

**Effective Date:** 02/12/2023

**Version Creation Date:** 08/29/2022

Approval and implementation dates for specific health plans may vary. Please consult the applicable health plan for more details. AIM Specialty Health disclaims any responsibility for the completeness or accuracy of the information contained herein.

## CLINICAL APPROPRIATENESS GUIDELINES

# GENETIC TESTING

Appropriate Use Criteria: Pharmacogenomic Testing

### Proprietary

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GEN09-0223.1-v2



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## Description and Application of the Guidelines

The AIM Clinical Appropriateness Guidelines (hereinafter “the AIM Clinical Appropriateness Guidelines” or the “Guidelines”) are designed to assist providers in making the most appropriate treatment decision for a specific clinical condition for an individual. As used by AIM, the Guidelines establish objective and evidence-based criteria for medical necessity determinations where possible. In the process, multiple functions are accomplished:

- To establish criteria for when services are medically necessary
- To assist the practitioner as an educational tool
- To encourage standardization of medical practice patterns
- To curtail the performance of inappropriate and/or duplicate services
- To advocate for patient safety concerns
- To enhance the quality of health care
- To promote the most efficient and cost-effective use of services

The AIM guideline development process complies with applicable accreditation standards, including the requirement that the Guidelines be developed with involvement from appropriate providers with current clinical expertise relevant to the Guidelines under review and be based on the most up-to-date clinical principles and best practices. Relevant citations are included in the References section attached to each Guideline. AIM reviews all of its Guidelines at least annually.

AIM makes its Guidelines publicly available on its website twenty-four hours a day, seven days a week. Copies of the AIM Clinical Appropriateness Guidelines are also available upon oral or written request. Although the Guidelines are publicly-available, AIM considers the Guidelines to be important, proprietary information of AIM, which cannot be sold, assigned, leased, licensed, reproduced or distributed without the written consent of AIM.

AIM applies objective and evidence-based criteria, and takes individual circumstances and the local delivery system into account when determining the medical appropriateness of health care services. The AIM Guidelines are just guidelines for the provision of specialty health services. These criteria are designed to guide both providers and reviewers to the most appropriate services based on a patient’s unique circumstances. In all cases, clinical judgment consistent with the standards of good medical practice should be used when applying the Guidelines. Guideline determinations are made based on the information provided at the time of the request. It is expected that medical necessity decisions may change as new information is provided or based on unique aspects of the patient’s condition. The treating clinician has final authority and responsibility for treatment decisions regarding the care of the patient and for justifying and demonstrating the existence of medical necessity for the requested service. The Guidelines are not a substitute for the experience and judgment of a physician or other health care professionals. Any clinician seeking to apply or consult the Guidelines is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient’s care or treatment.

The Guidelines do not address coverage, benefit or other plan specific issues. Applicable federal and state coverage mandates take precedence over these clinical guidelines. If requested by a health plan, AIM will review requests based on health plan medical policy/guidelines in lieu of the AIM Guidelines.

The Guidelines may also be used by the health plan or by AIM for purposes of provider education, or to review the medical necessity of services by any provider who has been notified of the need for medical necessity review, due to billing practices or claims that are not consistent with other providers in terms of frequency or some other manner.

## General Clinical Guideline

### Clinical Appropriateness Framework

Critical to any finding of clinical appropriateness under the guidelines for a specific diagnostic or therapeutic intervention are the following elements:

- Prior to any intervention, it is essential that the clinician confirm the diagnosis or establish its pretest likelihood based on a complete evaluation of the patient. This includes a history and physical examination and, where applicable, a review of relevant laboratory studies, diagnostic testing, and response to prior therapeutic intervention.
- The anticipated benefit of the recommended intervention should outweigh any potential harms that may result (net benefit).
- Current literature and/or standards of medical practice should support that the recommended intervention offers the greatest net benefit among competing alternatives.
- Based on the clinical evaluation, current literature, and standards of medical practice, there exists a reasonable likelihood that the intervention will change management and/or lead to an improved outcome for the patient.

If these elements are not established with respect to a given request, the determination of appropriateness will most likely require a peer-to-peer conversation to understand the individual and unique facts that would supersede the requirements set forth above. During the peer-to-peer conversation, factors such as patient acuity and setting of service may also be taken into account.

