Policy: MP239  
Section: Medical Benefit Policy  
Subject: Pharmacogenetic Testing

I. Policy: Pharmacogenetic Testing

II. Purpose/Objective:
To provide a policy of coverage regarding Pharmacogenetic Testing

III. Responsibility:
   A. Medical Directors
   B. Medical Management Department

IV. Required Definitions
1. Attachment – a supporting document that is developed and maintained by the policy writer or department requiring/authoring the policy.
2. Exhibit – a supporting document developed and maintained in a department other than the department requiring/authoring the policy.
3. Devised – the date the policy was implemented.
4. Revised – the date of every revision to the policy, including typographical and grammatical changes.
5. Reviewed – the date documenting the annual review if the policy has no revisions necessary.

V. Additional Definitions
Medical Necessity or Medically Necessary means Covered Services rendered by a Health Care Provider that the Plan determines are:

a. appropriate for the symptoms and diagnosis or treatment of the Member's condition, illness, disease or injury;
b. provided for the diagnosis, and the direct care and treatment of the Member's condition, illness disease or injury;
c. in accordance with current standards of good medical treatment practiced by the general medical community;
d. not primarily for the convenience of the Member, or the Member's Health Care Provider; and the most appropriate source or level of service that can safely be provided to the Member. When applied to hospitalization, this further means that the Member requires acute care as an inpatient due to the nature of the services rendered or the Member's condition, and the Member cannot receive safe or adequate care as an outpatient.

Medicaid Business Segment
Medical Necessity shall mean a service or benefit that is compensable under the Medical Assistance Program and if it meets any one of the following standards:
(i) the service or benefit will, or is reasonably expected to, prevent the onset of an illness, condition or disability.
(ii) the service or benefit will, or is reasonably expected to, reduce or ameliorate the physical, mental or development effects of an illness, condition, injury or disability.
(iii) the service or benefit will assist the Member to achieve or maintain maximum functional capacity in performing daily activities, taking into account both the functional capacity of the Member and those functional capacities that are appropriate for members of the same age.
INDICATIONS:
Pharmacogenetic testing is considered to be medically necessary when the identification of a specific gene marker is noted to be clinically necessary before initiation of therapy by the U.S. Food and Drug Administration as noted in the Indications section of the prescribing information. Examples include, but are not limited to any of the following:

- K-RAS for cetuximab (Erbitux) and/or panitumumab (Vectibix)
- BRAF for vemurafenib (Zelboraf), dabrafenib (Tafinlar), pembrolizumab (Keytruda) or encorafenib (Braftovi)
- BRAF and NRAS for cetuximab (Erbitux) or panitumumab (Vectibix).
- CTFR for ivacaftor (Kalydeco) or lumacaftor/ivacaftor (Orkambi)
- EGFR for cetuximab (Erbitux), erlotinib (Tarceva) osimertinib (Tagrisso), and/or afatinib dimaleate (Gilotrif)
- HER2/neu for traztuzumab (Herceptin) and/or lapatinib (Tykerb)
- Genotype 1 chronic hepatitis C for teleprevir (Incivik)
- ER for fulvestrant (Faslodex)
- GBA for velaglucerase alfa
- BCR/ABL1 for dasatinib, imatinib, nilotinib, ponatinib and/or bosutinib
- PDL1 for pembrolizumab (Keytruda), durvalumab (Imfinzi).
- HLA-B*5701 for Abacavir (Ziagen)
- HLA-B*1502 for persons of Asian ancestry prior to carbamazepine (Tegretol)
- HLA-B*5801 for allopurinol
- ALK for crizotinib (Xalkori) or ceritinib (Zykadia)
- DYPD gene mutation for capecitabine or 5-fluorouracil
- BRCA for olaparib (Lynparza), rucaparib (Rubraca).
- TPMT gene mutation or phenotypic assay for 6-mercaptopurine or azathioprine therapy (See MP311 for additional information)
- MGMT gene methylation assay for temozolomide (Temodar)
- NS3 Q80K for simprevir (Olysio)
- FTL3 mutation assay for midostaurin (Rydapt).
- CYP2D6 for tetrabenazine (Xenazine) greater than 50 mg per day, eliglustat (Cerdelga).

