Washington State Health Care Authority

Pharmacogenetic testing for patients being treated with oral anticoagulants

Final evidence report

April 16, 2018

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This health technology assessment report is based on research conducted by the Center for Evidence-based Policy (Center) under contract to the Washington State Health Care Authority (HCA). This report is an independent assessment of the technology question(s) described based on accepted methodological principles. The findings and conclusions contained herein are those of the authors, who are responsible for the content. These findings and conclusions do not necessarily represent the views of the Washington HCA and thus, no statement in this report shall be construed as an official position or policy of the HCA.

The information in this assessment is intended to assist health care decision makers, clinicians, patients, and policy makers in making evidence-based decisions that may improve the quality and cost-effectiveness of health care services. Information in this report is not a substitute for sound clinical judgment. Those making decisions regarding the provision of health care services should consider this report in a manner similar to any other medical reference, integrating the information with all other pertinent information to make decisions within the context of individual patient circumstances and resource availability.

About the Center for Evidence-based Policy

The Center is recognized as a national leader in evidence-based decision making and policy design. The Center understands the needs of policymakers and supports public organizations by providing reliable information to guide decisions, maximize existing resources, improve health outcomes, and reduce unnecessary costs. The Center specializes in ensuring that diverse and relevant perspectives are considered and appropriate resources are leveraged to strategically address complex policy issues with high-quality evidence and collaboration. The Center is based at Oregon Health & Science University in Portland, Oregon.

Conflict of Interest Disclosures: No authors have conflicts of interest to disclose. All authors have completed and submitted the Oregon Health & Science University form for Disclosure of Potential Conflicts of Interest, and none were reported.

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List of Abbreviations

ACC	American College of Cardiology
AFib	atrial fibrillation
AHA	American Heart Association
CI	confidence interval
CMS	Centers for Medicare & Medicaid Services
DVT	deep vein thrombosis
FDA	U.S. Food and Drug Administration
HR	hazard ratio
HTA	health technology assessment
INR	international normalized ratio
KQ	key question
NR	not reported
OR	odds ratio
RCT	randomized controlled trial
RR	risk ratio
VTE	venous thromboembolism

Executive Summary

Structured Abstract

Purpose

The purpose of this evidence report is to review the clinical utility and cost-effectiveness of pharmacogenetic testing to inform medication dosing for patients beginning treatment with oral anticoagulants.

Key Questions

The following main key questions guided this review:

1. Effectiveness: What is the clinical utility of genetic testing to inform treatment decisions for patients being treated with anticoagulants?
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 patient characteristics and clinical history?
4. What are the cost-effectiveness and other economic outcomes of genetic testing used to inform the selection or dosage of oral anticoagulant medication?

Data Sources

Center researchers conducted searches of Ovid MEDLINE, the Cochrane Database of Systematic Reviews, and the Cochrane Central Register of Controlled Trials for English-language studies published from each database's inception to January 3, 2018. Additional sources for health technology assessments (HTA) and evidence reviews were consulted and studies from reference lists were examined. Evidence sources and the AHRQ National Guideline Clearinghouse were searched for clinical practice guidelines. Center researchers searched the Centers for Medicare & Medicaid Services (CMS) website for the Medicare Coverage Database for National and Local Coverage Determinations (NCDs and LCDs) and private payers' websites for relevant coverage policies.

Study Selection

Two Center researchers screened all titles and abstracts for potential inclusion based on prespecified inclusion and exclusion criteria and performed dual full-text review for inclusion.

Data Extraction

Using standardized and piloted processes and forms, one Center researcher extracted data and a second researcher checked the extraction for accuracy. Two researchers independently assessed the risk of bias of included studies and methodological quality of clinical practice guidelines.

Data Synthesis

The search strategy yielded 1,007 unduplicated citations. A total of 18 studies met inclusion criteria: 13 randomized controlled trials (RCTs) for clinical utility and 5 economic studies. Center researchers applied the Grading of Recommendations, Assessment, Development, and Evaluation Working Group (GRADE) system to rate the overall quality of evidence on key clinical utility and economic outcomes.

Results

Three outcomes that Center researchers meta-analyzed represent patient-important outcomes: mortality, thromboembolic events, and major bleeding. In meta-analyses involving risk of death and thromboembolic events, there were no statistically significant differences between the pharmacogenetic testing group and controls. Center researchers found low quality of evidence for risk of death and moderate quality of evidence for thromboembolic events. Meta-analysis showed a 57% reduction for risk of major bleeding in the pharmacogenetic testing group compared to controls (risk ratio [RR], 0.43; 95% CI, 0.22 to 0.84; p = .01, I^2 = 0%). In subgroup meta-analysis by comparison group, the risk of major bleeding was statistically significantly lower for the those who received pharmacogenetic testing compared to a clinical algorithm to guide initial dosing (RR, 0.39; 95% CI, 0.19 to 0.81). Although the risk of major bleeding was lower for patients who received pharmacogenetic testing to guide initial dosing, compared to a fixed dose, the difference was not statistically significant (RR, 0.70; 95% CI, 0.14 to 3.53). Center researchers rated the quality of the body of evidence for major bleeding as moderate.

Two outcomes are intermediate or surrogate outcomes: the percentage of time in therapeutic range (PTTR) and overanticoagulation. The risk of overanticoagulation was 10% lower and PTTR was 3.11 percentage points higher in the pharmacogenetic testing intervention group compared to controls. However, neither estimate was statistically significantly different, and there was low quality of evidence for both outcomes. The PTTR finding could also be explained with a subgroup analysis examining the comparators used in the studies. A benefit was only observed when comparing the pharmacogenetic testing group to the fixed-dose warfarin group. No PTTR benefit was observed when comparing the pharmacogenetic testing group to the group that received clinical algorithm dosing of warfarin.

All of the identified economic studies had limitations, and the overall quality of evidence for cost-effectiveness was very low. No economic analysis considered clinical conditions other than AFib. No analysis was recent enough to be based upon a comprehensive effectiveness estimate from all of the RCTs identified in this report; the authors included 1 to 3 RCTs in populating their economic model assumptions. Three studies used a U.S. perspective, and all assumed a higher PTTR than meta-analysis found in this report. The cost of testing in U.S. perspective studies ranged from $175 to $475 in 2007 dollars. Despite these liberal assumptions, the authors of these 3 studies did not find the pharmacogenetic intervention cost-effective in 2007 U.S. dollars at a conventional threshold of $50,000, with estimates ranging from $60,725 to $171,800 per quality-adjusted life-year (QALY).

Center researchers identified 8 relevant clinical practice guidelines. Three recommend against the use of pharmacogenetic testing to initiate warfarin therapy, 2 recommend its use, and 3 have no recommendation. Neither the Medicare NCD nor the Noridian LCD provide coverage for pharmacogenetic testing except for enrollees who are participating in an RCT of warfarin treatment.

Limitations

Limitations of this systematic review and meta-analysis included differences among studies in terms of populations, underlying medical conditions, risk of outcomes, indications for treatment, comparators used, study outcome definitions and assessment, and the overall conduct of the study and system in which it was conducted. These study differences, and the clinical heterogeneity and issues of generalizability they can give rise to, should be carefully considered when interpreting the conclusions of this systematic review and meta-analysis. In addition, the small overall number of events for patient-important outcomes creates statistical instability. Most of these estimates could easily be changed by additional studies.

Conclusions

The available evidence makes balancing the benefits and harms from pharmacogenetic testing for polymorphisms to guide warfarin initiation challenging. Pharmacogenetic testing was associated with a slight, although not statistically significant, increase in the risk of mortality. A reduction in major bleeding among participants who received the pharmacogenetic test was the only clinical utility outcome that was statistically significantly different. Decreased risks were observed for thromboembolic events and overanticoagulation, but the findings were not statistically significant. There was a slight, although not statistically significant, increase in PTTR with receipt of the pharmacogenetic test, and this difference was limited to studies that used a fixed-dose comparator. It is particularly likely that additional research for the outcomes rated as having low quality of evidence could have an important effect on the observed findings.

Background

Anticoagulant drugs, commonly known as blood thinners, are used for patients with conditions such as atrial fibrillation (AFib), deep venous thrombosis (DVT), pulmonary embolism, or other complications from having a blood clot, or after surgery to prevent stroke.[1] Warfarin (Coumadin), approved for use in the U.S. by the Food and Drug Administration (FDA) 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.[4] Achieving effective anticoagulation can require time, laboratory testing, and dose adjustments, particularly for warfarin.[4]

Factors including patient diet, comorbidities, and drug interactions with other medications can lead to wide variation in warfarin dose requirements.[4] The effect of warfarin must be monitored carefully with blood testing that measures the time it takes for blood to clot using the prothrombin time test, which is reported as the International Normalized Ratio (INR). In the beginning stages, INR testing might need to occur frequently, even daily. After initial adjustment of dosing, a patient is usually tested monthly.[5,6]

Protocols for initial dosing of warfarin can call for a standard dose for most patients, or a dose based on a clinical algorithm that uses a patient's individual characteristics such as age, sex, ethnicity, weight, body surface area, comorbidities, and indication for warfarin use. Genotype testing can be included in the calculation of the initial warfarin dose to create a pharmacogenetic algorithm.

Technology Description

The most frequent genotypes included in pharmacogenetic algorithms for warfarin dosing are cytochrome P450 2C9 (*CYP2C9*), vitamin K epoxide reductase (*VKORC1*), and cytochrome P450 4F2 (*CYP4F2*). The CYP2C9 enzyme metabolizes warfarin, and polymorphisms in *CYP2C9* reduce enzymatic activity, which can lead to significantly lower doses of warfarin to achieve therapeutic levels in patients with these polymorphisms.[7] Warfarin blocks VKORC1 enzyme activity, and genetic variants in *VKORC1* result in the therapeutic dose of warfarin being reduced by approximately 25% per variant allele.[7] The CYP4F2 enzyme cleaves the phytal side chain of vitamin K, leading to inactive metabolites, and the genetic polymorphism in *CYP4F2* can increase the warfarin therapeutic dose by up to 12% per allele.[7]

Common variants in *CYP2C9, VKORC1*, and *CYP4F2* account for up to 18%, 30%, and 11%, respectively, of the variance in stable warfarin dose among populations of European ancestry.[8] Variants of these 3 genes explain less of the dose variability among patients of other ancestries because of differing allele frequencies across populations.[8] For example, *CYP2C9*2* is almost

absent in Asian populations.[8] Other *CYP2C9* alleles (e.g., *5, *6, *8, *11) occur almost exclusively in persons of African ancestry and contribute to dose variability in these populations.[8]

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 by the Washington State Health Care Authority 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 members determine coverage regarding selected genetic tests for patients with an indication for use of oral anticoagulant medications.

Methods

This evidence review is based on the final key questions published on January 26, 2018.

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 [TTR], 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 MEDLINE and Cochrane Library searches: Database inception to January 3, 2018

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?

Data Sources and Searches

Center researchers conducted a search of the peer-reviewed published literature using multiple online databases, including Ovid MEDLINE, the Cochrane Library Database of Systematic Reviews, and the Cochrane Central Register of Controlled Trials. RCTs and systematic reviews (with and without meta-analysis) and health technology assessments of RCTs that assessed clinical utility were considered for Key Questions 1, 2, and 3. Cost-effectiveness studies and other comparative economic evaluations, along with systematic reviews (with and without meta-analysis) reporting economic outcomes, were considered for Key Question 4. The Ovid MEDLINE search strategy is in Appendix A. Additional sources, including the Agency for Healthcare Research and Quality (AHRQ), the National Institute for Health and Care Excellence (NICE), and the Veterans Administration Evidence-based Synthesis Program, were searched for relevant systematic reviews, technology assessments, and clinical practice guidelines. Center researchers also screened reference lists of included RCTs and systematic reviews. In addition, Center researchers conducted searches of the AHRQ's National Guideline Clearinghouse (guidelines.gov) and websites of relevant professional organizations for clinical practice guidelines.

Center researchers conducted a search of PharmGKB, Stanford University's online resource for information about genetic variation on drug responses.[9] A general Internet search for appropriate published studies and relevant gray literature was also conducted. In addition, Center researchers searched the Centers for Medicare & Medicaid Services (CMS) website for the Medicare Coverage Database for National Coverage Determinations (NCDs) and Local Coverage Determinations (LCDs) applying to the state of Washington. The Aetna, Cigna, and Regence websites were searched for coverage policies for these private payers.

To identify relevant ongoing clinical trials, Center researchers searched the online database of clinical trials (ClinicalTrials.gov) maintained by the National Library of Medicine at the National

Institutes of Health. This search included terms related to oral anticoagulants (e.g., medication names) and pharmacogenetics.

Results

The search strategy located 1,007 unduplicated citations. After excluding 965 citations by dual assessment of title and abstract, 42 full-text articles were independently reviewed by 2 researchers; 24 of these articles did not meet predetermined inclusion criteria. A list of the excluded studies and reasons for exclusion are in Appendix I. All eligible RCTs and systematic reviews of RCTs assessed the clinical utility of pharmacogenetic testing for the dosing of warfarin.

After full-text review, 11 systematic reviews of RCTs were identified.[1,10-19] Among the studies included in these systematic reviews, 10 eligible RCTs were identified.[7,20-28] Three additional eligible RCTs were identified that were published after the most recent systematic review.[29-31] One of these more recent RCTs, published by Gage et al. in 2017, has the largest sample size (n = 1,650) of all the identified RCTs. Thus, Center researchers decided to conduct a systematic review and meta-analysis of the 13 eligible RCTs and to not include the systematic reviews as primary sources. One of the included RCTs[25] did not report any of the outcomes included in the meta-analysis. The 5 eligible economic studies focused on pharmacogenetic testing for the dosing of warfarin in the setting of AFib.[32-34]

Center researchers conducted meta-analyses for 5 outcomes. The first 3 of these are the main patient-important outcomes and the final 2 are intermediate or surrogate outcomes:

- Mortality (binary, unique event)
- Major bleeding (binary, unique event)
- Thromboembolic events (binary, unique event)
  Percentage of time in therapeutic range (PTTR) (continuous, as a percentage of follow-up time)
- INR greater than or equal to 4 (binary, unique event)

Using RevMan 5.3, Center researchers estimated pooled and subgroup mean differences and risk ratios and their 95% confidence intervals for continuous and binary outcomes, respectively, using the inverse variance statistical technique and random effects models for all outcomes. When there were sufficient numbers of studies and data, prespecified subgroup analyses included an assessment of multiple factors:

- Different comparators (i.e., clinical algorithm-guided based dosing compared to fixed dosing)
- Risk of bias (i.e., high compared to moderate compared to low)
- Sample size (i.e., greater than or equal to 400 total participants or less than 400 total participants)
- Number of genes tested in the pharmacogenetics test (i.e., 3 genes, 2 genes, or 1 gene)
- Country where the study was conducted (i.e., U.S. compared to other countries)

- Clinical indication (i.e., AFib, valve replacement, post-orthopedic surgery, or other indications)
- Race (i.e., 90% or more total participants were White, 90% or more total participants were Asian, or a combination of races)
- Follow-up period (i.e., greater than 30 days or 30 days or less)

Descriptions of each included RCT and the data abstracted from each RCT are provided in the main report and summarized in Appendix C, Tables 4 through 8. Table 9 in Appendix C displays data from included economic modeling studies. A brief summary of study characteristics is listed below in Table ES-1:

Table ES-1. Brief Summary of Study Characteristics

Citation Country	Study Duration Total # Subjects Randomized	Genotypes Tested	Indications for Anticoagulation	Treatment Dosing	Control Dosing
Anderson et al. 2007[27] U.S.	3 months 206	*CYP2C9*2/*3, VKORC1*	Orthopedic surgery, VTE, AFib	Regression equation based on authors' previous study; then doses adjusted based on INR	10 mg of warfarin on days 1 and 2; 5 mg on days 3 and 4; then doses adjusted based on the day 5 INR
Borgman et al. 2012[20] U.S.	12 weeks 34	*CYP2C9*2/*3, VKORC1*	VTE, AFib	Generally 5 mg on day 1; then doses according to PerMIT algorithm	Generally started at 5 mg per day; dose adjustments based on algorithm during first week; then doses adjusted based on INR
Burmester et al. 2011[7] U.S.	60 days 230	*CYP2C9*2/*3, VKORC1, CYP4F2*	AFib, VTE	Marshfield pharmaco-genetic model on days 1 and 2; then adjustments based on guidelines from ACC and AHA	Marshfield pharmacologic model on days 1 and 2, which allowed doses up to 10 mg; then adjustments based on guidelines from ACC and AHA
Caraco et al. 2008[24] Israel	1 month/ variable 283	*CYP2C9*2/*3*	VTE, AFib	Authors' algorithm for first 8 days; then adjustments based on ACC and AHA guidelines	Algorithm by Ageno et al.[35] for first 8 days that generally started at 5 mg; then adjustments based on guidelines from ACC and AHA

Citation Country	Study Duration Total # Subjects Randomized	Genotypes Tested	Indications for Anticoagulation	Treatment Dosing	Control Dosing
Gage et al. 2017[31] U.S.	90 days 1,650	*CYP2C9*2/*3, VKORC1, CYP4F2*	Hip or knee arthroplasty	Pharmacogenetic algorithm at WarfarinDosing.org for first 11 days	Clinical dosing algorithm at WarfarinDosing.org for first 11 days (algorithm allows 10 mg loading dose, but details not provided)
Hillman et al. 2005[23] U.S.	4 weeks 38	*CYP2C9*2/*3*	AFib, VTE, cardiac valve replacement, orthopedic surgery, other	Multivariable model by authors	5 mg on the first day; then doses adjusted based on INR
Huang et al. 2009[28] China	50 days 142	*CYP2C9*2/*3, VKORC1*	Cardiac valve replacement	Algorithm designed by authors; then doses adjusted based on INR	2.5 mg/day for the first 3 days; then doses adjusted based on INR
Jonas et al. 2013[22] U.S.	90 days 109	*CYP2C9*2/*3, VKORC1*	VTE, AFib, other	Washington University School of Medicine algorithm; then adjustments based on ACC and AHA guidelines	Washington University School of Medicine algorithm with only clinical variables (doses of 10 mg allowed, but details not provided); then adjustments based on guidelines from ACC and AHA
Kimmel et al. 2013[21] U.S.	6 months 1,015	*CYP2C9*2/*3, VKORC1*	VTE, AFib, other	Pharmacogenetic algorithm for first 5 days; then algorithm-predicted dose adjustments based on INR	Clinical algorithm for first 3 days with initial doses of about 2 to 12 mg; dose-revision algorithm for days 4 or 5; then algorithm-predicted dose adjustments based on INR
Pengo et al. 2015[30] Italy	30 days 200	*CYP2C9*2/*3, VKORC1, CYP4F2*	AFib	Pharmacogenetic algorithm by Zambon et al. for first 6 days; then PARMA software	5 mg/day for 4 days; clinical prediction model using day 5 INR for days 5 and 6; then PARMA software
Pirmohamed et al. 2013[26]	12 weeks 455	*CYP2C9*2/*3, VKORC1*	AFib, VTE	Slightly modified version of IWPC algorithm for first 3 days; algorithm	Dose based on age for first 3 days (over 75 years: 5 mg per day; 75

Citation Country	Study Duration Total # Subjects Randomized	Genotypes Tested	Indications for Anticoagulation	Treatment Dosing	Control Dosing
UK, Sweden				using day 4 INR for days 4 and 5; then doses adjusted based on INR	years and younger: 10 mg, 5 mg, 5 mg for days 1, 2, and 3, respectively); then doses adjusted based on INR
Wang et al. 2012[25] China	50 days 106	*CYP2C9*2/*3, VKORC1*	Cardiac valve replacement	Algorithm by Huang et al. for first 3 days; then dose adjustments based on INR	2.5 mg/day for first 3 days; then dose adjustments based on INR
Wen et al. 2017[29] Taiwan	90 days 320	*CYP2C9*3, VKORC1* *CYP2C9*2/*3, VKORC1*	AFib, VTE, other	Taiwan algorithm for first 3 days; then adjustments based on INR International Warfarin Pharmacogenetic Consortium algorithm for first 3 days; then dose adjustments based on INR	5 mg per day for first 3 days; then dose adjustments based on INR

Abbreviations. AFib: atrial fibrillation; VTE: venous thromboembolism; INR: international normalized ratio; ACC: American College of Cardiology; AHA: American Heart Association.

Key Question 1: Clinical Utility

Main Outcomes

Center researchers performed meta-analyses for prespecified primary outcomes (mortality, major bleeding, thromboembolic event, INR > 4, and the PTTR for anticoagulation) and conducted prespecified subgroup analyses detailed in the Methods section. The following meta-analysis results are presented for each major outcome, with relevant subgroups for each of the 5 outcomes.

In meta-analyses, 4 of the 5 outcomes presented in this section are expressed as risk ratios; 1 (PTTR) is expressed as a mean difference in the percentage of time within the defined therapeutic INR range. Forest plots are shown for each outcome below. For interpretation of forest plots with a mean difference (PTTR), results to the right of zero (no effect) displayed as a box (individual studies) or diamond shape (summary estimate) in the graph favor the pharmacogenetic intervention; results on the left favor controls. For interpretation of forest plots with risk ratios, results to the left of 1.0 (no effect) in the graph favor the pharmacogenetic intervention; results to the right favor controls.

Mortality

Seven trials[7,20-22,28,31] reported mortality as an outcome, of which 3[20,28,31] reported no deaths in either arm of the trial. None of the studies reported deaths directly related to the pharmacogenetic or comparator dosing method, but nearly all studies reported events as "all-cause" mortality or as unrelated to the intervention. Included studies were likely underpowered to detect this rare outcome, and 3 of the 7 studies that captured mortality observed zero events in both groups. In total, 9 deaths were reported among 1,786 (0.50%) participants in the intervention groups and 8 among 1,754 (0.46%) in the control groups, for a risk ratio of 1.17 (95% CI, 0.43 to 3.22) and $I^2 = 0\%$ in favor of the control group (see Figure ES-1). However, the risk ratio was not statistically significant and the confidence interval was wide. A subgroup analysis was performed, examining the possible effect of the control group using a clinical dosing algorithm or fixed-dose warfarin initiation. Neither subgroup had a statistically significant estimate, and confidence intervals were wide and overlapping. Given the low number of deaths reported, the meta-analysis was fairly unstable, and any additional mortality events occurring in either group could modify the estimate of effect. The overall anticipated absolute effect (Table ES-2) was 0.48 more deaths per 1,000 people with pharmacogenetic testing (95% CI, 4.1 more to 5.0 fewer deaths per 1,000 people). Center researchers rated the overall quality of evidence for the outcome of mortality as low.

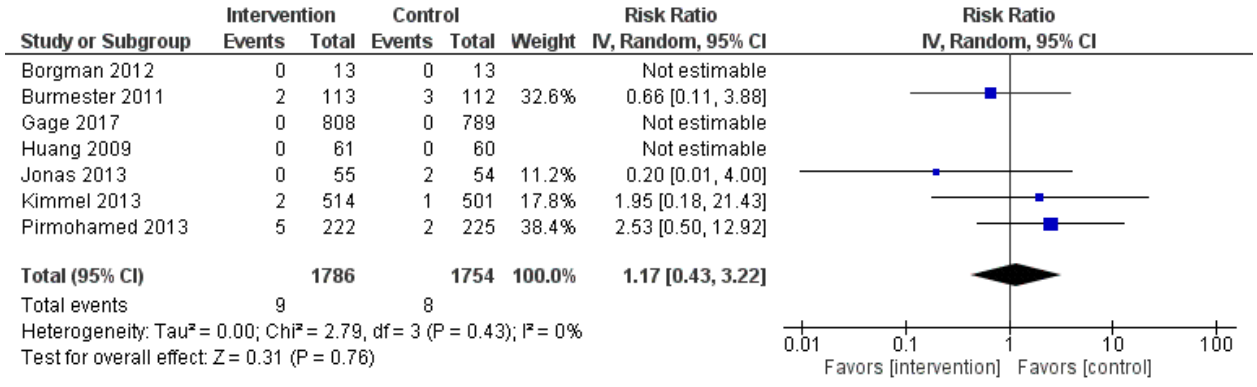


Figure ES-1. Meta-analysis of Pharmacogenetic Testing vs. Control for Mortality

Major Bleeding

Eleven RCTs included major bleeding as an outcome.[7,20-24,26,28-31] For purposes of the meta-analysis, Center researchers used the RCT authors' definition of major bleeding, which generally included bleeding that necessitated hospitalization or required interventions such as blood transfusion. Four trials did not report any major bleeding in either group.[20,26,28,30] The total number of events was small: 12 events among 2,187 participants in the intervention group (0.55%) and 29 events among 2,054 in the control group (1.4%). In the overall analysis participants enrolled in the intervention group were 57% less likely to experience major bleeding than those in the control group (RR, 0.43; 95% CI, 0.22 to 0.84; p = .01, $I^2 = 0\%$) (see Figure ES-2). The anticipated absolute effect (Table ES-2) was 8.6 fewer major bleeding events per 1,000

people with pharmacogenetic testing (95% CI, 2.7 to 14.4 fewer major bleeding episodes per 1,000 people).

