

Approval and implementation dates for specific health plans may vary. Please consult the applicable health plan for more details.

Clinical Appropriateness Guidelines

Genetic Testing

Appropriate Use Criteria: Pharmacogenetic Testing

Proprietary

© 2026 Carelon Medical Benefits Management, Inc. All rights reserved.

Table of Contents

Description and Application of the Guidelines	3
General Clinical Guideline	4
Clinical Appropriateness Framework	4
Simultaneous Ordering of Multiple Diagnostic or Therapeutic Interventions	4
Repeat Diagnostic Intervention	4
Repeat Therapeutic Intervention	5
Pharmacogenetic Testing	6
Clinical Indications	6
General Requirements	6
General Criteria for Pharmacogenetic Testing	6
Table 1	7
Table 2	7
Rationale	8
References	11
Codes	13
History	15

Description and Application of the Guidelines

The Carelon Clinical Appropriateness Guidelines (hereinafter “the Carelon 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. The Guidelines establish objective and evidence-based criteria for medical necessity determinations, where possible, that can be used in support of the following:

- 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 address patient safety concerns
- To enhance the quality of health care
- To promote the most efficient and cost-effective use of services

The Carelon guideline development process complies with applicable accreditation and legal 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. Resources reviewed include widely used treatment guidelines, randomized controlled trials or prospective cohort studies, and large systematic reviews or meta-analyses. Carelon reviews all of its Guidelines at least annually.

Carelon makes its Guidelines publicly available on its website. Copies of the Guidelines are also available upon oral or written request. Additional details, such as summaries of evidence, a list of the sources of evidence, and an explanation of the rationale that supports the adoption of the Guidelines, are included in each guideline document.

Although the Guidelines are publicly available, Carelon considers the Guidelines to be important, proprietary information of Carelon, which cannot be sold, assigned, leased, licensed, reproduced or distributed without the written consent of Carelon. Use of the Guidelines by any external AI entity without the express written permission of Carelon is prohibited.

Carelon 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 Carelon 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, and in the case of reviews for Medicare Advantage Plans, the Guidelines are only applied where there are not fully established CMS criteria. If requested by a health plan, Carelon will review requests based on health plan medical policy/guidelines in lieu of the Carelon Guidelines. Use of an FDA-approved or conditionally approved product does not constitute medical necessity or guarantee reimbursement by the respective health plan.

The Guidelines may also be used by the health plan or by Carelon 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 is likely to outweigh any potential harms, including from delay or decreased access to services that may result (net benefit).
- Widely used treatment guidelines and/or current clinical literature and/or standards of medical practice should support that the recommended intervention offers the greatest net benefit among competing alternatives.
- There exists a reasonable likelihood that the intervention will change management and/or lead to an improved outcome for the patient.

Providers may be required to submit clinical documentation in support of a request for services. Such documentation must a) accurately reflect the clinical situation at the time of the requested service, and b) sufficiently document the ordering provider's clinical intent.

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 justify a finding of clinical appropriateness. During the peer-to-peer conversation, factors such as patient acuity and setting of service may also be taken into account to the extent permitted by law.

Genetic tests not specifically mentioned in the guidelines are considered not medically necessary.

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 testing of the same anatomic location 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 diagnostic testing at the same facility due to technical issues

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

Repeat Therapeutic Intervention

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. Requests for ongoing services may depend on completion of previously authorized services in situations where a patient's response to authorized services is relevant to a determination of clinical appropriateness.

Pharmacogenetic Testing

Clinical Indications

General Requirements

Testing should be performed in a laboratory with established experience in this clinical domain that has met quality standards set by the Clinical Laboratory Improvement Amendments (CLIA) program overseen by the Centers for Medicare & Medicaid Services (CMS). Prior to using any test result findings for medical management, it is important to ensure that findings were obtained from not only a CLIA-certified lab but also one accredited by the College of American Pathologists (CAP) to issue a report of findings directly to ordering health care providers. Some states (e.g., New York) may have additional reporting requirements.

Germline genetic testing may be performed **only once per lifetime** for a given gene except when the individual is known to have been inadequately tested.

General Criteria for Pharmacogenetic Testing

For each of the following therapies and associated biomarkers (see [Table 1](#) and [Table 2](#)), 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 individual's underlying condition
- The pharmacogenetic 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 specific genetic polymorphisms relevant to guiding treatment for the individual's condition and expected treatment
- The pharmacogenetic testing is referenced in the corresponding FDA package insert for a drug or in NCCN guidelines
- Treatment is being considered for which the member's health plan has a drug-specific policy requiring additional, appropriately focused genetic biomarker testing otherwise not specified by the FDA label or NCCN 2A recommendation

Biomarkers are considered individually for drug treatment. The use of panel and multigene tests for polymorphisms to determine drug-metabolizer status is considered **not medically necessary**.

Table 1.

