Warfarin Sensitivity (CYP2C8, CYP2C9, CYP4F2, VKORC1) Genotyping

Warfarin (Coumadin) is an anticoagulant widely used throughout the world. Testing may be indicated for warfarin-naïve individuals prior to starting warfarin therapy, individuals with a personal or family history of difficulty with warfarin, and adherent patients taking warfarin but who are difficult to treat. Testing is also indicated for individuals currently on warfarin and required to discontinue therapy, such as prior to an invasive procedure or surgery, to estimate the time required to eliminate the drug.

Tests to Consider

Warfarin Sensitivity (CYP2C8, CYP2C9, CYP4F2, VKORC1) Genotyping 3001541

Method: Polymerase Chain Reaction/Fluorescence Monitoring

Identifies individuals with inherited variants that affect metabolism (*CYP2C8*, *CYP2C9*) and/or sensitivity (*CYP4F2*, *VKORC1*) to warfarin.

See Variants Tested table for more information.

Related Test

CYP2C8 and CYP2C9 3001501

Method: Polymerase Chain Reaction/Fluorescence Monitoring

Assesses genetic risk of abnormal drug metabolism for CYP2C8 and/or CYP2C9 substrates.

Disease Overview

Pathophysiology

- Warfarin is administered as a racemic mixture; s-warfarin is more potent than r-warfarin and is thought to mediate most of the anticoagulant activity of warfarin.
- Primary mechanism of action is to inhibit vitamin K epoxide reductase (VKOR)
  - VKOR recycles vitamin K and activates clotting factors II, VII, IX, and X
- Exerts anticoagulant effects by reducing the concentration of these activated clotting factors

Diagnostic Issues

- Individual response to warfarin varies:
  - Factors affecting response include age, gender, body mass, diet, concomitant medications, and genetic variants.
  - An estimated 40-63% of the variability in therapeutic warfarin dose is accounted for by the *CYP2C9**2 and *3 and the *VKORC1**2 variant alleles.
- Overdosing and underdosing can result in life-threatening events (eg, bleeding or thrombosis).
  - ~1% of individuals die due to bleeding complications associated with warfarin.
  - ~15% of individuals experience minor bleeding complications.
- Dose adjustments are often necessary
  - Usually based on international normalized ratio (INR)
  - May be difficult to achieve therapeutic INR in some individuals (eg, those requiring <21 mg per week or >49 mg per week to maintain INR).

Genetics

Genes Tested

CYP2C8, CYP2C9, CYP4F2, VKORC1

Variants Tested

Gene (Transcript)	Allele
CYP2C8 (NM_000770)	*CYP2C8*1C*: rs17110453, c.-370T>G
	*CYP2C8*2*: rs11572103, c.805A>T

Gene (Transcript)	Allele
	*CYP2C8*3*: rs10509681, c.1196A>G
	*CYP2C8*4*: rs1058930, c.792C>G
CYP2C9 (NM_000771)	*CYP2C9*2*: rs1799853, c.430C>T
	*CYP2C9*3*: rs1057910, c.1075A>C
	*CYP2C9*4*: rs56165452, c.1076T>C
	*CYP2C9*5*: rs28371686, c.1080C>G
	*CYP2C9*6*: rs9332131, c.818del
	*CYP2C9*8*: rs7900194, c.449G>A
	*CYP2C9*9*: rs2256871, c.752A>G
	*CYP2C9*11*: rs28371685, c.1003C>T
	*CYP2C9*12*: rs9332239, c.1465C>T
CYP4F2 (NM_001082)	*CYP4F2*3*: rs2108622, c.1297G>A
VKORC1 (NM_024006)	*VKORC1*2*: rs9923231, c.-1639G>A

Allele frequencies and phenotype predictions are available at www.pharmvar.org or www.pharmgkb.org.

Inheritance

Autosomal codominant

Test Interpretation

Sensitivity/Specificity

- Clinical sensitivity: genetic factors and known non-genetic factors account for ~50% of the variability in warfarin dose[1]
- Analytical sensitivity and specificity: >99%

Results

- Variant(s) detected:
  - *VKORC1*2* allele is associated with reduced expression of the warfarin target, vitamin K epoxide reductase (VKOR), and a reduced dose requirement
  - The *CYP4F2*3* allele is associated with an increased dose requirement
  - *CYP2C8/9* variants are associated with a reduced rate of warfarin catabolism, which is associated with a decreased dose requirement and an increased time required to achieve steady state
    - Loading doses may be required

        - Vulnerability to drug-drug interactions may also be increased
    - The *CYP2C* cluster variant (rs12777823), not currently detected in this test, is associated with a decreased dose requirement in African American individuals, but is not included in algorithms intended for other populations. The mechanism underlying the association is not well characterized, but this variant was included in Tier 2 variant recommendations from the Association of Molecular Pathology and the College of American Pathologists.
- No variants detected: predictive of *1 functional allele
- Genotype should be interpreted with clinical information.
- Genetic information and nongenetic factors can be used in combination with warfarin dose calculators, such as through www.WarfarinDosing.org.
- Additional dosing guidance is available through drug labeling and professional guidance documents, such as those published by the American College of Chest Physicians (CHEST) and the Clinical Pharmacogenetics Implementation Consortium (CPIC).

Limitations

- Only the targeted genetic variants will be detected by this panel, and assumptions about phase and content are made to assign alleles.
- Diagnostic errors can occur due to rare sequence variations.
- Risk of therapeutic failure or adverse reactions with CYP2C8 or CYP2C9 substrates may be affected by genetic and nongenetic factors that are not detected by this test.
- This result does not replace the need for therapeutic drug or clinical monitoring.

References

1. Clinical Pharmacogenetics Implementation Consortium. CPIC guideline for pharmacogenetics-guided warfarin dosing. [Last modified: Apr 2019; Accessed: Apr 2019]

Additional Resources

Kearon C, Akl EA, Ornelas J, et al. Antithrombotic therapy for VTE disease: CHEST Guideline and Expert Panel Report. Chest. 2016;149(2):315-352.

Pratt VM, Cavallari LH, Del Tredici AL, et al. Recommendations for clinical warfarin genotyping allele selection: a report of the Association for Molecular Pathology and the College of American Pathologists. J Mol Diagn. 2020;22(7):847-859.

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