Center researchers conducted a prespecified subgroup analysis by comparator, and major bleeding remained lower in the pharmacologically guided dosing group compared to the clinical algorithm group, with a 61% reduced risk of major bleeding (Figure ES-3). In subgroup meta-analysis by comparison group, the risk of major bleeding was statistically significantly lower for the patients who received pharmacogenetic testing compared to a clinical algorithm to guide initial dosing (RR, 0.39; 95% CI, 0.19 to 0.81). Although the risk of major bleeding was lower for patients who received pharmacogenetic testing to guide initial dosing, compared to a fixed dose the difference was not statistically significant (RR, 0.70; 95% CI, 0.14 to 3.53). The absolute differences in major bleeding were 11.1 (95% CI, 3.2 to 19.1) fewer major bleeding events per 1,000 people with pharmacogenetic testing in the clinical algorithm studies, and 2.1 (95% CI, -4.8 to 9.1) fewer major bleeding events per 1,000 people with pharmacogenetic testing in the fixed-dose comparator studies.

Overall, the subgroup analysis indicates that the major bleeding benefit of pharmacogenetically guided warfarin dosing seen in the main analysis cannot be explained by whether the control group was dosed according to a clinical algorithm or with a fixed-dose approach. However, the maximum allowed initial doses under clinical algorithms were higher (10 to 12 mg) among the 3 studies that contributed the most events within this subgroup.[7,21,31] In general, clinical practice guidelines recommend starting doses between 5 mg and 10 mg and being more cautious for patients with higher risks of bleeding such as the elderly, and those with impaired nutrition, liver disease, congestive heart failure, recent cardiopulmonary bypass, use of antiplatelet therapy, or other risk factors.[36,37]

The caveat remains that few events were reported overall, and that even when statistically significant, the confidence intervals were relatively wide. There is likely clinical heterogeneity among studies based on definitions of bleeding, indication for anticoagulation, length of follow up, and comorbid conditions. Center researchers rated the overall quality of evidence for this outcome as moderate.

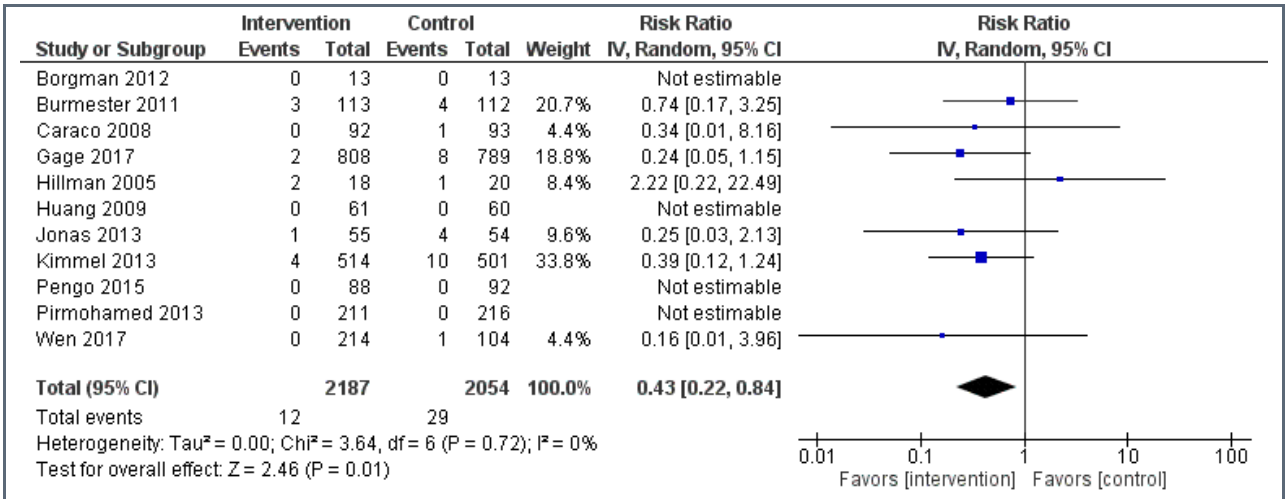


Figure ES-2. Meta-analysis of Pharmacogenetic Testing vs. Control for Major Bleeding

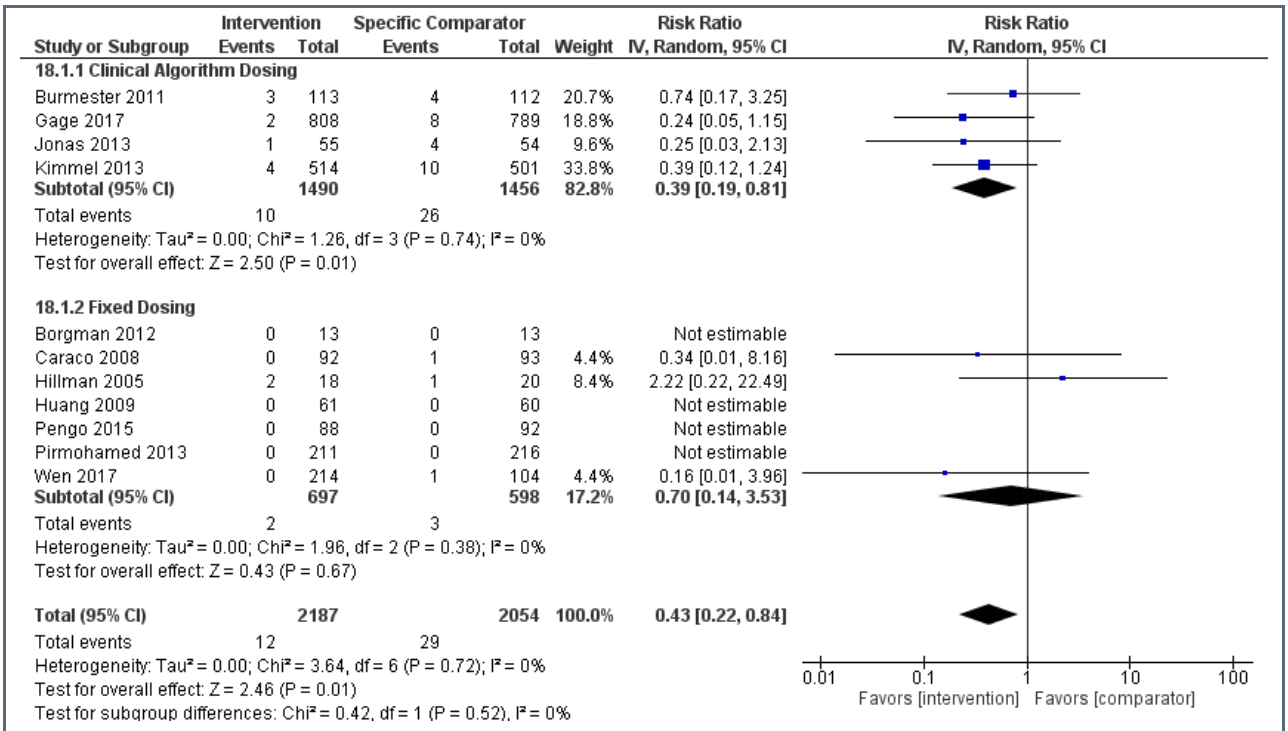


Figure ES-3. Meta-analysis of Pharmacogenetic Testing vs. Control by Comparator for Major Bleeding

Thromboembolic Events

A total of 11 trials[7,20-24,26,28-31] reported thromboembolic events (generally DVT or pulmonary embolism), although 5 of these trials[20,24,28-30] reported no events in either the intervention or control groups. The analysis was heavily weighted by the Gage et al. (2017) RCT in the meta-analysis. Gage et al. (2017) conducted a bilateral lower extremity duplex ultrasound study on all

asymptomatic patients at 1-month post-surgery. No other study screened for asymptomatic cases of thromboembolism and screening asymptomatic patients is not clinically recommended,[38] nor has it proven useful.[39,40] The Gage et al. (2017) RCT included 33 VTE events among 808 patients (4.1%) in the pharmacogenetically guided group and 38 events among 789 patients (4.8%) in the clinically guided group between days 1 and 60 after surgery (RR, 0.85; 95% CI, 0.54 to 1.34). Most of the identified VTEs were ascertained in asymptomatic patients by duplex ultrasound at 1-month post-surgery: 23 VTE events of 33 in the intervention group and 23 of 38 in the control group were asymptomatic DVTs found by ultrasound. All other trials reported only symptomatic VTE events. Thus, Gage et al. (2017) reported a relatively high proportion of events, and because of the large size of the study, the overall meta-analytic result (RR, 0.85; 95% CI, 0.56 to 1.28; p = .44, I^2 = 0%) for thromboembolic events is heavily influenced by the Gage et al. (2017) trial (see Figure ES-4). A subgroup analysis by comparator was also performed. Similar to the finding with some other outcomes, there was not a statistically significant difference in either subgroup. However, the differences between the fixed-dose and clinical algorithm comparators are likely clinically meaningful. The pharmacogenetic test performed 73% better than the fixed-dose comparator, and only 11% better than the clinical algorithm comparator. The anticipated absolute effect (Table ES-2) was 5.1 fewer thromboembolic events per 1,000 people with pharmacogenetic testing (95% CI, 3.6 more to 13.8 fewer per 1,000 people). When the analysis was restricted to symptomatic events only, by comparator, the anticipated absolute effect was 3.7 (95% CI, -4.8 to 12.2) fewer thromboembolic events per 1,000 among the clinical algorithm comparator studies and 5.0 (95% CI, -0.65 to 10.7) fewer events per 1,000 people among the fixed-dose comparator studies. Center researchers rated the overall quality of evidence for this outcome as moderate.

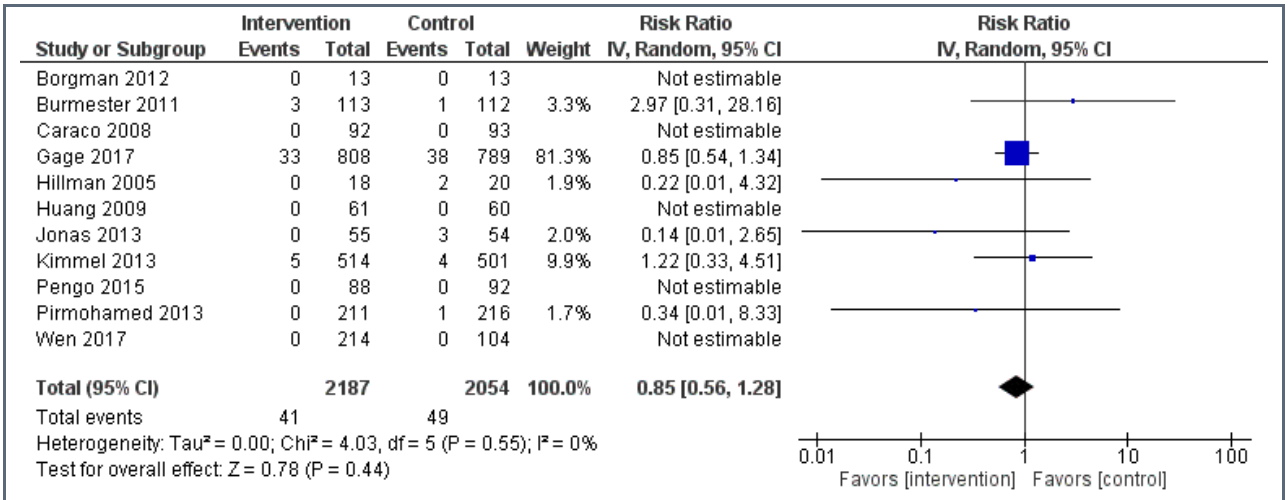


Figure ES-4. Meta-analysis of Pharmacogenetic Testing vs. Control for Thromboembolic Events

Percentage of Time in Therapeutic Range (PTTR)

All but 1[21,24-26,29,30] of the RCTs reported PTTR. Center researchers accepted any measure of PTTR as defined by the study for meta-analysis. A PTTR of greater than 60%, and preferably 75%, is associated with improved outcomes for patients, including mortality, major bleeding, stroke, and heart attack.[41] However, many factors influence PTTR, from individual patient characteristics to the frequency of INR measurement and the organization and effectiveness of anticoagulation services.[42] Center researchers were unable to ascertain a minimal clinically significant level for differences in PTTR and noted that 8[7,21-23,28-31] of 12 RCTs in this meta-analysis did not have PTTR results in either group that met the 60% threshold.

Five trials defined the therapeutic range as an INR of 2 to 3. Three trials[20,22,27] used an INR range of 1.8 to 3.2, and 1[28] used 1.8 to 3. Burmester et al. (2011) allowed an INR range of 2 to 3.5 and Hillman et al. (2005) did not report the range used. The PTTR was reported at different time intervals across studies. In general, these timeframes corresponded to the general study follow-up periods (see Table 4 and Table 7), and ranged from 14 to 90 days.

Although the main PTTR meta-analysis (Figure ES-5) found an increase of 3.1 percentage points more (95% CI, -0.28 to 6.50) time within the therapeutic range for subjects in the pharmacogenetic intervention groups, there was substantial statistical heterogeneity (I^2 = 78%). Center researchers conducted a prespecified set of subgroup analyses to explore sources of heterogeneity. A subgroup analysis by comparator (Figure ES-6) found no significant difference in the PTTR in studies using a clinical algorithm compared to a pharmacogenetically guided one (mean difference, 0.54%; 95% CI, -2.44 to 3.52; p = .72), whereas there was a not statistically significant difference favoring the pharmacogenetically guided group when it was compared to the fixed-dose comparators (mean difference, 4.97%; 95% CI, -0.50 to 10.45; p = .07). Although

the difference between these subgroups was not statistically significant, it is likely to be clinically meaningful given the tenfold difference between the point estimates. The pharmacogenetically guided algorithms used in the RCTs all included clinical factors in addition to genetic variant data. This subgroup meta-analysis determined that the PTTR advantage seen in the pharmacogenetic testing groups could largely be explained by the use of fixed-dose warfarin initiation rather than a clinical algorithm in the comparator group. When the RCT used a clinical algorithm, there was no longer any advantage to the addition of pharmacogenetic testing. In addition, the fixed-dosing subgroup of studies included all trials that Center researchers rated as having high risk of bias, which could also account for some of the observed benefit of the pharmacogenetic testing group within the overall analysis that was not seen in the subgroup analysis.

Subgroup analysis according to the number of genes tested, length of follow-up, and sample size did not demonstrate statistically significant differences. Another subgroup analysis by indication for anticoagulation found higher PTTR for pharmacogenetically guided dosing in patients who had orthopedic surgery in 1 trial[31] and valve replacement in another trial,[28] although there was no significant difference for AFib or trials with a mix of indications. A subgroup analysis by race found a similar effect for the White and Asian subgroups compared to the overall analysis, but a wider confidence interval and higher degree of statistical heterogeneity for studies with 90% or greater Asian population,[28,29] indicating that race could have some contribution to the statistical heterogeneity found in the main analysis. A subgroup analysis comparing studies conducted inside or outside of the U.S. did not find statistically significant differences, but the point estimate for studies outside the U.S. was about 5 times higher than for studies conducted in the U.S. This might in part reflect heterogeneity stemming from racial composition of the population, but might indicate some additional effect from the grouping of 3 studies[24,28,29] with high risk of bias and 2[26,30] with moderate risk of bias among studies conducted outside the U.S.

RCTs with a high risk of bias, all of which used a fixed-dosing approach in the control group, were more likely to favor the pharmacogenetically guided intervention compared to those with a low or moderate risk of bias. Although none of these subgroups were statistically significantly different, the groups with low and moderate risk of bias appear to be different, with estimates closer to the null (i.e., 0.00), compared to the high risk of bias group. These differences might also account for some of the heterogeneity in the main analysis. The overall quality of evidence for this outcome was rated as low.

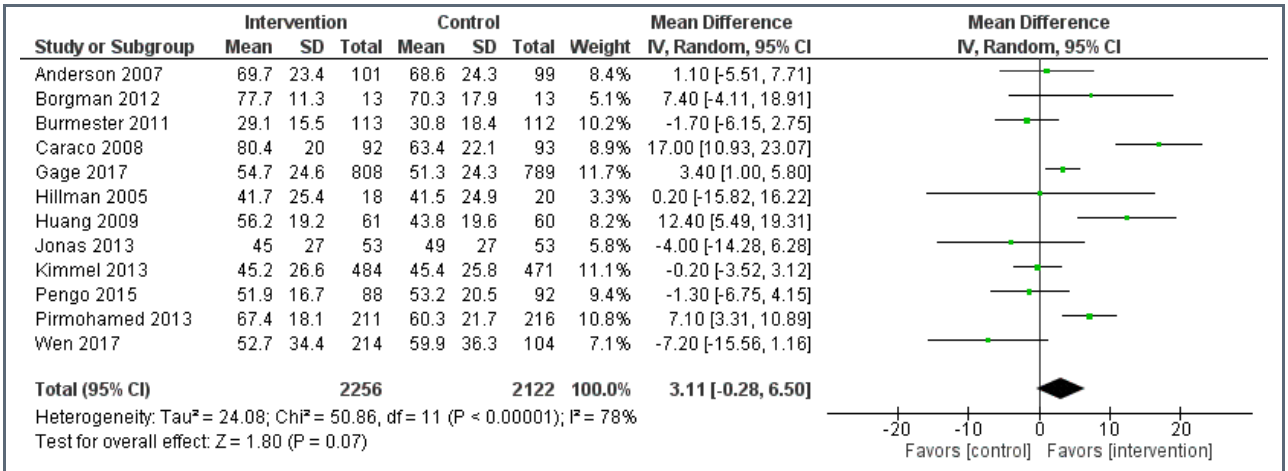


Figure ES-5. Meta-analysis of Pharmacogenetic Testing vs. Control for PTTR

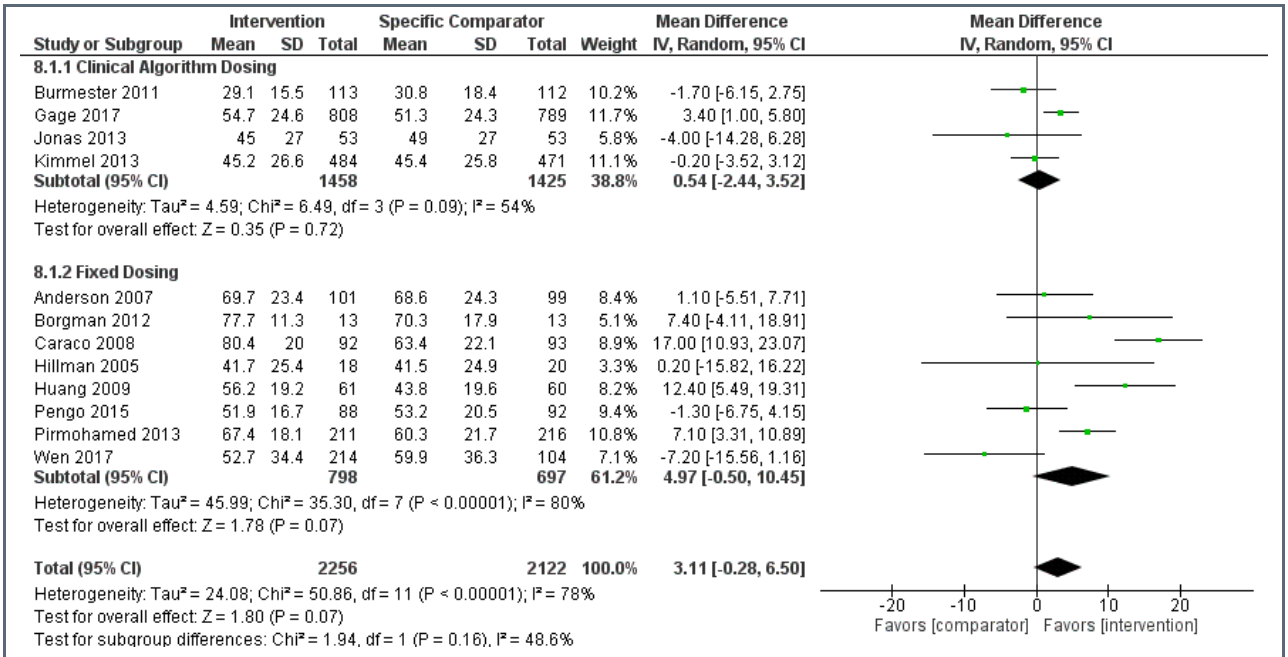


Figure ES-6. Meta-analysis of Pharmacogenetic Testing vs. Control by Comparator for PTTR

Overanticoagulation (INR ≥ 4)

Nine trials reported an INR measurement of 4 or more (INR ≥ 4) and 1 trial reported an INR of 3.5 or more (INR ≥ 3.5) and were included in the meta-analysis for this outcome. Studies did not report proportions of patients who had INRs at a level that might require therapeutic intervention, such as 7.[43] Most INR levels of 5 to 7 require only rechecking the INR or holding a dose,[43] but RCTs did not report data about bleeding events correlated with INR or about interventions required for high INR values. Trials reported INR in different time periods: 4 trials[20,21,23,31] reported whether the outcome had occurred by 1 month (ranging from 28 to 30

days) and 3 trials[22,26,29] reported occurrence by 3 months. Given that the trials had different lengths of follow-up, the timeframe for individuals to experience overanticoagulation varied. In the overall meta-analysis that included 10 trials, 340 events occurred among 2,095 participants in the pharmacogenetically guided group (16.2%) and 354 events occurred among 1,961 participants in the control group (18.1%). As shown in Figure ES-7, Center researchers observed a 9% improvement in favor of the pharmacogenetically guided intervention, but the difference was not statistically significant (RR, 0.91; 95% CI, 0.80 to 1.04; p = .16, I^2 = 0%). The anticipated absolute effect (Table ES-2) was 18.2 fewer people per 1,000 who experienced overanticoagulation with pharmacogenetic testing (95% CI, 5 more people to 41.5 fewer people per 1,000). Center researchers rated the overall quality of evidence for this outcome as low.

In the prespecified subgroup analysis by comparator, the pharmacogenetically guided intervention performed similarly to the clinically guided group (RR, 0.95; 95% CI, 0.78 to 1.15; p = .58). The estimate for the fixed-dose comparator group, although not statistically significant (RR, 0.83; 95% CI, 0.67 to 1.04; p = .11), was similar to the finding for PTTR in that the effect of pharmacogenetic testing was not seen in the clinical algorithm group, but was much closer to being present for the fixed-dose group of studies.

Overanticoagulation puts the patient at risk of bleeding.[43] There are likely to be "overshoots" during initiation of warfarin therapy, but with close monitoring, risks can be minimized.[43] A supratherapeutic INR that is less than 5.0 generally requires no action more aggressive than holding a dose or checking the INR again. Therefore, the clinical significance of the meta-analytic finding, even if it were statistically significant, is unclear.

