CYP2C19 & CYP2D6 Pharmacogenetic Testing

Policy Number: PG0436
Last Review: 07/01/2023

PARAMOUNT

HMO & PPO
MARKETPLACE
MEDICARE – ELITE, MAP

GUIDELINES

- This policy does not certify benefits or authorization of benefits, which is designated by each individual policyholder terms, conditions, exclusions and limitations contract. It does not constitute a contract or guarantee regarding coverage or reimbursement/payment. Self-Insured group specific policy will supersede this general policy when group supplementary plan document or individual plan decision directs otherwise.
- Paramount applies coding edits to all medical claims through coding logic software to evaluate the accuracy and adherence to accepted national standards.
- This medical policy is solely for guiding medical necessity and explaining correct procedure reporting used to assist in making coverage decisions and administering benefits.

SCOPE

X Professional
X Facility

DESCRIPTION

Drug efficacy and toxicity vary substantially between individuals. Drugs and doses are typically adjusted to meet individual requirements as needed by using trial and error, therefore clinical consequences may include a prolonged time to optimal therapy and serious adverse events. It has been found that inherited DNA sequence variation (polymorphisms) in genes for drug-metabolizing enzymes may have a significant effect on the efficacy or toxicity of a drug. This field of research is referred to as pharmacogenomics.

It has been proposed that genotype testing for certain genes to detect polymorphisms will allow physicians to predict side effects to drugs and to tailor a drug regimen based on an individual's genetic make-up. It may be that genotype testing will improve the choice of drug, or the dose of the drug, when the drug in question has a narrow therapeutic dose range, when the consequences of treatment failure are severe, and/or when serious adverse reactions are more likely in individuals with certain polymorphisms.

Pharmacogenetic testing has been proposed to predict individual response to a variety of *CYP2C19*-metabolized drugs including clopidogrel, proton pump inhibitors, and tricyclic antidepressants, among others. In certain scenarios, an individual patient may benefit from genetic testing in determining dosage and likely response to specific medications.

Pharmacogenetic testing has been proposed to predict individual response to a variety of *CYP2D6*-metabolized drugs including tamoxifen, antidepressants, opioid analgesics, and tetrabenzine for chorea, among others. In certain scenarios, an individual patient may benefit from this genetic testing in determining dosage and likely response to specific medications.

The impact of polymorphisms has been the focus of study with a wide variety of drugs and for many diseases and conditions. The use of this type of science is just starting to be investigated, and its impact on actual medical practice is not yet fully understood.

POLICY

Paramount Commercial Insurance Plans, Medicare Advantage Plans, and Paramount Advantage Medicaid

- **CYP2C19 (81225) and CYP2D6 (81226) Pharmacogenetic Testing requires prior authorization for all product lines.**

Related Policies
- **PG0390 Genetic Testing for Warfarin Dose**
- **PG0368 Pharmacogenomic Testing for Mental Health Conditions**

COVERAGE CRITERIA

Paramount Commercial Insurance Plans and Paramount Advantage Medicaid

CYP2C19 genotyping is considered medically necessary to determine the drug-metabolizer status of individuals who meet either of the following criteria:
- The individual is currently undergoing treatment with clopidogrel (Plavix) and has not been tested; OR
- The use of clopidogrel (Plavix) is being proposed

Repeat CYP2C19 genotyping has no proven value, and therefore is limited to once per lifetime.

CYP2D6 genotyping is considered medically necessary when the following criteria are met:
- Individual has been diagnosed with Gaucher type I disease; AND
- Prior to initiation of eliglustat (Cerdelga)

CYP2D6 genotyping is considered medically necessary to guide medical treatment and/or dosing for individuals for whom initial therapy is planned with:
- Tetrabenazine (Xenazine) doses greater than 50 mg/day, or re-initiation of therapy with doses greater than 50 mg/day for the treatment of chorea associated with Huntington's disease.

Repeat CYP2D6 genotyping has no proven value, and therefore is limited to once per lifetime.

CYP2C19 and CYP2D6 genotyping is considered investigational at this time for the following medications including, but may not be limited to, the following:
- Proton pump inhibitors
- Antidepressants other than those listed above
- Antipsychotics
- Antiepileptics
- Donepezil or Galantamine for Alzheimer's disease
- Tamoxifen
- Warfarin

CYP2C19 and CYP2D6 genotyping for any indications other than those listed above are considered investigational and not medically necessary including, but may not be limited to, the following:
- General population screening

Medicare Advantage Plans

The clinical record must clearly show the use of or intent to prescribe a drug that has known drug-gene interactions that require a PGx test to be ordered to define the safe use of that drug in that patient.

If a treating clinician orders a single gene test or a test for a particular allele(s), but as a matter of operational practicality, the laboratory tests that single gene or allele on a platform that looks for variants in other genes / alleles as well, that particular test done in that particular instance is considered a single gene / allele test for coverage purposes. In this scenario the provider may bill for the component of the test that was reasonable and necessary (in this example, the single gene test).