Therapies and associated biomarkers considered medically necessary for genotyping with CPIC Level of Evidence 1A and/or FDA labeling guidance indicating testing is required or testing recommended

Biomarker	Drug	Therapeutic Area
ApoE ε4	donanemab-azbt, lecanemab	Neurology
CFTR	deutivacaftor, elexacaftor, ivacaftor, lumacaftor, tezacaftor, vanzacaftor*	Pediatrics, Pulmonary*
CYP2C19	clopidogrel	Cardiology
CYP2C9	deuruxolitinib	Dermatology
CYP2C9	siponimod	Neurology
CYP2D6	eliglustat	Hematology
CYP2D6	tetrabenazine	Neurology
DPYD	capecitabine, fluorouracil	Oncology
G6PD	rasburicase	Hematology
G6PD	primaquine, tafenoquine	Infectious diseases
HLA-A*02:01	tebentafusp-tebn	Oncology
HLA-B*1502, HLA-A*3101	carbamazepine, oxcarbazepine	Neurology
HLA-B*5701	abacavir	Infectious diseases
HLA-B*58:01	allopurinol	Rheumatology
LMNA, ZMPSTE24	lonafarnib	Pediatrics
NAGS	carglumic acid	Gastroenterology
POLG	divalproex sodium, valproic acid	Neurology
TPMT, NUDT15	mercaptopurine, thioguanine	Hematology
TPMT, NUDT15	azathioprine	Rheumatology**

*Co-packaged deutivacaftor, tezacaftor, and vanzacaftor; elexacaftor, ivacaftor, and tezacaftor; lumacaftor and ivacaftor

See the [FDA table of pharmacogenomic biomarkers](#) in drug labeling or the [Clinical Pharmacogenetics Implementation Consortium \(CPIC Guidelines\)](#) for additional information about genes and drugs that have been evaluated.

Table 2.

Therapies and associated biomarkers considered medically necessary for genotyping with CPIC Level of Evidence 1A and actionable pharmacogenetic gene-drug association and/or FDA labeling guidance

Biomarker	Drug	Therapeutic Area
CYP2C19	abrocitinib	Dermatology
CYP2C19	citalopram	Psychiatry
CYP2C19	clobazam	Neurology
CYP2C9	celecoxib, piroxicam	Rheumatology
CYP2C9, HLA-B*1502	fosphenytoin, phenytoin	Neurology
CYP2D6	deutetrabenazine, dextromethorphan and quinidine	Neurology

Biomarker	Drug	Therapeutic Area
CYP2D6	aripiprazole, aripiprazole lauroxil, atomoxetine, brexpiprazole, iloperidone, pitolisant, venlafaxine	Psychiatry
NAT2	amifampridine	Neurology
UGT1A1*28	belinostat	Oncology
UGT2B17, CYP2C19	belzutifan	Oncology

See the [FDA table of pharmacogenomic biomarkers](#) in drug labeling or the [Clinical Pharmacogenetics Implementation Consortium \(CPIC Guidelines\)](#) for additional information about genes and drugs that have been evaluated.

Rationale

Overview

Pharmacogenetic 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 drug pharmacodynamics. Moreover, genetic determinates of excretion or drug metabolism influence pharmacokinetics.¹ 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.² While there is enthusiasm for pharmacogenetic testing and growth in direct-to-consumer marketing, there have 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.^{3, 4}

The Clinical Pharmacogenetics Implementation Consortium (CPIC) was developed in 2009 as a shared project between the Pharmacogenomics Knowledge Base (PharmGKB)⁵ 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.⁶ The objectives, processes, and work of CPIC is supported by the College of American Pathologists (CAP). CPIC guidelines are meant to help clinicians understand how genetic tests can be used to optimize therapy versus whether a test should be ordered. CPIC employs a level of evidence review for each drug-genotype association and grades the level of evidence. Designation for level of evidence in CPIC is based on the number, quality, and consistency of individual studies pertaining to the specific drug-genotype pairing. Drugs listed in the [Table 1](#) have a PharmGKB level of evidence of 1A by CPIC and/or the drugs in [Table 1](#) include a notice on the FDA label requiring or recommending pharmacogenetic testing with the associated drug.

The US Food and Drug Administration (FDA) also maintains a searchable table of pharmacogenomic biomarkers in drug labeling. With notable exceptions, pharmacogenetics is best used to assess the risk of general suboptimal response; however, there are some instances where the FDA is explicit in recommending genotyping ahead of prescribing. The drugs listed in [Table 1](#) have support for genotyping as either required or recommended based on the FDA drug label and may be included in a boxed warning in the package insert.

The drugs listed in [Table 2](#) have CPIC Level of Evidence 1A with actionable pharmacogenetic gene-drug association and/or FDA labeling guidance describing genotype-specific dosing guidance and/or genotype associated adverse reactions in the warnings and precautions section of the FDA package insert. Testing for genotypes noted in [Table 2](#) may not be required in all cases and should always be used along with clinical evaluation when prescribing or adjusting dosage. This type of testing does not override the need for clinical assessment and judgement.⁷ Of note, a large pragmatic trial conducted in the United States (the INGENIOUS trial) evaluated pharmacogenetic testing for 26 drug-gene pairs to determine whether the occurrence of adverse drug events within 1 year would be significantly reduced, and no difference was observed. Lessons learned from this study include that trials evaluating pharmacogenetic genotyping in response to de novo pharmacogenetic actionable prescriptions are likely to require more effective clinical decision support, faster return of results or preemptive testing, consent prior to randomization, larger sample sizes, and assurance that participants are enrolled from providers' clinics that will follow the pharmacogenetic recommendations.⁸

