


<b>MEDICAL POLICY</b>	<b>Genetic Testing: Cytochrome <i>P450</i> and <i>VKORC1</i> Polymorphisms (All Lines of Business Except Medicare)</b>
<b>Effective Date: 10/1/2021</b>	Medical Policy Number: 313
 10/1/2021	Medical Policy Committee Approved Date: 7/2021; 9/2021
Medical Officer	Date

See Policy CPT/HCPCS CODE section below for any prior authorization requirements

**SCOPE:**

Providence Health Plan, Providence Health Assurance, Providence Plan Partners, and Ayin Health Solutions as applicable (referred to individually as “Company” and collectively as “Companies”).

**APPLIES TO:**

All lines of business except Medicare

**BENEFIT APPLICATION**

Medicaid Members

*Oregon:* Services requested for Oregon Health Plan (OHP) members follow the OHP Prioritized List and Oregon Administrative Rules (OARs) as the primary resource for coverage determinations. Medical policy criteria below may be applied when there are no criteria available in the OARs and the OHP Prioritized List.

**POLICY CRITERIA**

- I. Cytochrome *P450* genotyping may be considered **medically necessary and covered** when any of the following are met (A.-D.):
  - A. For *CYP2C9* genotyping, both of the following are met (1. and 2.):
    - 1. Patient is an adult with relapsing forms of multiple sclerosis, including clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease; **and**

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2. Patient is being considered for treatment with siponimod (Mayzent®).
- B. For *CYP2C19* genotyping, the patient is being considered for treatment with clopidogrel (Plavix®) with any of the following indications (1.-4.):
  1. Acute coronary syndrome
  2. Recent myocardial infarction
  3. Recent stroke
  4. Established peripheral arterial disease.
- C. For *CYP2D6* genotyping, either of the following are met (1. or 2.):
  1. Patient with Gaucher disease type I is being considered for treatment with eliglustat (Cerdelga™); **or**
  2. Patient with Huntington disease is being considered for treatment with tetrabenazine (Xenazine®).
- D. For *CYP27A1* genotyping, patients with cerebrotendinous xanthomatosis who are being considered for treatment with Chenodal (chenodiol).
- II. Cytochrome *P450* genotyping is considered **investigational and not covered** when criterion I. above is not met.
- III. Genetic panel tests that include more than one *CYP450* gene for evaluating drug-metabolizer status are considered **investigational and not covered**.
- IV. Vitamin K epoxide reductase subunit C1 (*VKORC1*) genotyping is considered **investigational and not covered** for the treatment of any indication.
- V. Genetic panel tests that include one or more genes for which clinical utility has not been established are considered **investigational and not covered**, including but not limited to the following tests (A.-I.):
  - A. GeneSight® Psychotropic- Assurex Health, Inc
  - B. Mental Health DNA Insight™- Pathway Genomics®
  - C. Neuro IDGenetix- AltheaDx, Inc.
  - D. Pain Panel- Alpha Genomix
  - E. PGxOne™ Plus Pharmacogenomics Test -Admera Health
  - F. Polypharmacy Panel- Genelex Corporation
  - G. Polypharmacy Comprehensive Panel- Genelex Corporation
  - H. Psychiatry/ADHD Panel - Alpha Genomix
  - I. RightMed Comprehensive Test – OneOme
  - J. Versiti Coagulation Disorder Panel- Versiti Diagnostic Laboratories

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K. Versiti Comprehensive Bleeding Disorder Panel- Versiti Diagnostic Laboratories

Link to [Policy Summary](#)