Generally, pharmacogenetic testing such as mutation analysis or genotyping is considered to be medically necessary when:

- The member is a candidate for a targeted therapy as noted above; and
- The testing methodology used to investigate and identify the genetic mutation or biomarker has been proven to be clinically valid and analytically valid; and
- The test result has been proven to have clinical utility and will have a direct impact on the decision making and/or the member’s clinical outcome.

MEDICARE BUSINESS SEGMENT:
Pharmacogeneomic testing for warfarin metabolism is eligible for coverage once per patient lifetime, corresponding to CYP2C9 and VKORC1 genotypes, respectively. Alleles CYP2C9 and VKORC1 for warfarin dosing are coverable per NCD 90.1 via coverage with evidence development. (http://www.cms.gov/medicare-coverage-database/details/ncddetails.aspx?NCDId=333&ncdver=1&bc=BAAAqAAAAAAA&)

Pharmacogeneomic testing of CYP2C19 for clopidogrel metabolism is eligible for coverage in individuals with acute coronary syndrome undergoing a percutaneous coronary intervention who are initiating or re-initiating clopidogrel therapy.

Pharmacogeneomic testing of CYP2D6 is eligible for coverage in individuals in whom:

- Amitriptyline or nortriptyline is initiated for depressive disorder; or
- Tetrabenazine dosing greater than 50 mg/day

MEDICAID BUSINESS SEGMENT:
Pharmacogeneomic testing of CYP2C19 for clopidogrel metabolism is eligible for coverage as an Option 2 program exception once per patient lifetime when the request for this test is for an insured individual with documented moderate to high risk for an acute coronary event.

EXCLUSIONS:
Unless otherwise mandated, the Plan does NOT provide coverage for the use of the following pharmacogenetic testing because they are considered experimental, investigational or unproven. The Geisinger Technology Assessment Committee evaluated this technology and concluded that there is insufficient evidence in the peer-reviewed published
medical literature to establish the effectiveness of this test on health outcomes when compared to established tests or technologies.

- CYP2D6 gene mutation for any of the following
  - Opioid analgesics
  - Antidepressants for treatment of depression (including SSRI’s) (not applicable to Medicare)
  - Anti-psychotics for treatment of schizophrenia
  - Tamoxifen resistance
- CYP2C9 for warfarin metabolism (not applicable to Medicare/Medicaid)
- VKORC1 for warfarin metabolism (not applicable to Medicare/Medicaid)
- CYP1A2
- CYP3A4
- CYP3A5
- CYP2B6
- OPRM1 (µ-opioid receptor)
- OPRK1 (k-opioid receptor)
- DRD1 (dopamine receptor)
- DRD2 (dopamine receptor)
- DRD4 (dopamine receptor)
- DAT1 or SLC6A3 (dopamine transporter)
- DBH (dopamine beta-hydroxylase)
- SLCO1B1 genotyping to improve statin prescribing and patient adherence
- TYMS (thymidylate synthetase) (eg, 5-fluorouracil/5-FU drug metabolism)
- IFNL3 (prediction of virological response to pegylated-interferon-alpha and ribavirin combination therapy)
- MTHFR (5, 10-methylenetetrahydrofolate reductase) (eg, hereditary hypercoagulability) gene analysis
- HTR2A (eg, citalopram metabolism) gene analysis, common variants
- HTR2C (eg, citalopram metabolism) gene analysis, common variants
- UGT1A1 for irinotecan treatment
- UGT2B15 (uridine diphosphate glycosyltransferase 2 family, member 15)
- COMT (catechol-O-methyltransferase)
- CYP2C19 for any of the following:
  - Clopidogrel resistance (covered for Medicare in individuals with acute coronary syndrome. May be considered for program exception for the MA business segment as noted above)
  - Antidepressants
  - Barbiturates
  - Proton pump inhibitors
  - Mephenytoin

