Clinical Use Guidelines

Pharmacogenomic Testing for Drug Toxicity and Response

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Introduction

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

Procedures Addressed

The inclusion of any procedure code in this table is provided for informational purposes and is not a guarantee of coverage nor an indication that prior authorization is required.

Procedures addressed by this guideline	Procedure codes
5HT2C (Serotonin Receptor) Gene Variants	81479
5-Fluorouracil (5-FU) Toxicity and Chemotherapeutic Response	81232 81346
Ankyrin G Gene Variants	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
CYP2C9 Genotyping	81227
CYP2C19 Genotyping	81225
CYP4F2 Genotyping	81479
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

Procedures addressed by this guideline	Procedure codes
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
Cytochrome P450 1A2 Genotype	0031U
DPYD Genotyping	81232
DRD2 (Dopamine Receptor) Gene Variants	81479
DRD4 dopamine D4 receptor p450	81479
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
Focused Pharmacogenomics Panel	0029U
Genomind Professional PGx Express	0175U
HLA-B*1502 Genotyping	81381
HLA-B*5701 Genotyping	81381
IFNL3 rs12979860 Gene Variant	81283
INFINITI Neural Response Panel	0078U
KIF6 Gene Variants	81479
Mental Health DNA Insight	81225 81226 81479
MTHFR Gene Variants	81291
NAT2 Gene Variants	81479
NT (NUDT15 and TPMT) Genotyping Panel	0169U
OPRM1 Gene Variants	81479

Procedures addressed by this guideline	Procedure codes
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
RightMed PGx16 Test	0347U
Serotonin Receptor Genotype (HTR2A and HTR2C)	0033U
SLC6A4 (5-HTTLPR) Serotonin Transporter Variants	81479
TPMT Genotyping	81335
Thiopurine Methyltransferase (TPMT) and Nudix Hydrolase (NUDT15) Genotyping	0034U
UGT1A1 Targeted Variant Analysis	81350
VKORC1 Genotyping	81355
Warfarin Response Genotype	0030U
Warfarin responsiveness testing by genetic technique using any method	G9143
Investigational and experimental tests that make use of molecular and genomic technologies	81479, 84999, 81599, and others

What Are Pharmacogenomic Tests?

Definition

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 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]

Criteria

Criteria: General Coverage Guidance

Pharmacogenomic tests may be indicated 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: Companion or Complementary Diagnostic Testing

Testing for purposes of medication usage will be approved when the following criteria are met:

- **Testing is being performed in a CLIA-certified laboratory, AND**
- **Testing of the requested gene has not previously been performed, AND**
- **A medication's FDA label requires results from the genetic test to effectively or safely use the therapy in question, AND**
- **Healthcare providers can use the test results to directly impact medical care for the individual, OR**
- **The member meets all criteria listed in the below table titled *Select Pharmacogenomic Tests Covered with Criteria***

Select Pharmacogenomic Tests Covered with Criteria

The following pharmacogenomic tests and indications are covered when the member meets the applicable criteria below.

Gene	Indication	Criteria
CYP2C19	Clopidogrel use	Currently on clopidogrel therapy or use of clopidogrel therapy is being proposed for a patient at moderate to high risk for a poor outcome, such as: • Experiencing symptoms consistent with ACS when percutaneous coronary intervention is an option, and/or • Considering a drug-eluting stent

Gene	Indication	Criteria
CYP2D6	Tetrabenazine response	Member has a diagnosis of Huntington's disease, AND Treatment with tetrabenazine is being considered in a dosage greater than 50mg per day. Note: CYP2D6 tests denoted by CPT codes 0071U–0076U, are typically not medically necessary. Requests for these tests will be reviewed on a case by case basis.
CYP2D6	Deutetrabenazine response	Member has a diagnosis of Huntington's disease, AND Treatment with deutetrabenazine is being considered in a dosage greater than 36mg per day. Note: CYP2D6 tests denoted by CPT codes 0071U–0076U, are typically not medically necessary. Requests for these tests will be reviewed on a case by case basis.
CYP2D6	Eliglustat response	Member has a diagnosis of Gaucher disease, AND Treatment with eliglustat is being considered. Note: CYP2D6 tests denoted by CPT codes 0071U–0076U, are typically not medically necessary. Requests for these tests will be reviewed on a case by case basis.
DPYD	5-FU Toxicity	DPYD testing for genetic variants DPYD*2A (rs3918290), DPYD*13 (rs55886062), and rs67376798 A (on the positive chromosomal strand) is indicated in individuals considering or currently on therapy with any 5-FU containing drug including, but not limited to: • 5-fluorouracil (Fluorouracil®, Adrucil®) • capecitabine (Xeloda®) • fluorouracil topical formulations (Carac®, Efudex®, Fluoroplex®)

