

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: Pharmacogenomic Testing

Proprietary

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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.

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. Pharmaceuticals, radiotracers, or medical devices used in any of the diagnostic or therapeutic interventions listed in the Guidelines must be FDA approved or conditionally approved for the intended use. However, 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.

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 on-going 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.

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 individual'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. Therapies and associated biomarkers

| Biomarker | Drug | Therapeutic Area |
|-------------|----------------------------------|---------------------|
| ApoE ε4 | lecanemab | Neurology |
| 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 |

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

Rationale

Overview

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.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 pharmacogenomic 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 Base⁵ 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 US Food and Drug Administration (FDA) also maintains a [searchable table of pharmacogenomic biomarkers](#) in drug labeling. 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.⁷ There are some instances where the FDA is explicit in recommending genotyping ahead of prescribing. However, 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.

Pharmacogenetic testing to guide psychopharmacologic prescribing

One area of enthusiasm 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 baseline demographic factors, and also 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.⁸ 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.⁹ 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.¹⁰ Moreover, pharmacogenomic-guided treatment was evaluated in the PRIME study¹¹, 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.¹²⁻¹⁶

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.¹⁷⁻¹⁹ Likewise, systematic reviews of the available studies in this realm are unequivocal that the evidence of clinical utility are lacking in this realm.^{20,21}

DYPD testing and fluoropyrimidine prescribing

Another area of controversy in the field of pharmacogenomics is the role of DPYD testing for patients being treated with cytolytic 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 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.^{22,23} The NCCN and the FDA recognize the increased risk of severe fluoropyrimidine toxicity in known DPYD carriers but do not recommend routine testing. The FDA label for fluorouracil warns 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. While dose adjustment of fluoropyrimidines based on DPYD genotype (or any other reason) has been shown to diminish toxicity, it is not certain that dose reductions do not result in inferior 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.^{24,25} 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. Several reviews are available from international sources.^{22,26} 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 pharmacogenomic 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 and concerns were observed that some patients had minimal toxicity and may be under-dosed with the pharmacogenomic-driven pre-emptive dose reductions.^{27, 28}

While there are some proponents of DPYD testing in the United States²⁹, overall, preemptive DPYD testing has not become generally accepted in the United States for a variety of reasons.³⁰ Among clinicians and researchers, the primary reasons for not testing are the perceived low prevalence of DPYD deficiency, lack of professional clinical guidelines in the United States recommending testing, and a lack of knowledge around which test to order and what to do with the result. The major barrier to implementation of preemptive testing is the concern among oncologists and their patients related to the potential for dose reduction resulting from this testing, leading 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.³¹

The accumulation of soluble and insoluble aggregated amyloid-beta (Aβ) may initiate or potentiate pathologic processes in Alzheimer's disease. The Clarity-AD trial³² is the sentinel trial that led to the decision of the US FDA to approve lecanemab for treatment of early Alzheimer's disease.³³ 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.³⁴ Monitoring guidelines for these events do not involve testing for APOE ε4, as that testing is used only to inform the decision about whether or not to initiate the drug.

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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

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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] |
| 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 |
| 81310 | NPM1 (nucleophosmin) (eg, acute myeloid leukemia) gene analysis, exon 12 variants |
| 81335 | TPMT (thiopurine S-methyltransferase) (eg, drug metabolism), gene analysis, common variants (eg, *2, *3) |
| 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 |
| 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) |
| 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) |
| 81232 | DPYD (dihydropyrimidine dehydrogenase) (eg, 5-fluorouracil/5-FU and capecitabine drug metabolism), gene analysis, common variant(s) (eg, *2A, *4, *5, *6) |
| 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) |
| 81306 | NUDT15 (nudix hydrolase 15) (eg, drug metabolism) gene analysis, common variant(s) (eg, *2, *3, *4, *5, *6) |
| 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) |

| Code | Not Medically Necessary |
|-------|--|
| 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) |
| 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 |
| 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]) |
| 0034U | TPMT (thiopurine S-methyltransferase), NUDT15 (nudix hydroxylase 15)(eg, thiopurine metabolism), gene analysis, common variants (ie, TPMT *2, *3A, *3B, *3C, *4, *5, *6, *8, *12; NUDT15 *3, *4, *5) |
| 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 |
| 0169U | NUDT15 (nudix hydrolase 15) and TPMT (thiopurine S-methyltransferase) (eg, drug metabolism) gene analysis, common variants |
| 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 |
| 0380U | Drug metabolism (adverse drug reactions and drug response), targeted sequence analysis, 20 gene variants and CYP2D6 deletion or duplication analysis with reported genotype and phenotype |
| 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 |
| 0423U | Psychiatry (eg, depression, anxiety), genomic analysis panel, including variant analysis of 26 genes, buccal swab, report including metabolizer status and risk of drug toxicity by condition |
| 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 |

| Code | Not Medically Necessary |
|-------|--|
| 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 |
| 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 |
|-----------------------------|-------------|----------------|--|
| Revised | 01/23/2024 | 10/20/2024 | Independent Multispecialty Physician Panel (IMPP) review. Added APO E4 testing. Added CPT codes 81310 and 81401 (MNWCM), and HCPCS code S3852 (MNWCM). Added references. |
| 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. |