Unless otherwise mandated, the Plan does NOT provide coverage for the use of any of the following pharmacogenetic testing panels because they are considered experimental, investigational or unproven:

- AIBioTech CardioloGene Genetic Panel
- AIBioTech Pain Management Panel
- AIBioTech PsychiaGene Genetic Panel
- AIBioTech Urologene Panel
- GeneSight ADHD
- GeneSight Psychotropic
- GeneSight Analgesic
- Genececept Assay
- SureGene Test for Antipsychotic and Antidepressant Response
- Millenium Pharmacogenetic Testing
- Proove Drug Metabolism Panel
- Proove Narcotic Risk Assay
- YouScript Panel
- PharmaRisk Basic
- PharmaRisk Psychiatric Panel
- Molecular Testing Labs Psychotropic Medication Panel
- Physicians Choice Laboratory Services Pharmacogenetic Testing
- NeuroIDGenetics
- CardioIDGenetics
- OnDose testing to allow area under the curve (AUC)-targeted 5-fluorouracil dosing
**CODING ASSOCIATED WITH:** Pharmacogenetic Testing

The following codes are included below for informational purposes and may not be all inclusive. Inclusion of a procedure or device code(s) does not constitute or imply coverage nor does it imply or guarantee provider reimbursement. Coverage is determined by the member specific benefit plan document and any applicable laws regarding coverage of specific services. Please note that per Medicare coverage rules, only specific CPT/HCPCS Codes may be covered for the Medicare Business Segment. Please consult the CMS website at [www.cms.gov](http://www.cms.gov) or the local Medicare Administrative Carrier (MAC) for more information on Medicare coverage and coding requirements.