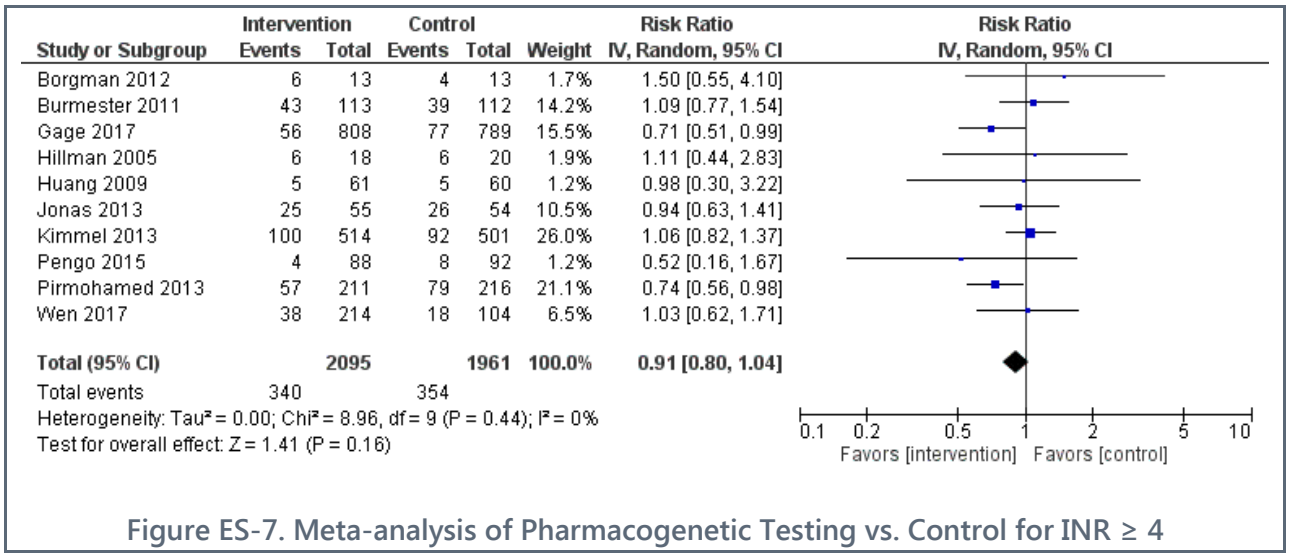


Figure ES-7. Meta-analysis of Pharmacogenetic Testing vs. Control for INR ≥ 4

Key Question 2: Harms

Harms outcomes are reflected in several items described under Key Question 1. Mortality, major bleeding, and VTE are all adverse outcomes and occurred with pharmacogenetically guided warfarin dosing and all comparators, including clinically guided and fixed-dose warfarin initiation. Although the main analyses for major bleeding, VTE events, overanticoagulation, and

PTTR all had point estimates indicating benefit for pharmacogenetic dosing none of these differences was statistically significant, with the exception of major bleeding. There was a 57% lower risk of bleeding in the pharmacogenetically guided groups overall, although the total number of events was small. Patients with an indication for oral anticoagulation to prevent VTE have increased risk of VTE if they are not sufficiently anticoagulated and, on the other hand, increased risks of bleeding if they are sufficiently anticoagulated. These are not direct harms of pharmacogenetic testing, but represent known risks of both anticoagulation and the patient's underlying indication and comorbid health factors.

Key Question 3: Special Populations

Three subgroup analyses, by clinical indication and by race, for the major bleeding, PTTR and overanticoagulation outcomes are relevant to this question. These subgroup analyses were not performed for the other outcomes because the number of studies and outcome events were more limited. The subgroup analyses by race should be considered exploratory because of the inability to conduct individual patient meta-analysis and the limited racial information included in most studies. Racial composition of individual studies is detailed in Table 6 of Appendix C. There were no statistically significant subgroup differences by race (White vs. Asian vs. racially and ethnically mixed study populations) for either PTTR or overanticoagulation. For both outcomes, the point estimates favored the pharmacogenetic intervention for White participants (PTTR: mean difference 2.3%, 95% CI, -0.46 to 5.23, I^2 = 51%, and INR ≥ 4; RR, 0.84; 95% CI, 0.68 to 1.04; I^2 = 21%). For the subgroup analysis of major bleeding, by race, the risk, although favoring the intervention, was not statistically significantly different for White or Asian subgroups. However, for the two studies with other race combinations,[21,22] the difference was statistically significant in favor of the intervention (RR, 0.35; 95% CI, 0.13 to 0.97; I^2 = 0%).

The subgroup analyses of PTTR according to the indication for anticoagulation (AFib, orthopedic surgery for hip or knee replacement, heart valve replacement, and mixed other indications) demonstrated a benefit for the pharmacogenetic intervention for both orthopedic surgery (mean difference, 3.4%; 95% CI, 1.00 to 5.80) and valve replacement (mean difference, 12.40; 95% CI, 5.49 to 19.31). However, for the orthopedic surgery subgroup, the 95% CI touched 1.0, and was very similar to the overall point estimate from the main analysis. The point estimate for the valve replacement subgroup was about 3 times higher than the main effect estimate, which might indicate a true effect in that clinical setting, but could also be due in part to differences in the comparator employed, country of study, participants' age and race, and length of follow-up. Both estimates were based on only 1 study each, Gage et al. (2017) for orthopedic surgery (rated as having a low risk of bias) and Huang et al. (2009) for valve replacement (rated as having a high risk of bias). In the subgroup analyses of overanticoagulation, a difference in favor of the pharmacogenetic intervention was noted for the orthopedic surgery subgroup, but for no other subgroups (RR, 0.71; 95% CI, 0.51 to 0.99); only Gage et al. (2017) contributed data to this subgroup. Because of reporting of race by the various RCTs, a subgroup meta-analysis of any outcome for Black patients could not be performed. However, Gage et al. (2017) did report the PTTR for Black patients compared to all other races enrolled in the RCT and found a statistically

significant effect only for the group of patients of other races (91% of the study participants were White and 6.4% were Black). For participants of other races, the mean difference for PTTR was 3.7% (95% CI, 1.2 to 6.1, p = .003), and for Black participants there was no difference from the pharmacogenetic intervention (mean difference 0.2%, 95% CI, -8.9 to 9.4, p = .96). This finding might reflect the lack of prevalence of CYP2C9 alleles *2 and *3 in African American populations. The Kimmel et al. (2013) study, conducted among patients largely with indications of AFib and VTE, reported that clinically guided dosing resulted in improved PTTR among Black patients compared to the pharmacogenetic intervention.

Key Question 4: Cost-Effectiveness and Other Economic Outcomes

Five economic modeling studies published between 2009 and 2017 were identified.[32-34,44,45] Center researchers rated 2 studies[34,45] as having a high risk of bias and 3[32,33,44] a moderate risk of bias. The economic modeling studies were generally older than larger and more recent RCTs. Each incorporated effectiveness estimates based on 1 to 3 older RCTs. When one of the modeling studies stated specific assumptions about incorporating PTTR, the estimate was generally higher and more in favor of pharmacogenetically guiding dosing than in the meta-analysis in this report, which found a mean difference of 3.11 percentage points (95% CI, -0.28 to 6.50). All 5 studies assumed a hypothetical population of patients initiating warfarin therapy for AFib and did not consider other clinical indications for anticoagulation.[32-34,44,45] Three studies[33,34,45] assumed a U.S. perspective (either societal or third-party payer), 1[32] assumed a UK health service perspective, and 1[44] was conducted with estimates for the UK and Swedish health system perspectives. The cost of testing among U.S. perspective studies ranged from $175 to $475 in 2007 U.S. dollars. All 5 studies reported costs per quality-adjusted life-year (QALY). Cost/QALY ranged from $60,725 to $171,800 in 2007 U.S. dollars. More recent estimates applicable to the U.S. setting were not found. Cost/QALY pertaining to the UK NHS ranged from £6,702 (2014 £) to £13,266 (2011 £). Center researchers rated the overall quality of evidence from these economic modeling studies as very low.

Summary

Thirteen RCTs and 5 economic modeling studies contributed data to this summary of the clinical and economic impact of pharmacogenetic testing compared to other dosing strategies for the initiation of warfarin anticoagulation. Table ES-2 presents a summary of the quantity of data, quality of evidence, and relative and anticipated absolute effects of pharmacogenetic dosing initiation of warfarin compared to alternative dosing methods.

All studies had some limitations, and the overall quality of evidence rating was low for 3 clinical outcomes (i.e., mortality, PTTR, mortality, and INR ≥ 4) and moderate for 2 other (i.e., major bleeding and thromboembolic events). The 2 outcomes (PTTR and overanticoagulation) that were reported most robustly across studies are intermediate outcomes. The outcome of thromboembolic events showed a small, not statistically significant difference in favor of pharmacogenetic testing. Conversely, overall mortality showed a small, not statistically significant difference in favor of other dosing initiation strategies. Major bleeding was the only

clinical outcome with a statistically significant difference, although the absolute differences are small, and several factors diminish our confidence in both the internal and external validity of this finding.

There is possible value for pharmacogenetic testing among certain subgroups, including patients undergoing scheduled hip or knee replacement or heart valve replacement. Particular racial subgroups might derive more or less benefit from testing based on the prevalence of particular genetic variants in that racial subgroup. It does not appear that currently there is demonstrated benefit for Black patients.

These conclusions should be evaluated in light of several limitations. RCTs were likely not powered to detect patient-important outcomes, such as mortality, and there were few events for mortality, major bleeding, and thromboembolism, which contributed to statistical imprecision. PTTR and overanticoagulation were reported more robustly and given the continuous nature of PTTR, more likely to be adequately powered. Although these outcomes can be validly measured, they are relatively poor surrogates for patient-important outcomes. Although there was a statistically significant difference of 3.11% in the mean PTTR favoring pharmacogenetic testing, this finding is of questionable clinical significance and highly influenced by study comparator, When a clinical algorithm was used, there was essentially no difference compared to use of a pharmacogenetic algorithm. A similar trend was seen with the outcome of overanticoagulation, although the effect was not as pronounced. Other limitations include differences in outcome definitions across studies, the follow-up period for each outcome, clinical indications, and differences among study population. Studies were also conducted in a variety of health systems, both domestic and international, which further contributes to clinical heterogeneity and limits generalizability to the U.S. setting: some outcomes such as PTTR had markedly different results between U.S.- and non-U.S.-based studies. These limitations contribute to both lower quality of evidence ratings and the ability to widely generalize findings.

Cost-effectiveness analyses were also limited by a lack of recent RCT data to inform model parameters, and more basic issues with adherence to best practices in cost-effectiveness study methodology. Because of their publication dates, the 3 modeling studies that were U.S. based in 2007 dollars could not have incorporated the growing body of literature about pharmacogenetic testing for warfarin therapy initiation. Costs of genetic tests might be quite different than the estimates incorporated into the models because costs of genetic tests generally have tended to decrease over time.[46] None of the 3 U.S.-based studies found pharmacogenetic testing to be cost-effective at a threshold of $50,000, and 2 found pharmacogenetic testing to not be cost-effective at a threshold of $100,000. The overall quality of economic study evidence was rated as very low.

Table ES-2. GRADE Summary of Evidence

Outcome	Number of Participants Studies	Quality of Evidence	Estimated Effect Size (95% CI)	Anticipated Absolute Effects	
				Risk with and without Pharmacogenetic Testing and 95% CI (per 1,000 people)	Risk Difference and 95% CI (per 1,000 people)
Clinical utility—Mortality	n = 3,540 k = 7	Low ●●○○	RR, 1.17 (95% CI, 0.43 to 3.22)	5.0 (2.5 to 9.7) 4.6 (2.1 to 9.1)	0.48 (-4.1 to 5.0) fewer deaths without pharmacogenetic testing
Clinical utility—Major Bleeding	n = 4,241 k = 11	Moderate ●●●○	RR, 0.43 (95% CI, 0.22 to 0.84)	5.5 (3.0 to 9.7) 14.1 (9.8 to 20.3)	8.6 (2.7 to 14.6) fewer episodes of major bleeding with pharmacogenetic testing
Clinical utility—Thromboembolic Events	n = 4,241 k = 11	Moderate ●●●○	RR, 0.85 (95% CI, 0.56 to 1.28)	18.8 (13.8 to 25.4) 23.9 (18.0 to 31.5)	5.1 (-3.6 to 13.8) fewer thromboembolic events with pharmacogenetic testing
Clinical utility—Time in Therapeutic Range	n = 4,378 k = 12 <u>Subgroups</u> Clinical dosing algorithm comparator n = 2,883 k = 4 Fixed-dose comparator n = 1,495 k = 8	Low ●●○○	Mean difference (MD), 3.11 (95% CI, -0.28 to 6.50) <u>Subgroups</u> Clinical dosing algorithm comparator MD, 0.54 (95% CI, -2.44 to 3.52) Fixed-dose comparator MD, 4.97 (95% CI, -0.50 to 6.50)	Not applicable	Not applicable

Outcome	Number of Participants Studies	Quality of Evidence	Estimated Effect Size (95% CI)	Anticipated Absolute Effects	
				Risk with and without Pharmacogenetic Testing and 95% CI (per 1,000 people)	Risk Difference and 95% CI (per 1,000 people)
Clinical utility—INR > 4	n = 3,056 k = 10	Low ●●○○	RR, 0.90 (95% CI, 0.79 to 1.03)	162.3 (147.1 to 178.7) 180.5 (164.1 to 198.2)	18.2 (-5.0 to 41.5) people per 1,000 had lower risk of over-anticoagulation with pharmacogenetic testing

Clinical Practice Guidelines

Center researchers identified 8 clinical practice guidelines that have been published since 2012. Three of the guidelines include recommendations against the use of pharmacogenetic testing for anticoagulant therapy. Three guidelines did not contain any recommendation about pharmacogenetic tests.[47-49] The American College of Chest Physicians 2012 guideline *Evidence-Based Management of Anticoagulant Therapy*, rated as having good methodological quality, includes a strong recommendation against the routine use of pharmacogenetic testing for use of warfarin.[36] The 2013 guidelines on antithrombotic therapy indications and management from the Scottish Intercollegiate Guidelines Network (SIGN), also rated as having good methodological quality, include a Grade A recommendation against pharmacogenetic testing before the initiation of therapy.[37] The Australasian Society of Thrombosis and Haemostasis's 2013 update guideline, rated as having poor methodological quality, provides a strong recommendation that pharmacogenetic testing to guide warfarin dosing is not necessary.[50]

Two guidelines include recommendations for the use of pharmacogenetic testing for warfarin dosing. The Clinical Pharmacogenetics Implementation Consortium (CPIC) 2017 update guideline, rated as having poor methodological quality, recommends that warfarin maintenance dosage for adults be based on genetic information.[8] These guidelines recommend that pharmacogenetically guided dosing use a validated published algorithm (e.g., algorithms by IWPC,[51] Gage et al.,[52] EU-PACT,[26] and Lenzini et al.[53]).

The Canadian Pharmacogenomics Network for Drug Safety published a guideline on genetic testing of *CYP2C9* and *VKORC1* for warfarin therapy in 2015.[54] This guideline, also rated as having poor methodological quality, has a moderate-strength recommendation that testing of all warfarin-naive patients for *VKORC1* (21639G.A), *CYP2C9*2*, and *CYP2C9*3* should be considered before initiation of therapy and within the first 2 weeks of therapy.[54] In addition, such pharmacogenetic testing should be considered for all patients who are at increased risk of

bleeding complications, who consistently show out-of-range INRs, or who experience adverse events while receiving warfarin.[54]

Of the 8 identified guidelines, 3 of them[36,37,50] include recommendations on the initial dose of warfarin when not using pharmacogenetic testing. The American College of Chest Physicians guideline *Evidence-Based Management of Anticoagulant Therapy* suggests initiating warfarin at 10 mg daily for the first 2 days for relatively healthy outpatients.[36] Another guideline by the American College of Chest Physicians, *Oral Anticoagulant Therapy*, discusses flexibility in determining the starting dose of warfarin.[38] These guidelines suggest that initial doses between 5 and 10 mg are effective, with appropriate dosing varying by inpatient or outpatient status, age, concomitant treatments, and comorbidities.[38]

The SIGN guidelines state that the initial treatment dose for acute thromboembolism is generally 10 mg warfarin, but recommend varying the initial dose based on age, body weight, comorbidities, and other factors.[37] The Australasian Society of Thrombosis and Haemostasis guidelines recommend avoiding high loading doses of warfarin and starting at 5 mg daily or even lower in elderly patients.[50]

Selected Payer Coverage Determinations

Medicare

The 1 Medicare NCD identified does not provide coverage for pharmacogenetic testing, unless the beneficiary is enrolled in an RCT of anticoagulation therapy with warfarin.[55] The beneficiaries enrolled in such a study must have not been previously tested for *CYP2C9* or *VKORC1* alleles and must have received fewer than 5 days of warfarin in the anticoagulation regimen for which the testing is ordered.[55] This NCD includes a statement that it has been or is currently being reviewed under the NCD process.[55] Center researchers identified 1 Medicare LCD by Noridian that applies to Washington.[56] This LCD includes the same coverage determination as the 1 identified NCD.[55]

Private Payers

The Aetna policy on pharmacogenetic and pharmacodynamic testing considers genotyping for *CYP2C9* or *VKORC1* polymorphisms to inform warfarin dosing to be experimental and investigational.[57] The Regence policy on *CYP450* genotyping states that *CYP2C9* and *VKORC1* genotyping for the purpose of warfarin dose management is considered investigational.[58] The Cigna policy on pharmacogenetic testing does not cover genotyping for *CYP2C9* or *VKORC1*.[59]

Conclusions

The goal of anticoagulant therapy is to prevent thromboembolism while minimizing the risk of bleeding.[43] Warfarin management is complex because of its narrow therapeutic range and the large number of variables that can influence anticoagulation.[43] Among these variables are age, height, weight, comorbidities, diet, drug interactions, and genetic variation.[43] This systematic review and meta-analysis was conducted to inform policy decisions in the state of Washington

regarding whether pharmacogenetic testing for the initiation of warfarin therapy has clinical utility and cost-effectiveness compared to other management strategies.

Three meta-analytic outcomes represent end outcomes of importance to patients: mortality, thromboembolic events, and major bleeding. Meta-analyses involving morality and thromboembolic events were not statistically significantly different, either in main analyses or in prespecified subgroup analyses. The overall quality of evidence for mortality was low and moderate for thromboembolic events. Major bleeding was 61% less likely with the pharmacogenetic intervention in studies that used a clinical algorithm comparator. However, no statistically significant difference was observed among studies using a fixed-dose comparator. The quality of evidence was moderate for this finding.

Although major bleeding was the 1 outcome analyzed that favored pharmacogenetic testing, there are caveats to this finding. Among 11 RCTs, there were a total of 12 major bleeding events for 2,187 patients in the pharmacogenetic groups and 29 events among 2,054 in the comparator groups. Six RCTs had either zero or 1 major bleeding event in either study group. The addition of these 6 RCTs to the meta-analysis is recommended to improve the overall precision of results, and the absolute risk differences do take this into consideration. However, having no or few events in several RCTs included for this analysis also creates a situation in which outlier studies can have more influence, particularly with a small total number of events. These studies all had slightly different definitions of major bleeding and different lengths of follow-up during which the outcome could be detected. Studies that were influential in the meta-analyses allowed relatively high doses of warfarin under their clinical algorithms, although bleeding outcomes by initiation doses, underlying risk factors, or INR at the time of bleeding were not reported. These issues point to a degree of clinical heterogeneity, which makes application of this finding to practice uncertain even with statistical significance.

The two additional meta-analytic outcomes are intermediate or surrogate outcomes: PTTR and overanticoagulation. These 2 outcomes were unfortunately more robustly reported across RCTs than were the patient-important outcomes. Neither of these outcomes demonstrated a statistically significant difference with pharmacogenetic testing. Center researchers had low confidence in both findings based on the quality of evidence.

There were 5[32-34,44,45] modeling studies to contribute to evaluating the cost-effectiveness of pharmacogenetic testing for warfarin therapy in the setting of AFib. All of these studies had limitations, and the overall quality of evidence was very low. Only 3 of the studies were conducted using a U.S. perspective. Most assumed a higher PTTR than was found in the meta-analysis, and had cost per QALY estimates ranging from $60,725 to $171,800 in 2007 U.S. dollars. Only 1 of these study estimates demonstrated cost-effectiveness at a conventional threshold of $50,000 and none found cost-effectiveness at a threshold of $100,000.

Center researchers identified 8 relevant clinical practice guidelines.[8,36,37,47-50,54] Of these, 3 guidelines, including the American College of Chest Physicians 2012 guideline *Evidence-Based*

Management of Anticoagulant Therapy,[36] recommend against the use of pharmacogenetic testing to initiate warfarin therapy, 2 guidelines (both developed by societies that promote genomics) recommend its use,[8,54] and 3 have no recommendation.[47-49] Neither the Medicare NCD nor the Noridian LCD provide coverage for pharmacogenetic testing except for enrollees participating in RCTs of warfarin treatment, and no relevant private payers cover the testing. In summary, the evidence on pharmacogenetic testing for warfarin therapy is limited, with only some evidence that it might decrease episodes of major bleeding. Neither good-quality practice guidelines nor payer coverage policies support its use.

Center researchers did not identify studies involving oral anticoagulants other than warfarin that were eligible for inclusion. The trials registry site www.ClinicalTrials.gov lists ongoing studies that involve pharmacogenetic testing and direct-acting oral anticoagulants (see Appendix G).

Technical Report

Background

Anticoagulant drugs, commonly known as blood thinners, are used for patients with conditions such as atrial fibrillation (AFib), deep venous thrombosis (DVT), pulmonary embolism, or other complications from having a blood clot, or after surgery to prevent stroke.[1] Warfarin (Coumadin), approved for use in the U.S. by the Food and Drug Administration (FDA) 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] Excessive bleeding from using anticoagulants can occur in any area of the body, and the most serious bleeding is usually gastrointestinal or intracerebral.[5] Warfarin use is the most common cause of medication-related emergency department visits in the U.S.[60]

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.[4] Achieving effective anticoagulation can require time, laboratory testing, and dose adjustments, particularly for warfarin.[4] The newer DOACs do not require such close monitoring and have more predictable dosing profiles, fewer interactions with other drugs, and more rapid onset and offset of action compared to warfarin.[61] DOACs include factor II inhibitors (e.g., dabigatran) and factor Xa inhibitors (e.g., apixaban, betrixaban, edoxaban, and rivaroxaban).[61] Potential limitations of DOACs include class-specific or drug-specific cautions and contraindications, reduced adherence with lack of regular monitoring, and higher costs than warfarin.[61]

The formation of a clot in the body is a complex process that involves multiple substances called clotting factors. Warfarin decreases the body's ability to form blood clots by blocking the formation of vitamin K-dependent clotting factors.[5] Individual patient characteristics can affect warfarin's anticoagulation effect on the body, including diet, comorbidities, and interactions with other medications, which can lead to wide variation in warfarin dose requirements.[4] Thus, the effect of warfarin must be monitored carefully with blood testing that measures the time it takes for blood to clot using the prothrombin time test, which is reported as the International Normalized Ratio (INR). In the beginning stages, INR testing might need to occur frequently, even daily. After initial adjustment of dosing, a patient is usually tested every 2 to 4 weeks, and the daily dose of warfarin can be adjusted to keep the INR within the target range, which varies by clinical condition, but is typically between 2.0 and 3.0.[5,6]

Protocols for initial dosing of warfarin can call for a standard dose for most patients, or a dose based on a clinical algorithm that uses a patient's individual characteristics. The use of different initial warfarin dose strategies is somewhat controversial and varies in different regions of the world based on experience and local standards.[8] The clinical algorithms can include a patient's age, sex, ethnicity, weight, body surface area, comorbidities, and indication for warfarin use.

Genotype testing can be included in the calculation of initial warfarin dose to create a pharmacogenetic algorithm.