Pharmacogenetic testing to guide psychopharmacologic prescribing

One area of significant interest for exploring the role of pharmacogenetic testing is in the realm of psychiatry, particularly the use of testing to guide antidepressant prescribing. While it is known that genetic variants contribute to the variance in response to drug treatments for depression, the relative contribution of genetic versus nongenetic patient- and clinician-specific factors is largely unknown. Factors that are important for antidepressant response may include baseline depression severity and demographic factors, as well as age of onset of depression and chronicity, comorbid psychiatric and medical conditions, and social determinants of health. Rigorously conducted clinical trials have not yet shown the clinical utility of such testing. In particular, the GUIDED trial was a randomized, double-blind, clinical trial evaluating the GeneSight pharmacogenomic intervention which did not find a statistically significant difference in response rates or remission rates when those tested were compared to those without testing.⁹ The GUIDED trial was a prospective study of 1167 outpatients with depression and no suicidal risk or significant comorbidity and inadequate response to at least one prior psychotropic medication.¹⁰ Usual care for subsequent therapy was compared to use of GeneSight (a proprietary combinatorial pharmacogenomics algorithm). This study was negative for the primary endpoint related to HAM-D₁₇ scores at 8 weeks, and disappointing response rates were seen in both study arms. Some of the 25 secondary endpoints that were tested without correction for multiplicity of testing were reported as statistically significant but clinical significance was questionable.¹¹ Moreover, pharmacogenomic-guided treatment was evaluated in the PRIME study¹², a pragmatic randomized trial conducted in the primary care clinics of 22 Department of Veterans Affairs medical centers that randomized 1944 subjects who were initiating or switching treatment with a single antidepressant. In this study, the rate of symptom remission was again not meaningful clinically (e.g., a gain of less than 2% in the proportion of patients achieving remission at 24 weeks, or approximately 0.5 points on the PHQ-9 scale), despite this difference achieving statistical significance in this large study sample. Also, the study was not blinded, a large proportion (25%-31%) did not initiate antidepressants within 30 days of randomization, and antidepressants were frequently prescribed in the pharmacogenomic-guided group after being identified as at risk for drug-gene interactions. There are several smaller prospective studies that show minimal differences in outcomes (if any) and have significant methodological limitations.¹³⁻¹⁷

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.¹⁸⁻²⁰ Likewise, systematic reviews of the available studies in this realm are unequivocal that the evidence of clinical utility are lacking in this realm.²¹⁻²⁴ Prospective trials are ongoing, including a large pragmatic randomized trial to assess gene-based prescribing of selective serotonin reuptake inhibitors (SSRIs) in the treatment of depression.²⁵

DPYD testing and fluoropyrimidine prescribing

Another area of controversy in the field of pharmacogenetics is the role of dihydropyrimidine dehydrogenase gene (DPYD) testing for patients treated with cytotoxic chemotherapy using fluoropyrimidines such as 5-fluorouracil or oral capecitabine. 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 but sometimes severe, life-threatening adverse reactions including neutropenia, diarrhea, mucositis, and neurotoxicity. Fluoropyrimidine toxicity is due in part to inherited polymorphisms in the dihydro-pyrimidine dehydrogenase enzyme (DPD), encoded by DPYD, which is responsible for 5-FU elimination. Approximately 3%-5% of White populations have partial DPD deficiency, and 0.2% of White populations have complete DPD deficiency. Per the FDA package insert for capecitabine and fluorouracil, four main DPYD variants have been associated with impaired DPD activity in White populations when present as homozygous or compound heterozygous variants: **c.1905+1G>A (DPYD *2A), c.1679T>G (DPYD *13), c.2846A>T, and c.1129-5923C>G (Haplotype B3). DPYD*2A and DPYD*13 are no function variants, and c.2846A>T and c.1129-5923C>G are decreased function variants.** The decreased function DPYD variant c.557A>G is observed in individuals of African ancestry.²⁶ This is not a complete listing of all DPYD variants that may result in DPD deficiency. 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.^{27, 28}

The NCCN issued updated guidance in 2025 stating “Testing for DPYD genetic variants **should be considered prior to fluoropyrimidine therapy**. After discussions regarding risk assessment, patients may choose DPYD genetic testing. However, no specific test is recommended at this time and there are insufficient data to inform dose adjustments for many of the DPYD variants.”²⁹ This updated guidance from NCCN represents a change from the prior NCCN guidance which stated that routine DPYD testing prior to fluoropyrimidine therapy was “not recommended.”

The FDA package inserts for capecitabine and fluorouracil each contain a section on patient counseling instructing physicians to inform patients of the potential for serious and life-threatening adverse reactions due to DPD deficiency and to discuss with patients whether they should be tested for genetic variants of DPYD that are associated with an increased risk of serious adverse reactions from the use of capecitabine and/or fluorouracil. Furthermore, discussion of testing for genetic variants of DPYD prior to initiating capecitabine and/or fluorouracil to reduce the risk of serious adverse reactions if the patient’s clinical status permits and based on clinical judgement is noted. Both drug labels warn clinicians to withhold or permanently discontinue fluorouracil based on clinical assessment of the onset, duration, and severity of the observed toxicities in patients with evidence of acute early-onset or unusually severe toxicity. The label does not suggest DPYD guided dosing and mentions that currently available tests may vary in accuracy and design and that an FDA-authorized test for the detection of genetic