### Simultaneous Ordering of Multiple Diagnostic or Therapeutic Interventions

Requests for multiple diagnostic or therapeutic interventions at the same time will often require a peer-to-peer conversation to understand the individual circumstances that support the medical necessity of performing all interventions simultaneously. This is based on the fact that appropriateness of additional intervention is often dependent on the outcome of the initial intervention.

Additionally, either of the following may apply:

- Current literature and/or standards of medical practice support that one of the requested diagnostic or therapeutic interventions is more appropriate in the clinical situation presented; or
- One of the diagnostic or therapeutic interventions requested is more likely to improve patient outcomes based on current literature and/or standards of medical practice.

### Repeat Diagnostic Intervention

In general, repeated pharmacogenomic testing for the same indication should be limited to evaluation following an intervention, or when there is a change in clinical status such that additional testing is required to determine next steps in management. At times, it may be necessary to repeat a test using different techniques or protocols to clarify a finding or result of the original study.

Repeated testing for the same indication using the same or similar technology may be subject to additional review or require peer-to-peer conversation in the following scenarios:

- Repeated pharmacogenomic testing by the same laboratory due to technical issues
- Repeated pharmacogenomic testing requested at a different laboratory due to provider preference or quality concerns
- Repeated pharmacogenomic testing area based on persistent symptoms with no clinical change, treatment, or intervention since the previous study
- Repeated pharmacogenomic testing by different providers for the same member over a short period of time

## Repeat Therapeutic Intervention

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In general, repeated therapeutic intervention in the same anatomic area is considered appropriate when the prior intervention proved effective or beneficial and the expected duration of relief has lapsed. A repeat intervention requested prior to the expected duration of relief is not appropriate unless it can be confirmed that the prior intervention was never administered.

# Pharmacogenomic Testing

## Clinical Indications

For each of the following FDA-approved therapies and associated biomarkers (see [Table 1](#)), one genotyping for the appropriate biomarker is considered **medically necessary** when **ALL** the following conditions are met:

- The medication for which genotyping is being done is the most appropriate treatment for the member's underlying condition
- The pharmacogenomic test has demonstrated analytical and clinical validity and clinical utility for the individual, including consideration of the frequency of relevant alleles in the individual's subgroup (when applicable)
- The biomarker testing is focused on the specific genetic polymorphisms relevant to guiding treatment for the individual's condition and expected treatment.

**Table 1**

Biomarker	Drugs	Therapeutic Area
CFTR	ivacaftor	Pediatrics
CYP2C19	clopidogrel	Cardiology
CYP2C9	siponimod	Neurology
CYP2D6	eliglustat	Pediatrics
CYP2D6	tetrabenazine	Neurology
G6PD	rasburicase	Hematology
G6PD	tafenoquine, primaquine	Infectious Diseases
HLA-B*1502	carbamazepine, oxcarbazepine	Neurology
HLA-B*5701	abacavir	Infectious Diseases
HLA-B*58:01	allopurinol	Rheumatology
NAGS	carglumic acid	Gastroenterology
POLG	divalproex sodium, valproic acid	Neurology
TPMT	mercaptopurine, thioguanine	Hematology

Excerpted from  
<https://cpicpgx.org/genes-drugs/>

## Rationale

Pharmacogenomic testing refers to genotype testing for polymorphisms in order to identify variants of specific genes associated with drug pharmacodynamics or metabolism. Such testing is sometimes used to guide the dosing or choice of particular drugs in an individual with the goal of optimizing the response to therapy and/or minimizing the likelihood of an adverse drug effect. Polymorphisms in the genes encoding the drug target can influence the drug pharmacodynamics. Moreover, genetic determinates of excretion or drug metabolism influence pharmacokinetics.<sup>1</sup> Although about 15% of all prescriptions in the United States have potential influence from pharmacogenetics, evidence is available to support genotype-guided prescribing for a limited number of drugs, and sometimes only for specific subpopulations. In some cases, there are race-based screening recommendations that can be difficult to apply because of wide variability in allele frequencies even within ethnic groups along with difficulty in discerning race ancestry and due to mixed ancestry. At the same time, imperatives to use resources judiciously warrant selective screening to target high prevalence groups when they can be accurately identified.<sup>2</sup>