Technology Description

The most frequent genotypes included in pharmacogenetic algorithms for warfarin dosing are cytochrome P450 2C9 (*CYP2C9*), vitamin K epoxide reductase (*VKORC1*), and cytochrome P450 4F2 (*CYP4F2*). The CYP2C9 enzyme metabolizes warfarin, and polymorphisms in *CYP2C9* reduce enzymatic activity, which can lead to significantly lower doses of warfarin to achieve therapeutic levels in patients with these polymorphisms.[7] Warfarin blocks VKORC1 enzyme activity, which catalyzes the reduction of vitamin K_1 and its epoxide.[7] The reduced form of these compounds serves as a cofactor for the gamma glutamyl carboxylase that generates the active form of clotting factors II, V, VII, and IX.[7] Genetic variants in *VKORC1* result in the therapeutic dose of warfarin being reduced by approximately 25% per variant allele.[7] The CYP4F2 enzyme cleaves the phytal side chain of vitamin K, leading to inactive metabolites, and the genetic polymorphism in *CYP4F2* can increase the warfarin therapeutic dose by up to 12% per allele.[7]

Genetic variations may also be associated with risk of bleeding. A systematic review by Yang et al. (2013) assessed the associations of genotypes in *CYP2C9* and *VKORC1* on hemorrhagic complications among patients being treated with warfarin.[62] Compared to *CYP2C9* wild genotype (*CYP2C9*1*), both *CYP2C9*2* and *CYP2C9*3* were associated with significantly higher risk of hemorrhagic complications.[62] After stratification by *CYP2C9* allele status, significantly higher risk for hemorrhagic complications was found only in carriers of at least 1 copy of *CYP2C9*3* (*1/*3 HR, 2.05; 95% CI, 1.36 to 3.10; $p < .001$; *3/*3 HR, 4.87; 95% CI, 1.38 to 17.14; $p = .01$).[62] No significant association was found between *VKORC1* genotypes and hemorrhagic complications.[62] *VKORC1* genotypes were associated with risk of overanticoagulation within 30 days, but not for overanticoagulation after 30 days.[62]

The systematic review by Chen et al. (2016) assessed the association between *CYP4F2* polymorphism and the risk of hemorrhagic complications in warfarin-treated patients.[63] Compared with wild-type homozygotes (*CYP4F2*1*1*), patients with the *CYP4F2*3* variant had a reduced rate of total bleeding events, although the difference was not significant (OR, 0.86; 95% CI, 0.71 to 1.05; $p = .15$).[63] When the authors conducted a sensitivity analysis by excluding the lowest-quality study from the meta-analysis, the risk of bleeding was significantly different between patients with *CYP4F2*3* compared to *CYP4F2*1*1* (OR, 0.80; 95% CI, 0.64 to 0.99; $p = .04$).[63]

Common variants in *CYP2C9, VKORC1*, and *CYP4F2* account for up to 18%, 30%, and 11%, respectively, of the variance in stable warfarin dose among populations of European ancestry.[8] Variants of these 3 genes explain less of the dose variability among patients of other ancestries because of differing allele frequencies across populations.[8] For example, *CYP2C9*2* is almost absent in Asian populations.[8] Other *CYP2C9* alleles (e.g., *5, *6, *8, *11) occur almost exclusively in persons of African ancestry and contribute to dose variability for patients with African ancestry.[8]

FDA Medication Guide

The FDA Medication Guide for warfarin includes a warning that use of warfarin can cause major or fatal bleeding.[64] The FDA Medication Guide states that the dosage and administration of warfarin must be individualized for each patient, and regular monitoring of INR is needed in all treated patients.[64] The appropriate initial dosing of warfarin varies widely for different patients; known factors that influence warfarin dose variability include age, race, body weight, sex, concomitant medications, comorbidities, and *CYP2C9* and *VKORC1* genotypes.[64]

The FDA Medication Guide provides dosing recommendations with genotype testing, as shown in the following table, which displays 3 ranges of expected maintenance warfarin doses for patient subgroups with different combinations of *CYP2C9* and *CYP2C9* gene variants. The FDA Medication Guide states, "If the patient's CYP2C9 and/or *CYP2C9* genotype are known, consider these ranges in choosing the initial dose. Patients with CYP2C9 *1/*3, *2/*2, *2/*3, and *3/*3 may require more prolonged time (2 to 4 weeks) to achieve maximum INR effect for a given dosage regimen than patients without these CYP variants."[64(p. 6)]

Three Ranges of Expected Maintenance Warfarin Daily Doses Based on CYP2C9 and VKORC1 Genotypes

VKORC1	CYP2C9					
	*1/*1	*1/*2	*1/*3	*2/*2	*2/*3	*3/*3
GG	5-7 mg	5-7 mg	3-4 mg	3-4 mg	3-4 mg	0.5-2 mg
AG	5-7 mg	3-4 mg	3-4 mg	3-4 mg	0.5-2 mg	0.5-2 mg
AA	3-4 mg	3-4 mg	0.5-2 mg	0.5-2 mg	0.5-2 mg	0.5-2 mg

Note. Ranges are derived from multiple published clinical studies. VKORC1 –1639G>A (rs9923231) variant is used in this table. Other co-inherited VKORC1 variants may also be important determinants of warfarin dose.[64(p. 6)]Source. Table adapted from FDA.[64(p. 6)]

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 by the Washington State Health Care Authority 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 members determine coverage regarding selected genetic tests for patients with an indication for use of oral anticoagulant medications.

Washington State Utilization and Cost Data

This section, provided by Washington State Health Care Authority (HCA) staff, describes claims data analyzed by the HCA to understand the current use of pharmacogenetic testing for oral anticoagulants among patients served by Washington state agencies.

Populations

The ***Pharmacogenetic testing for patients being treated with oral anticoagulants*** analysis includes member utilization and cost data from the following agencies: PEBB/UMP (Public Employees Benefit Board Uniform Medical Plan); PEBB Medicare; and the HCA Medicaid (Fee-for-Service) and the MCO Medicaid (Managed Care) programs. The Department of Labor and Industries (LNI) Workers' Compensation Plan had no claims that matched the parameters of this study.

The analysis period was three calendar years, 2015 to 2017. Primary study inclusion criteria included having experienced at least one of the CPT/HCPCS codes from Table A and a diagnosis related to heart disease or hypertension.

HCA Data Analysis Methods

Anticoagulant testing counts were based on an individual experiencing a paid, provider-patient face-to-face meeting, on a specific date, including at least one of the CPT codes from Table A and having a cardiac/hypertension condition.

Table A
Procedure (CPT/HCPCS) descriptions

CPT/ HCPCS	Description
81227	CYP2C9 (cytochrome P450, family 2, subfamily C, polypeptide 9) (e.g., drug metabolism), gene analysis, common variants (e.g., *2, *3, *5, *6)
81355	VKORC1 (vitamin K epoxide reductase complex, subunit 1) (e.g., warfarin metabolism), gene analysis, common variant(s) (e.g., -1639G>A, c.173+1000C>T)

Table B
Definitions for utilization and cost tables

Allowed dollars by total treatments with diagnosis - Annual paid dollars for all tests

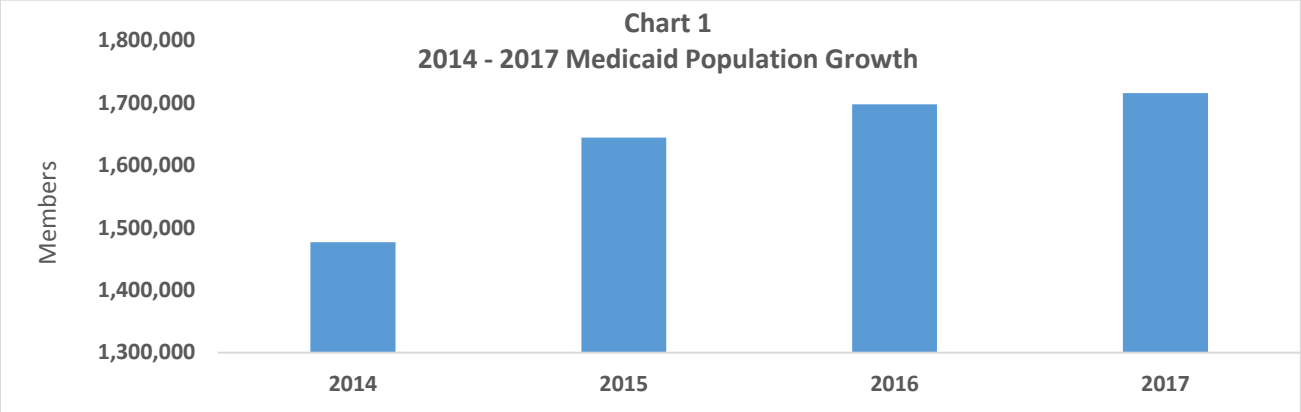
Average allowed dollars/test dollars - Total paid dollars for one service on a specific date.

Unique patients - Unduplicated patient by year, reported by agency

Total treatments with diagnosis and allowed dollars - Treatment defined as a single patient-provider face-to-face on a specific date and includes a hypertension related diagnosis on the claim.

Demographics

The following graphs depict the fluctuations in the study populations, PEBB and Medicaid (HCA and Managed Care). Each agency population is analyzed over a four-year period.



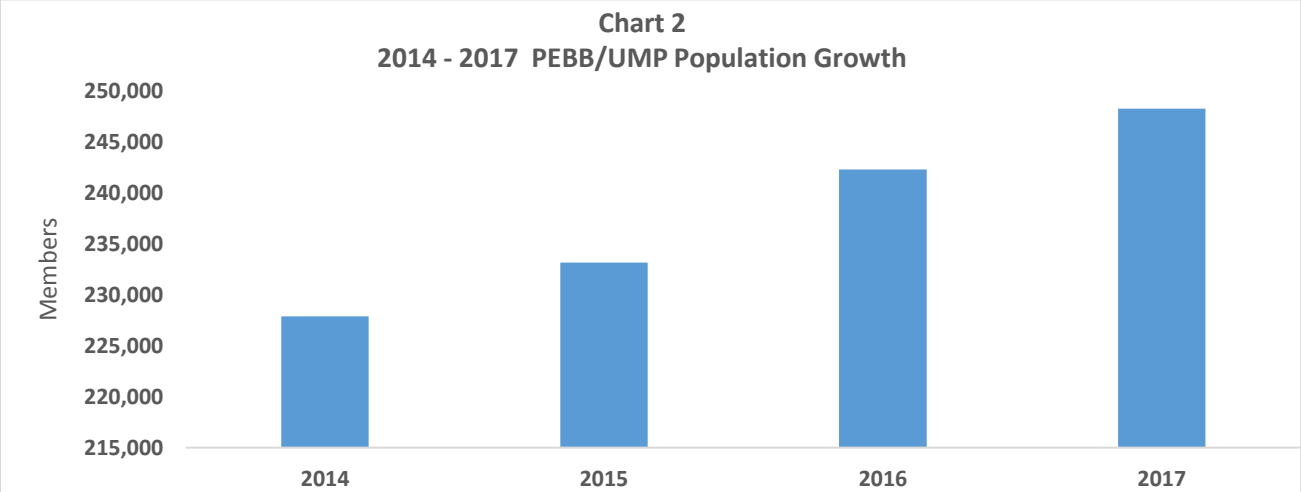


Chart 3

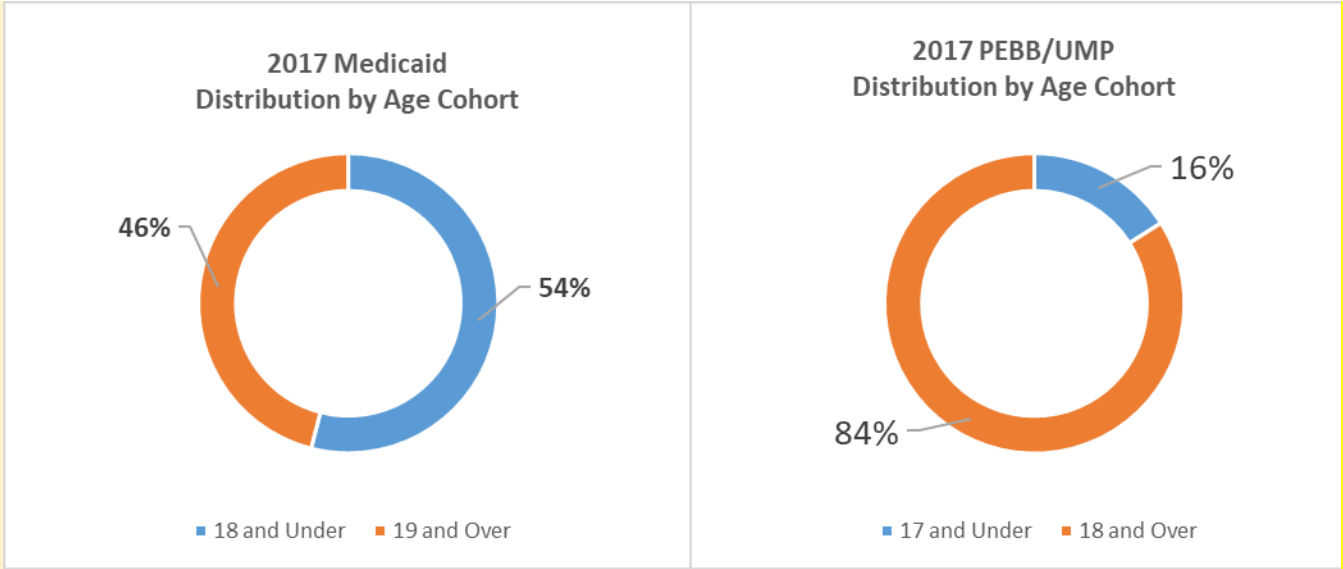


Table C
2015–2017 Utilization Allowed Dollars: Pharmacogenetic testing for patients being treated with anticoagulants
Medicaid MCO and Medicaid HCA (Fee-for-service), PEBB/UMP and Medicare/PEBB^^

	2015	2016	2017^
Unique Patients	36	61	26
Total Treatments with Diagnosis and Allowed Dollars	36	61	26
Dollars Allowed by Total Treatments w/Diagnosis	$3,662	$2,723	$877

^ 2017 lacks 90 days of claims run-out.
^^ Due to low number, utilization and costs information from participating agencies are shown in aggregate

Table D
2015–2017 Average Allowed Dollars/Test
Pharmacogenetic testing for patients being treated with anticoagulants
Medicaid MCO and Medicaid HCA (Fee-for-service), PEBB/UMP and Medicare/PEBB

	CPT 81227	CPT 81355
PEBB/UMP	$142	$0#
PEBB/Medicare	$156	$63
Medicaid HCA/MCO	$143	$80

Cannot be determined from claim.

Table E
2015–2017 Distribution of Primary Diagnosis by Count—
Line-Level, Paid and Unpaid Claims
PEBB/UMP, PEBB Medicare, Medicaid HCA and MCO for Anticoagulant Testing

Dx: Line Level Descriptions	Sum
Essential (primary) hypertension	25
Obesity (morbid and other)	24
Hypothyroidism, unspecified	21
Pure hypercholesterolemia	15
TYPE 2 Diabetes Mellitus	5
Mixed hyperlipidemia	4
Angina pectoris, unspecified	3
Benign hypertension	3
Other forms of acute ischemic heart disease	3
Secondary hypertension, unspecified	2

Methods

This evidence review is based on the final key questions published on January 26, 2018.

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 [TTR], 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 MEDLINE and Cochrane Library searches: Database inception to January 3, 2018

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:
    c. Patient characteristics (e.g., age, sex, race/ethnicity)?
    d. 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?

Analytic Framework

The analytic framework shown in Figure 1 guided the selection, synthesis, and interpretation of available evidence.

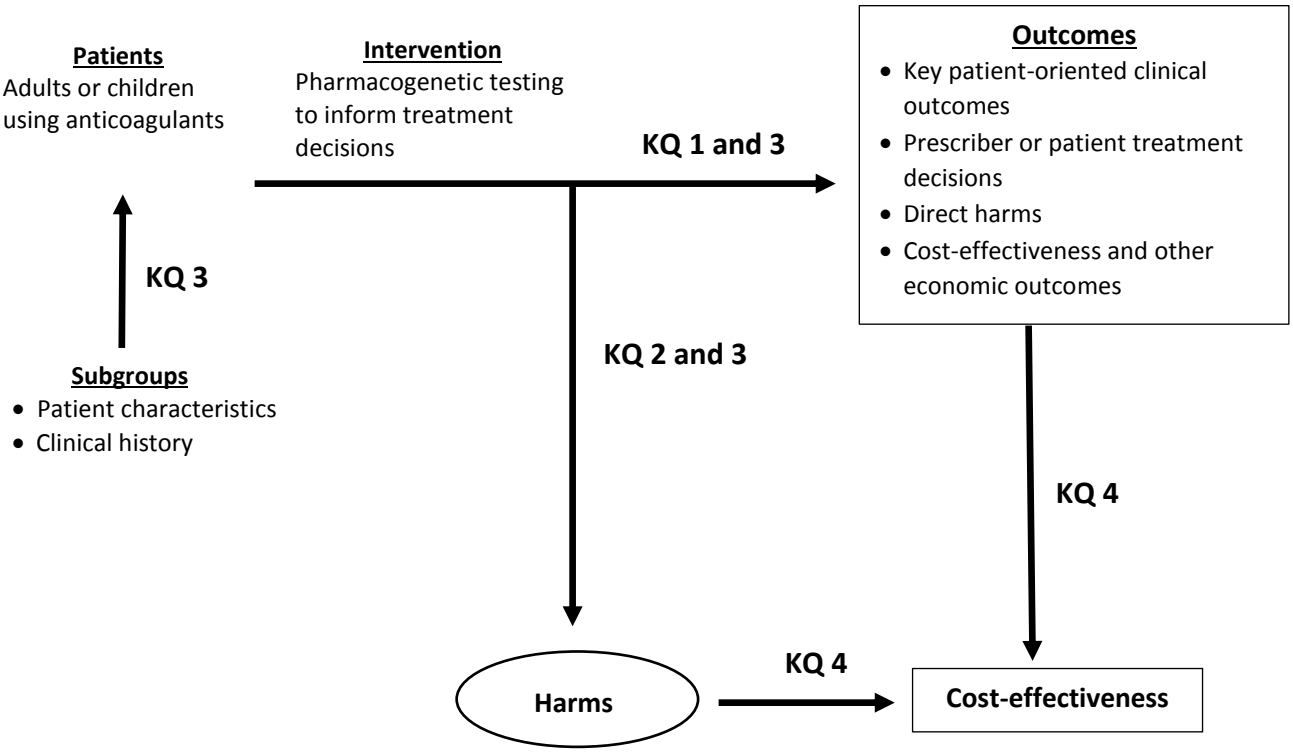


Figure 1. Analytic Framework

Eligible Studies

Table 1 summarizes the study inclusion and exclusion criteria.

Table 1. Study Inclusion and Exclusion Criteria

For clinical utility studies (KQ 1, 2, and 3), include study if all of the following criteria are met:	Rationale
Study population is composed of adults and/or children with an indication for oral anticoagulant therapy.	The clinical population of interest for whom the test may be employed.
The interventions are genetic tests that are used to guide dosing of oral anticoagulant medications.	These tests were of interest to the requester and are available and being used in the U.S.
Comparator included usual care without genetic testing to guide dosing of oral anticoagulant medications.	Without a comparison group, a study is not able to measure the effect of the intervention test on the outcomes of interest.
At least one outcome is a measure of direct clinical utility, including patient management decision (by care provider and/or patient); clinical outcomes	Outcomes of interest are defined to inform the requestor's decision-making needs. Patient-oriented end outcomes rather than surrogate or

For clinical utility studies (KQ 1, 2, and 3), include study if all of the following criteria are met:	Rationale
such as mortality, morbidity, or quality of life measures resulting from patient management decisions resulting from the test; harms such as inaccurate test results influencing patient management decisions; and (for KQ4 only) cost-effectiveness or other economic outcomes resulting from use of the test.	intermediate outcomes are required to inform this decision. Studies that assess only analytic or clinical validity are excluded because they do not yield information about their usefulness to patients and clinicians in practice.
Settings for data collection included clinical facilities (inpatient or outpatient) in any country with substantial applicability to the U.S. setting.	The clinical utility of a genetic test could be expected to vary based on the underlying health system and care within that system, and so only settings with direct applicability to the U.S. will be included.
Study designs include systematic reviews (with and without meta-analysis) and health technology assessments that meet inclusion criteria for this review, and randomized controlled trials. Systematic reviews, meta-analyses, and health technology assessments must be of low or moderate risk of bias.	Study designs are selected to minimize bias. Randomized controlled trials and systematic reviews and meta-analyses of them generally offer the lowest risk of bias because they are designed to minimize the effects of confounding factors on the outcomes.
Other criteria: Publication in English Publication date 2007 or later Publication available for full-text review Data from study publication is extractable	Report authors and users of report use English language. Scoping indicated that studies of gene expression profile tests likely to be eligible were not published before 2007 or were captured in systematic reviews published after that date. Studies must be available for review. Data included in publication must be reported in a way that can be used and analyzed in the report.

Abbreviation. KQ: key question.

Data Sources and Searches

Center researchers conducted a search of the peer-reviewed published literature using multiple online databases. RCTs and systematic reviews (with and without meta-analysis) and health technology assessments of RCTs that assessed clinical utility were considered for Key Questions 1, 2, and 3. Cost-effectiveness studies and other comparative economic evaluations, along with systematic reviews (with and without meta-analysis) reporting economic outcomes, were considered for Key Question 4. The following electronic databases were searched to identify relevant peer-reviewed studies:

- Ovid MEDLINE and In-Process & Other Non-Indexed Citations
- Cochrane Database of Systematic Reviews
- Cochrane Central Register of Controlled Trials

The Ovid MEDLINE search strategy is in Appendix A. Center researchers also screened reference lists of relevant studies and used lateral search functions such as *related articles* and *cited by*. These additional sources were searched:

- Agency for Healthcare Research and Quality (AHRQ)
- National Institute for Health and Care Excellence (NICE)—Evidence
- Veterans Administration Evidence-based Synthesis Program

Center researchers searched these sources for systematic reviews and clinical practice guidelines using the same search terms outlined for the evidence search. In addition, searches of the AHRQ's National Guideline Clearinghouse (guidelines.gov) and websites of relevant professional organizations for guidelines were conducted. These searches included terms related to oral anticoagulants (e.g., medication names) and pharmacogenetics. Guidelines published in the past 5 years were considered for inclusion.

Center researchers conducted a search of PharmGKB, Stanford University's online resource for information about genetic variation on drug responses.[9] A general Internet search for appropriate published studies and relevant gray literature was also conducted. In addition, Center researchers searched the Centers for Medicare & Medicaid Services (CMS) website for the Medicare Coverage Database for National Coverage Determinations (NCDs) and Local Coverage Determinations (LCDs) applying to the state of Washington. The Aetna, Cigna, and Regence websites were searched for coverage policies for these private payers.

To identify relevant ongoing clinical trials, Center researchers searched the online database of clinical trials (ClinicalTrials.gov) maintained by the National Library of Medicine at the National Institutes of Health. This search included terms related to oral anticoagulants (e.g., medication names) and pharmacogenetics. Information in this database is provided by the sponsor or principal investigator of clinical studies. Studies are generally registered in the database when they begin, with information updated as the study progresses.

Screening

Two Center researchers screened titles and abstracts and had discussions to reach agreement on exclusion. For studies that the 2 researchers could not agree on whether to exclude by title and abstract screening, a full-text review for inclusion criteria was performed. The 2 researchers had discussions to reach agreement on inclusion after the full-text review, and any remaining disagreement among these assessments was settled by a third researcher.

Data Abstraction and Quality Assessment

One Center researcher used standardized procedures to extract relevant data from each of the included trials, and at least 1 other investigator cross-checked the data for accuracy.

Two independent Center researchers evaluated trials for methodological risk of bias. The 2 researchers had discussions to reach agreement on the risk-of-bias assessments, and any remaining disagreement among these assessments was settled by a third independent

researcher. Each trial was assessed using Center instruments adapted from national and international standards and assessments for methodological quality.[65-70] A rating of high, moderate, or low risk of bias was assigned to each included study, based on adherence to recommended methods and potential for bias affecting internal and external biases. The risk-of-bias criteria for all of the study types are in Appendix B.