variants of DPYD is not currently available. While dose adjustment of fluoropyrimidines based on DPYD genotype (or any other reason) has been shown to diminish toxicity, it is uncertain whether dose reductions result in diminished efficacy. The Clinical Pharmacogenetics Implementation Consortium (CPIC) and the Dutch Pharmacogenetics Working Group (DPWG) have both published guidance for dosing fluoropyrimidines based on DPYD phenotype.^{30, 31} Some other countries have more widely implemented preemptive DPYD testing for patients scheduled to receive a fluoropyrimidine, sometimes with publicly funded and uniform testing approaches. A Joint Consensus Recommendation of the Association for Molecular Pathology, American College of Medical Genetics and Genomics, Clinical Pharmacogenetics Implementation Consortium, College of American Pathologists, Dutch Pharmacogenetics Working Group of the Royal Dutch Pharmacists Association, European Society for Pharmacogenomics and Personalized Therapy, Pharmacogenomics Knowledgebase, and Pharmacogene Variation Consortium includes the four aforementioned DPYD variants as Tier 1 variants for testing.³²

Since April 2020, pretherapeutic screening for accessing the deficiency of the DPD enzyme by genotyping the dihydropyrimidine dehydrogenase gene (DPYD) is required by the European Medicine Agency (EMA) prior to the administration of fluoropyrimidine-based chemotherapy. Between 1 June 2020 to 1 May 2024, a total of 2,798 DPYD requests were analyzed in the Galicia autonomous community of Spain. DPYD genotyping results revealed a 3.15% prevalence of heterozygosity for at least one of the four DPYD variants.³³

A secondary analysis of the PREPARE randomized clinical trial looking at the clinical benefits and utility of pretherapeutic DPYD and UGT1A1 testing in gastrointestinal cancer was reported in 2024. This non prespecified secondary analysis stems from Pre-Emptive Pharmacogenomic Testing for Preventing Adverse Drug Reactions (PREPARE), a multicenter, controlled, open, block-randomized, crossover implementation trial conducted from March 7, 2017, to June 30, 2020, and includes data from Italy according to a sequential study design.³⁴ The study population included 563 patients (intervention, 252; control [standard of care], 311) with gastrointestinal cancer (age ≥18 years) who were eligible for fluoropyrimidine and/or irinotecan treatment. Participants with actionable variants (DPYD*2A, DPYD*13, DPYD c.2846A>T, and DPYD c.1236G>A for fluoropyrimidines, and UGT1A1*28, UGT1A1*6, and UGT1A1*27 for irinotecan) received drug or dose adjustments based on Dutch Pharmacogenetics Working Group recommendations. 1232 patients were enrolled in Italy, with 563 included in the analysis. In the intervention arm, carriers of any actionable genotype exhibited a 90% lower risk of clinically relevant toxic effects compared with the control arm. The control arm presented higher toxic effect management costs per patient (\$4159; 95% CI, \$1510-\$6810) compared with patients in the intervention arm (\$26; 95% CI, 0-\$312) (P = .004) and a higher rate of hospitalization (34.8% vs 11.8%; P = .12). Three-year overall survival did not differ significantly between arms, while quality-adjusted life-years significantly improved in the intervention arm. The pharmacogenetics-informed approach did not manifest a detrimental effect on treatment intensity in actionable genotype. Notably, this study evaluated both DPYD testing and UGT1A1 testing. Several other reviews are available from international sources.^{27, 35} These studies confirm the validity of various DPYD variants and their association with increased risk of toxicity. The absolute risks remain small, and the root of the controversy over pharmacogenetic testing in this setting is related to implementation science and net benefits and costs of the strategy accounting for not only toxicities but also cancer treatment outcomes over time. Observational studies of this approach have been conducted and confirm that toxicity can be reduced but also show that serious adverse events occur despite dose reductions in some individuals, while other patients had minimal toxicity and may be underdosed with the pharmacogenetic-driven preemptive dose reductions.^{36, 37}

There are some proponents of DPYD testing in the United States³⁸, and NCCN has moved from a position stating that DPYD testing is not recommended to a position that testing for DPYD genetic variants **should be considered prior to fluoropyrimidine therapy**. Additionally, the FDA package inserts for both capecitabine and fluorouracil contain patient counseling recommendations to discuss possible DPYD testing with patients.

A meta-analysis that evaluated 36 prospective and retrospective studies looking at the four main DPYD variants found that carriers of DPYD variants were found to be significantly correlated with treatment-related mortality.³⁹ Although preemptive DPYD testing has not become generally accepted in the United States for a variety of reasons,⁴⁰⁻⁴³ there has been a movement by the NCCN for physicians to discuss DPYD genetic testing with patients who are candidates for 5-FU and capecitabine. Additionally, in the package insert for each drug, the FDA recommends counseling and consideration of DPYD genotype testing and details the four most common DPYD variants. Preliminary results from a single-center, retrospective cohort study looking at patients who had a DPYD test result before administration of the first fluoropyrimidine versus those who had a DPYD test after their first dose of fluoropyrimidine or no had no DPYD test at all were compared.⁴⁴ Among 1,281 patients in the study, 90-day all-cause mortality and dihydropyrimidine dehydrogenase (DPD)-related deaths were numerically but not statistically significantly lower in the preemptively tested cohort compared with the standard cohort. Among patients with DPD deficiency in the preemptive cohort, 84.6% received an empiric FP dose reduction, and dose escalation was attempted in 52.2% of these cases. These findings suggest that preemptive DPYD testing may enhance patient safety by enabling tailored dosing strategies, although it did not significantly reduce mortality in this study. Prospective studies are required to further demonstrate long-term benefits of dosing strategies. The major barrier to implementation of preemptive testing is concern among oncologists and their patients related to potential dose reduction, which could lead ultimately to reduced treatment efficacy.