### CPT/HCPCS CODES

All Lines of Business Except Medicare	
Prior Authorization Required	
0028U	CYP2D6 (cytochrome P450, family 2, subfamily D, polypeptide 6) (eg, drug metabolism) gene analysis, copy number variants, common variants with reflex to targeted sequence analysis
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 (List separately in addition to code for primary procedure)
0072U	CYP2D6 (cytochrome P450, family 2, subfamily D, polypeptide 6) (eg, drug metabolism) gene analysis, targeted sequence analysis (ie, CYP2D6-2D7 hybrid gene) (List separately in addition to code for primary procedure)
0073U	CYP2D6 (cytochrome P450, family 2, subfamily D, polypeptide 6) (eg, drug metabolism) gene analysis, targeted sequence analysis (ie, CYP2D7-2D6 hybrid gene) (List separately in addition to code for primary procedure)
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) (List separately in addition to code for primary procedure)
0075U	CYP2D6 (cytochrome P450, family 2, subfamily D, polypeptide 6) (eg, drug metabolism) gene analysis, targeted sequence analysis (ie, 5' gene duplication/multiplication) (List separately in addition to code for primary procedure)
0076U	CYP2D6 (cytochrome P450, family 2, subfamily D, polypeptide 6) (eg, drug metabolism) gene analysis, targeted sequence analysis (ie, 3' gene duplication/ multiplication) (List separately in addition to code for primary procedure)
81225	CYP2C19 (cytochrome P450, family 2, subfamily C, polypeptide 19) (eg, drug metabolism), gene analysis, common variants (eg, *2, *3, *4, *8, *17)
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)

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81227	CYP2C9 (cytochrome P450, family 2, subfamily C, polypeptide 9) (eg, drug metabolism), gene analysis, common variants (eg, *2, *3, *5, *6)
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 variants (eg, *2, *3, *4, *5, *6, *7)
81355	VKORC1 (vitamin K epoxide reductase complex, subunit 1) (eg, warfarin metabolism), gene analysis, common variant(s) (eg, -1639G>A, c.173+1000C>T)
81401	Molecular pathology procedure level 2
81402	Molecular pathology procedure level 3
81404	Molecular pathology procedure level 5
81405	Molecular pathology procedure level 6
<b>Not Covered</b>	
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)
0270U	Hematology (congenital coagulation disorders), genomic sequence analysis of 20 genes, blood, buccal swab, or amniotic fluid
0272U	Hematology (genetic bleeding disorders), genomic sequence analysis of 51 genes, blood, buccal swab, or amniotic fluid, comprehensive
<b>Unlisted Codes</b>	
All unlisted codes will be reviewed for medical necessity, correct coding, and pricing at the claim level. If an unlisted code is billed related to services addressed in this policy then <b>prior-authorization is required.</b>	
81479	Unlisted molecular pathology procedure
81599	Unlisted multianalyte assay with algorithmic analysis

## DESCRIPTION

### Pharmacogenetics

Pharmacogenetics, also called pharmacogenomics, is a relatively new field that is rapidly growing. Pharmacogenetics is the study of how genetic variation influences an individual's response to medications. These genetic variants may be inherited and present at birth, or they may be acquired such as those acquired by tumors in oncologic indications. Inherited genetic variants may be rare (observed in <5% of the general population), or they may be more common (observed in ≥5% of the population) in which case they are called polymorphisms. Variants in genes may help determine how well an individual responds to a drug or whether side effects or adverse reactions are experienced. Variations in genes

may also help determine how quickly an individual might metabolize a drug. This may help determine whether or not a particular drug will be effective and what the effective dose might be.

### Cytochrome *P450* Polymorphisms

The cytochrome *P450* family (*CYP450*) is a family of enzymes involved in drug metabolism. Cytochrome *P450* genotyping has been proposed as a means of optimizing drug selection and dosing based on patients' predicted drug metabolism. The most well-studied enzymes in this family include *CYP2D6*, *CYP2C19* and *CYP2C9*.

## REVIEW OF EVIDENCE

A review of the ECRI, Hayes, Cochrane, and PubMed databases was conducted regarding the use of genetic testing for cytochrome *P450* polymorphisms through June 2021.

### Cytochrome *P450* Polymorphisms

Due to the size of the cytochrome *P450* gene family (almost 60 genes) and the sheer number of classes of medications that different groups of CYP genes help metabolize, the following evidence section provides a general overview of the most recent highly-studied indications for which select CYP genes have been evaluated. This section does not contain evidence regarding the use multi-gene panels (containing three or more CYP genes) for pharmacogenetic purposes.