Center researchers assigned each outcome a summary judgment for the overall quality of evidence based on the system developed by the Grading of Recommendations, Assessment, Development, and Evaluation Working Group (GRADE).[71,72] The GRADE system defines the overall quality of a body of evidence for an outcome in the following manner:

- **High**: Raters are very confident that the estimate of the effect of the intervention on the outcome lies close to the true effect. Typical sets of studies are RCTs with few or no limitations, and the estimate of effect is likely stable.
- **Moderate**: Raters are moderately confident in the estimate of the effect of the intervention on the outcome. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is different. Typical sets of studies are RCTs with some limitations or well-performed nonrandomized studies with additional strengths that guard against potential bias and have large estimates of effects.
- **Low**: Raters have little confidence in the estimate of the effect of the intervention on the outcome. The true effect may be substantially different from the estimate of the effect. Typical sets of studies are RCTs with serious limitations or nonrandomized studies without special strengths.
- **Very low**: Raters have no confidence in the estimate of the effect of the intervention on the outcome. The true effect is likely to be substantially different from the estimate of effect. Typical sets of studies are nonrandomized studies with serious limitations or inconsistent results across studies.
- **Not applicable**: Researchers did not identify any eligible articles.

Two independent Center researchers evaluated the methodological quality of eligible clinical practice guidelines. The 2 researchers had discussions to reach agreement on the quality assessments, and any remaining disagreement among these assessments was settled by a third independent researcher. The methodological quality of clinical practice guidelines was rated as good, fair, or poor. The assessment criteria for the methodological quality of clinical practice guidelines are in Appendix B.

Search Results

The search strategy located 1,007 unduplicated citations. After excluding 965 citations by dual assessment of title and abstract, 42 full-text articles were independently reviewed by 2 researchers; 24 of these articles did not meet predetermined inclusion criteria. Table 1 is a detailed list of criteria and their rationale. The search results are summarized in a Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) study flow diagram in Figure 2. A list of the excluded studies and reasons for exclusion are in Appendix I.

All eligible RCTs and systematic reviews of RCTs assessed the clinical utility of pharmacogenetic testing for the dosing of warfarin.

After full-text review, 11 systematic reviews of RCTs were identified.[1,10-19] Among the studies included in these systematic reviews, 10 eligible RCTs were identified.[7,20-28] Three additional eligible RCTs were identified that were published after the most recent systematic review.[29-31] One of these more recent RCTs, published by Gage et al. in 2017, has the largest sample size (n = 1,650) of all the identified RCTs. Thus, Center researchers decided to conduct a systematic review and meta-analysis of the 13 eligible RCTs and to not include the systematic reviews as primary sources. One of the included RCTs[25] did not report any of the outcomes included in the meta-analysis.

The 5 eligible economic studies focused on pharmacogenetic testing for the dosing of warfarin in the setting of AFib.[32-34]

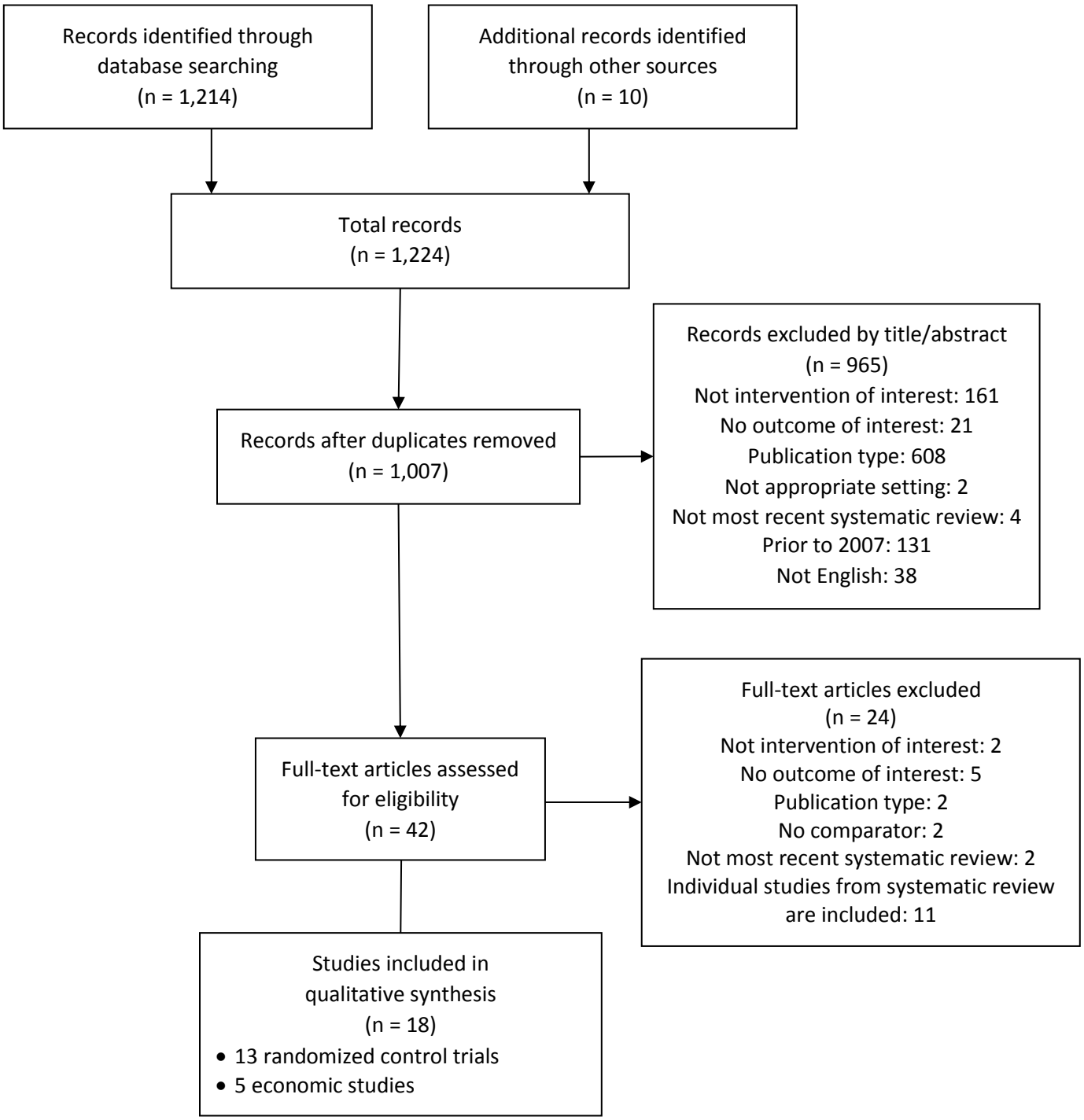


Figure 2. PRISMA Study Flow Diagram

Statistical Analysis

Center researchers conducted meta-analyses for 5 outcomes, which are displayed below with their data type:

- Percentage of time in therapeutic range (PTTR) (continuous, as a percentage of follow-up time)
- INR greater than or equal to 4 (binary, unique event)

- Thromboembolic events (binary, unique event)
- Mortality (binary, unique event)
- Major bleeding (binary, unique event)

Using RevMan 5.3, Center researchers estimated pooled and subgroup mean differences and risk ratios and their 95% confidence intervals for continuous and binary outcomes, respectively. Center researchers used the inverse variance statistical technique and random effects models for all outcomes. Center researchers took the longest follow-up period that was identified in published documents for all outcomes. Subgroup analyses included an assessment of multiple factors:

- Different comparators (i.e., clinical algorithm-guided based dosing compared to fixed dosing)
- Risk of bias (i.e., high compared to moderate compared to low)
- Sample size (i.e., greater than or equal to 400 total participants or less than 400 total participants)
- Number of genes tested in the pharmacogenetics test (i.e., 3 genes, 2 genes, or 1 gene)
- Country where the study was conducted (i.e., U.S. compared to other countries)
- Clinical indication (i.e., AFib, valve replacement, post-orthopedic surgery, or other indications)
- Race (i.e., 90% or more total participants were White, 90% or more total participants were Asian, or a combination of races)
- Follow-up period (i.e., greater than 30 days or 30 days or less)

All subgroup analyses were conducted for PTTR and INR greater than or equal to 4. Only exploratory analyses of different comparators were conducted for thromboembolic events, mortality, and major bleeding. Center researchers conducted sensitivity analyses assessing different follow-up periods in Wen 2017[29] and inclusion of Huang 2009[28] within meta-analyses of INR. Huang 2009[28] had available data only on INR greater than or equal to 3.5 instead of INR greater than or equal to 4.

Using RevMan 5.3, Center researchers created forest plots to graphically display the findings for the overall and subgroup meta-analyses. Funnel plots were also created using RevMan 5.3 to qualitatively assess publication bias for PTTR and INR greater than or equal to 4. Center researchers entered data into the meta-analyses when zero events for a particular outcome in both the pharmacogenetic testing group and control group occurred. Although these data contribute to the total participants in each group and are displayed within the forest plots, RevMan 5.3 does not account for these findings in the pooled estimate (Cochrane Support Team, email, February 26, 2018). Including zero total events trials in the meta-analysis moves the pooled effect estimate closer to the null, but also narrows the confidence interval and results in decreased heterogeneity.[73] Biostatisticians recommend inclusion of zero event trials because of these factors.[73] Nevertheless, Center researchers calculated the incidence for each binary

outcome by group and the risk difference between the 2 groups for these outcomes. These measures take into consideration zero event data. The findings are displayed in Table 3.

For PTTR, if a mean difference was greater than zero, then the pharmacogenetic test was favorable compared to the control. If the mean difference was less than zero, then the control was favorable compared to the pharmacogenetic test. If the mean difference was zero, then there was no difference between the pharmacogenetic test and control. For all other outcomes, if a risk ratio was below 1.00, then the pharmacogenetic test was favorable to the control. If a risk ratio was above 1.00, then the control was favorable to the pharmacogenetic test. If the risk ratio was 1.00, then there was no difference between the pharmacogenetic test and control. Center researchers used an alpha level of .05 to determine statistical significance for all overall meta-analyses. Center researchers assessed all overall and subgroup meta-analyses for statistical and clinical heterogeneity. Statistical heterogeneity was considered present if an I^2 statistic was greater than or equal to 50% with a Chi-square test that had a p value of less than or equal to 0.10.

When trials had more than 2 groups, Center researchers calculated weighted means for comparable groups (e.g., same intervention, same comparator) and pooled standard deviations. When relevant statistics to conduct a meta-analysis were missing, Center researchers attempted to calculate the statistics using available data (e.g., 95% confidence interval, sample size, number of events reported in 1 group), and we contacted study authors for the data. For the GRADE summary of evidence table (Table 3), Center researchers calculated the anticipated risks and 95% confidence intervals in the intervention and control groups and the risk differences and 95% confidence intervals between these 2 groups using OpenEpi software.[74]

Evidence Summary

The section below summarizes the study characteristics and study participant characteristics for each of the included RCTs.

RCT Descriptions

Anderson et al., 2007

Anderson et al. (2007) conducted an RCT comparing pharmacogenetic dosing to standard empiric dosing using the Kovacs 10 mg initiation nomogram.[27] The target INR was 2 to 3. Exclusion criteria included pregnancy, lactation, rifampin use, and comorbidities (e.g., renal or hepatic insufficiency) that would preclude standard dosing.[27] Group assignment was masked to all except for a research assistant and the pharmacist.[27] Over half of the 200 patients enrolled had an orthopedic procedure as the indication for anticoagulation, and the study included patients with DVT or pulmonary embolism, AFib, or other diagnoses.[27] Nearly all patients were White.[27] Patients were generally initiated on warfarin therapy while hospitalized.[27] Participants in the pharmacogenetic study arm were statistically significantly older, had any *CYP2C9* genetic variant, and a higher proportion had hypertension.[27] After study initiation, the standard dose arm received 10 mg of warfarin on days 1 and 2 and 5 mg on days 3 and 4.[27] Doses were then

adjusted based on the day 5 INR.[27] The pharmacogenetic study arm was dosed according to a regression equation that included *CYP2C9* and *CYP2C9* genotype, age, weight, and sex.[27] Regression scores were converted to 14-dose increments between 1 mg and 8 mg.[27] Twice the predicted dose was given on days 1 and 2, and subsequent doses were modified based on the measured INR, using the standard arm predicted dose multiplied by the regression coefficient.[27] Outcomes were collected for 3 months or until warfarin therapy ended (usually at 1 month for patients with an orthopedic indication).[27] The primary outcome was the proportion of out-of-range INR values (defined as < 1.8 or > 3.2).[27] Center researchers assessed this trial as having a moderate risk of bias because of inadequate allocation concealment, unclear masking of outcome assessment, and an unclear description of the statistical analysis.

Borgman et al., 2012

Borgman et al. (2012) conducted a pilot RCT of 26 patients to test the feasibility of a genotype-guided warfarin dosing tool (PerMIT) that incorporated *CYP2C9* and *CYP2C9* polymorphism information compared to standard care by the University of Utah thrombosis service, employing the Kovacs algorithm.[20] Exclusion criteria included pregnancy and significant comorbidities such as hepatic or renal insufficiency.[20] Enrolled patients had a mix of indications for anticoagulation, were warfarin naïve, and had a projected treatment duration of at least 12 weeks.[20] The 2 teams responsible for anticoagulation in each study arm were aware of patient allocation.[20] The standard care arm was generally started at 5 mg per day, but clinician discretion was allowed.[20] Patients in the PerMIT group were also generally started on 5 mg on day 1, but were dosed according to the PerMIT algorithm thereafter unless the patient's clinician objected.[20] The target INR range was 2 to 3 and values of 1.8 to 3.2 were considered acceptable.[20] INRs were routinely measured in the first week on days zero, 3, and 5; twice in the second week; once in weeks 3 and 4 of therapy; and monthly thereafter.[20] No primary endpoint was designated, but the study measured outcomes such as TTR and time to stable therapeutic dose.[20] Center researchers assessed this trial as having a high risk of bias because of factors including unclear randomization, inadequate allocation concealment, lack of masking, inadequate statistical analysis, and some authors having an equity interest in the test provider.

Burmester et al., 2011

At the Marshfield Clinic in Wisconsin, Burmester et al. (2011) conducted an RCT of a pharmacogenetically guided warfarin initiation, using an algorithm that incorporated *CYP2C9*, *CYP2C9*, and *CYP4F2* polymorphisms.[7] The comparator group's dosing was determined by the standard Marshfield Clinic clinical algorithm, which allows standard initiation doses up to 10 mg.[7] Most of the 230 randomized participants (80%) were hospitalized at the initiation of the study.[7] Most of the 230 randomized patients (80%) were hospitalized at the initiation of anticoagulation; the indications for anticoagulation included AFib for 49% of the intervention group and 43% of the control group.[7] Other indications included thromboembolic disease and heart valve surgery.[7] All patients identified as White.[7] Target INRs ranged from 2 to 3.5, depending on the clinical indication.[7] Participants received initial dosing on days 1 and 2, based on the predicted dose from either the pharmacogenetic algorithm or the clinical algorithm.[7]

Subsequent dose adjustments were based on guidelines from the American College of Cardiology (ACC) and American Heart Association (AHA).[7] The primary study outcomes were prediction error and TTR during the first 14 days of therapy.[7] Patients were followed for 60 days after randomization.[7] Center researchers assessed this trial as having a moderate risk of bias because of inadequate statistical analysis description, partial funding from a test manufacturer, and authors who were patent holders for the technology involved in the genomic test.

Caraco et al., 2008

Caraco et al. (2008) conducted an RCT that allocated patients based on whether the identity number was odd or even (a method of pseudo-randomization).[24] This study was conducted in Israel and enrolled 283 patients, although 92 were excluded, leaving 185 in the analysis (65.4%).[24] The racial composition of participants was not reported.[24] Approximately two-thirds of enrollees had a VTE indication and the remainder received anticoagulants because of AFib.[24] The locally developed intervention-dosing algorithm contained information about the *CYP2C9* genotype, although details about the other factors considered by that algorithm were not specified except that all doses were lowered by 25% for patients who were concurrently taking amniodarone.[24] The authors noted that the comparator dosing algorithm was a computer-generated system developed by Ageno et al. (2000).[35] Although no details were provided about the starting doses used in the study by Caraco et al. (2008),[24] the typical starting dose in the Ageno et al. (2000) study was 5 mg.[35] The primary outcomes were the time required to reach a therapeutic INR (INR > 2) and the time required to reach stable anticoagulation.[24] Patients were followed until a stable dose of warfarin was achieved, which was generally about 1 month, but could vary.[24] Center researchers assessed this trial as having a high risk of bias because of the study authors' use of pseudo-randomization, inadequate allocation concealment and statistical analysis description, and lack of outcome assessor masking.

Gage et al., 2017

Gage et al. (2017) conducted a U.S. multicenter RCT named GIFT (Genetic Informatics Trial of Warfarin to Prevent DVT) that randomized 1,650 patients and analyzed 1,597 patients (96.8%) who were initiating warfarin therapy to prevent postsurgical DVT after having elective hip or knee arthroplasty.[31] The trial included only patients over age 65 and excluded patients for factors such as previously known genotype status or warfarin dose, baseline INR greater than 1.35, bleeding disorder or serious non-traumatic bleeding event in the previous 2 years, or another indication for warfarin therapy (e.g., AFib).[31] The mean age of patients was over 70 years and more than 90% were White.[31]

Patients were randomized to warfarin dosing based on a genotype-guided algorithm compared to a clinically based algorithm on days 1 through 11 post-surgery.[31] Randomization was stratified by race, given that the prevalence of *CYP2C9* *2 and *3 polymorphisms varies by race.[31] The genotype-guided group received warfarin dosing in the first 11 days of the study as guided by a web application (WarfarinDosing.org) that incorporated information on all genetic variants.[31] The pharmacogenetic algorithm incorporated information about the patient's

CYP2C9, *CYP2C9*, and *CYP4F2* genotypes.[31] Patients in the control group were dosed according to the web-based clinical algorithm without addition of genetic information.[31] Warfarin dosing was open-label, but investigators, clinicians, and patients were masked to group assignment.[31] Clinicians could deviate from the algorithm-predicted daily dose, although dose deviations of ≥ 1 mg per day for doses > 3 mg or ≥ 0.5 mg per day for doses ≤ 3 mg per day were recorded as outcomes.[31]

The primary outcome was a composite of major bleeding, INR greater or equal to 4, VTE, and death.[31] All patients without a symptomatic DVT underwent a lower extremity duplex ultrasound study for screening at approximately 1 month after surgery to detect asymptomatic DVT.[31] Patients were followed for 90 days post-surgery.[31] Center researchers assessed this trial as having a low risk of bias. Center researchers noted only minor biases: the GenMarkDx company had loaned the genotyping platform to the central laboratory involved in the study, and several authors disclosed commercial research funding and other income.

Hillman et al., 2005

Hillman et al. (2005) conducted a feasibility RCT of 38 patients with a mix of indications for oral anticoagulation from the Marshfield Clinic in Wisconsin.[23] The study authors compared intervention dosing based on a multivariable model that included age, body surface area, diabetes and other comorbidities, the clinical indication, and the *CYP2C9* genotype to a standard initiation warfarin dosing regimen of 5 mg per day on the first day, with subsequent doses adjusted according to the INR.[23] Exclusion criteria included previous use of warfarin, antiphospholipid antibodies, liver or renal disease, non-White race, and age under 40 years.[23] These exclusions were employed because the algorithm was developed on patients without these characteristics.[23] A primary outcome was not designated because the study was done primarily to assess the feasibility of the pharmacogenetically guided algorithm in practice, but the authors did report PTTR and INR > 4 for the first 28 days after initiation.[23] Center researchers assessed this trial as having a high risk of bias because of unclear randomization and allocation concealment, lack of masking, and midstudy protocol changes.

Huang et al., 2009

Huang et al. (2009) conducted an RCT of a pharmacogenetically guided warfarin dosing algorithm compared to a standard initiation protocol of 2.5 mg per day for the first 3 days of therapy.[28] Subsequent dose adjustments were based on INR values.[28] The genetic protocol involved testing for *CYP2C9* and *CYP2C9* genotypes, but details about how genetic polymorphisms were incorporated into the dosing algorithm were not provided.[28] The authors randomized 142 participants and 121 (85.2%) were analyzed.[28] The study was conducted in China, all patients were ethnically Chinese, and all had an indication of heart valve replacement.[28] The patient group was relatively young, with a mean age in the early 40s.[28] The primary outcome was the time required to reach a stable maintenance dose of warfarin, and patients were followed for 50 days post-randomization.[28] Center researchers assessed this trial as having a high risk of bias because of unclear randomization and allocation concealment,

inadequate detail about the genetic dosing protocol, lack of masking, and lack of detail about potential author conflicts of interest.

Jonas et al., 2013

In North Carolina, Jonas et al. (2013) randomized 109 patients to initial anticoagulation according to the Washington University School of Medicine (WUSOM) algorithm with *CYP2C9* and *CYP2C9* genotype information compared to the WUSOM algorithm without the addition of genotype data.[22] Allowed warfarin doses ranged from 0.5 to 10 mg per day.[22] Subsequent dosing was determined for both groups based on consensus guidelines from the ACC and AHA.[22] Patients with a history of warfarin use and a known dose requirement, those who received more than 3 doses prior to confirming enrollment, and pregnant women were excluded.[22] The study population was 27% Black and 73% White, with indications for anticoagulation including AFib, DVT or pulmonary embolism, and a small minority with heart valve replacement or other indications.[22] The primary outcomes were the number of anticoagulation visits required and PTTR; patients were followed for 90 days.[22] Center researchers assessed this trial as having a low risk of bias, without any significant limitations.

Kimmel et al., 2013

Kimmel et al. (2013) conducted a U.S. multicenter RCT named COAG (Clarification of Optimal Anticoagulation through Genetics) that randomized 1,015 patients and analyzed 955 patients (94.1%).[21] Inpatients and outpatients were initiated on warfarin; approximately 60% had DVT or pulmonary embolism as the primary indication for anticoagulation, and 22% had AFib or a flutter.[21] Exclusion criteria included a variety of factors that would be likely to limit adherence (e.g., alcohol or substance misuse, dementia), previously known warfarin dose or relevant genotype, abnormal baseline INR, and contraindication to warfarin therapy for at least 3 months.[21] Patients were assigned in a 1:1 ratio—stratified by whether race was self-reported as Black or non-Black (27% were black)—to a dosing algorithm that incorporated *CYP2C9* and *CYP2C9* genotype information or to a clinical dosing algorithm.[21] In each study arm, patients received the algorithm-determined dose for each of the first 3 days of therapy, and a dose determined by a dose-revision algorithm that incorporated genotypes in the intervention group and did not for the control group for days 4 or 5, or both.[21] After day 5, doses were adjusted based on the algorithm-predicted dose adjusted for INR measurement.[21] Patients and clinicians were masked to the actual dose in the first month of therapy because the drug was encapsulated.[21] The range of initiation doses received by patients in the control group was about 2 mg to 12 mg, although the typical or average dose was not reported.[21] The primary study outcome was PTTR from day 4 or 5 through 28 days of therapy, and patients were followed for 6 months after initiation of therapy.[21] Center researchers assessed this study as having a low risk of bias, although several authors had research grants, consulting contracts, or equity interests with commercial entities.

