criteria is met:
  - Documentation is provided that the requested testing is required to obtain health plan coverage for the medication being considered for treatment, or
  - A medication's FDA label requires results from the genetic test to effectively or safely use the therapy in question, with specific actions recommended based on the tested genotype (e.g., the label states the drug is contraindicated, recommends consideration of an alternative therapy, and/or requires dosage adjustments), or
  - The member meets criteria for one of the following tests covered without FDA label requirements:
    - DPYD testing for genetic variants DPYD*2A (rs3918290), DPYD*13 (rs55886062), and rs67376798 A (on the positive chromosomal strand) is requested for an individual considering or currently on therapy with any 5-FU containing drug including, but not limited to: 5-fluorouracil (Fluorouracil®, Adrucil®), capecitabine (Xeloda®), or fluorouracil topical formulations (Carac®, Efudex®, Fluoroplex®).

Targeted testing will be covered only for the number of genes or tests necessary to establish drug response.

- When available and cost-efficient, a tiered approach to testing, with reflex to more detailed testing and/or different genes, is recommended.
- When requested with a single procedure code, all components of the test must individually meet the above medical necessity criteria in order to be considered for reimbursement (e.g., CYP2D6 tests denoted by CPT codes 0071U–0076U, which test for other CYP2D6 findings in addition to the common gene variants, are typically not medically necessary).

Testing of any pharmacogenomic gene variants for general drug response or response to broad categories of drugs (e.g., psychotherapeutic, cardiovascular, etc.) would

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not meet the above criteria for targeted testing, and is therefore not eligible for reimbursement.

Targeted Pharmacogenomic Tests Considered Not Medically Necessary

The following tests and indications (i.e. gene/drug interactions) have not demonstrated clinical utility at the time this guideline was updated.[4-44] These tests are considered not medically necessary for these specific indications. This list is not intended to be all-inclusive.*

- CNT (CEP72, TPMT and NUDT15) genotyping panel from RPRD Diagnostics for response to thiopurines and/or vincristine CPT: 0286U
- CYP2C19 gene variants for the management of H. pylori CPT: 81225
- CYP2C9 gene variants for warfarin response CPT: 81227
- CYP2D6 gene variants for tamoxifen response CPT: 81226
- Warfarin Response Genotype from Mayo Clinic CPT: 0030U

Note:

*Please note that some targeted tests and procedure codes in this list may be coverable for other indications. When a test is requested for the purposes of assessing response to a drug not listed here, please see Criteria: Targeted Pharmacogenomic Tests above.

Criteria: Single-Gene Pharmacogenomic Tests Considered Experimental, Investigational, or Unproven

The following single-gene pharmacogenomic tests have not demonstrated clinical utility for any indication at the time this guideline was updated and are considered experimental, investigational, or unproven, and therefore not eligible for reimbursement. This list is not intended to be all-inclusive.†

- 5HT2C (Serotonin Receptor; HTR2C) gene variants CPT: 81479
- ADRB2 (Beta-2-Adrenergic Receptor) gene variants CPT: 81479
- COMT (Catechol Methyl Transferase) gene variants CPT: 81479
- Catechol-O-Methyltransferase (COMT) Genotype from Mayo Clinic CPT: 0032U
- CYP1A2 (Cytochrome P450 1A2) (CYP1A2) gene variants CPT: 81479
- Cytochrome P450 1A2 (CYP1A2) Genotype from Mayo Clinic CPT: 0031U
- CYP2B6 (Cytochrome P450 2B6) gene variants CPT: 81479
- CYP2C8 (Cytochrome P450 2C8) gene variants CPT: 81479
- CYP3A4 (Cytochrome P450 3A4) gene variants CPT: 81230
- CYP3A5 (Cytochrome P450 3A5) gene variants CPT: 81231
- CYP4F2 (Cytochrome P450 4F2) gene variants CPT: 81479
- IFNL3 (IL28B) rs12979860 gene variant CPT: 81283