APOE ε4 allele testing in Alzheimer's disease

APOE ε4 has a worldwide prevalence of 14% and is the strongest known genetic susceptibility factor for sporadic Alzheimer disease (OR, 8-12 for ε4/ε4 vs ε3/ε3). Nevertheless, APOE ε4 is neither necessary nor sufficient for the development of Alzheimer disease dementia, and meta-analyses indicate low sensitivity (53%) and specificity (67%) of APOE ε4 for identifying patients who will progress from mild cognitive impairment to Alzheimer disease dementia. For this reason, testing is not currently recommended in the clinical evaluation of cognitive impairment.⁴⁵

The accumulation of soluble and insoluble aggregated amyloid-beta (Aβ) may initiate or potentiate pathologic processes in Alzheimer's disease. The Clarity AD trial⁴⁶ is the sentinel trial that led to the decision of the US FDA to approve lecanemab for treatment of early Alzheimer's disease.⁴⁷ Lecanemab is a humanized IgG1 monoclonal antibody that binds with high affinity to Aβ soluble protofibrils, and the Clarity AD trial showed that it was associated with moderately less decline on measures of cognition and function in patients with early Alzheimer's disease than placebo at 18 months, but was associated with adverse events. In this trial, 15.8% of patients were found to be homozygous carriers of APOE ε4, and these individuals had a higher risk of symptomatic amyloid-related imaging abnormalities (ARIA), with 13/141 (9.2%) affected compared to the lowest risk patients (non-carriers of APOE ε4) who had a risk of 1.4%. This led to a statement in the FDA label that suggests that provider consider testing for APOE ε4 status to when deciding to initiate treatment with lecanemab. Since the safety and efficacy of lecanemab are known only for patients like those participating in the phase 2 and phase 3 lecanemab trials, appropriate use recommendations adhere closely to the inclusion and exclusion criteria of the trials.⁴⁸ Monitoring guidelines for these events do not involve testing for APOE ε4, as that testing is used only to inform the decision about whether to initiate the drug.

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.
2. Goodman CW, Brett AS. Race and Pharmacogenomics—Personalized Medicine or Misguided Practice? *Jama*. 2021;325(7):625–6.
3. FDA. The FDA Warns Against the Use of Many Genetic Tests with Unapproved Claims to Predict Patient Response to Specific Medications: FDA Safety Communication. 2018.
4. FDA. Warning Letter: Inova Genomics Laboratory. 2019.
5. PharmGKB [April 11, 2024]. Available from: <https://www.pharmgkb.org/>.
6. Relling MV, Klein TE, Gammal RS, et al. The Clinical Pharmacogenetics Implementation Consortium: 10 Years Later. *Clin Pharmacol Ther*. 2020;107(1):171–5.
7. Wake DT, Ilbawi N, Dunnenberger HM, et al. Pharmacogenomics: Prescribing Precisely. *Med Clin North Am*. 2019;103(6):977–90.
8. Eadon MT, Rosenman MB, Zhang P, et al. The INGENIOUS trial: Impact of pharmacogenetic testing on adverse events in a pragmatic clinical trial. *Pharmacogenomics J*. 2023;23(6):169–77.
9. 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.
10. Greden JF, Parikh SV, Rothschild AJ, et al. Impact of pharmacogenomics on clinical outcomes in major depressive disorder in the GUIDED trial: A large, patient- and rater-blinded, randomized, controlled study. *J Psychiatr Res*. 2019;111:59–67.
11. Goldberg JF, Rosenblat JD, McIntyre RS, et al. Letter to the Editor: Clinical versus statistical significance of pharmacogenomic-guided antidepressant therapy: What's really being measured and marketed? *J Psychiatr Res*. 2019;114:208–9.
12. Oslin DW, Lynch KG, Shih MC, et al. Effect of Pharmacogenomic Testing for Drug-Gene Interactions on Medication Selection and Remission of Symptoms in Major Depressive Disorder: The PRIME Care Randomized Clinical Trial. *Jama*. 2022;328(2):151–61.
13. Kang Z, Qin Y, Sun Y, et al. Multigenetic Pharmacogenomics-Guided Treatment vs Treatment As Usual Among Hospitalized Men With Schizophrenia: A Randomized Clinical Trial. *JAMA Netw Open*. 2023;6(10):e2335518.
14. McCarthy MJ, Chen Y, Demodena A, et al. A prospective study to determine the clinical utility of pharmacogenetic testing of veterans with treatment-resistant depression. *J Psychopharmacol*. 2021;35(8):992–1002.
15. Pérez V, Salavert A, Espadaler J, et al. Efficacy of prospective pharmacogenetic testing in the treatment of major depressive disorder: results of a randomized, double-blind clinical trial. *BMC Psychiatry*. 2017;17(1):250.
16. Tiwari AK, Zai CC, Altar CA, et al. Clinical utility of combinatorial pharmacogenomic testing in depression: A Canadian patient- and rater-blinded, randomized, controlled trial. *Transl Psychiatry*. 2022;12(1):101.
17. Vos CF, Ter Hark SE, Schellekens AFA, et al. Effectiveness of Genotype-Specific Tricyclic Antidepressant Dosing in Patients With Major Depressive Disorder: A Randomized Clinical Trial. *JAMA Netw Open*. 2023;6(5):e2312443.
18. Brown LC, Stanton JD, Bharthi K, et al. Pharmacogenomic Testing and Depressive Symptom Remission: A Systematic Review and Meta-Analysis of Prospective, Controlled Clinical Trials. *Clin Pharmacol Ther*. 2022;112(6):1303–17.
19. Bunka M, Wong G, Kim D, et al. Evaluating treatment outcomes in pharmacogenomic-guided care for major depression: A rapid review and meta-analysis. *Psychiatry Res*. 2023;321:115102.
20. Ontario Health. Multi-gene Pharmacogenomic Testing That Includes Decision-Support Tools to Guide Medication Selection for Major Depression: A Health Technology Assessment. *Ont Health Technol Assess Ser*. 2021;21(13):1–214.