Pengo et al., 2015

In Italy, Pengo et al. (2015) conducted an RCT that randomized 200 patients with AFib and analyzed 180 (90%).[30] The authors compared the locally developed pharmacogenetic algorithm

developed by Zambon et al. (2011)[75] that incorporated *CYP2C9*, *CYP2C9*, and *CYP4F2* genotyping to standard fixed dosing. In the intervention arm, patients received a loading dose on the first day and maintenance doses on days 2 through 6 based on the genetic algorithm.[30] Patients in the control group were initiated with 5 mg per day for 4 days.[30] On days 5 and 6, doses were based on a clinical prediction model using the day 5 INR result.[30] From day 7, the dose in both groups was determined by the attending clinician with the assistance of PARMA software.[30] The PARMA algorithm was derived from mathematical models based on data of dosage recommendations from expert medical teams.[76] Patients were given a daily dose of low-molecular-weight heparin enoxaparin from the day of enrollment until warfarin initiation; genotyping was performed only once per week.[30] Patients who were concurrently taking amniodarone or CYP-450-inducing drugs such as rifampin or carbamazepine, had a baseline INR > 1.2, or could become pregnant were excluded from the study.[30] All of the study participants identified as White and had an anticoagulation indication of AFib.[30] The primary outcome measures evaluated in the first 19 days of the study were the number of out-of-range INR values (INR < 2 or INR > 3) and the PTTR.[30] Center researchers assessed this study as having a moderate risk of bias because of unclear allocation concealment and lack of masking of data collectors.

Pirmohamed et al., 2013

Pirmohamed et al. (2013) conducted an RCT in 2 centers in Sweden and 3 centers in the UK (mostly university/academic hospitals and their outpatient facilities) that was named EU-PACT (European Pharmacogenetics of Anticoagulant Therapy).[26] The authors randomized 455 patients and analyzed 427 (93.8%).[26] Randomization blocks were stratified by center and indication for anticoagulation.[26] Nearly all participants identified as White, and 72% had AFib or fibrillation and 27% had VTE as indications for anticoagulation.[26] Exclusion criteria included presence of a mechanical heart valve, previously known *CYP2C9* or *CYP2C9* genotype, previous treatment with a coumarin anticoagulant, severe cognitive impairment, pregnancy, or lactation.[26] The warfarin initiation loading dose for days 1 through 3 was determined by an algorithm that incorporated *CYP2C9* and *CYP2C9* genotype variants and was a slightly modified version of the IWPC algorithm.[26] In the intervention group, dosing on days 4 and 5 was determined by a dose-revision algorithm that incorporated the INR from day 4.[26] Within the control group, patients 75 years of age and younger received a daily warfarin loading dose of 10 mg for the first day and 5 mg on days 2 and 3.[26] For patients older than 75 years of age, the fixed loading dose was 5 mg per day for the first 3 days.[26] Subsequent dose adjustments for both groups were based on usual clinical practice, which was not detailed in the paper or supplementary materials.[26] The primary outcome was PTTR during the first 12 weeks of therapy.[26] Center researchers assessed this study as having a moderate risk of bias because of unclear allocation concealment and lack of masking of data collectors.

Wang et al., 2012

Wang et al.[25] (2012) conducted an RCT of a pharmacogenetic algorithm developed by Huang et al.[28] The study enrolled 106 and analyzed 101 Han Chinese patients (95.3%) who were having a

single or double mechanical heart valve replacement.[25] Warfarin dosing began 3 days postoperatively.[25] Pharmacogenetically guided doses were limited to 3.5 mg per day for the first 3 days of therapy and subsequent dose adjustments were based on the measured INR.[25] Patients in the control group initiated therapy with a fixed dose of 2.5 mg per day and the dose was then adjusted based on the subsequent INR.[25] The investigators excluded patients who were deemed inappropriate for the study including patients with an out-of-range baseline INR (< 0.8 or > 1.2); women who could become pregnant; and individuals with chronic liver, kidney, or hematological disease.[25] The primary outcome was the time required to reach a stable maintenance dose, and patients were followed for 50 days after initiation of warfarin therapy.[25] Center researchers assessed this study as having a high risk of bias because of unclear allocation concealment, lack of masking of patients and data collectors, and lack of detail about the funding source.

Wen et al., 2017

Wen et al. (2017) conducted an RCT comparing 2 pharmacogenetic warfarin dosing algorithms with a fixed-dose initiation protocol.[29] A total of 320 Han Chinese patients over age 20 with a mix of AFib, VTE, and other indications for anticoagulation were randomized in a 1:1:1 ratio to the 3 groups, and 318 were analyzed (99.4%).[29] The exclusion criteria included previous warfarin treatment, vitamin K deficiency, pregnancy, and hemorrhagic tendencies or hemorrhagic diseases.[29] The IWPC algorithm and the Taiwan algorithm incorporated information about the patient's *CYP2C9* and *CYP2C9* genotypes in the formulas.[29] In the pharmacogenetic arms, patients were initiated on therapy with a loading dose of 1.5 times the calculated dose.[29] The control arm received a fixed loading dose of 5 mg per day for the first 3 days of therapy.[29] Subsequent dose adjustments after the fourth day were based on the measured INR.[29] The primary study outcome was PTTR during the 3 months after warfarin initiation.[29] Center researchers assessed this study as having a high risk of bias because of unclear allocation concealment, inadequate detail about the genetic dosing protocol, lack of masking, and 1 author holding the European patent for a *CYP2C9* gene test.

Key Question 1: Effectiveness

Thirteen RCTs met final inclusion criteria and were published between 2007 and 2017. All included RCTs used warfarin as the oral anticoagulant and no studies were identified that used pharmacogenetic testing for non-vitamin K antagonist anticoagulants. Seven RCTs were conducted in the U.S.,[7,20-23,27,31] 2 in China,[25,28] and 1 each in Taiwan,[29] Israel,[24] and Italy,[30] with a multicenter trial in the UK and Sweden.[26] One study included only patients who were undergoing hip or knee arthroplasty,[31] 2 included only patients having heart valve replacement,[25,28] and 1 was performed in a population with AFib or flutter[30] as the sole indication for anticoagulation. In the remaining RCTs, there were a mix of reasons for anticoagulation, but most patients had AFib or flutter or VTE (either DVT or pulmonary embolism).[7,20-24,26,27,29]

Most participants were in their late 50s to early 70s, although participants in the 2 heart valve replacement trials[25,28] were in their early 40s. The trials by Huang et al., Wang et al., and Wen et al. were conducted in exclusively Asian populations. In 8 trials[7,20,23,26,27,30,31] the population was more than 90% White, and the racial composition was more mixed in the other 2 trials.[21,22] Most trials had relatively small sample sizes; only 3 randomized more than 400 participants.[21,26,31] These 3 RCTs, the GIFT,[31] COAG,[21] and EU-PACT[26] trials, accounted for approximately two-thirds of all participants across the 13 trials. Two trials were pilot or feasibility trials and enrolled fewer than 40 participants each.[20,23]

The pharmacogenetic intervention included an analysis of 1 gene (*CYP2C9*) in 2 studies,[23,24] 2 genes (*CYP2C9* and *CYP2C9*) in 7 trials,[20-22,25-29] and 3 genes (*CYP2C9*, *CYP2C9*, and *CYP4F2*) in 3 trials.[7,30,31] Four trials[7,21,22,31] employed a clinically-based algorithm to guide warfarin dosing in the control group, and the others used a variety of fixed-dose regimens for initiation of anticoagulation. Follow-up periods ranged from 1 to 6 months. Five trials reported outcomes with at least 30 days of follow-up.[20,22,26,28,29] Center researchers conducted dual, independent risk-of bias-assessments using common criteria for RCTs (see Appendix B for risk-of-bias assessment instrument details and Appendix D for ratings, by domain, for each trial). Three trials[21,22,31] were judged to be at a low risk of bias, 4[7,26,27,30] were at a moderate risk of bias, and 6[20,23-25,28,29] were at a high risk of bias.

Main Outcomes

Center researchers performed meta-analysis for prespecified primary outcomes (mortality, major bleeding, thromboembolic events, INR > 4, and the PTTR for anticoagulation) and conducted prespecified subgroup analyses as detailed in the Methods section. The Wang et al. (2017) RCT did not report any of the major outcomes included in the meta-analysis, but did report other outcomes that are narratively summarized in this report in the section on additional outcomes reported. The following meta-analysis results are presented for each major outcome, with relevant subgroups for each of the 5 outcomes.

Forest plots are used to graphically present meta-analytic results. The forest plot figures that are discussed in detail within the narrative are presented in the following sections, and other figures are in Appendix E. Funnel plots used to evaluate the possibility of publication bias were produced for outcomes that had sufficient data (PTTR and overanticoagulation), and are in Appendix E.

In meta-analyses, 4 of the 5 outcomes presented in this section are expressed as risk ratios; 1 (PTTR) is expressed as a mean difference in the percentage of time within the defined therapeutic INR range. For interpretation of forest plots with a mean difference (PTTR), results to the right of zero (no effect) displayed as a box (individual studies) or diamond shape (summary estimate) in the graph favor the pharmacogenetic intervention; results on the left favor controls. For interpretation of forest plots with risk ratios, results to the left of 1.0 (no effect) in the graph favor the pharmacogenetic intervention; results to the right favor controls.

Mortality

Seven trials[7,20-22,28,31] reported mortality as an outcome, of which 3[20,28,31] reported no deaths in either arm of the trials. Deaths reported were either classed as all-cause or specifically not related to the study in most of these trials, but the nature of the deaths was not specified in the trials by Jonas et al. (2013)[22] and Kimmel et al. (2013).[21] Included studies were likely underpowered to detect this rare outcome, and 3 of the 7 studies that captured mortality observed zero events in both groups. In total, 9 deaths were reported among 1,786 (0.50%) participants in the intervention groups and 8 among 1,754 (0.46%) in the control groups, for a risk ratio of 1.17 (95% CI, 0.43 to 3.22) in favor of the control group (see Figure 3). However, the risk ratio was not statistically significant and the confidence interval was wide. Center researchers did not detect any statistical heterogeneity in the analysis (I^2 = 0% and Chi^2 = 2.79; p = .43). One subgroup analysis was performed, examining the possible effect of the control group using a clinical dosing algorithm or fixed-dose warfarin initiation (see Figure 4). Neither subgroup had a statistically significant estimate, and confidence intervals were wide and overlapping. Nevertheless, compared to pharmacogenetically guided therapy, the risk ratio for clinical algorithm-based trials had an estimate that was slightly in favor of the intervention (RR, 0.72; 95% CI, 0.20 to 2.62), and for trials using a fixed dose, the risk ratio was slightly in favor of the control (RR, 2.53; 95% CI, 0.50 to 12.92). Despite these observed differences, the Chi^2 test for subgroups was not statistically significantly different (p = .24). Another subgroup analysis examined the effect of follow-up period (greater than 30 days vs. 30 days or fewer) on outcomes, but also did not find significant differences.

Given the low number of deaths reported, the meta-analysis is fairly unstable and any additional mortality events occurring in either group could modify the estimate of effect. Furthermore, follow-up was never more than 6 months, and so there is no information regarding the longer-term overall mortality risk from these interventions. The anticipated absolute effect (Table 3) was 0.48 more deaths per 1,000 people with pharmacogenetic testing (95% CI, 4.1 more to 5.0 fewer deaths per 1,000 people). Center researchers rated the overall quality of evidence for this outcome as low.

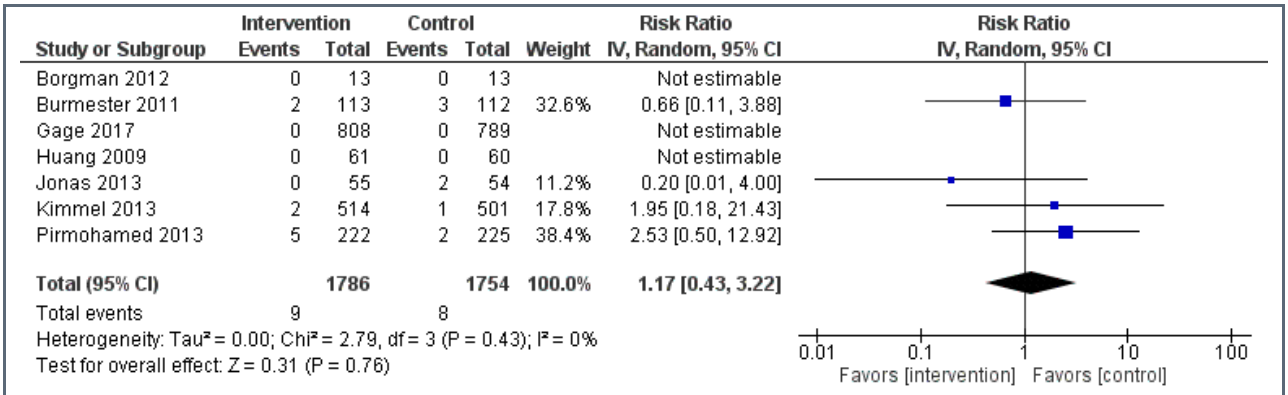


Figure 3. Meta-analysis of Pharmacogenetic Testing vs. Control for Mortality

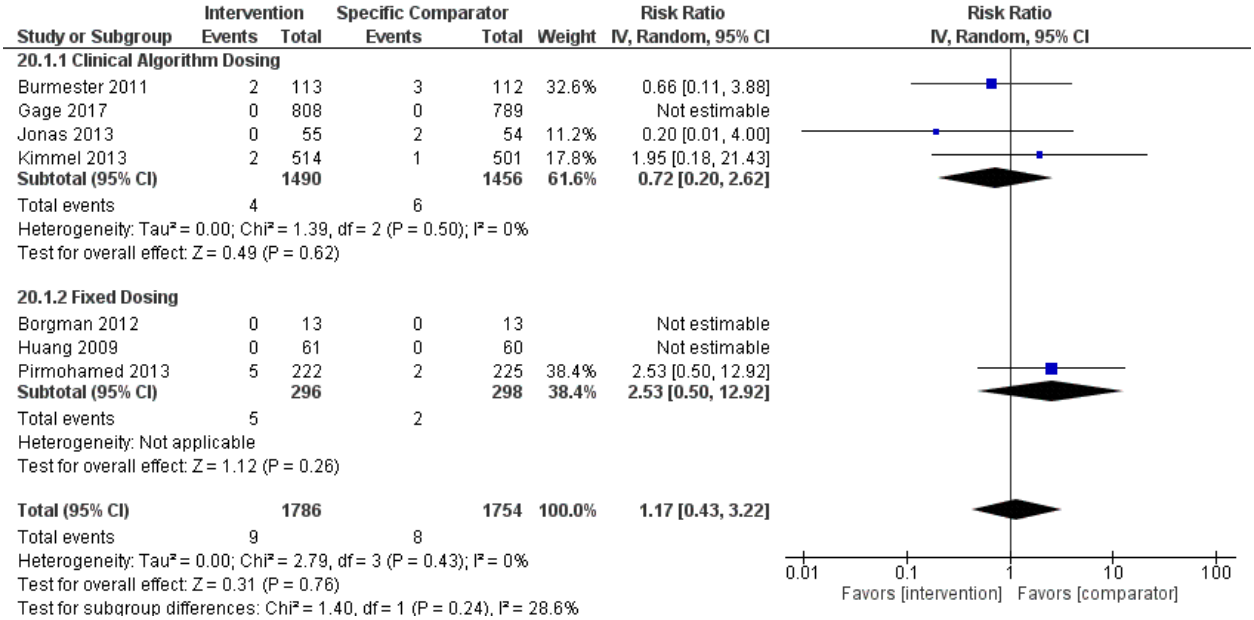


Figure 4. Meta-analysis of Pharmacogenetic Testing vs. Control by Comparator for Mortality

Major Bleeding

Eleven RCTs included major bleeding as an outcome.[7,20-24,26,28-31] For purposes of the meta-analysis, Center researchers used the RCT authors' definition of major bleeding, which generally included bleeding that necessitated hospitalization or required interventions. Burmester et al. (2011) reported major bleeding in several ways, and Center researchers selected their primary method of bleeding events reporting adjudicated by the trial's Data Safety Monitoring Board.[7] Trials typically included intracranial and gastrointestinal bleeding or bleeding resulting in a transfusion, surgery, or hospitalization in the definition of major bleeding. Four trials did not report major bleeding in either group.[20,26,28,30] The total number of events was small: 12 events

among 2,187 participants in the intervention group (0.55%) and 29 events among 2,054 in the control group (1.4%). As shown in Figure 5, participants enrolled in the intervention group were 57% less likely to experience major bleeding than those in the control group (RR, 0.43; 95% CI, 0.22 to 0.84; p = .01) in the main analysis. No statistical heterogeneity was identified (I^2 = 0% and Chi^2 = 3.64; p = .72). The anticipated absolute effect (Table 3) was 8.6 fewer major bleeding events per 1,000 people with pharmacogenetic testing (95% CI, 2.7 to 14.4 fewer major bleeding episodes per 1,000 people). Center researchers rated the overall quality of evidence for this outcome as moderate because of imprecision.

As shown in Figure 6, a prespecified subgroup analysis by comparator was conducted. The risk of major bleeding was statistically significantly lower for the patients who received pharmacogenetic testing compared to a clinical algorithm to guide initial dosing (RR, 0.39; 95% CI, 0.19 to 0.81). Although the risk of major bleeding was lower for patients who received pharmacogenetic testing to guide initial dosing, compared to a fixed dose the difference was not statistically significant (RR, 0.70; 95% CI, 0.14 to 3.53). The test for differences between subgroups was also not statistically significant (p = .52). The absolute differences in major bleeding were 11.1 (95% CI, 3.2 to 19.1) fewer major bleeding events per 1,000 people with pharmacogenetic testing in the clinical algorithm studies, and 2.1 (95% CI, -4.8 to 9.1) fewer major bleeding events per 1,000 people with pharmacogenetic testing in the fixed-dose comparator studies.

Overall, the subgroup analysis indicates that the major bleeding benefit of pharmacogenetically guided warfarin dosing seen in the main analysis cannot be explained by whether the control group was dosed according to a clinical algorithm or with a fixed-dose approach. However, the maximum allowed initial doses under clinical algorithms were higher (10 to 12 mg) among the 3 studies that contributed the most events within this subgroup.[7,21,31] In general, clinical practice guidelines recommend starting doses between 5 mg and 10mg and being more cautious for patients with higher risks of bleeding such as the elderly, and those with impaired nutrition, liver disease, congestive heart failure, recent cardiopulmonary bypass, use of antiplatelet therapy, or other risk factors.[36,37]

The caveat remains that very few events were reported overall, and that even when statistically significant, the confidence intervals were relatively wide.

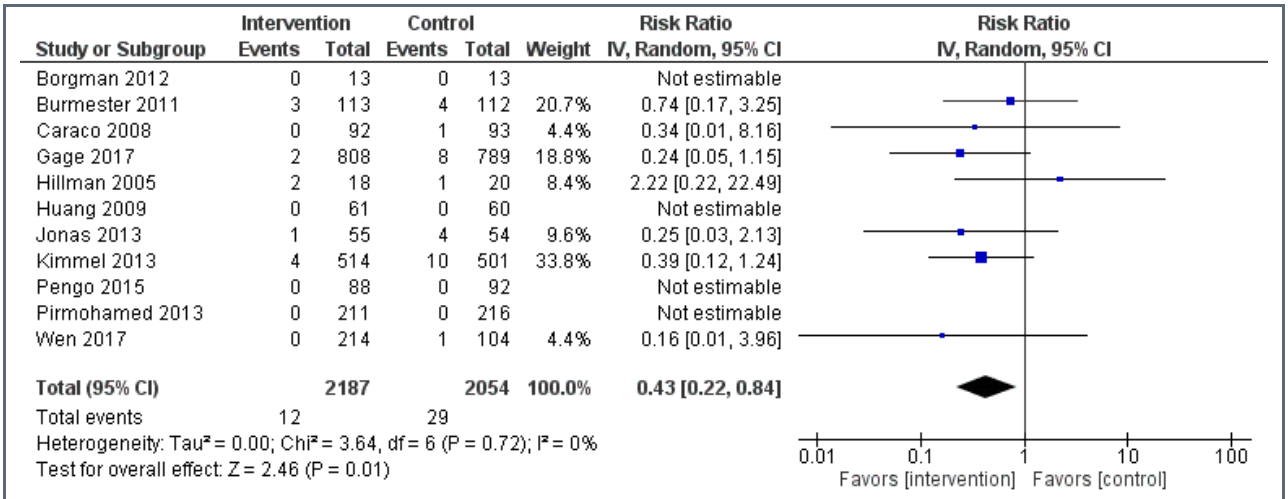


Figure 5. Meta-analysis of Pharmacogenetic Testing vs. Control for Major Bleeding

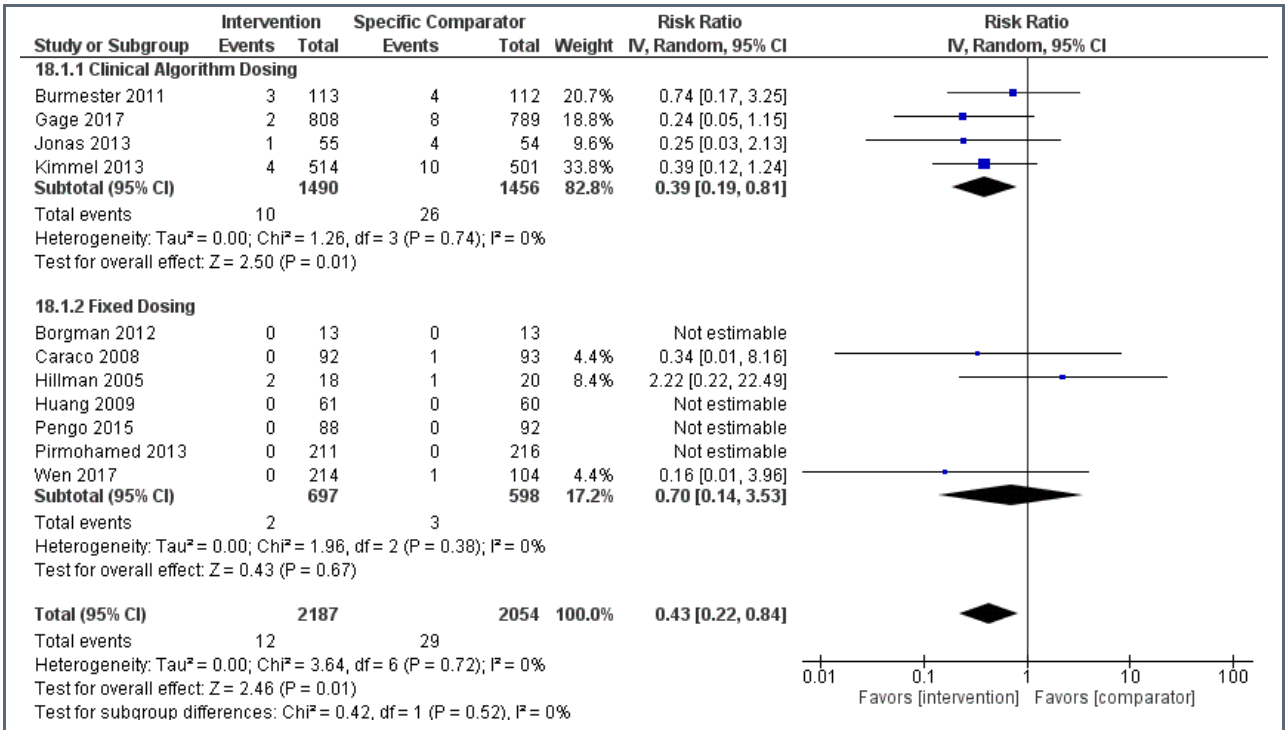


Figure 6. Meta-analysis of Pharmacogenetic Testing vs. Control by Comparator for Major Bleeding

Thromboembolic Events

A total of 11 trials[7,20-24,26,28-31] reported thromboembolic events (generally DVT or pulmonary embolism), although 5 of these trials[20,24,28-30] reported no events in either the intervention or control group. The analysis was heavily weighted by the Gage et al. (2017) RCT with 81.3% of the total weight in the meta-analysis. Gage et al. (2017) conducted a bilateral lower extremity duplex ultrasound study on all asymptomatic patients at 1-month post-surgery. The RCT included 33 total VTE events among 808 patients (4.1%) in the pharmacogenetically guided group and 38 events among 789 patients (4.8%) in the clinically guided group between days 1 and 60 after surgery (RR, 0.85; 95% CI, 0.54 to 1.34; p = .48). Most of the VTE events were ascertained in asymptomatic patients by duplex ultrasound at 1-month post-surgery: 23 VTE events of 33 in the intervention group and 23 of 38 in the control group were asymptomatic DVTs found by ultrasound. There were 10 (1.2%) symptomatic DVT or pulmonary embolism events in the intervention group and 15 (1.9%) in the control group. All other trials reported only symptomatic VTE events. Using a different type of outcome ascertainment, Gage et al. (2017) reported a relatively high proportion of events, and because of the large size of the study, the overall meta-analytic result (RR, 0.85; 95% CI, 0.56 to 1.28; p = .44) for thromboembolic events is heavily influenced by the Gage et al. (2017) trial (see Figure 7). No statistical heterogeneity was detected in the analysis (I^2 = 0%).