The Clinical Pharmacogenetics Implementation Consortium (CPIC) was developed in 2009 as a shared project between the Pharmacogenomics Knowledge Base (PharmGKB, <http://www.pharmgkb.org>) and the National Institutes of Health (NIH). The CPIC is focused on facilitating the translation of research findings into clinical actions for selected gene/drug pairs with sufficient evidence.<sup>3</sup> With notable exceptions, pharmacogenomics is best used to assess the risk of general suboptimal response. This type of testing does not override the need for clinical assessment and judgement.<sup>4</sup>

While there is considerable enthusiasm for pharmacogenomic testing and tremendous growth in direct-to-consumer marketing, there has also been actions taken by the FDA and other groups to warn patients that selecting or changing drug treatment in response to genetic test results can also lead to potentially serious health consequences ([see FDA warning letter, April 4, 2019](#); [FDA warning letter November 1, 2018](#)). One area where there has been particular enthusiasm is the realm of psychiatry, particularly with use of pharmacogenetic testing to guide antidepressant therapy. While it is known that genetic variants contribute to the variance in response to drug treatments for depression, rigorously conducted clinical trials have not yet shown the clinical utility of such testing. Meta-analyses and non-industry technical assessments of the existing literature have shown notable risks of bias in existing studies, a high degree of between study heterogeneity, and significant methodological limitations. In particular, the randomized, double-blind, clinical trial evaluating the GeneSight pharmacogenomic intervention did not find a statistically significant difference in response rates or remission rates when those tested were compared to those without testing.<sup>5</sup> Systematic reviews of the available studies in this realm are unequivocal that the evidence of clinical utility are lacking in this realm.<sup>6,7</sup>

One area of controversy in the field of pharmacogenomics is the role of DPYD testing for patients being treated with cytolytic chemotherapy using 5-fluorouracil. 5-fluorouracil (5-FU) and capecitabine are commonly used in solid tumors including colorectal, pancreatic, esophageal, head and neck, and breast cancer, and use of these drugs is associated with infrequent severe, life-threatening toxicities including neutropenia, diarrhea, and mucositis. Fluoropyrimidine toxicity is due in part to inherited polymorphisms in the dihydropyrimidine dehydrogenase enzyme, encoded by DPYD, which is responsible for 5-FU elimination. Approximately 5% of patients carry one of five DPYD polymorphisms that increase toxicity risk. DPYD variant carriers who receive standard fluoropyrimidine doses have ~70% risk of severe toxicity and ~3% risk of fatal toxicity, and these risks are even higher in the ~1/250 patients who carry two DPYD variants.<sup>8,9</sup> The NCCN and the FDA recognize the increased risk of severe fluoropyrimidine toxicity in known DPYD carriers but do not recommend routine testing. While some countries have mandated preemptive DPYD testing for patients scheduled to receive a fluoropyrimidine, preemptive DPYD testing is rarely conducted for a variety of reasons.<sup>10</sup> In the SWOG cancer research group, a survey was conducted of 59 US-based medical oncologists within the SWOG gastrointestinal and breast committees. Those data indicate that the primary reasons for not testing are the perceived low prevalence of DPYD deficiency, lack of clinical guidelines recommending testing, and a lack of knowledge around which test to order and what to do with the result. There is also concern among the oncology community related to the potential for dose reduction resulting from this testing, leading ultimately to reduced treatment efficacy.

The clinical utility of pharmacogenomic testing is not established for most instances of its use, and thus it is considered not medically necessary unless otherwise specified. There are some instances where the FDA is explicit in recommending genotyping ahead of prescribing.