- MTHFR (5,10-Methylenetetrahydrofolate Reductase) gene variants CPT: 81291
- OPRM1 (Opioid Receptor, Mu-1) gene variants CPT: 81479
- Statin Induced Myopathy Genotype (SLCO1B1) CPT: 81328
- TYMS (Thymidylate Synthetase) gene variants CPT: 81346
- VEGF (Vascular Endothelial Growth Factor) gene variants CPT: 81479
- VKORC1 (Vitamin K Epoxide Reductase Complex, Subunit 1) gene variants CPT: 81355

Note:

†Please note that some tests in this list may be coverable at the time of request due to an update in the FDA drug label. When a test is requested for the purposes of assessing response to a specific drug, please see Criteria: Targeted Pharmacogenomic Tests above.

Criteria: Pharmacogenomic Panels Considered Experimental, Investigational, or Unproven

Multi-gene pharmacogenomic panels that assess general drug response or response to broad categories of medications (e.g., psychotherapeutic, cardiovascular, etc.), regardless of the number of genes included or how they are billed, are considered experimental, investigational, or unproven (E/I/U) and therefore not eligible for reimbursement. The following are examples of panels that are considered E/I/U. This list is not intended to be all-inclusive.

- AvertD [Opioid use disorder risk assessment, genotyping of 15 single nucleotide polymorphisms (SNPs) by microarray analysis, buccal swab, algorithm reported as risk score for developing opioid use disorder in individuals not previously treated with opioid drugs and considering a 4-30 day prescription by AutoGenomics/SOLVD Health] CPT: 81599
- Drug metabolism (eg, pharmacogenomics) genomic sequence analysis panel, must include testing of at least 6 genes, including CYP2C19, CYP2D6, and CYP2D6 duplication/deletion analysis CPT 81418
- EffectiveRX Comprehensive Panel [Drug metabolism (adverse drug reactions and drug response), buccal specimen, gene-drug interactions, variant analysis of 33 genes, including deletion/duplication analysis of CYP2D6, including reported phenotypes and impacted gene-drug interactions from RCA Laboratory Services] CPT: 0438U
- Focused Pharmacogenomics Panel from Mayo Clinic CPT: 0029U
- GeneSight Psychotropic [Psychiatry (eg, depression, anxiety, attention deficit hyperactivity disorder [ADHD]), genomic analysis panel, variant analysis of 15 genes, including deletion/duplication analysis of CYP2D6 from Myriad Genetics] CPT: 0345U

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- Genomind Pharmacogenetics Report – Full [Psychiatry (eg, depression, anxiety), genomic analysis panel, including variant analysis of 26 genes, buccal swab, report including metabolizer status and risk of drug toxicity by condition from Genomind, Inc] CPT: 0423U
- Genomind Professional PGx Express CPT: 0175U
- IDgenetix [Psychiatry (eg, depression, anxiety, attention deficit hyperactivity disorder [ADHD]), genomic analysis panel, variant analysis of 15 genes, including deletion/duplication analysis of CYP2D6 from Castle Biosciences, Inc] CPT: 0411U
- Medication Management Neuropsychiatric Panel (EffectiveRX Neuropsychiatric Panel) [Drug metabolism (depression, anxiety, attention deficit hyperactivity disorder [ADHD]), gene-drug interactions, variant analysis of 16 genes, including deletion/duplication analysis of CYP2D6, reported as impact of gene-drug interaction for each drug from RCA Laboratory Services LLC d/b/a GENETWORx] CPT: 0392U
- Mental Health DNA Insight [Proprietary test from Pathway Genomics] CPT: 81225, 81226, 81479
- MyGenVar Pharmacogenomics Test [Drug metabolism, whole blood, pharmacogenomic genotyping of 40 genes and CYP2D6 copy number variant analysis, reported as metabolizer status from Geisinger Medical Laboratories] CPT: 0516U
- Pain Medication DNA Insight [Proprietary test from Pathway Genomics] CPT: 81225, 81226, 81227, 81291, 81479
- RightMed Comprehensive Test [Drug metabolism or processing (multiple conditions), whole blood or buccal specimen, DNA analysis, 27 gene report, with variant analysis including reported phenotypes and impacted gene-drug interactions from OneOme, LLC] CPT: 0349U
- RightMed Comprehensive Test Exclude F2 and F5 [Drug metabolism or processing (multiple conditions), whole blood or buccal specimen, DNA analysis, 25 gene report, with variant analysis and reported phenotypes from OneOme, LLC] CPT: 0348U
- RightMed Gene Report [Drug metabolism or processing (multiple conditions), whole blood or buccal specimen, DNA analysis, 27 gene report, with variant analysis and reported phenotypes from OneOme, LLC] CPT: 0350U
- RightMed Gene Test Exclude F2 and F5 [Drug metabolism (adverse drug reactions and drug response), genomic analysis panel, variant analysis of 25 genes with reported phenotypes from OneOme LLC] CPT: 0434U
- RightMed Mental Health Gene Report [Drug metabolism, psychiatry (eg, major depressive disorder, general anxiety disorder, attention deficit hyperactivity disorder [ADHD], schizophrenia), whole blood, buccal swab, and pharmacogenomic genotyping of 14 genes and CYP2D6 copy number variant analysis and reported phenotypes from OneOme, LLC] CPT: 0476U
- RightMed Mental Health Medication Report [Drug metabolism, psychiatry (eg, major depressive disorder, general anxiety disorder, attention deficit hyperactivity

