Washington State Health Care Authority

FINAL Key questions and background

Pharmacogenetic testing for patients being treated with anticoagulants

Background

Anticoagulant drugs, commonly known as blood thinners, are used for patients with conditions such as atrial fibrillation, deep venous thrombosis, or orthopedic surgery to prevent stroke, pulmonary embolism, or other complications from having a blood clot.[1] Warfarin, approved for use in the U.S. in 1954, is the most commonly prescribed oral anticoagulant, although use of direct oral anticoagulants (DOACs) is increasing.[2] When prescribing anticoagulants, the risk of thrombosis from the underlying condition needs to be weighed against the risk of bleeding from anticoagulation.[3] Clinical decisions about which of these agents to use depend on the underlying indication for anticoagulation and other considerations such as the patient's creatinine clearance (a measure of renal function), other medications used, and history of serious bleeding. Achieving effective anticoagulation can require time, laboratory testing, and dose adjustments, particularly for warfarin.[4] For example, diet, comorbidities, and interactions with other medications can lead to wide variation in warfarin dose requirements.[4] Genetic variations are known to change patient response to various medications, and efforts to personalize therapy according to genetic differences have gained momentum.[1] This report will examine the clinical usefulness of genetic tests to guide initiation or dosage adjustments for oral anticoagulant drugs.

Policy context

There are a growing number of genetic tests and panels of genetic tests designed to inform decisions on the selection and dosage of oral anticoagulant medications. Potential benefits of these tests are more appropriate treatment decisions and better patient outcomes, including avoiding treatment-related side effects. This topic was selected for a health technology assessment because of low concerns for the safety of these tests, high concerns for efficacy, and medium/high concerns for cost.

This evidence review will help to inform Washington's independent Health Technology Clinical Committee as the committee determines coverage regarding selected genetic tests for patients with an indication for use of oral anticoagulant medications.

Proposed scope

Population: Adults and children initiating or changing dosage of oral anticoagulant medications

Interventions: Genetic testing to inform the selection or dosage of oral anticoagulant medications

Comparators: Usual care without genetic testing

Outcomes:

- Patient-oriented clinical outcomes (e.g., death, stroke, time in therapeutic range, overanticoagulation, bleeding, quality of life as measured by validated instruments)
- Consequences of treatment decisions (including decisions by prescribers or patients to use, not use, or continue use of specific medications) on response to treatment and adverse effects as a result of treatment
- Direct harms, such as consequences of inaccurate test results
- Cost-effectiveness and other economic outcomes