### *CYP2B6*

#### *Antiretroviral Therapies*

The evidence regarding the clinical value of *CYP2B6* genotyping to guide antiretroviral therapies is inconclusive. Nonrandomized studies have reported on associations between *CYP2B6* polymorphisms and early efavirenz discontinuation<sup>1</sup>, and suicide risk<sup>2</sup>. These studies both suffered from nonrandomized study design. In addition, one study suffered from high attrition rate (35%) and lack of reporting on medication adherence.<sup>1</sup> While the other study was a post-hoc analysis of small open-label clinical trials that did not specifically focus on suicidality. Both studies concluded that additional studies were needed to further evaluate these associations. Conversely, one large observational cohort (n=801 patients followed over 6 months) reported that *CYP2B6* "slow metabolism" polymorphisms were not associated with any of the treatment endpoints (death, loss to care, HIV RNA above 25 copies/ml at six months, or CNS toxicity).<sup>3</sup> This study was limited by lack of data on medication adherence and data on cognitive functioning in relation to the CNS adverse effects reported.

One study reported on how reduction of efavirenz based on genotype led to continued suppression of HIV-1 (n=18 patients, as evidenced by low viral load) and that CNS-related symptoms improved with dose reduction on 10 of these patients.<sup>4</sup> However, the lack of blinding of the patients with high efavirenz plasma levels may have caused a placebo effect regarding efavirenz-associated CNS symptoms. The authors concluded that double-blind, placebo-controlled studies would be appropriate.

Small nonrandomized studies have reported on associations between specific *CYP2B6* polymorphisms and nevirapine-induced Stevens-Johnson syndrome (SJS), and association between other *CYP2B6* polymorphisms and increased immunological response as measured by CD4 counts.<sup>5,6</sup> The latter study also assessed associations between *CYP2B6* genotypes and plasma viral load, and genotypic drug resistance in plasma/genital secretions, but found none. These studies were limited by small sample size, weak, if any associations, limited follow-up and sub-optimal or unreported medication adherence.

#### *Methadone*

A recent meta-analysis evaluated the impact ABCB1 and *CYP2B6* genetic polymorphisms on methadone metabolism, dose and treatment response in patients with opioid addiction, including seven studies.<sup>7</sup> Although the analysis found that methadone plasma concentration was higher in homozygous carriers of the *CYP2B6*\*6 haplotype when compared to non-carriers, *CYP2B6*\*6 carriers were not found to be significantly different from non-carriers with respect to dose, response to treatment (including abstinence from illicit opioid use) or medication adherence. The reviewers also found no significant association between the ABCB1 polymorphism and methadone plasma concentrations, methadone dose, or methadone response.

#### *CYP2C9*

#### *Warfarin*

Please see the “Systematic Reviews of Pharmacogenetic Testing for Various Indications: Oral Anticoagulants” section below.

#### *Other Indications*

Systematic reviews have been published evaluating the clinical utility of *CYP2C9* genotyping for guiding decisions for a variety of medications including benzodiazepines<sup>8</sup>, nonsteroidal anti-inflammatory drugs<sup>9</sup>, and phenytoin.<sup>10,11</sup> Many of these reviews reported a lack of association between the genotypes evaluated and clinical outcomes including adverse events medication-related events. Limitations of the primary literature for each indication included study heterogeneity in terms of statistical analyses used, covariates considered and outcomes evaluated. Methodological limitations of primary studies included nonrandomized study designs, inclusion of select ethnicities, and studies being insufficiently powered to detect associations between genotypes and outcomes assessed. Large-scale, high-quality randomized trials are still needed to confirm any findings of associations between *CYP2C9* genotypes and clinical outcomes for these indications.

