

Warfarin DoseAdvise™ Genetic Test

Warfarin therapy and limitations

- Prescribed to over 1 million U.S. patients per year, warfarin is a difficult drug to manage due to its narrow therapeutic index and wide interindividual variability in anticoagulation response and therapeutic dose.
- Life-threatening events can result from under-dosing (thrombosis) or over-dosing (bleeding).
- On average, patients are over-anticoagulated (above therapeutic INR range) 30% of the time during the first month of warfarin initiation, increasing risk of bleeding events.
- Fatal bleeding occurs in 1% of patients per year and major bleeding events in 2-7% of patients per year.
- Warfarin is currently underutilized, particularly for prevention of stroke in patients with atrial fibrillation, due to its associated risks.

Contribution of genetics to warfarin dose variability

- Common variations in two genes, CYP2C9 (*2 and *3) and VKORC1 (-1639G>A), significantly decrease warfarin maintenance dose requirements.
- CYP2C9 and VKORC1 genotype together account for 35-40% of the variability in warfarin dose requirement. Combining genotype with clinical factors accounts for 55-60% of the variability in dose, making greatly improved estimates of optimal dose possible.
- An FDA advisory committee, the Clinical Pharmacology Subcommittee, supports the use of lower doses of warfarin for patients with genetic variations in CYP2C9 or VKORC1 that lead to reduced activities.

Frequencies of gene variants detected by the Warfarin DoseAdvise™ Genetic Test

- CYP2C9 *2 and *3 variants
(20-30% of Caucasians and 5% or less of Asians and African Americans carry at least one variant).
- VKORC1 (-1639G>A) variant
(65% of Caucasians, 99% of Asians, and 20% of African Americans carry at least one copy of this variant).

Benefits of integrating pharmacogenetic testing into warfarin therapy

- Allows individualization of warfarin therapy by assisting prediction of the optimal therapeutic dose for each patient.
- May shorten the time to achieve stable therapeutic dosing, reduce the number of dose adjustments necessary, and improve the percent of time in the target INR range.
- Predicted to increase safety and efficacy of warfarin therapy.
- One study estimated that the use of CYP2C9 genotyping has the potential to avoid 85,000 serious bleeding events and 17,000 strokes annually and to significantly reduce health care spending.

Test methodology

- PCR amplification and fluorescent signal amplification by Invader assay.

Sensitivity and specificity

- Analytic: >99.9%; Clinical: 35-40% of the variability in warfarin dose is due to genetic variants in CYP2C9 and VKORC1 detected by this test.
- This test detects the common variants in CYP2C9 and VKORC1 that confer warfarin sensitivity. It does not identify patients with warfarin resistance.

CPT Codes

- 83891, 83900, 83901, 83892 x 6, 83896 x 9, 83903 x 3, 83908 x 3, 83912