Center researchers conducted a subgroup analysis by comparator was also performed, as shown in Figure 8. Neither the trials with clinical algorithm control groups (RR, 0.89; 95% CI, 0.58 to 1.35) nor the trials with fixed-dose control groups (RR, 0.27; 95% CI, 0.03 to 2.38) showed a statistically significant difference between groups. The anticipated absolute effect (Table 3) was 5.1 fewer thromboembolic events per 1,000 people with pharmacogenetic testing (95% CI, 3.6 more to 13.8 fewer per 1,000 people). When the analysis was restricted to symptomatic events only, by comparator, the anticipated absolute effect was 3.7 (95% CI, -4.8 to 12.2) fewer thromboembolic events per 1,000 among the clinical algorithm comparator studies and 5.0 (95% CI, -0.65 to 10.7) fewer events per 1,000 people among the fixed-dose comparator studies. Center researchers rated the overall quality of evidence for this outcome as moderate.

Center researchers conducted a sensitivity analysis by removing the asymptomatic thromboembolic events from the Gage et al. (2017) RCT (Figure 9). The subgroup analysis excluding asymptomatic VTE events from Gage et al.[31] did not find a statistically significant difference (RR, 0.73; 95% CI, 0.40 to 1.34; I^2 = 0%). Analyzed by comparator, there were not statistically significant differences (clinical algorithm subgroup: RR, 0.81; 95% CI, 0.40 to 1.66; I^2 = 9%; fixed-dose comparator: RR, 0.27; 95% CI, 0.03 to 2.38; I^2 = 0%). The point estimates showed the same pattern as in the main analyses without the exclusion of asymptomatic thromboembolic events, more strongly favoring the intervention among the group of studies that used a fixed-dose comparison group.

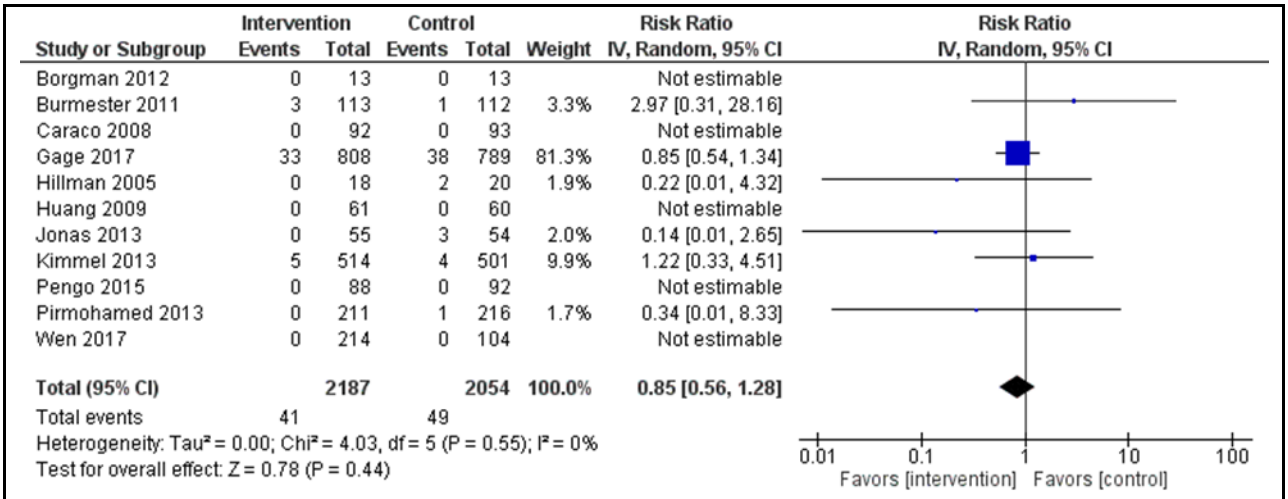


Figure 7. Meta-analysis of Pharmacogenetic Testing vs. Control for Thromboembolic Events

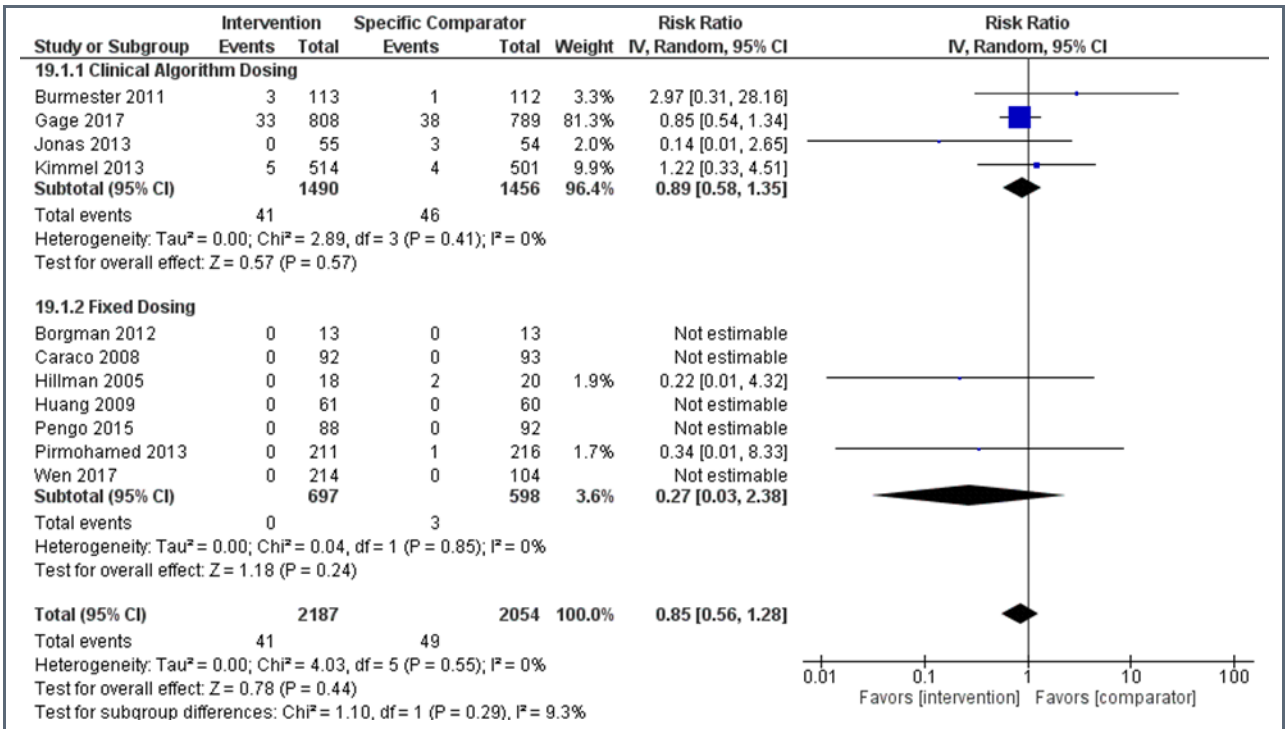


Figure 8. Meta-analysis of Pharmacogenetic Testing vs. Control by Comparator for Thromboembolic Events

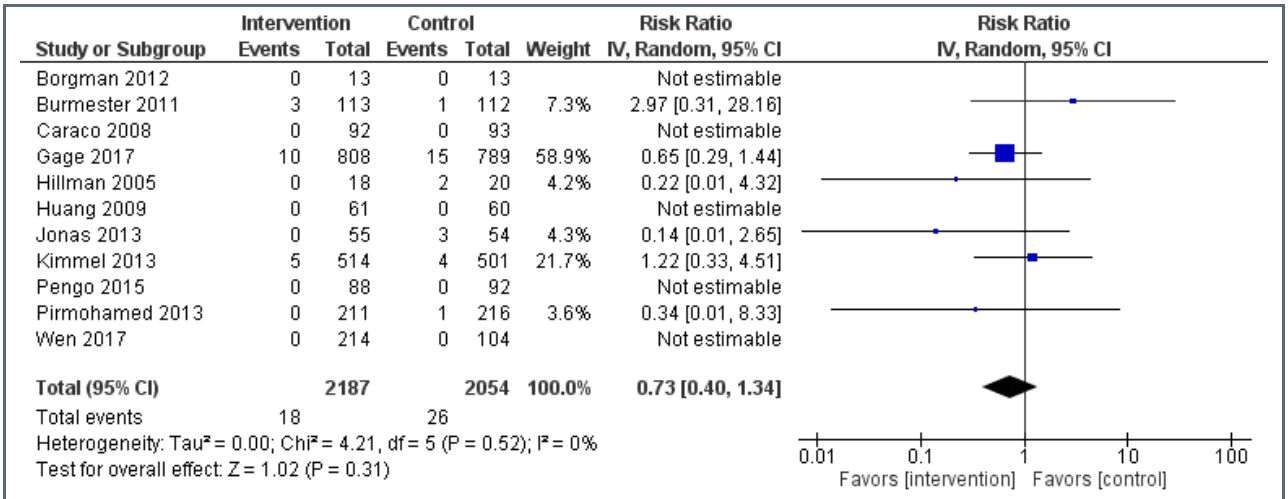


Figure 9. Meta-analysis of Pharmacogenetic Testing vs. Control for Thromboembolic Events With Asymptomatic Events from Gage et al. RCT Excluded

Percentage of Time in Therapeutic Range (PTTR)

All but 1[21,24-26,29,30] of the RCTs reported PTTR. Center researchers accepted any PTTR as defined by the study for meta-analysis. A PTTR of greater than 60%, and preferably 75%, is associated with improved outcomes for patients, including mortality, major bleeding, stroke, and heart attack.[41] However, many factors influence PTTR, from individual patient characteristics to the frequency of INR measurement and the organization and effectiveness of anticoagulation services.[42] Center researchers were unable to ascertain a minimal clinically significant level for differences in PTTR and noted that 8[7,21-23,28-31] of 12 RCTs in this meta-analysis did not have PTTR results in either group that met the 60% threshold.

Five trials defined the therapeutic range as an INR of 2 to 3. Gage et al. (2017) also used a 2 x 2 factorial for a target INR of 1.8 or 2.5 and used therapeutic ranges for this outcome of 1.5 to 2.1 and 2 to 3, respectively. Three trials[20,22,27] used an INR range of 1.8 to 3.2, and 1[28] used 1.8 to 3. Burmester et al. (2011) allowed an INR range of 2 to 3.5 and Hillman et al. (2005) did not report the range used.

The PTTR was also reported at different time intervals across studies. In general, these timeframes corresponded to the general study follow-up periods (see Table 4 and Table 7), and ranged from 14 to 90 days. Wen et al. (2017) reported PTTR separately for week 1 and week 2 and weeks 3 to 4, 5 to 9, and 10 to 12, but not an overall PTTR for the entire 12 weeks. For purposes of the meta-analysis, the PTTR for weeks 5 to 9 was included because it was the longest period of time for which the outcome was reported. Because the INR is generally more variable at the beginning of warfarin anticoagulation (generally within the first month of therapy), it would be reasonable to expect that trials that measured the PTTR over a longer period of time might find a higher proportion of in-range INRs. Center researchers planned a

subgroup analysis examining follow-up outcome reporting periods of ≤ 30 days or > 30 days to evaluate the possible contribution of time-of-outcome reporting to the overall effect.

In the overall analysis shown in Figure 10, the pharmacogenetically guided group had 3.1 percentage points more time in follow-up in the therapeutic range (mean difference, 3.11%; 95% CI, -0.28 to 6.50; p = .07), although the difference was not statistically significant and the analysis had significant heterogeneity (I^2 = 78%; Chi^2 = 50.86; p < .0001). The overall quality of evidence for this outcome was rated as low.

Center researchers conducted a prespecified set of subgroup analyses to explore sources of heterogeneity. A subgroup analysis by comparator (Figure 11) found no significant difference in the PTTR in studies using a clinical algorithm compared to a pharmacogenetically guided one (mean difference, 0.54%; 95% CI, -2.44 to 3.52; p = .72). Although the mean difference was larger and in favor of the pharmacogenetically guided group compared to the fixed-dose comparators (mean difference, 4.97 percentage points; 95% CI, -0.50 to 10.45; p = .07), this difference was only marginally significant. Although the difference between these subgroups was not statistically significant (Chi^2 = 1.94; p = .16), it is likely to be clinically meaningful given the tenfold difference between the point estimates. Additionally, only moderate statistical heterogeneity occurred in the clinical algorithm group (I^2 = 54%; Chi^2 = 6.49; p = .09), indicating that some of the statistical heterogeneity in the overall analysis was explained by the difference in comparators (i.e., clinical algorithm and fixed dosing). The fixed-dosing subgroup included all trials that Center researchers rated as having high risk of bias, which could account for some of the observed benefit of the pharmacogenetic testing group.

The subgroup analysis according to the number of genes tested (Figure 12) found a small inverse dose-response relationship. All of the estimates favored the pharmacogenetically guided intervention, although none of the estimates were statistically significant. With 1, 2, and 3 genes tested, the mean differences were 10.3%, 2.62%, and 0.65%, respectively. No meaningful difference was seen in the subgroup analysis by length of follow-up reporting for the PTTR outcome (Figure 13); the point estimates for ≤ 30 days and > 30 days were not statistically different, but favored the genetic intervention and were similar to the main effect estimate. Studies with a larger sample size (≥ 400 participants) had similar point estimates to studies with fewer participants, and both estimates were similar to the main effect estimate (Figure 14).

As shown in Figure 15, the subgroup analysis by indication for anticoagulation found higher PTTR for pharmacogenetically guided dosing in patients who had orthopedic surgery in 1 trial[31] (mean difference, 3.40%; 95% CI, 1.00 to 5.80; p = .005) and valve replacement in another trial[28] (mean difference, 12.40; 95% CI, 5.49 to 19.31; p = .0004), although there was no significant difference for AFib (mean difference, -1.30%; 95% CI, -6.75 to 4.15; p = .64) or trials with a mix of indications (mean difference, 2.49%; 95% CI, -2.19 to 7.17; p = .30). A subgroup analysis by race (Figure 16) found a similar effect for the White and Asian subgroups compared to the overall analysis, but a wider confidence interval and higher degree of statistical heterogeneity for

studies with a 90% or greater Asian population,[28,29] indicating that race could have some contribution to the statistical heterogeneity found in the main analysis.

A subgroup analysis comparing studies conducted inside or outside of the U.S. (Figure 17) did not find statistically significant differences, but the point estimate for studies outside the U.S. was about 5 times higher than for studies conducted in the U.S. (mean difference, 5.82%; 95% CI, -1.59 to 13.22; p = .12 vs. 1.12%; 95% CI, -1.02 to 3.26; p = .31). This might in part reflect heterogeneity stemming from the racial composition of the population, but might indicate some additional effect from the grouping of 3 studies[24,28,29] with high risk of bias and 2[26,30] with moderate risk of bias among studies conducted outside the U.S.

As shown in Figure 18, RCTs with a high risk of bias, all of which used a fixed-dosing approach in the control group, were more likely to favor the pharmacogenetically guided intervention (mean difference, 6.57%; 95% CI, -2.94 to 16.07; p = .18) compared to those with a low risk of bias (mean difference, 1.24%; 95% CI, -2.15 to 4.64; p = .47) or a moderate risk of bias (mean difference, 1.49%; 95% CI, -3.25 to 6.23; p = .54). Although none of these subgroups were statistically significantly different, the groups with low and moderate risk of bias appear to be different, with estimates closer to the null (i.e., 0.00), compared to the high risk of bias group. These differences might account for some of the heterogeneity in the main analysis in that the lowest level of statistical heterogeneity is in the low risk of bias trials (I^2 = 53%; Chi^2 = 4.30; p = .12).

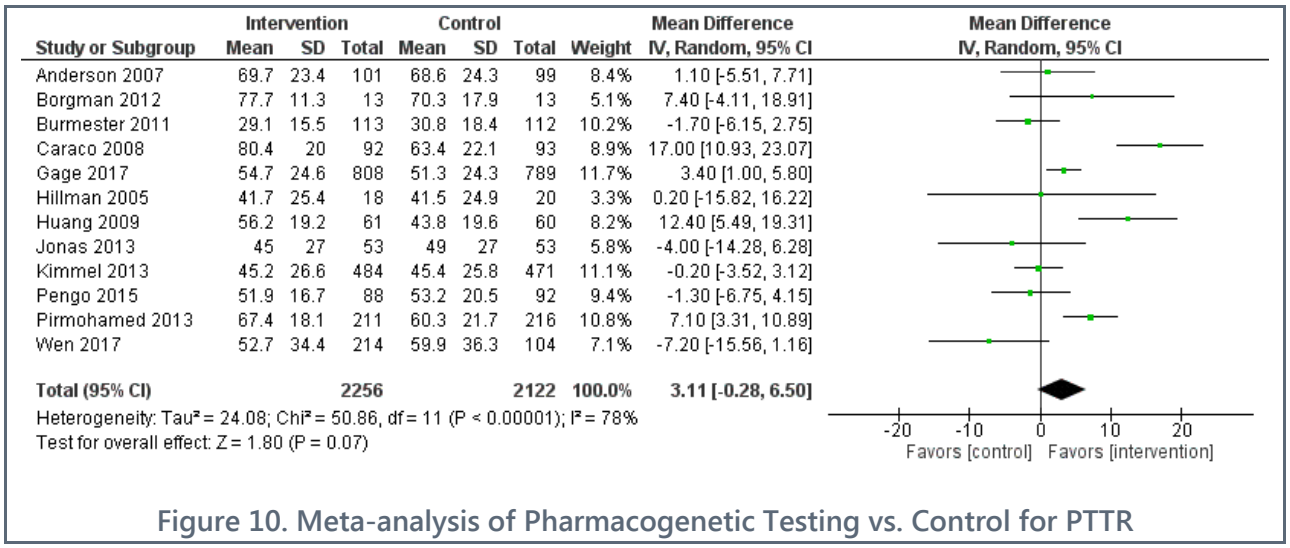


Figure 10. Meta-analysis of Pharmacogenetic Testing vs. Control for PTTR

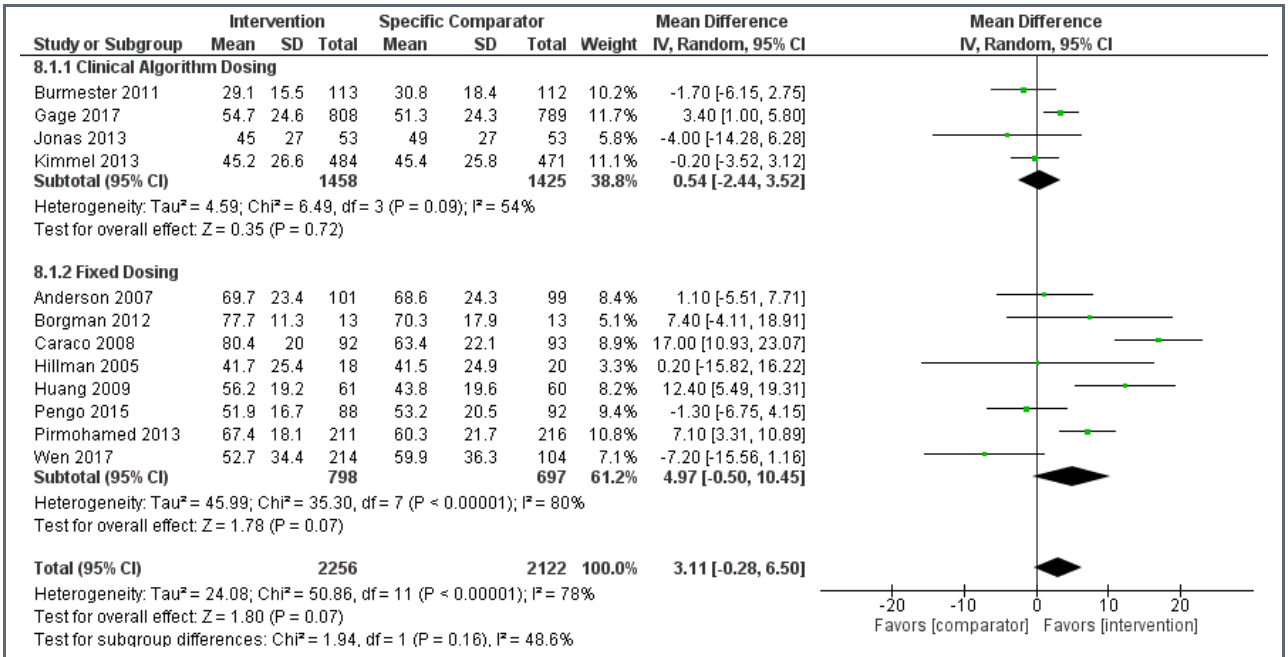


Figure 11. Meta-analysis of Pharmacogenetic Testing vs. Control by Comparator for PTTR

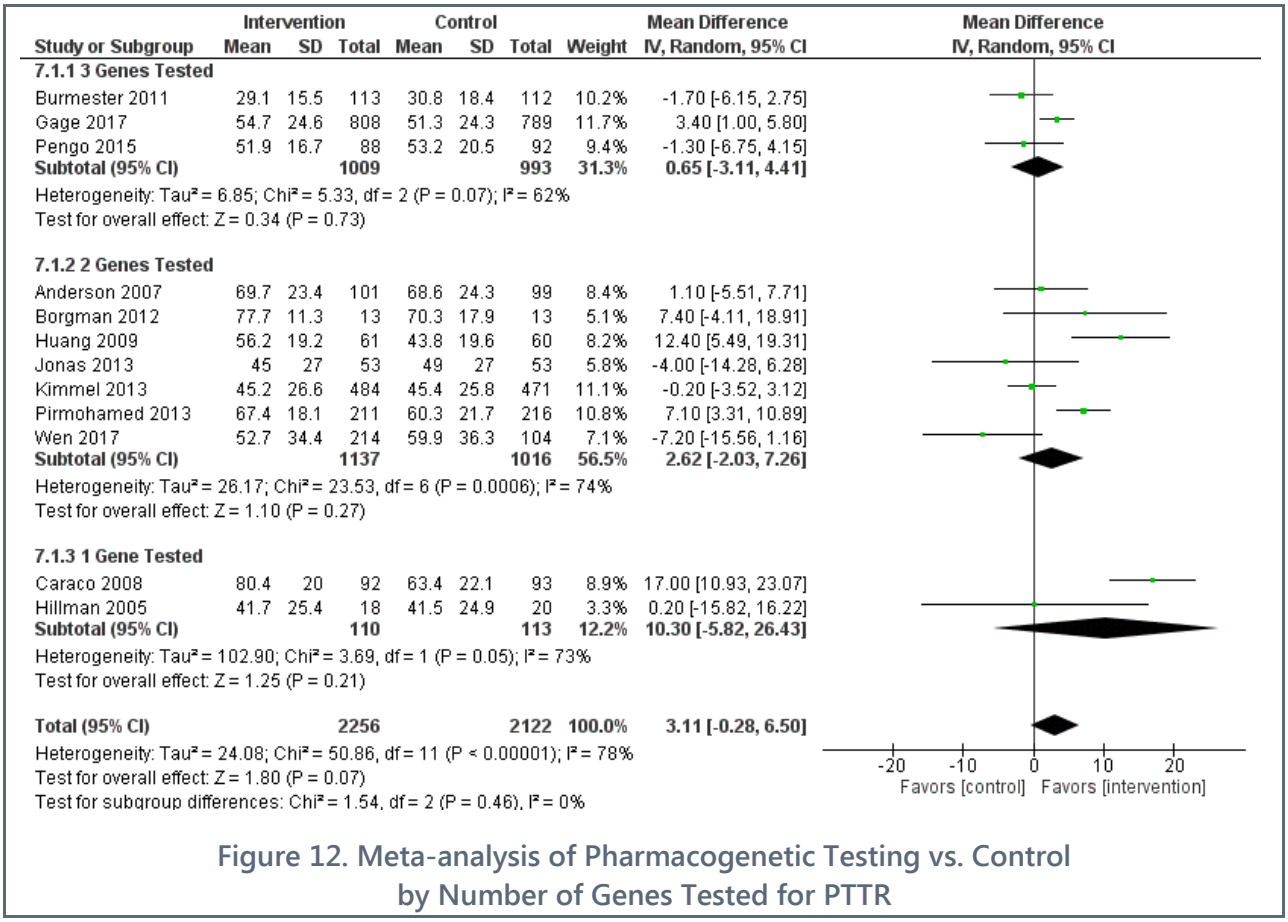


Figure 12. Meta-analysis of Pharmacogenetic Testing vs. Control by Number of Genes Tested for PTTR