#### *CYP2C19*

Recent systematic reviews have been published evaluating the clinical utility of *CYP2C19* genotyping for guiding decisions for a variety of medications including phenytoin<sup>11,12</sup>, voriconazole<sup>13,14</sup>, proton pump inhibitors<sup>15,16</sup>, clopidogrel<sup>17,18</sup>, and treatments for *Helicobacter pylori*.<sup>19</sup> Many of these reviews reported

a lack of association between the genotypes evaluated and clinical outcomes including fungal/bacterial eradication and medication efficacy rates, or adverse medication-related events such as hepatotoxicity. Limitations of the primary literature for each indication included nonrandomized study designs, small sample sizes leading to underpowered studies, and heterogeneity in the patient populations and ethnicities evaluated and statistical analyses used. Larger, high-quality randomized trials are still needed to confirm any findings of associations between *CYP2C19* genotypes and clinical outcomes for these indications.

### *CYP2D6*

#### *Breast Cancer*

The evidence evaluating *CYP2D6* genotyping to determine drug metabolizer status and predict cancer-related outcomes in patients with breast cancer treated with tamoxifen is conflicting. One systematic review of the clinical effectiveness of genotyping for *CYP2D6* for the management of women with breast cancer treated with tamoxifen, included 25 cohorts.<sup>20</sup> This review reported that while six cohorts suggested that extensive metabolizers appeared to have better outcomes than either poor or intermediate metabolizers in terms of relapse/recurrence; three cohorts reported poorer outcomes for extensive metabolizers. The reviewers noted heterogeneity across the studies in terms of the patient populations, alleles tested and outcomes evaluated, concluding that the data was limited and conflicting. A more recent systematic review also found that results of studies reporting associations between *CYP2D6* and tamoxifen outcomes were not robust.<sup>21</sup> Similar conclusions of insufficient and conflicting evidence of clinical utility were drawn by additional reviews on this topic.<sup>22,23</sup> Several large scale RCTs included in these reviews reported a weak or no association between *CYP2D6* genotype and various outcomes including breast cancer occurrence<sup>24</sup>, breast cancer specific survival<sup>25</sup>, disease recurrence<sup>26</sup>, and breast cancer-free interval.<sup>27</sup> The reviews concluded that additional prospective studies are necessary to fully establish the value of *CYP2D6* genotyping in women with breast cancer considering tamoxifen.

#### *Other conditions:*

The clinical value of *CYP2D6* genotyping has been evaluated in the context of many different medications but remains inconclusive. Systematic reviews have been published evaluating the clinical utility of *CYP2D6* genotyping for decisions for a variety of medications including metoprolol<sup>28,29</sup>, donepezil<sup>30</sup>, tramadol<sup>31</sup>, opioid treatment for pain,<sup>32</sup> risperidone and other antipsychotics.<sup>33,34</sup> However, most of the primary studies suffer the same limitations described above for the *CYP2D6*/tamoxifen studies, with the large majority of studies being retrospective reviews, case series, or small non-randomized case-control studies. In general, while some studies report modest associations between *CYP2D6* genotyping and clinically relevant outcomes, such as clinical response, adverse effects, and pain reduction; most outcomes were not significant. Adequately powered prospective randomized studies are warranted to clarify the role of *CYP2D6* genotyping in practice.

#### *Oral Anticoagulants*

In 2017, a systematic review by Zhang et al. studied *CYP2C9* polymorphisms on pediatric warfarin maintenance dosage requirements in 507 patients (N=8 studies), reporting that *CYP2C9* \*1/\*2, *CYP2C9* \*1/\*3, and *CYP2C9* genotypes were significantly associated with lower warfarin maintenance dose requirements in this population. Limitations of this study included small sample size and lack of ethnic diversity in subjects. Also in 2017, Tang et al. systematically reviewed studies on *VKORC1* polymorphisms and warfarin maintenance dosing in relation to age and ethnicity, including 9578 (N= 53 studies).<sup>35</sup> The authors reported that Caucasian carriers of *VKORC1* polymorphisms required a higher mean daily warfarin dose compared with Asian carriers. However, age was found to be a confounding variable, as it was also strongly associated with warfarin dosing requirements. Both reviews focused on select patient populations, limiting the applicability of results to other populations and ethnicities. Of note, neither review reported on whether results from genotyping affected patient outcomes such as incidence of bleeding or thromboembolic events.