disorder [ADHD], schizophrenia), whole blood, buccal swab, and pharmacogenomic genotyping of 14 genes and CYP2D6 copy number variant analysis, including impacted gene-drug interactions and reported phenotypes from OneOme, LLC] CPT: 0477U
- RightMed Oncology Gene Report [Oncology, whole blood or buccal, DNA single-nucleotide polymorphism (SNP) genotyping by real-time PCR of 24 genes, with variant analysis and reported phenotypes from OneOme LLC] CPT: 0460U
- RightMed Oncology Medication Report [Oncology, pharmacogenomic analysis of single-nucleotide polymorphism (SNP) genotyping by real-time PCR of 24 genes, whole blood or buccal swab, with variant analysis, including impacted gene-drug interactions and reported phenotypes from OneOme LLC] CPT: 0461U
- RightMed PGx16 Test [Drug metabolism or processing (multiple conditions), whole blood or buccal specimen, DNA analysis, 16 gene report, with variant analysis and reported phenotypes from OneOme, LLC] CPT: 0347U
- Tempus nP [Neuropsychiatry (eg, depression, anxiety), genomic sequence analysis panel, variant analysis of 13 genes, saliva or buccal swab, report of each gene phenotype from Tempus Labs, Inc] CPT: 0419U
- UCSF Pharmacogenomics Panel [Drug metabolism (adverse drug reactions and drug response), genotyping of 16 genes (ie, ABCG2, CYP2B6, CYP2C9, CYP2C19, CYP2C, CYP2D6, CYP3A5, CYP4F2, DPYD, G6PD, GGCX, NUDT15, SLCO1B1, TPMT, UGT1A1, VKORC1), reported as metabolizer status and transporter function from University of California San Francisco Genomic Medicine Laboratory] CPT: 0533U

Other Considerations

For pharmacogenomic tests that look for changes in germline DNA (i.e., not tumor DNA or viral DNA), testing will be allowed once per lifetime per gene. Exceptions may be considered if technical advances in testing or the discovery of novel genetic variants demonstrate significant advantages that would support a medical need to retest.

Testing performed in a CLIA-certified laboratory will be considered for coverage. The use of a specific FDA approved companion diagnostic is not necessary for coverage to be considered.

Test-specific guidelines may be available for some pharmacogenomic tests. Please refer to the guidelines manual for a list of test-specific guidelines. For tests without a specific guideline, use the above criteria.

For information on somatic mutation testing in solid tumor tissue or hematological malignancies, please refer to the guideline, *Somatic Mutation Testing*, as this testing is not addressed here.

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