<table>
<thead>
<tr>
<th>Code</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>
<tr>
<td>81220</td>
<td>CFTR (cystic fibrosis transmembrane conductance regulator) (eg, cystic fibrosis) gene analysis; common variants (eg, ACMG/ACOG guidelines)</td>
</tr>
<tr>
<td>81221</td>
<td>CFTR (cystic fibrosis transmembrane conductance regulator) (eg, cystic fibrosis) gene analysis; known familial variants</td>
</tr>
<tr>
<td>81222</td>
<td>CFTR (cystic fibrosis transmembrane conductance regulator) (eg, cystic fibrosis) gene analysis; duplication/deletion variants</td>
</tr>
<tr>
<td>81227</td>
<td>CYP2C9 gene analysis, common variants</td>
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<tr>
<td>81225</td>
<td>CYP2C19 gene analysis, common variants</td>
</tr>
<tr>
<td>81355</td>
<td>VKORC1 gene analysis, common variants</td>
</tr>
<tr>
<td>81226</td>
<td>CYP2D6 (cytochrome P450, family 2, subfamily D, polypeptide 6) (eg, drug metabolism), gene analysis, common variants</td>
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<tr>
<td>81235</td>
<td>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)</td>
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<tr>
<td>81245</td>
<td>FLT3 (fms-related tyrosine kinase 3) (eg, acute myeloid leukemia), gene analysis; internal tandem duplication (ITD) variants (ie, exons 14, 15)</td>
</tr>
<tr>
<td>81246</td>
<td>FLT3 (fms-related tyrosine kinase 3) (eg, acute myeloid leukemia), gene analysis; tyrosine kinase domain (TKD) variants (eg, D835, I836)</td>
</tr>
<tr>
<td>81288</td>
<td>MLH1 (mutL homolog 1, colon cancer, nonpolyposis type 2) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; promoter methylation analysis</td>
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<tr>
<td>81371</td>
<td>HLA class I and II typing, low resolution (eg, antigen equivalents); HLA-A, -B, and -DRB1 (eg, verification typing)</td>
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<tr>
<td>81376</td>
<td>HLA class II typing, low resolution (eg, antigen equivalents); one locus (eg, HLA-DRB1, -DRB3/4/5, -DQB1, -DQA1, -DPB1, or -DPA1), each</td>
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<tr>
<td>81381</td>
<td>HLA class I typing, high resolution (ie, alleles or allele groups); one allele or allele group (eg, B*57:O1P), each</td>
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<tr>
<td>81276</td>
<td>KRAS (kristen rat sarcome viral oncogene homolog) (eg, carcinoma) gene analysis; additional variant(s) (eg, codon 61, codon 146)</td>
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<tr>
<td>81275</td>
<td>KRAS (v-Ki-ras2 Kirsten rat sarcoma viral oncogene) (eg, carcinoma) gene analysis, variants in codons 12 and 13</td>
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<tr>
<td>81287</td>
<td>MGMT (O-6-methylguanine-DNA methyltransferase) (eg, glioblastoma multiforme), methylation analysis</td>
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<tr>
<td>81350</td>
<td>UGT1A1 (UDP glucuronosyltransferase 1 family, polypeptide A1) (eg, irinotecan metabolism), gene analysis, common variants</td>
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<tr>
<td>81381</td>
<td>HLA Class I typing, high resolution (ie, alleles or allele groups); 1 allele or allele group (eg, B*57:01P), each</td>
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<tr>
<td>81400-81408</td>
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<tr>
<td>81210</td>
<td>BRAF (v-raf murine sarcoma viral oncogene homolog B1) (eg, colon cancer), gene analysis, V600E variant</td>
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<tr>
<td>81240</td>
<td>F2 (prothrombin, coagulation factor II) (eg, hereditary hypercoagulability) gene analysis, 20210G&gt;A variant</td>
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<tr>
<td>81241</td>
<td>F5 (coagulation factor V) (eg, hereditary hypercoagulability) gene analysis, leiden variant</td>
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<tr>
<td>81291</td>
<td>MTHFR (5, 10-methylenetetrahydrofolate reductase) (eg, hereditary hypercoagulability) gene analysis, common variants (eg, 677T, 1298C)</td>
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<tr>
<td>82172</td>
<td>apolipoprotein, each</td>
</tr>
<tr>
<td>82777</td>
<td>galectin-3</td>
</tr>
<tr>
<td>81283</td>
<td>IFNL3 interferon lambda, gene analysis</td>
</tr>
<tr>
<td>81328</td>
<td>SLCO1B1 solute carrier organic anion transporter family, member 1B1</td>
</tr>
<tr>
<td>81335</td>
<td>TPMT (thiopurine S-methyltransferase, gene analysis, common variants</td>
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<tr>
<td>81346</td>
<td>TYMS (thymidylate synthase, gene analysis (eg, 5-FU drug metabolism)</td>
</tr>
<tr>
<td>81232</td>
<td>DPYD dihydropyrimidine dehydrogenase gene analysis</td>
</tr>
<tr>
<td>81230</td>
<td>CYP3A4 gene analysis</td>
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<tr>
<td>81231</td>
<td>CYP3A5 gene analysis</td>
</tr>
<tr>
<td>84431</td>
<td>Thromboxane metabolite(s), including thromboxane if performed, urine</td>
</tr>
</tbody>
</table>
cellular function assay involving stimulation (eg, mitogen or antigen) and detection of biomarker (eg, ATP)

Enzyme activity in blood cells, cultured cells or tissue, not elsewhere specified, nonradioactive substrate, each specimen

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

Drug metabolism (adverse drug reactions and drug response), targeted sequence analysis (ie, CYP1A2, CYP2C19, CYP2C9, CYP2D6, CYP3A4, CYP3A5, CYP4F2, SLCO1B1, VKORC1 and rs12777823)

Drug metabolism (warfarin drug response), targeted sequence analysis (ie, CYP2C9, CYP4F2, VKORC1, rs12777823)

CYP1A2 (cytochrome P450 family 1, subfamily A, member 2)(eg, drug metabolism) gene analysis, common variants (ie, *1F, *1K, *6, *7)