## References

1. Lin B, Chung WK. Cases in Precision Medicine: The Role of Pharmacogenetics in Precision Prescribing. *Ann Intern Med.* 2019;170(11):796-804. Epub 2019 May 21. PMID: 31108507
2. Goodman CW, Brett AS. Race and Pharmacogenomics-Personalized Medicine or Misguided Practice? *JAMA.* 2021;325(7):625-6. Epub 2021 Jan 26. PMID: 33492362
3. Relling MV, Klein TE, Gammal RS, et al. The Clinical Pharmacogenetics Implementation Consortium: 10 Years Later. *Clin Pharmacol Ther.* 2020;107(1):171-5. Epub 2019 Sep 29. PMID: 31562822
4. Wake DT, Ilbawi N, Dunnenberger HM, et al. Pharmacogenomics: Prescribing Precisely. *Med Clin North Am.* 2019;103(6):977-90. Epub 2019 Oct 5. PMID: 31582008
5. Winner JG, Carhart JM, Altar CA, et al. A prospective, randomized, double-blind study assessing the clinical impact of integrated pharmacogenomic testing for major depressive disorder. *Discov Med.* 2013;16(89):219-27. Epub 2013 Nov 16. PMID: 24229738
6. Rosenblat JD, Lee Y, McIntyre RS. Does Pharmacogenomic Testing Improve Clinical Outcomes for Major Depressive Disorder? A Systematic Review of Clinical Trials and Cost-Effectiveness Studies. *J Clin Psychiatry.* 2017;78(6):720-9. Epub 2017 Jan 10. PMID: 28068459
7. Health Quality Ontario. Pharmacogenomic Testing for Psychotropic Medication Selection: A Systematic Review of the Assurex GeneSight Psychotropic Test. *Ont Health Technol Assess Ser.* 2017;17(4):1-39. PMID: 28515818
8. Meulendijks D, Henricks LM, Sonke GS, et al. Clinical relevance of DPYD variants c.1679T>G, c.1236G>A/HapB3, and c.1601G>A as predictors of severe fluoropyrimidine-associated toxicity: a systematic review and meta-analysis of individual patient data. *Lancet Oncol.* 2015;16(16):1639-50. Epub 2015 Nov 26. PMID: 26603945
9. Lee AM, Shi Q, Pavey E, et al. DPYD variants as predictors of 5-fluorouracil toxicity in adjuvant colon cancer treatment (NCCTG N0147). *J Natl Cancer Inst.* 2014;106(12). Epub 2014 Nov 9. PMID: 25381393
10. Ciccolini J. DPD deficiency in patients treated with fluorouracil. *Lancet Oncol.* 2015;16(16):1574-6. Epub 2015 Nov 26. PMID: 26603944

## Codes

The following code list is not meant to be all-inclusive. Authorization requirements will vary by health plan. Please consult the applicable health plan for guidance on specific procedure codes.

Specific CPT codes for services should be used when available. Nonspecific or not otherwise classified codes may be subject to additional documentation requirements and review.

### CPT/HCPCS

CPT® (Current Procedural Terminology) is a registered trademark of the American Medical Association (AMA). CPT® five digit codes, nomenclature and other data are copyright by the American Medical Association. All Rights Reserved. AMA does not directly or indirectly practice medicine or dispense medical services. AMA assumes no liability for the data contained herein or not contained herein.