Gene	Indication	Criteria
HLA-B*1502	Carbamazepine response	HLA-B*1502 variant testing is indicated in individuals with Asian ancestry prior to initiation of or during the first nine months of treatment with carbamazepine therapy.
HLA-B*1502	Oxcarbazepine response	HLA-B*1502 variant testing is indicated in individuals with Asian ancestry prior to initiation of or during the first nine months of treatment with oxcarbazepine therapy.
HLA-B*5701	Abacavir hypersensitivity	HLA-B*5701 testing is indicated in individuals with HIV-1 prior to the initiation of any abacavir-containing therapy.
TPMT	Thiopurine response	TPMT testing by phenotyping or genotyping is indicated in individuals considering treatment with any thiopurine drug: • azathioprine (AZA, Imuran®, Azasan®) • 6-mercaptopurine (6-MP, Mercaptopurinum®, Purinethol®) • thioguanine (6-TG, Tabloid®, Thioguanine®)
UGT1A1	Irinotecan response	UGT1A1 variant analysis is indicated in individuals with metastatic and/or recurrent colorectal cancer prior to the initiation of irinotecan therapy.

Criteria: Investigational And/or Experimental Single Gene Tests

Single Gene Tests: The following pharmacogenomic tests and indications are considered investigational and/or experimental and, therefore, not eligible for reimbursement.[3-24] This list is not intended to be all inclusive.*

- 5HT2C (Serotonin Receptor) gene variants CPT: 81479
- Ankyrin G gene variants CPT: 81479
- COMT (Catechol Methyl Transferase) gene variants CPT: 81479
- Catechol-O-Methyltransferase (COMT) Genotype from Mayo Clinic CPT: 0032U
- CYP450 gene variants (including, but not limited to CYP1A2, CYP2D6, CYP2C9, CYP2C19, CYP3A4, CYP3A5) for psychotherapeutic, cardiovascular, or general drug response CPT: 81225, 81226, 81227, 81230, 81231, 81479
- Cytochrome P450 1A2 Genotype from Mayo Clinic CPT: 0031U
- CYP2C19 testing for the management of H. pylori CPT: 81225

- **CYP2C9, VKORC1, and/or CYP4F2 Testing for Warfarin Response CPT: 81227, 81355, 81479**
- **CYP2D6 testing for tamoxifen response CPT: 81226**
- **DRD2 (Dopamine Receptor) gene variants CPT: 81479**
- **DRD4 dopamine D4 receptor p450 CPT: 81479**
- **IFNL3 rs12979860 gene variant CPT: 81283**
- **KIF6 gene variants CPT: 81479**
- **MTHFR gene variants CPT: 81291**
- **NAT2 gene variants CPT: 81479**
- **OPRM1 gene variants CPT: 81479**
- **Serotonin Receptor Genotype (HTR2A and HTR2C) from Mayo Clinic CPT: 0033U**
- **SLC6A4 (5-HTTLPR) serotonin transporter variants CPT: 81479**
- **Warfarin Response Genotype from Mayo Clinic CPT: 0030U**

Note ***Please note that some single gene tests may be coverable under a narrow set of indications. Please see the Companion or Complementary Diagnostic Testing criteria above.**

Criteria: Investigational And/or Experimental Panel Tests

Pharmacogenomic panels, regardless of how they are billed, are considered investigational and/or experimental and, therefore, are not eligible for reimbursement. The following are examples of panels that are considered investigational and/or experimental. This list is not intended to be all inclusive:

- **5-Fluorouracil (5-FU) Toxicity and Chemotherapeutic Response [Proprietary panel of DPYD and TYMS gene variants to assess risk of 5-fluorouracil toxicity from ARUP Laboratory] CPT: 81232 and 81346**
- **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**
- **Focused Pharmacogenomics Panel from Mayo Clinic CPT: 0029U**
- **Genomind Professional PGx Express CPT: 0175U**
- **Mental Health DNA Insight [Proprietary test from Pathway Genomics] CPT: 81225, 81226, 81479**
- **INFINITI® Neural Response Panel [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 from Prescient Medicine Holdings, Inc.] CPT: 0078U

- NT (NUDT15 and TPMT) Genotyping Panel from RPRD Diagnostics CPT: 0169U
- CNT (CEP72, TPMT and NUDT15) genotyping panel from RPRD Diagnostics CPT: 0286U
- Thiopurine Methyltransferase (TPMT) and Nudix Hydrolase (NUDT15) Genotyping from Mayo Clinic CPT: 0034U
- 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 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

Other Considerations

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.

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 are available for some pharmacogenomic tests. Please refer to the guidelines manual for a list of test-specific guidelines (for example: *GeneSight Psychotropic Test*). For tests without a specific guideline, use the General Coverage Guidance above.

For information on somatic mutation testing in solid tumor tissue, please refer to the guideline, *Somatic Mutation Testing - Solid Tumors*. For information on somatic mutation testing in hematological malignancies, please refer to the guideline, *Somatic Mutation Testing - Hematological Malignancies*. Somatic mutation testing is not addressed here.

References

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