Clinical Policy Title: Pharmocogenetic testing for warfarin (Coumadin®) sensitivity

Clinical Policy Number: 02.01.13

Effective Date: September 1, 2013
Initial Review Date: May 15, 2013
Most Recent Review Date: May 18, 2016
Next Review Date: May 2017

Related policies:

CP# 05.01.02 Patient self-testing of prothrombin international normalized ratio (INR) measurement

ABOUT THIS POLICY: Prestige Health Choice has developed clinical policies to assist with making coverage determinations. Prestige Health Choice’s clinical policies are based on guidelines from established industry sources, such as the Centers for Medicare & Medicaid Services (CMS), state regulatory agencies, the American Medical Association (AMA), medical specialty professional societies, and peer-reviewed professional literature. These clinical policies, along with other sources, such as plan benefits and state and federal laws and regulatory requirements, including any state- or plan-specific definition of “medically necessary,” and the specific facts of the particular situation are considered by Prestige Health Choice when making coverage determinations. In the event of conflict between this clinical policy and plan benefits and/or state or federal laws and/or regulatory requirements, the plan benefits and/or state and federal laws and/or regulatory requirements shall control. Prestige Health Choice’s clinical policies are for informational purposes only and not intended as medical advice or to direct treatment. Prestige Health Choice’s clinical policies are reflective of evidence-based medicine at the time of review. As medical science evolves, Prestige Health Choice will update its clinical policies as necessary. Prestige Health Choice’s clinical policies are not guarantees of payment.

Coverage policy

Prestige Health Choice considers the use of pharmocogenetic testing for warfarin (Coumadin®) sensitivity to be investigational and, therefore, not medically necessary.

Limitations:

Coverage determinations are subject to benefit limitations and exclusions as delineated by the state Medicaid authority. The Florida Medicaid website can be accessed at http://ahca.myflorida.com/Medicaid/.

There are no covered uses for pharmocogenetic testing for warfarin sensitivity.

Alternative covered services:
Laboratory testing for prothrombin time (PT) and International Normalized Ratio (INR) values.

**Background**

Warfarin (trade names: Coumadin®; Jantoven®; Marevan®) is an anticoagulant prescribed to prevent or treat thromboembolic events in high-risk individuals. The drug has a narrow therapeutic window with variable responses to dosing. Individuals usually receive a starting dose of 2 mg to 5 mg and are frequently monitored until reaching a stable international normalized ratio (INR) value of 2.0 – 3.0. Genetic variants present in the form of alleles have an influence on an individual’s response to treatment with warfarin.

Pharmacogenomics and pharmacogenetics are bodies of science that involve genetics, and at times the terms are used interchangeably. However, there are differences between the two:

- Pharmacogenomics pertains to the science of the many genes that determine drug behavior.
- Pharmacogenetics examines the link between an individual’s genetic make-up and their response to a pharmaceutical product. The results of a pharmacogenetic test are used in an attempt to predict an individual’s response to a specific pharmaceutical before it is used in a therapy regimen.

Warfarin elimination from the body relies almost exclusively upon the metabolic conversion of inactive metabolites by cytochrome P450 (CYP) enzymes in liver (hepatic) cells. The principal cytochrome P450 enzyme that modulates the anticoagulant activity of warfarin is CYP2C9. The VKORC1 gene encodes the vitamin K epoxide reductase enzyme, the drug target of warfarin. Different races present different variances with allele types, and different allele types have varying warfarin sensitivity.

An individual may undergo testing of CYP2C9 or VKORC1 alleles in an attempt to predict the individual’s response to warfarin prior to the initiation of drug therapy. Though pharmacogenetic testing is used to gain a better approximation of the optimal initial dosing of warfarin, it does not remove the need for PT/INR testing as the standard diagnostic test for assessing an individual’s reaction to warfarin dosing. The U.S. Food and Drug Administration (FDA) has approved several genetic tests for warfarin sensitivity.

**Searches**

Prestige Health Choice searched PubMed and the databases of:

- UK National Health Services Centre for Reviews and Dissemination.
- The Centers for Medicare & Medicaid Services (CMS).
We conducted searches on April 26, 2016. Search terms were: “Warfarin (MeSH),” “Pharmacogenetics (MeSH),” and free text terms “pharmacogenetic” and “warfarin.”

We included:

- **Systematic reviews**, which pool results from multiple studies to achieve larger sample sizes and greater precision of effect estimation than in smaller primary studies. Systematic reviews use predetermined transparent methods to minimize bias, effectively treating the review as a scientific endeavor, and are thus rated highest in evidence-grading hierarchies.
- **Guidelines based on systematic reviews.**
- **Economic analyses**, such as cost-effectiveness, and benefit or utility studies (but not simple cost studies), reporting both costs and outcomes — sometimes referred to as efficiency studies — which also rank near the top of evidence hierarchies.