21. 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.
22. 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.
23. Li D, Pain O, Chiara F, et al. Metabolic activity of CYP2C19 and CYP2D6 on antidepressant response from 13 clinical studies using genotype imputation: a meta-analysis. *Transl Psychiatry.* 2024;14(1):296.
24. Milosavljević F, Molden PE, Ingelman-Sundberg PM, et al. Current level of evidence for improvement of antidepressant efficacy and tolerability by pharmacogenomic-guided treatment: A Systematic review and meta-analysis of randomized controlled clinical trials. *Eur Neuropsychopharmacol.* 2024;81:43–52.
25. Hines LJ, Wilke RA, Myers R, et al. Rationale and design for a pragmatic randomized trial to assess gene-based prescribing for SSRIs in the treatment of depression. *Clin Transl Sci.* 2024;17(6):e13822.
26. FDA USFDA. FDA Table of Pharmacogenomic Biomarkers in Drug Labeling. 2024.
27. 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.
28. 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).
29. NCCN. Colon Cancer, Version 3.2025. NCCN Clinical Practice Guidelines in Oncology. 2025.
30. Amstutz U, Henricks LM, Offer SM, et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for Dihydropyrimidine Dehydrogenase Genotype and Fluoropyrimidine Dosing: 2017 Update. *Clin Pharmacol Ther.* 2018;103(2):210–6.
31. Lunenburg C, van der Wouden CH, Nijenhuis M, et al. Dutch Pharmacogenetics Working Group (DPWG) guideline for the gene-drug interaction of DPYD and fluoropyrimidines. *Eur J Hum Genet.* 2020;28(4):508–17.
32. Pratt VM, Cavallari LH, Fulmer ML, et al. DPYD Genotyping Recommendations: A Joint Consensus Recommendation of the Association for Molecular Pathology, American College of Medical Genetics and Genomics, Clinical Pharmacogenetics Implementation Consortium, College of American Pathologists, Dutch Pharmacogenetics Working Group of the Royal Dutch Pharmacists Association, European Society for Pharmacogenomics and Personalized Therapy, Pharmacogenomics Knowledgebase, and Pharmacogene Variation Consortium. *J Mol Diagn.* 2024.
33. Gil-Rodríguez A, Recarey-Rama S, Rodríguez-Viyuela A, et al. Balance of care activity after EMA recommendation for DPYD gene testing in Galicia. *Front Pharmacol.* 2025;16:1523536.
34. Roncato R, Bignucolo A, Peruzzi E, et al. Clinical Benefits and Utility of Pretherapeutic DPYD and UGT1A1 Testing in Gastrointestinal Cancer: A Secondary Analysis of the PREPARE Randomized Clinical Trial. *JAMA Netw Open.* 2024;7(12):e2449441.
35. Sharma BB, Rai K, Blunt H, et al. Pathogenic DPYD Variants and Treatment-Related Mortality in Patients Receiving Fluoropyrimidine Chemotherapy: A Systematic Review and Meta-Analysis. *Oncologist.* 2021;26(12):1008–16.
36. Morris SA, Moore DC, Musselwhite LW, et al. Addressing barriers to increased adoption of DPYD genotyping at a large multisite cancer center. *Am J Health Syst Pharm.* 2023;80(19):1342–9.
37. Wang L, Howlett S, Essapen S. Treating patients with dihydropyrimidine dehydrogenase (DPD) deficiency with fluoropyrimidine chemotherapy since the onset of routine prospective testing-The experience of a large oncology center in the United Kingdom. *Semin Oncol.* 2022;49(2):170–7.
38. Baker SD, Bates SE, Brooks GA, et al. DPYD Testing: Time to Put Patient Safety First. *J Clin Oncol.* 2023;41(15):2701–5.
39. de Moraes FCA, de Almeida Barbosa AB, Sano VKT, et al. Pharmacogenetics of DPYD and treatment-related mortality on fluoropyrimidine chemotherapy for cancer patients: a meta-analysis and trial sequential analysis. *BMC Cancer.* 2024;24(1):1210.
40. Ciccolini J. DPD deficiency in patients treated with fluorouracil. *Lancet Oncol.* 2015;16(16):1574–6.
41. Jacobson JO, Rempel G, Chen A, et al. Design and Implementation of an Opt-Out, End-to-End, Preemptive DPYD Testing Program for Patients Planned for a Systemic Fluoropyrimidine. *JCO Oncol Pract.* 2024;20(8):1115–22.
42. Tamraz B, Venook AP. DPYD Pharmacogenetics: To Opt-in or to Opt-out. *JCO Oncol Pract.* 2024:Op2400255.
43. Tracksdorf T, Smith DM, Pearse S, et al. Strategies for DPYD testing prior to fluoropyrimidine chemotherapy in the US. *Support Care Cancer.* 2024;32(8):497.
44. Yu L, Espiritu J, Patel K, et al. Clinical Implications of a Large-Scale Voluntary Preemptive DPYD Testing Program for Patients Planned for a Systemic Fluoropyrimidine: Preliminary Results. *JCO Oncol Pract.* 2025:Op2500170.
45. Choudhury P, Ramanan VK, Boeve BF. APOE ε4 Allele Testing and Risk of Alzheimer Disease. *Jama.* 2021;325(5):484–5.
46. van Dyck CH, Swanson CJ, Aisen P, et al. Lecanemab in Early Alzheimer's Disease. *N Engl J Med.* 2023;388(1):9–21.
47. Reardon S. FDA approves Alzheimer's drug lecanemab amid safety concerns. *Nature.* 2023;613(7943):227–8.
48. Cummings J, Apostolova L, Rabinovici GD, et al. Lecanemab: Appropriate Use Recommendations. *J Prev Alzheimers Dis.* 2023;10(3):362–77.