In 2018, the Washington Health Care Authority published a technology assessment on the clinical utility of pharmacogenetic testing (including *CYP2C9*, *VKORC1*, and *CYP4F2*) for patients being treated with oral anticoagulants, including 13 randomized controlled trials.<sup>36</sup> The reviewers reported that risk of death and thromboembolic events were not significantly different between the pharmacogenetic testing group and controls. The risk of major bleeding in patients who received pharmacogenetic testing to guide initial dosing compared to patients started on a fixed dose, was not statistically significant (RR of 0.70; 95% CI, 0.14 to 3.53). Similar conclusions were drawn regarding risk of bleeding by a second good quality systematic review of 18 trials, also published in 2018.<sup>37</sup> The quality of evidence was determined to be low for risk of death, and moderate for thromboembolic events and major bleeding. Additional intermediate/surrogate outcomes were evaluated: the percentage of time in therapeutic range (PTTR) and over-anticoagulation. However, neither estimate was statistically significantly different and the quality of evidence for both outcomes was determined to be low.

The assessment noted several limitations of the evidence-base, including, “differences among studies in terms of populations, underlying medical conditions, risk of outcomes, indications for treatment, comparators used, study outcome definitions and assessment, and the overall conduct of the study and system in which it was conducted ... In addition, the small overall number of events for patient-important outcomes creates statistical instability. Most of these estimates could easily be changed by additional studies.” The assessment concluded that, “the available evidence makes balancing the benefits and harms from pharmacogenetic testing for polymorphisms to guide warfarin initiation challenging .... It is particularly likely that additional research for the outcomes rated as having low quality of evidence could have an important effect on the observed findings.”

### *Pain Management*

Systematic reviews have been published evaluating the clinical utility of pharmacogenetics for pain management, evaluating a variety of genes and a number of medications, including opioids and other analgesics. Some of the genes evaluated include ABCB1, COMT, *CYP2D6*, *CYP3A4*, *CYP3A5*, OPRM1, and UGT2B7. These studies have focused on a variety of pain indications including post-operative pain<sup>38-42</sup>, chronic cancer pain<sup>43</sup>, labor pain<sup>44</sup>, post-partum pain<sup>45</sup>, and mixed pain indications.<sup>46</sup>



Limitations of the primary literature include heterogeneity between studies in terms of outcomes evaluated and data analyses, differences in experimental setup (exact polymorphisms or haplotypes studied, phenotypes studied), and conflicting results as some studies reported associations between some genetic variants and clinical outcomes while others report a lack of significance. Large-scale, high-quality randomized trials are still needed to confirm any findings of associations between genes tested for pharmacogenetic purposes and outcomes related to pain.

### Multigene Panels

Several systematic reviews were identified addressing the GeneSight Psychotropic (Myriad Genetics, Inc.) and Neuro IDgenetix (AltheaDx, Inc.) tests for guiding medication selection for patients with psychiatric disorders or acute or chronic pain.<sup>47-49</sup> Studies published to date suffer from high risk of bias, short term follow up, and lack of significant results in primary analyses. Future studies are needed comparing use of GeneSight Psychotropic to true standard practice in a randomized, controlled, blinded trial design with long term follow up.