**Findings**

There is insufficient evidence in the literature to warrant recommending routine warfarin sensitivity pharmacogenetic testing for initial dosing for individuals prior to receiving warfarin therapy. The predictive values for CYP2C9 genotype testing and VKOR SNPs testing are approximately 96 percent to 98 percent and 83 percent to 85 percent, respectively. The inconsistency in the predictive values of these tests has an impact on any determination for standard of care. Clinical variables such as age, race, smoking status, concomitant drugs and weight account for a great degree of variability in warfarin response (Hirsh, 2001).

Algorithms should be developed that incorporate genetic variation (genotype) to warfarin sensitivity and other significant factors to predict the best likely, stable starting warfarin dose to limit high INR values. More studies are needed that show warfarin pharmacogenetic testing actually reduces the risk and incidence of serious bleeding and mortality. More evidence and outcomes from large prospective clinical trials are needed that link genotype to warfarin dosing recommendations before endorsing warfarin sensitivity genotype testing (Flockhart, 2008; Holbrook, 2012; Ruaño, 2010).

**Policy update:**

In 2014, we identified one new cost-effectiveness analysis and two new randomized controlled trials (RCTs) but no new systematic reviews or guidelines for this policy update. The two RCTs provided conflicting results. One large RCT found no improvement in anticoagulation control during the first four weeks of therapy using genotype-guided dosing of warfarin and no between-group differences in rates of the combined outcome of any INR ≥ 4, major bleeding or thromboembolism. However, they noted a significant interaction between dosing strategy and race; among African American patients, the mean percentage of time in the therapeutic range was lower in the genotype-guided group than in the clinically guided group (P = 0.003) (Kimmel, 2013).
Conversely, in another study pharmacogenetic-based dosing was associated with both significantly less time to reach a therapeutic INR and higher percentage of time in the therapeutic INR range than standard dosing during the initiation of warfarin therapy (Pirmohamed, 2013). A cost-effectiveness analysis based on a clinical trial simulation found pharmacogenetic-guided warfarin therapy and apixaban (Eliquis®; Bristol Meyers Squibb) appear to be more cost effective than clinically-guided warfarin treatment (Pink 2014).

In 2015, we identified two new meta-analyses with conflicting results. While Tang (2014) found some benefit with pharmacogenetic dosing of warfarin and its analogues, Stergiopoulos (2014) found a pharmacogenetic dosing strategy did not result in increased time of the INR in the therapeutic range, fewer patients with an INR greater than 4, or a reduction in major bleeding or thromboembolic events compared with clinical dosing algorithms.

In 2016, we identified two new meta-analyses for this policy (Tang, 2015; Liao, 2015). Patients who receive a loading dose of warfarin often reach a supratherapeutic INR level that can place a patient at risk for bleeding and prolonged hospital stay. While pharmacogenetic warfarin dosing offered no clear advantage over clinical dosing based on patient variables, it was superior to using a fixed initial standard loading dose. Meta-analyses note the variation in study populations, lengths of follow-up, genotype-based and single clinical algorithms, and outcomes which challenge the ability to draw firm conclusions from the evidence base. In light of these results, there remains insufficient evidence in the literature to warrant recommending routine warfarin sensitivity genotype testing for initial dosing for individuals prior to receiving warfarin therapy.

Summary of clinical evidence:

<table>
<thead>
<tr>
<th>Citation</th>
<th>Content, Methods, Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Tang (2015)</strong></td>
<td>Key points:</td>
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<tr>
<td>Pharmacogenetic (PG) versus standard versus clinically guided dosing</td>
<td>• Meta-analysis of eight RCTs (number of subjects not reported).</td>
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<tr>
<td></td>
<td>• Primary outcome: percentage of time within the therapeutic INR range.</td>
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<td></td>
<td>• Secondary outcomes: INR ≥ 4 events, major bleeding events and thromboembolic events.</td>
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<td></td>
<td>• PG-guided dosing significantly increased the effectiveness and safety of Coumarin therapy compared with standard dosing but did not have advantages compared with clinically-guided dosing.</td>
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<tr>
<td><strong>Liao (2015)</strong></td>
<td>Key points:</td>
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<tr>
<td>PG + clinical algorithm versus single clinical algorithm dosing</td>
<td>• Meta-analysis of seven RCTs (1,910 total participants).</td>
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<td></td>
<td>• Primary outcome: percentage of time within the therapeutic INR range (TTR).</td>
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<td></td>
<td>• PG-guided group had improved outcomes compared with a fixed initial standard dose, but not with a non-fixed initial dose.</td>
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<td></td>
<td>• No significant difference in rate of adverse events or death.</td>
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<td></td>
<td>• Further experiments needed to confirm these findings.</td>
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<tr>
<td><strong>Pink (2014)</strong></td>
<td>Key points:</td>
</tr>
<tr>
<td>Citation</td>
<td>Content, Methods, Recommendations</td>
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<td>-------------------------------</td>
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<tr>
<td>Cost-effectiveness analysis</td>
<td>• Clinical trial simulation of S-warfarin used to predict TTR for different dosing algorithms based on data from meta-analyses.</td>
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<td>• Neither dabigatran nor rivaroxaban were cost-effective options.</td>
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<td></td>
<td>• In relation to clinically dosed warfarin, pharmacogenetics-guided warfarin and apixaban had incremental cost-effectiveness ratios of £13,226 and £20,671 per quality adjusted life year gained, respectively.</td>
</tr>
<tr>
<td>Stergiopoulos (2014)</td>
<td>Key points:</td>
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<tr>
<td>PG-guided initial dosing</td>
<td>• Meta-analysis of nine RCTs (2812 total patients).</td>
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<td>versus clinical dosing</td>
<td>• Follow-up ranged from four weeks to six months.</td>
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<tr>
<td>protocols</td>
<td>• A PG-guided dosing strategy did not result in a greater percentage of TTR, fewer patients with an INR &gt; 4, or a reduction in major bleeding or thromboembolic events compared with clinical dosing algorithms.</td>
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<tr>
<td>Tang (2014)</td>
<td>Key points:</td>
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<tr>
<td>PG-guided versus</td>
<td>• Systematic review and meta-analysis of 10 RCTs and prospective cohort studies (5,299 total patients), including eight RCTs addressing initial warfarin dosing.</td>
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<tr>
<td>clinical or standard initial</td>
<td>• PG-based warfarin dosing increased the rate of TTR and reduced the risk for bleeding complications in persons starting warfarin therapy.</td>
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<tr>
<td>dosing protocols</td>
<td>• No difference in number of patients with an INR &gt; 4.</td>
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</tbody>
</table>

**Glossary**

**Allele** — One of two or more alternative forms of a gene that arise by mutation and are found at the same place on a chromosome. It may or may not produce different observable phenotypic traits.

**Chromosome** — The part of a cell that contains the genetic material.

**Gene** — A biological, hereditary unit, capable of reproducing, that is affixed to a specific location on a chromosome.

**Pharmacogenetics** — The study of how an individual’s genetic makeup, or genotype, affects the body’s response to drugs.

**Phenotype** — An organism’s observable characteristics or traits, e.g., biological or physiological properties. A phenotype results from the expression of an organism’s genes, as well as the influence of environmental factors and the interactions between the two.

**Single nucleotide polymorphisms (SNPS)** — Components in genes that have the potential to affect warfarin metabolism and activity and may predict an individual’s response to warfarin.

**Warfarin** — An anticoagulant (blood thinner). Warfarin reduces the formation of blood clots.
References

Professional society guidelines/other:


Peer-reviewed references:


Moreau C, Bajolle F, Siguret V, et al. Vitamin K antagonists in children with heart disease: height and


**Clinical trials:**

Searched ClinicalTrials.gov on April 27, 2016 using terms warfarin AND (pharmacogenetic OR dose) | Open Studies. 80 studies found, two relevant.


**CMS National Coverage Determinations (NCDs):**

Local Coverage Determinations (LCDs):

No LCDs identified as of the writing of this policy.

Commonly submitted codes

Below are the most commonly submitted codes for the service(s)/item(s) subject to this policy. This is not an exhaustive list of codes. Providers are expected to consult the appropriate coding manuals and bill accordingly.

<table>
<thead>
<tr>
<th>CPT Code</th>
<th>Description</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>81227</td>
<td>CYP2C9 (cytochrome P450, family 2, subfamily C, polypeptide 9) (e.g., drug metabolism), gene analysis, common variants (e.g., *2, *3, *5, *6).</td>
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<tr>
<td>81355</td>
<td>VKORC1 (vitamin K epoxide reductase complex, subunit 1) (eg, warfarin metabolism), gene analysis, common variants (e.g., -1639/3673).</td>
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</tbody>
</table>

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<thead>
<tr>
<th>HCPCS Level II</th>
<th>Description</th>
<th>Comment</th>
</tr>
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<tbody>
<tr>
<td>G9143</td>
<td>Warfarin responsiveness testing by genetic technique using any method, any number of specimen(s).</td>
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</tbody>
</table>

Refer to the Policy Coding Appendices for ICD-10 codes.
Policy Number 02.01.05 Appendix — ICD-9.