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.

May Be Medically Necessary When Criteria are Met

Code	May Be Medically Necessary When Criteria are Met
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]
81232	DPYD (dihydropyrimidine dehydrogenase) (eg, 5-fluorouracil/5-FU and capecitabine drug metabolism), gene analysis, common variant(s) (eg, *2A, *4, *5, *6)
81247	G6PD (glucose-6-phosphate dehydrogenase) (eg, hemolytic anemia, jaundice), gene analysis; common variant(s) (eg, A, A-)
81248	G6PD (glucose-6-phosphate dehydrogenase) (eg, hemolytic anemia, jaundice), gene analysis; known familial variant(s)
81249	G6PD (glucose-6-phosphate dehydrogenase) (eg, hemolytic anemia, jaundice), gene analysis; full gene sequence
81306	NUDT15 (nudix hydrolase 15) (eg, drug metabolism) gene analysis, common variant(s) (eg, *2, *3, *4, *5, *6)
81335	TPMT (thiopurine S-methyltransferase) (eg, drug metabolism), gene analysis, common variants (eg, *2, *3)
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)]
81380	HLA Class I typing, high resolution (ie, alleles or allele groups); HLA Class I typing, high resolution (ie, alleles or allele groups)
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]
81401	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)
81479	Unlisted molecular pathology procedure
0034U	TPMT (thiopurine S-methyltransferase), NUDT15 (nudix hydrolase 15) (eg, thiopurine metabolism) gene analysis, common variants (ie, TPMT *2, *3A, *3B, *3C, *4, *5, *6, *8, *12; NUDT15 *3, *4, *5)
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)
0169U	NUDT15 (nudix hydrolase 15) and TPMT (thiopurine S-methyltransferase) (eg, drug metabolism) gene analysis, common variants
S3852	DNA analysis for APOE epsilon 4 allele for susceptibility to Alzheimer's disease

Not Medically Necessary

Code	Not Medically Necessary
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)
81240	F2 (prothrombin, coagulation factor II) (eg, hereditary hypercoagulability) gene analysis, 20210G>A variant
81241	F5 (coagulation Factor V) (eg, hereditary hypercoagulability) gene analysis, Leiden variant
81283	IFNL3 (interferon, lambda 3) (eg, drug response), gene analysis, rs12979860 variant
81291	MTHFR (5,10-methylenetetrahydrofolate reductase) (eg, hereditary hypercoagulability) gene analysis, common variants (eg, 677T, 1298C)
81328	SLCO1B1 (solute carrier organic anion transporter family, member 1B1) (eg, adverse drug reaction), gene analysis, common variant(s) (eg, *5)
81346	TYMS (thymidylate synthetase) (eg, 5-fluorouracil/5-FU drug metabolism), gene analysis, common variant(s) (eg, tandem repeat variant)
81355	VKORC1 (vitamin K epoxide reductase complex, subunit 1) (eg, warfarin metabolism), gene analysis, common variant(s) (eg, -1639G>A, c.173+1000C>T)
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
0030U	Drug metabolism (warfarin drug response), targeted sequence analysis (ie, CYP2C9, CYP4F2, VKORC1, rs12777823)
0032U	COMT (catechol-O-methyltransferase) (drug metabolism) gene analysis, c.472G>A (rs4680) variant
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
0205U	Ophthalmology (age-related macular degeneration), analysis of 3 gene variants (2 CFH gene, 1 ARMS2 gene), using PCR and MALDI-TOF, buccal swab, reported as positive or negative for neovascular age-related macular-degeneration risk associated with zinc supplements
0286U	CEP72 (centrosomal protein, 72-KDa), NUDT15 (nudix hydrolase 15) and TPMT (thiopurine S-methyltransferase) (eg, drug metabolism) gene analysis, common variants - CNT (CEP72, NUDT15 and TPMT) Genotyping Panel
0345U	Psychiatry (eg, depression, anxiety, attention deficit hyperactivity disorder [ADHD]), genomic analysis panel, variant analysis of 15 genes, including deletion/duplication analysis of CYP2D6
0347U	Drug metabolism or processing (multiple conditions), whole blood or buccal specimen, DNA analysis, 16 gene report, with variant analysis and reported phenotypes
0348U	Drug metabolism or processing (multiple conditions), whole blood or buccal specimen, DNA analysis, 25 gene report, with variant analysis and reported phenotypes
0349U	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
0350U	Drug metabolism or processing (multiple conditions), whole blood or buccal specimen, DNA analysis, 27 gene report, with variant analysis and reported phenotypes
0392U	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
0411U	Psychiatry (eg, depression, anxiety, attention deficit hyperactivity disorder [ADHD]), genomic analysis panel, variant analysis of 15 genes, including deletion/duplication analysis of CYP2D6
0419U	Neuropsychiatry (eg, depression, anxiety), genomic sequence analysis panel, variant analysis of 13 genes, saliva or buccal swab, report of each gene phenotype
0434U	Drug metabolism (adverse drug reactions and drug response), genomic analysis panel, variant analysis of 25 genes with reported phenotypes
0438U	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
0460U	Oncology, whole blood or buccal, DNA single-nucleotide polymorphism (SNP) genotyping by real-time PCR of 24 genes, with variant analysis and reported phenotypes
0461U	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
0476U	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