- 81225 .....CYP2C19 (cytochrome P450, family 2, subfamily C, polypeptide 19) (eg, drug metabolism), gene analysis, common variants (eg, \*2, \*3, \*4, \*8, \*17) [for clopidogrel metabolism]
- 81226 .....CYP2D6 (cytochrome P450, family 2, subfamily D, polypeptide 6) (eg, drug metabolism), gene analysis, common variants (eg, \*2, \*3, \*4, \*5, \*6, \*9, \*10, \*17, \*19, \*29, \*35, \*41, \*1XN, \*2XN, \*4XN) [for eliglustat or tetrabenazine metabolism]
- 81227 .....CYP2C9 (cytochrome P450, family 2, subfamily C, polypeptide 9) (eg, drug metabolism), gene analysis, common variants (eg, \*2, \*3, \*5, \*6) [for siponimod (Mayzent) metabolism]
- 81230 .....CYP3A4 (cytochrome P450 family 3 subfamily A member 4) (eg, drug metabolism), gene analysis, common variant(s) (eg, \*2, \*22)
- 81231 .....CYP3A5 (cytochrome P450 family 3 subfamily A member 5) (eg, drug metabolism), gene analysis, common variant(s) (eg, \*2, \*3, \*4, \*5, \*6, \*7)
- 81232 .....DPYD (dihydropyrimidine dehydrogenase) (eg, 5-fluorouracil/5-FU and capecitabine drug metabolism), gene analysis, common variant(s) (eg, \*2A, \*4, \*5, \*6)
- 81346 .....TYMS (thymidylate synthetase) (eg, 5-fluorouracil/5-FU drug metabolism), gene analysis, common variant(s) (eg, tandem repeat variant)
- 81350 .....UGT1A1 (UDP glucuronosyltransferase 1 family, polypeptide A1) (eg, drug metabolism, hereditary unconjugated hyperbilirubinemia [Gilbert syndrome]), gene analysis, common variants (eg, \*28, \*36, \*37) [when specified for drug metabolism (irinotecan)]
- 81355 .....VKORC1 (vitamin K epoxide reductase complex, subunit 1) (eg, warfarin metabolism), gene analysis, common variant(s) (eg, -1639G>A, c.173+1000C>T)
- 81381 .....HLA Class I typing, high resolution (ie, alleles or allele groups); one allele or allele group (eg, B\*57:01P), each [when specified as Human Leukocyte Antigen B\*57:01P (HLA-B\*5701) for abacavir metabolism, Human Leukocyte Antigen B\*58:01 (HLA-B\*58:01) for allopurinol metabolism, or Human Leukocyte Antigen B\*1502 (HLA-B\*1502) for carbamazepine metabolism]
- 81418 .....Drug metabolism (eg, pharmacogenomics) genomic sequence analysis panel, must include testing of at least 6 genes, including CYP2C19, CYP2D6, and CYP2D6 duplication/deletion analysis
- 81479 .....Unlisted molecular pathology procedure
- 0029U.....Drug metabolism (adverse drug reactions and drug response), targeted sequence analysis (ie, CYP1A2, CYP2C19, CYP2C9, CYP2D6, CYP3A4, CYP3A5, CYP4F2, SLCO1B1, VKORC1 and rs12777823)
- 0030U.....Drug metabolism (warfarin drug response), targeted sequence analysis (ie, CYP2C9, CYP4F2, VKORC1, rs12777823)
- 0031U.....CYP1A2 (cytochrome P450 family 1, subfamily A, member 2) (eg, drug metabolism) gene analysis, common variants (ie, \*1F, \*1K, \*6, \*7)
- 0032U.....COMT (catechol-O-methyltransferase) (drug metabolism) gene analysis, c.472G>A (rs4680) variant
- 0033U.....HTR2A (5-hydroxytryptamine receptor 2A), HTR2C (5-hydroxytryptamine receptor 2C) (eg, citalopram metabolism) gene analysis, common variants (ie, HTR2A rs7997012 [c.614-2211T>C], HTR2C rs3813929 [c.-759C>T] and rs1414334 [c.551-3008C>G])
- 0070U.....CYP2D6 (cytochrome P450, family 2, subfamily D, polypeptide 6) (eg, drug metabolism) gene analysis, common and select rare variants (ie, \*2, \*3, \*4, \*4N, \*5, \*6, \*7, \*8, \*9, \*10, \*11, \*12, \*13, \*14A, \*14B, \*15, \*17, \*29, \*35, \*36, \*41, \*57, \*61, \*63, \*68, \*83, \*xN)
- 0071U.....CYP2D6 (cytochrome P450, family 2, subfamily D, polypeptide 6) (eg, drug metabolism) gene analysis, full gene sequence
- 0072U.....CYP2D6 (cytochrome P450, family 2, subfamily D, polypeptide 6) (eg, drug metabolism) gene analysis, targeted sequence analysis (ie, CYP2D6-2D7 hybrid gene)

0073U.....CYP2D6 (cytochrome P450, family 2, subfamily D, polypeptide 6) (eg, drug metabolism) gene analysis, targeted sequence analysis (ie, CYP2D7-2D6 hybrid gene)

0074U.....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)

0075U.....CYP2D6 (cytochrome P450, family 2, subfamily D, polypeptide 6) (eg, drug metabolism) gene analysis, targeted sequence analysis (ie, 5' gene duplication/multiplication)

0076U.....CYP2D6 (cytochrome P450, family 2, subfamily D, polypeptide 6) (eg, drug metabolism) gene analysis, targeted sequence analysis (ie, 3' gene duplication/ multiplication)

0078U.....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

0173U.....Psychiatry (ie, depression, anxiety), genomic analysis panel, includes variant analysis of 14 genes

0175U.....Psychiatry (eg, depression, anxiety), genomic analysis panel, variant analysis of 15 genes

## History

Status	Review Date	Effective Date	Action
Created	08/29/2022	02/12/2023	Independent Multispecialty Physician Panel (IMPP) review. Original effective date.