## CLINICAL PRACTICE GUIDELINES

### National Comprehensive Cancer Network (NCCN)

#### *Breast Cancer Diagnosis and Treatment*

The NCCN breast cancer guidelines (v 4.2021) recommends against *CYP2D6* genotype testing for patients considering tamoxifen, and states that coadministration of strong inhibitors of *CYP2D6* should be used with caution.<sup>50</sup> In the guidelines' discussion section, authors also state:

“Given the limited and conflicting evidence at this time, the NCCN Breast Cancer Panel does not recommend *CYP2D6* testing as a tool to determine the optimal adjuvant endocrine strategy. This recommendation is consistent with the ASCO Guidelines.”<sup>50</sup>

### American Society of Clinical Oncology

In 2016, the ASCO published a guideline on the use of biomarkers to guide adjuvant systemic therapy decisions for women with early-stage invasive breast cancer. Authors recommended against cytochrome *P450 2D6* (*CYP2D6*) polymorphisms to guide adjuvant endocrine therapy selection.<sup>51</sup>

### Clinical Pharmacogenetics Implementation Consortium (CPIC)

In 2017, the CPIC issued a guideline for pharmacogenetics-guided warfarin dosing.<sup>52</sup> Authors stated that although there is substantial evidence associating *CYP2C9* and *VKORC1* variants with warfarin dosing, randomized clinical trials have demonstrated inconsistent results in terms of clinical outcomes.

## POLICY SUMMARY

There is a lack of evidence and clinical practice guideline support for most CYP genotyping. However, there are several indications for which there is sufficient evidence that genetic testing for mutations in select CYP genes may be necessary to determine whether a patient is a candidate for a particular therapy. These situations include:

- *CYP2C9* for Mayzent® (siponimod) for relapsing forms of multiple sclerosis (MS), including clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults.
- *CYP2C19* genotyping for Plavix® (clopidogrel) for patients with conditions outlined by the FDA (acute coronary syndrome, recent myocardial infarction, recent stroke, or established peripheral arterial disease)
- *CYP2D6* genotyping for patients with Huntington's chorea to inform treatment with Xenazine® (tetrabenazine)
- *CYP2D6* genotyping for patients with Gaucher disease, type 1 to inform treatment with Cerdelga™ (eliglustat)
- *CYP27A1* genotyping for patients with Cerebrotendinous xanthomatosis to inform treatment with Chenodal (chenodiol)

For *VKORC1* genotyping and all other CYP gene genotyping, including tests for guiding medication selection for patients with psychiatric disorders or acute or chronic pain (e.g. GeneSight Psychotropic), there is insufficient evidence that testing for genetic variants in any of the CYP genes to inform medication choice or dosing will lead to improved outcomes for any indication.

## INSTRUCTIONS FOR USE

Company Medical Policies serve as guidance for the administration of plan benefits. Medical policies do not constitute medical advice nor a guarantee of coverage. Company Medical Policies are reviewed annually and are based upon published, peer-reviewed scientific evidence and evidence-based clinical practice guidelines that are available as of the last policy update. The Companies reserve the right to determine the application of Medical Policies and make revisions to Medical Policies at any time. Providers will be given at least 60-days' notice of policy changes that are restrictive in nature.

The scope and availability of all plan benefits are determined in accordance with the applicable coverage agreement. Any conflict or variance between the terms of the coverage agreement and Company Medical Policy will be resolved in favor of the coverage agreement.

## REGULATORY STATUS

Several test kits for *CYP450* genotyping have been cleared for marketing by the FDA (FDA product code: NTI). These include, but may not be limited to the following:

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## Genetic Testing: Cytochrome *P450* and *VKORC1* Polymorphisms (All Lines of Business Except Medicare)

- The AmpliChip® (Roche Molecular Systems, Inc.)
- The xTAG® *CYP2D6* Kit (Luminex Molecular Diagnostics)
- The INFINITI *CYP2C19* Assay (AutoGenomics Inc.)
- Verigene *CYP2C19* Nucleic Acid Test
- The Spartan RX *CYP2C19* Test System (Spartan Bioscience)
- The xTAG® *CYP2C19* Kit v3 (Luminex Molecular Diagnostics)

### Mental Health Parity Statement

Coverage decisions are made on the basis of individualized determinations of medical necessity and the experimental or investigational character of the treatment in the individual case. In cases where medical necessity is not established by policy for specific treatment modalities, evidence not previously considered regarding the efficacy of the modality that is presented shall be given consideration to determine if the policy represents current standards of care.

## REFERENCES

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