Time period for literature search: 2007 to the present

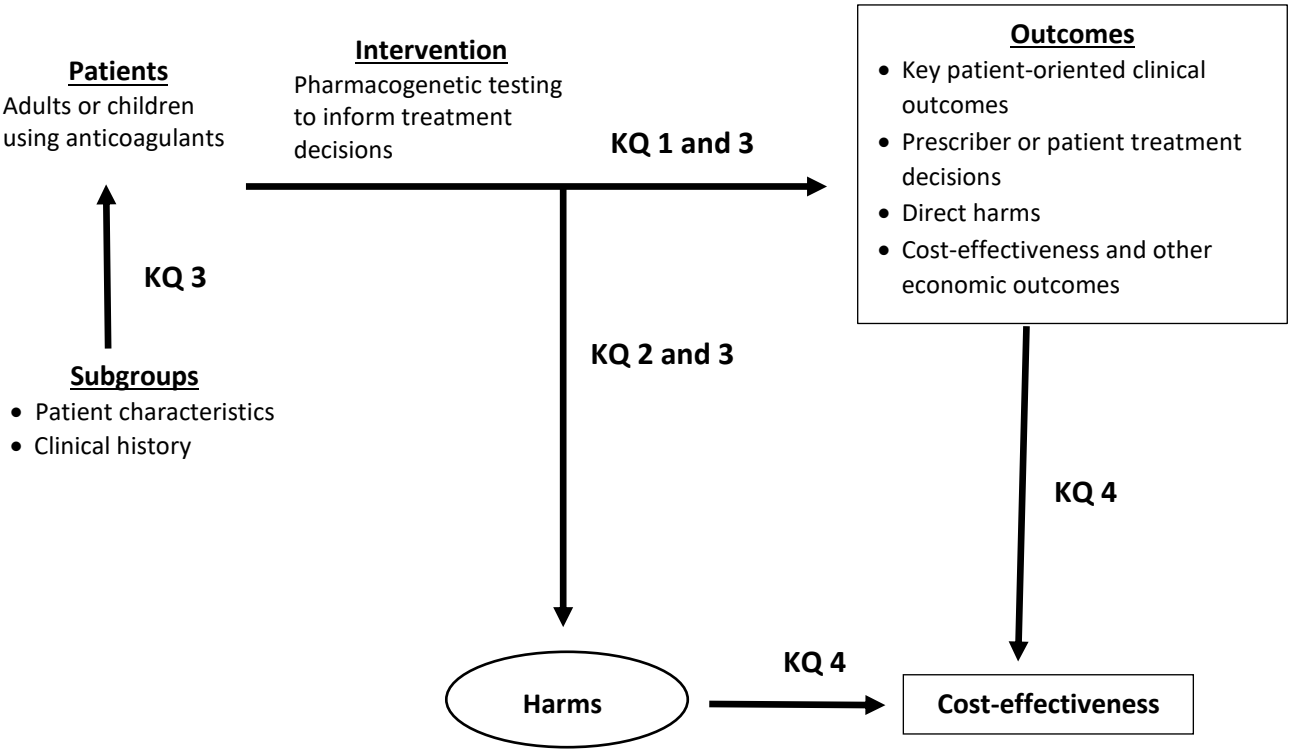
Key questions

1. Effectiveness: What is the clinical utility of genetic testing to inform treatment decisions for patients being treated with anticoagulants?
    a. Do treatment decisions guided by genetic testing result in clinically meaningful improvements in important patient outcomes (e.g., death and stroke) or reductions in adverse events (e.g., bleeding) compared with usual care without genetic testing?
    b. Does genetic testing to inform the selection or dose of medications change the drug or dosage selected by prescribers or patients compared with usual care without genetic testing?
2. Harms: What direct harms are associated with conducting genetic testing when it is used to inform the selection or dosage of oral anticoagulant medication?
3. Special populations: Compared with usual care without genetic testing, do important patient outcomes or harms after genetic testing vary by:
    a. Patient characteristics (e.g., age, sex, race/ethnicity)?
    b. Clinical history (e.g., medical comorbidities, underlying condition requiring anticoagulation, severity of illness, concurrent medication use, whether treatment decision is initial or subsequent)?
4. What are the cost-effectiveness and other economic outcomes of genetic testing used to inform the selection or dosage of oral anticoagulant medication?

Eligible studies

Randomized controlled trials (RCTs) and good-quality systematic reviews (with or without meta-analyses) of RCTs that assess listed clinical utility outcomes will be considered for Key Questions 1, 2, and 3. Methodologically robust cost-effectiveness studies and other prospective comparative economic evaluations, along with good-quality systematic reviews of these types of studies, will be considered for Key Question 4. If multiple systematic reviews and/or meta-analyses are available, then the one(s) that are most recent, comprehensive, robust, and applicable will be selected for inclusion. Studies will be required to be published in English and applicable to the U.S. setting.

Analytic framework



The analytic framework below will guide the selection, synthesis, and interpretation of available evidence.

References

1. Shi C, Yan W, Wang G, Wang F, Li Q, Lin N. Pharmacogenetics-based versus conventional dosing of warfarin: a meta-analysis of randomized controlled trials. *PloS One*. 2015;10(12):e0144511.
2. Harter K, Levine M, Henderson SO. Anticoagulation drug therapy: a review. *The Western Journal of Emergency Medicine*. 2015;16(1):11-17.

3. Michigan Anticoagulation Quality Improvement Initiative. Anticoagulation toolkit. 2017; http://anticoagulationtoolkit.org/sites/default/files/toolkit_pdfs/toolkitfull.pdf

4. Emery JD. Pharmacogenomic testing and warfarin: what evidence has the GIFT trial provided? *JAMA*. 2017;318(12):1110-1112.

Public comment and response

See Draft key questions: Comment and response document published separately.