Code	Not Medically Necessary
0477U	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
0516U	Drug metabolism, whole blood, pharmacogenomic genotyping of 40 genes and CYP2D6 copy number variant analysis, reported as metabolizer status
0533U	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
0650U	Drug metabolism (adverse drug reactions and drug response), genotyping of 9 genes (ie, CYP2D6, CYP2C19, G6PD, SLCO1B1, HLA-B*58:01, NAT2, CYP2C9, VKORC1, ABCG2), reported as metabolizer status and transporter function
0652U	Drug metabolism (adverse drug reactions), DNA analysis of 13 genes by targeted genotyping, using saliva or buccal swab, reported as diplotype and metabolizer status
G9143	Warfarin responsiveness testing by genetic technique using any method, any number of specimen(s)

ICD-10 Diagnosis

Refer to the ICD-10 CM manual

History

Status	Review Date	Effective Date	Action
Updated codes 07/01/2026	n/a	Unchanged	CPT code update: added new 0650U, 0652U, removed termed 0029U, 0031U, 0423U (NMN).
Revised	10/09/2025	06/14/2026	Independent Multispecialty Physician Panel (IMPP) review. Added General Requirements section with statement clarifying that testing be performed in a CLIA-certified lab accredited by the College of American Pathologists. Clarified that diagnostic testing occurs only once per lifetime per individual. Expanded list of drug therapies and biomarkers considered medically necessary and split into two tables. Provided clarification on use of panel and multigene tests in determining drug-metabolizer status. Added references. Moved CPT code 81350 from NMN to MNWCM.
Updated codes 01/01/2026	n/a	Unchanged	CPT code update: removed termed 0033U (NMN).
Revised	07/17/2025	11/15/2025 except for Anthem BCBS OH Medicaid	IMPP review. Guideline renamed from Pharmacogenomic to Pharmacogenetic Testing. Added criterion for testing when the specific test is referenced in the FDA package insert or in NCCN guidelines. Added DPYD biomarker testing for capecitabine and fluorouracil treatment to the list of therapies and biomarkers considered medically necessary for genotyping. Added references. Moved CPT code 81232 from NMN to MNWCM.
Revised	10/28/2024	07/26/2025	IMPP review. Added donanemab-azbt, deuruxolitinib, and NUDT15 to the list of therapies and associated biomarkers considered medically necessary for genotyping. Added references. Moved CPT codes 81306, 0034U, and 0169U from NMN to MNWCM.
Updated codes 04/01/2025	n/a	Unchanged	CPT code update: added 0533U (NMN).
Updated codes 01/01/2025	n/a	Unchanged	CPT code update: removed termed 0380U (NMN).
Revised	01/23/2024	10/20/2024	IMPP review. Added APO E4 testing. Added CPT codes 81401 (MNWCM) and HCPCS code S3852 (MNWCM). Added references.

Status	Review Date	Effective Date	Action
Updated codes 10/01/2024	n/a	Unchanged	Added CPT codes 81380 (MNWCM), 0476U, 0477U, 0516U (NMN). Removed 0078U (NMN).
Updated codes 07/01/2024	n/a	Unchanged	Added CPT codes 0460U and 0461U (NMN).
Updated codes 03/17/2024	n/a	Unchanged	Split code list into those considered medically necessary when criteria are met (MNWCM) and not MN. Added NMN CPT codes 81240, 81241, 81291, 0205U, 0380U, 0392U, 0411U, 0419U, 0423U, 0434U, 0438U. Removed 81250, 0258U, 0290U, 0291U, 0292U, 0293U. Added required language to General Clinical Guideline per new Medicare regulations.
Created	08/29/2022	02/12/2023	IMPP review. Original effective date.