A multi-gene panel is considered reasonable and necessary if more than one single gene on that panel would be considered reasonable and necessary for safe use of the medication in question or if multiple drugs are being considered (each fulfilling the criteria of actionable gene-drug interactions identified above) that have different

relevant genes. Additionally, a gene panel must contain at a minimum all the necessary relevant gene/allele content required for their indicated use to meet clinical utility requirements. Such minimum criteria are determined by experts including relevant associations such as the Association for Molecular Pathology and are considered during the technical assessment. A multi-gene panel is not considered reasonable and necessary if only a single gene on the panel is considered reasonable and necessary.

If two or more single genes are tested, rather than a multi-gene panel, then the record must reflect that a clinician individually ordered each gene, and each single gene must individually be reasonable and necessary at the time they are ordered.

The ordering provider of a PGx test is restricted to providers who have the licensure, qualifications, and necessary experience / training to both diagnose the condition being treated and also to prescribe medications (the provider must be able to do both) for the condition either independently or in an arrangement as required by all the applicable state laws.

Test components that are not reasonable and necessary

- Genes not identified as having actionable use are not considered reasonable and necessary. The algorithms employed in combinatorial testing are also not currently considered reasonable and necessary components of multi-gene testing.

Paramount Commercial Insurance Plans, Medicare Advantage Plans, and Paramount Advantage Medicaid
Technical requirements

- The treating clinician receiving the laboratory report must be able to use the genetic information presented to guide treatment. To accomplish this, the laboratory must clearly report the clinical significance of the resultant genotype, based on empirical data or validated methodologies, as an annotation or interpretation. For clarity, the report should document the specific genotype-drug interaction that lead to the resultant interpretation.
- A lab may test for a reference allele as a matter of exclusion (e.g. report that a patient has a reference allele when alternate alleles are not found). However, in such cases, the report must identify which allele is the reference allele and that the reference allele is reported as a matter of exclusion.

Noncovered Indications

- PGx testing is not covered when a treating clinician is not considering treatment with a medication that has an actionable drug-gene interaction, or when the use of a medication with a drug-gene interaction is not reasonable and necessary.

Special Documentation Requirements
In order for any of the above services to be covered, the patient's medical record must clearly reflect the following:

- The patient has a diagnosis for which pharmacologic therapy is reasonable and necessary, and the drug or drugs that the clinician is considering using must be reasonable and necessary for the treatment of the patient's diagnosis.
- The clinician has made an initial personalized decision for the patient based on the patient's diagnosis, the patient's other medical conditions, other medications the patient is taking, professional judgement, clinical science and basic science pertinent to the drug (e.g. mechanism of action, side effects), the patient's past medical history and when pertinent family history and the patient's preferences and values.
- The provider performing the service must have a record of what drug(s) is/are being considered and for what indication(s) to ensure the test performed is reasonable and necessary.

CODING/BILLING INFORMATION
The inclusion or exclusion of a code in this section does not necessarily indicate coverage. Codes referenced in this clinical policy are for informational purposes only.
Codes that are covered may have selection criteria that must be met.
Payment for supplies may be included in payment for other services rendered.

CPT CODES

81225	CYP2C19 (cytochrome P450, family 2, subfamily C, polypeptide 19) (e.g., drug metabolism), gene analysis, common variants (e.g., *2, *3, *4, *8, *17)
81226	CYP2D6 (cytochrome P450, family 2, subfamily D, polypeptide 6) (e.g., drug metabolism), gene analysis, common variants (e.g., *2, *3, *4, *5, *6, *9, *10, *17, *19, *29, *35, *41, *1XN, *2XN, *4XN)

Paramount reserves the right to review and revise our policies periodically when necessary. When there is an update, we will publish the most current policy to https://www.paramounthealthcare.com/services/providers/medical-policies/ .

REVISION HISTORY EXPLANATION
ORIGINAL EFFECTIVE DATE: 05/24/2018

Date	Explanation & Changes
05/24/2018	• CYP2C19 (81225) and CYP2D6 (81226) genotyping requires prior authorization for all product lines • Policy created to reflect most current clinical evidence per The Technology Assessment Working Group (TAWG).
12/28/2020	• Medical policy placed on the new Paramount Medical policy format
03/03/2023	• Medical policy updated to reflect Medicaid coverage to Anthem as of 02/01/2023
07/01/2023	• Medical Policy updated to reflect the most current CMS guidelines for the Medicare Advantage product plans coverage criteria. • Medical policy updated to align the Commercial product plans to align with Paramount's medical policy PG0368, Pharmacogenomic Testing for Mental Health Conditions

REFERENCES/RESOURCES

Centers for Medicare and Medicaid Services, CMS Manual System and other CMS publications and services

American Medical Association, *Current Procedural Terminology (CPT®)* and associated publications and services

Centers for Medicare and Medicaid Services, Healthcare Common Procedure Coding System, HCPCS Release and Code Sets

U.S. Preventive Services Task Force, http://www.uspreventiveservicestaskforce.org/
Industry Standard Review

Hayes, Inc.

Industry Standard Review