COMT (catechol-O-methyltransferase) (drug metabolism) gene analysis, c.472G>A (rs4680) variant


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)

CYP2D6 (cytochrome P450, family 2, subfamily D, polypeptide 6) (eg, drug metabolism) gene analysis, targeted sequence analysis (ie, CYP2D6-hyphen2D7 hybrid gene) (List separately in addition to code for primary procedure)

CYP2D6 (cytochrome P450, family 2, subfamily D, polypeptide 6) (eg, drug metabolism) gene analysis, targeted sequence analysis (ie, CYP2D7-hyphen2D6 hybrid gene) (List separately in addition to code for primary procedure)

CYP2D6 (cytochrome P450, family 2, subfamily D, polypeptide 6) (eg, drug metabolism) gene analysis, targeted sequence analysis (ie, non-hyphen duplicated gene when duplication/multiplication is trans) (List separately in addition to code for primary procedure)

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)

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)

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

LINE OF BUSINESS:
Eligibility and contract specific benefits, limitations and/or exclusions will apply. Coverage statements found in the line of business specific benefit document will supersede this policy. For Medicare, applicable LCD’s and NCD’s will supercede this policy. For PA Medicaid Business segment, this policy applies as written.

REFERENCES:


Hayes Inc. GTE database STA2R SureGene Test for Antipsychotic and Antidepressant Response for Pharmacogenetic Testing (SureGene LLC) Jan 2014


Hayes Inc. GTE database Cytochrome P450 3A5 (CYP3A5) Testing for Predict Response to Tacrolimus No, 2013

Hayes Inc. GTE database UGT1A1 Sequence Variant Testing for Predicting Response to Irinotecan Therapy in Colorectal Cancer Jan. 2013

Hayes Inc. GTE database Cytochrome P450 Genotyping to Predict Response to Pain Medications for Response to Pain Medications Feb. 2014


Hayes Inc. GTE database Cytochrome P450 (CYP450) Genotyping to Predict Response to Antidepressant and Antipsychotic Medications for Pharmacogenetic Testing Nov. 2012

Hayes Inc. GTE database CYP2C9 and VKORC1 Variant Testing for Management of Warfarin Dose Initiation Jun 2012

Hayes, Inc. GTE database Genetic testing to predict allopurinol toxicity. 2017


Ziagen® Product Information, Research Triangle Park, NC. GlaxoSmithKlein

Tegretol® [Product Information], East Hanover, NJ. Novartis Pharmaceuticals Corp

Abbott Laboratories. Press Release: Abbott Introduces New ALK Genetic Test for Specific Form of Non-Small-Cell Lung Cancer Abbott Park, IL

U.S. Food and Drug Administration (FDA). Fatal hypersensitivity reactions, respiratory symptoms, and Ziagen (abacavir sulfate). FDA Medwatch. The FDA Safety Information and Adverse Event Reporting Program. Rockville, MD

Piller C. Proove Biosciences, which sold dubious DNA tests to predict addiction risk, sells off assets as CEO departs amid criminal probe. STAT, August 31, 2017


U.S. Food and Drug Administration (FDA). FDA approves new uses for two drugs administered together for the treatment of BRAF-positive anaplastic thyroid cancer. Silver Spring, MD: FDA; May 4, 2018

U.S. Food and Drug Administration (FDA). FDA approves encorafenib and binimetinib in combination for unresectable or metastatic melanoma with BRAF mutations. Silver Spring, MD: FDA; June 27, 2018

This policy will be revised as necessary and reviewed no less than annually.

Devised: 03/2010

Revised: 8/13 (added coverage for Medicare business segment), 9/14 (expanded policy scope), 4/15 (added panels to exclusions); 7/15 (added Medicare coverage); 8/17 (add indications and exclusions); 8/18 (add indications and exclusions); 8/19 (add indications and exclusions)

Reviewed: 3/11, 3/12, 3/13, 9/16