Medical Policy
Genetic Testing for Warfarin Dose

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Policy Number: 214
BCBSA Reference Number: 2.04.48
NCD/LCD: National Coverage Determination (NCD), Pharmacogenic Testing for Warfarin Response (90.1)

Related Policies
None

Policy
Commercial Members: Managed Care (HMO and POS), PPO, and Indemnity

Genotyping to determine cytochrome p450 2C9 (CYP2C9) and vitamin K epoxide reductase subunit C1 (VKORC1) genetic variants is considered INVESTIGATIONAL for the purpose of managing the administration and dosing of warfarin, including use in guiding the initial warfarin dose to decrease time to stable international normalized ratio and reduce the risk of serious bleeding.

Medicare HMO BlueSM and Medicare PPO BlueSM Members

Medical necessity criteria and coding guidance can be found through the link below:
National Coverage Determination (NCD), Pharmacogenic Testing for Warfarin Response (90.1)

For medical necessity criteria and coding guidance for Medicare Advantage members living outside of Massachusetts, please see the Centers for Medicare and Medicaid Services website for information regarding your specific jurisdiction at https://www.cms.gov.

Prior Authorization Information
Pre-service approval is required for all inpatient services for all products.
See below for situations where prior authorization may be required or may not be required for outpatient services.
Yes indicates that prior authorization is required.
No indicates that prior authorization is not required.
N/A indicates that this service is primarily performed in an inpatient setting.
Outpatient

<table>
<thead>
<tr>
<th>Commercial Managed Care (HMO and POS)</th>
<th>This is not a covered service.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Commercial PPO and Indemnity</td>
<td>This is not a covered service.</td>
</tr>
<tr>
<td>Medicare HMO BlueSM</td>
<td>No</td>
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<tr>
<td>Medicare PPO BlueSM</td>
<td>No</td>
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</tbody>
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**CPT Codes / HCPCS Codes / ICD Codes**

Inclusion or exclusion of a code does not constitute or imply member coverage or provider reimbursement. Please refer to the member’s contract benefits in effect at the time of service to determine coverage or non-coverage as it applies to an individual member.

Providers should report all services using the most up-to-date industry-standard procedure, revenue, and diagnosis codes, including modifiers where applicable.

The following codes are included below for informational purposes only; this is not an all-inclusive list.

The following CPT/HCPCS codes are considered investigational for **Commercial Members:** Managed Care (HMO and POS), PPO, and Indemnity:

**CPT Codes**

<table>
<thead>
<tr>
<th>CPT codes:</th>
<th>Code Description</th>
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<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) (e.g., warfarin metabolism), gene analysis, common variants (e.g., -1639/3673)</td>
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**HCPCS Codes**

<table>
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<tr>
<th>HCPCS codes:</th>
<th>Code Description</th>
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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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**Description**

Warfarin is administered to prevent and treat thromboembolic events in high-risk patients; warfarin dosing is a challenging process, due to the narrow therapeutic window, variable response to dosing, and serious bleeding events in 5% or more of patients (depending on definition). Patients are typically given a starting dose of 2 to 5 mg and monitored frequently with dose adjustments until a stable international normalized ratio (INR) value (a standardized indicator of clotting time) between 2 and 3 is achieved. During this adjustment period, a patient is at high risk of bleeding.

Stable or maintenance warfarin dose varies among patients by more than an order of magnitude. Factors influencing stable dose include body mass index, age, interacting drugs, and indication for therapy. Warfarin, which is primarily metabolized in the liver by the CYP2C9 enzyme, exerts an anticoagulant effect by inhibiting the protein vitamin K epoxide reductase complex, subunit 1 (VKORC1). Three single nucleotide variants (SNVs), two in the CYP2C9 gene and one in the VKORC1 gene play key roles in determining the effect of warfarin therapy on coagulation. CYP2C9*1 metabolizes warfarin normally, CYP2C9*2 reduces warfarin metabolism by 30%, and CYP2C9*3 reduces warfarin metabolism by 90%. Because warfarin given to patients with *2 or *3 variants will be metabolized less efficiently, the drug will remain in circulation longer, so lower warfarin doses will be needed to achieve anticoagulation. Recent genome-wide association studies have also identified that a SNV in the CYP4F2 gene has been reported to account for a small proportion of the variability in stable dose (the CYP4F2 gene encodes a protein involved in vitamin K oxidation).
Using the results of \textit{CYP2C9} and \textit{VKORC1} genetic testing to predict a warfarin starting dose that approximates a likely maintenance dose may benefit patients by decreasing the risk of serious bleeding events and the time to stable INR. Algorithms have incorporated not only genetic variation but also other significant patient characteristics and clinical factors to predict the best starting dose.

\textbf{Summary}

Variants in the \textit{CYP2C9} and \textit{VKORC1} genes result in differences in warfarin metabolism. Using information about an individual’s \textit{CYP2C9} and \textit{VKORC1} genotypes may help in personalizing warfarin dosing and could reduce the time to dose stabilization and selection of appropriate maintenance dose that might avoid consequences of too much or too little anticoagulation.

For individuals with conditions requiring warfarin treatment who are being managed with genetic testing for \textit{CYP2C9} and \textit{VKORC1} variants to determine warfarin dose, the evidence includes multiple randomized controlled trial (RCTs), systematic reviews of the RCTs, and cohort studies. Relevant outcomes are test accuracy and validity, other test performance measures, morbid events, medication use, and treatment-related morbidity. The evidence on clinical validity from several retrospective and prospective cohort studies has shown that algorithms incorporating genetic variants and clinical factors explain greater variance in warfarin dosing over that predicted by clinical factors alone. However, the incremental gain using genetic testing depends on multiple factors, including ethnicity. Further, there is no consensus on a single algorithm that could be generalized to a diverse population. Multiple smaller randomized trials and meta-analyses of these trials have examined the clinical utility of genetic tests to guide warfarin dose and reported inconsistent results. Two large adequately powered RCTs attempted to address this inconsistency but reported contrasting results. Of these 2 trials, the larger U.S.-based RCT found no utility in adding genetic testing to a clinical dosing algorithm. The percentage of time in the therapeutic international normalized ratio range was similar when genetic testing was and was not added. The evidence is insufficient to determine the effects of the technology on health outcomes.

\textbf{Policy History}

<table>
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<tr>
<th>Date</th>
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| 8/2017   | BCBSA National medical policy review.  
Background and summary updated.  8/2017 |
| 1/2016   | New references added from BCBSA National medical policy. |
| 11/2015  | Added coding language. |
| 2/2015   | New references added from BCBSA National medical policy. |
| 2/2013   | New references from BCBSA National medical policy. |
No changes to policy statements. |
No changes to policy statements. |

\textbf{Information Pertaining to All Blue Cross Blue Shield Medical Policies}

Click on any of the following terms to access the relevant information:
\texttt{Medical Policy Terms of Use}
\texttt{Managed Care Guidelines}
\texttt{Indemnity/PPO Guidelines}
\texttt{Clinical Exception Process}
\texttt{Medical Technology Assessment Guidelines}

\textbf{References}