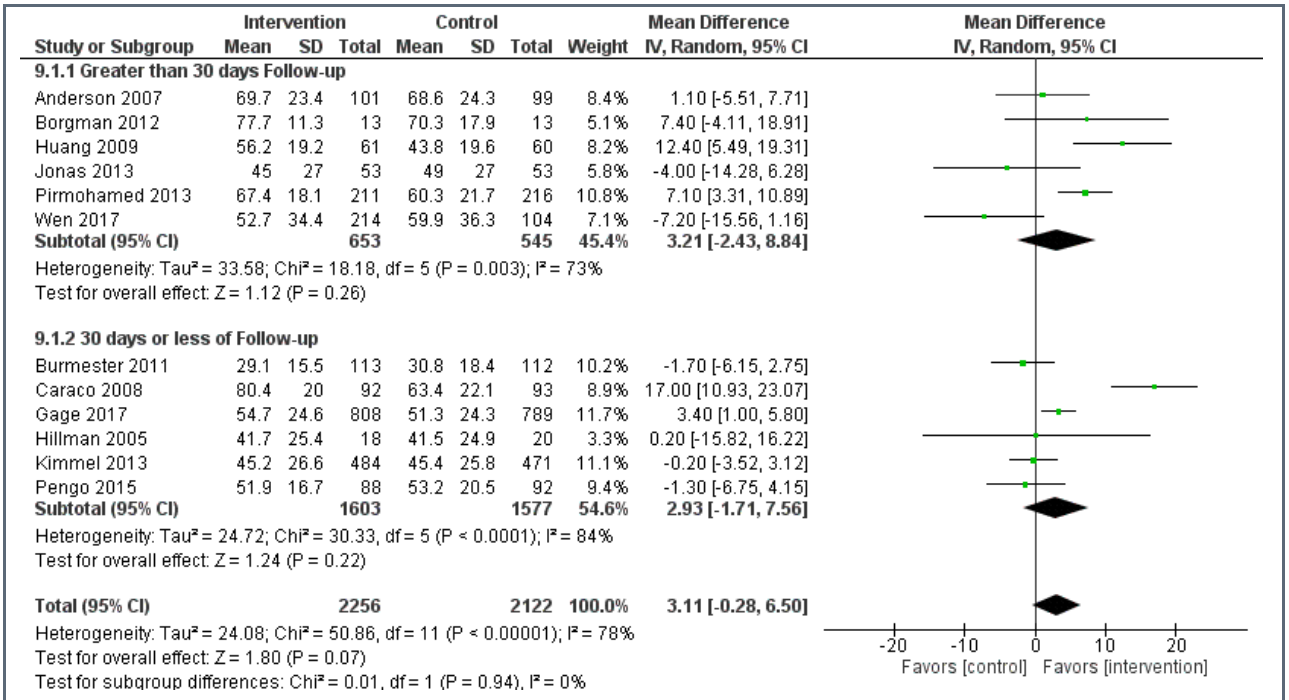


Figure 13. Meta-analysis of Pharmacogenetic Testing vs. Control by Length of Follow-up for PTTR

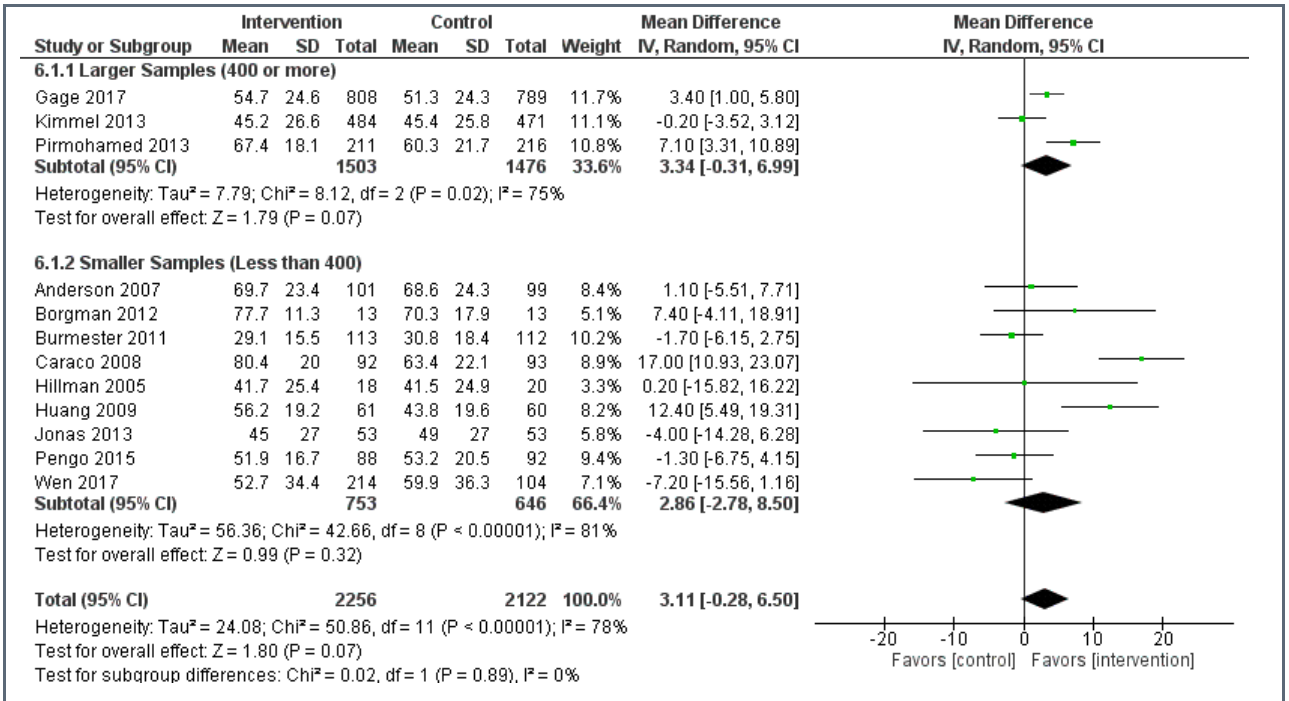


Figure 14. Meta-analysis of Pharmacogenetic Testing vs. Control by Sample Size for PTTR

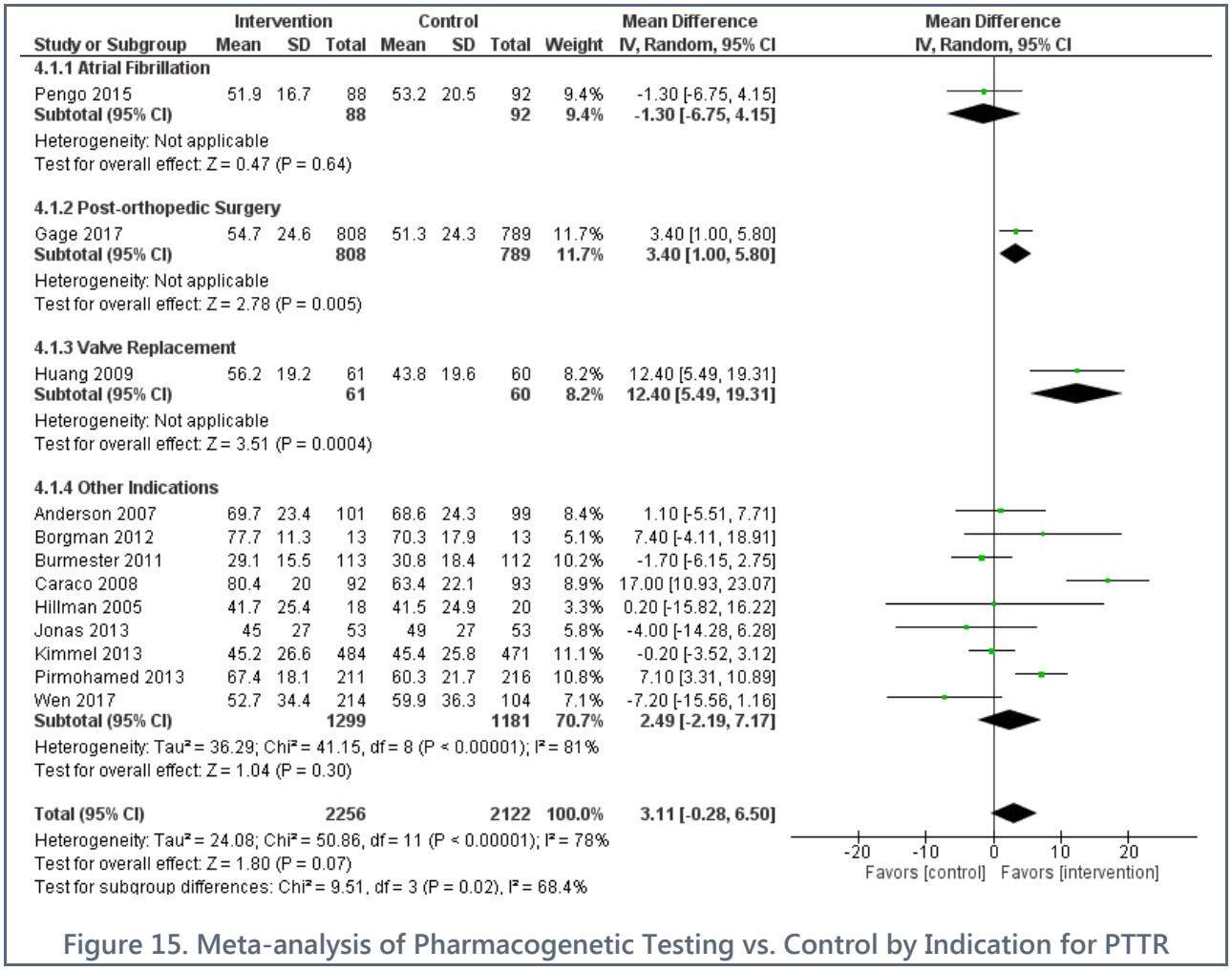


Figure 15. Meta-analysis of Pharmacogenetic Testing vs. Control by Indication for PTTR

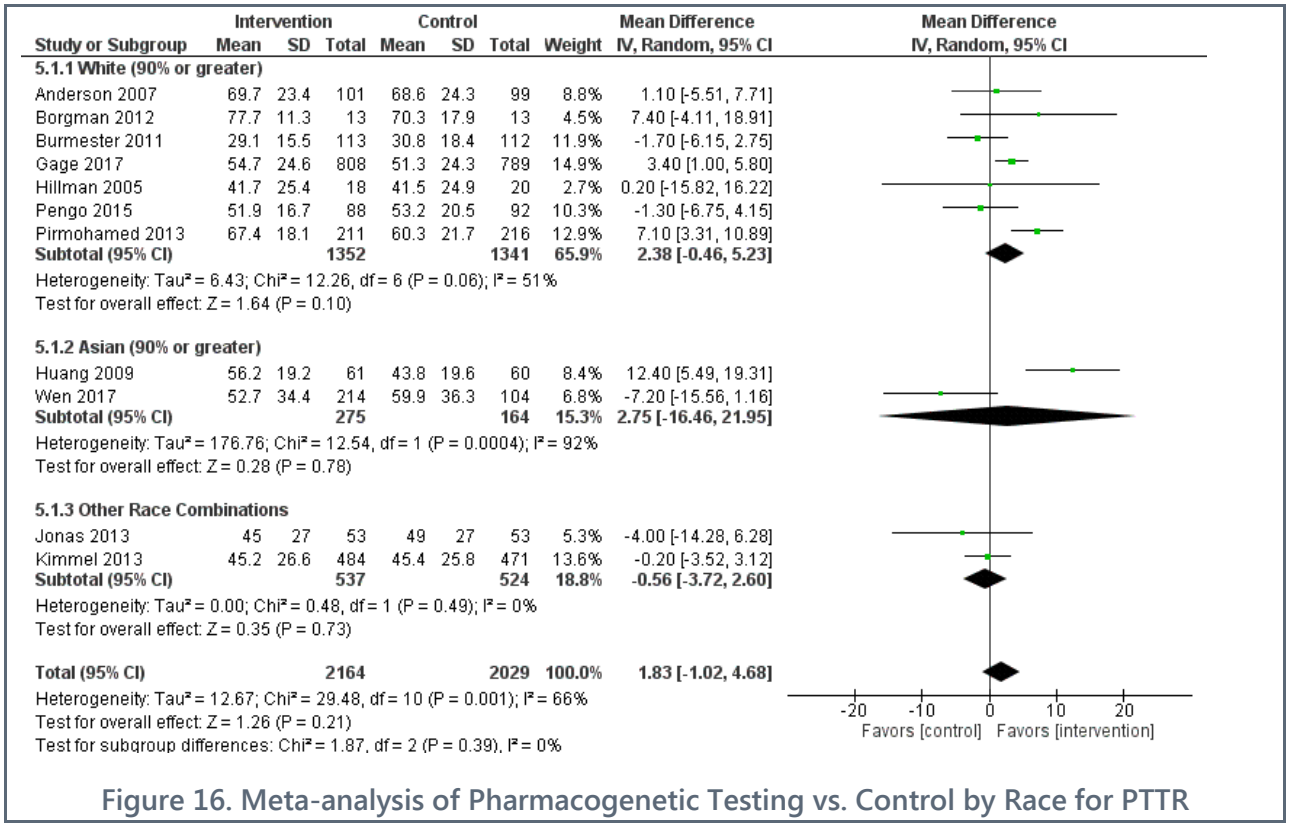


Figure 16. Meta-analysis of Pharmacogenetic Testing vs. Control by Race for PTTR

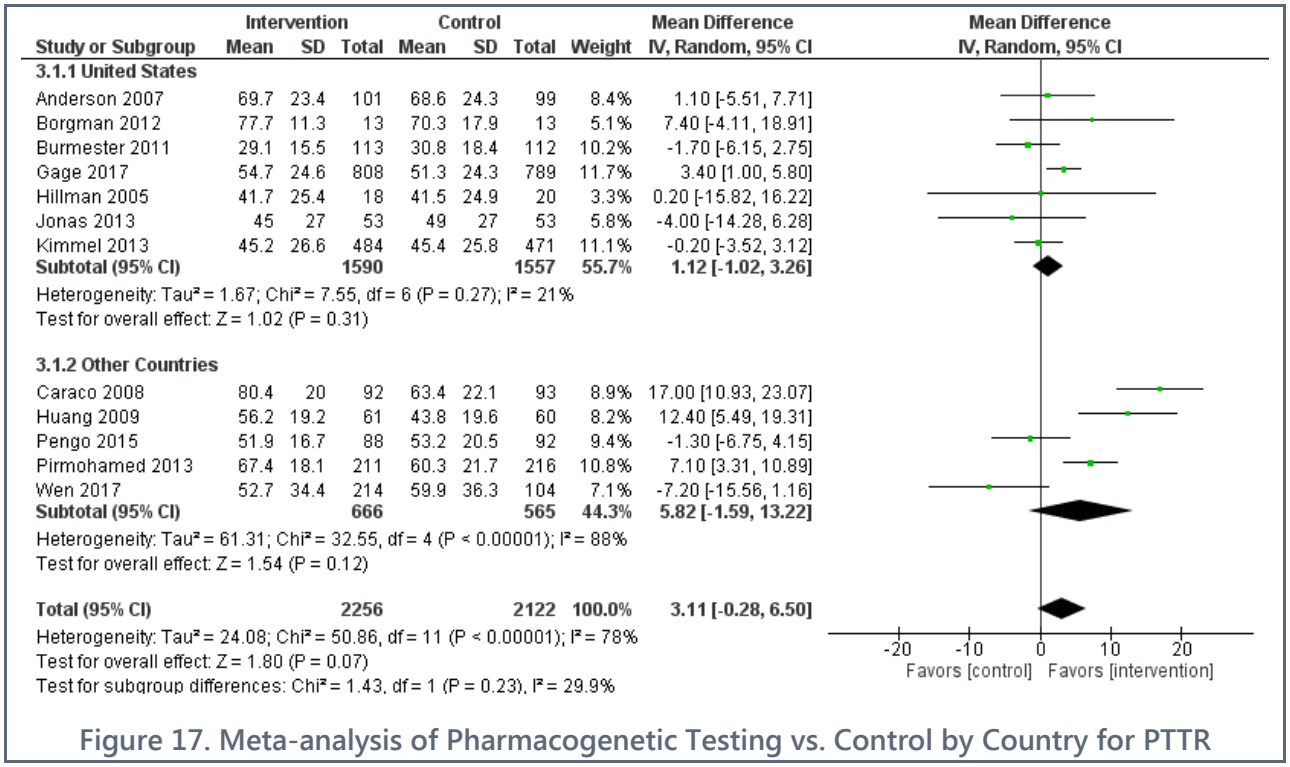


Figure 17. Meta-analysis of Pharmacogenetic Testing vs. Control by Country for PTTR

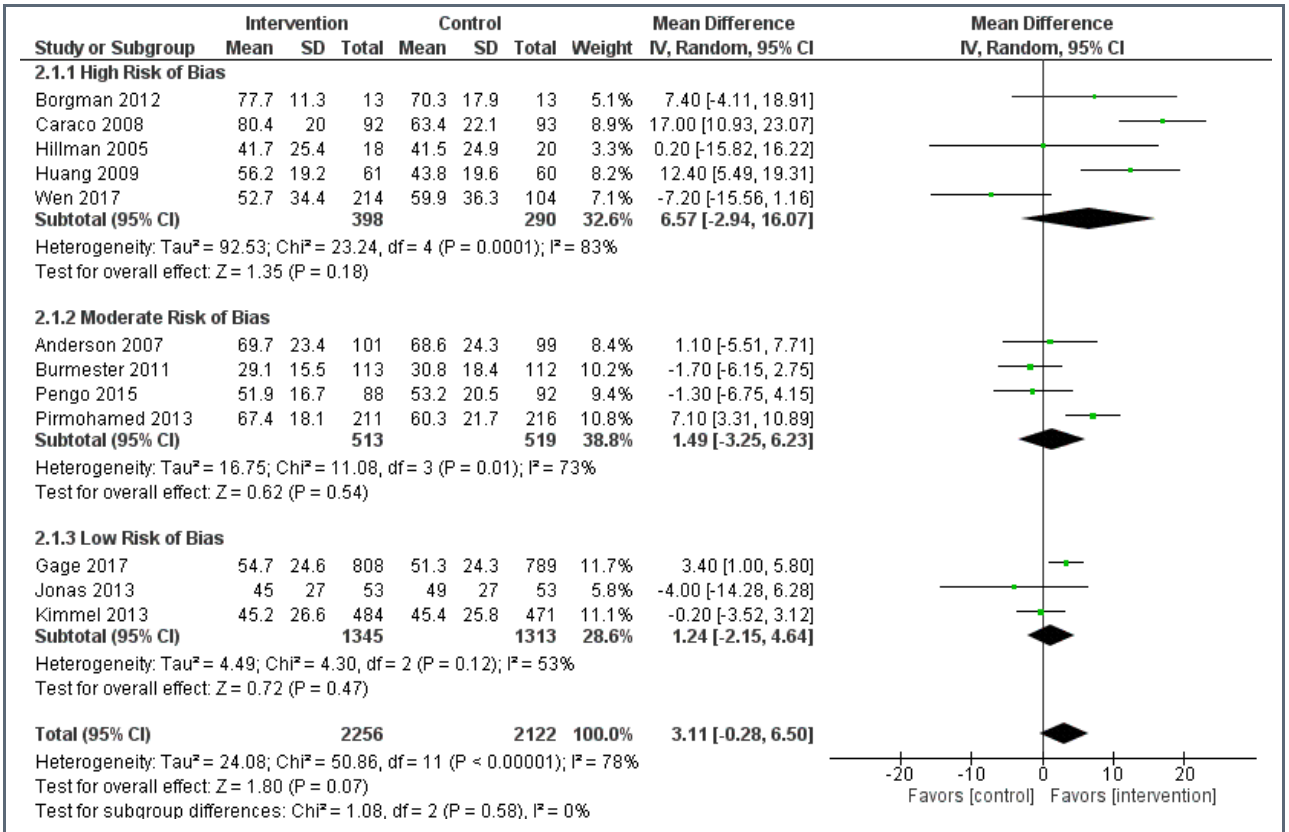


Figure 18. Meta-analysis of Pharmacogenetic Testing vs. Control by Risk of Bias for PTTR

Overanticoagulation (INR ≥ 4)

Nine trials reported an INR measurement of 4 or more (INR ≥ 4) and 1 trial reported an INR of 3.5 or more (INR ≥ 3.5) and were included in the meta-analysis for this outcome. Studies did not report proportions of patients who had INRs at a level that might require therapeutic intervention, such as level 7.[43] Most INR levels of 5 to 7 require only rechecking the INR or holding a dose,[43] but RCTs did not report data about bleeding events correlated with INR or about interventions required for high INR values. Trials reported INR for different time periods. For example, 4 trials[20,21,23,31] reported whether the outcome had occurred by 1 month (ranging from 28 to 30 days), and 3 trials[22,26,29] reported occurrence of the outcome by 3 months (ranging from 84 to 90 days). Given that the trials had different lengths of follow-up, the timeframe for individuals to experience overanticoagulation varied somewhat among trials. When Huang et al. (2009) was grouped with the other 9 trials, there was not a meaningful difference in the estimated effect for the main analysis or any of the subgroup analyses. The effect sizes and the confidence intervals did not change or changed by a very small amount (e.g., 0.01) with or without this trial.

In the overall meta-analysis that included 10 trials, 340 events occurred among 2,095 participants in the pharmacogenetically guided group (16.2%) and 354 events occurred among 1,961 participants in the control group (18.1%). As shown in Figure 19, Center researchers

observed a 9% improvement in favor of the pharmacogenetically guided intervention, but the difference was not statistically significant (RR, 0.91; 95% CI, 0.80 to 1.04; p = .16). No statistical heterogeneity was detected in this analysis (I^2 = 0%). The anticipated absolute effect (Table 3) was 18.2 fewer people per 1,000 who experienced overanticoagulation with pharmacogenetic testing (95% CI, 5 more people to 41.5 fewer people per 1,000). Center researchers rated the overall quality of evidence for this outcome as low.

Several prespecified subgroup analyses were also performed. In the subgroup analysis by comparator (see Figure 20), the pharmacogenetically guided intervention performed more similarly to the clinically guided group (RR, 0.95; 95% CI, 0.78 to 1.15; p = .58). The estimate for the fixed-dose comparator group was also not statistically significant, but was lower than the main analysis (RR, 0.83; 95% CI, 0.67 to 1.04; p = .11). No significant difference was found between these 2 subgroups (p = .39). The subgroup analysis conducted by indication for anticoagulation (see Figure 21) found a statistically significant effect in favor of the intervention among patients who had orthopedic surgery (RR, 0.71; 95% CI, 0.51 to 0.99; p = .04). Gage et al. (2017) was the only study to contribute to this outcome. No statistically significant differences were found for AFib, valve replacement, or other indications.

In another subgroup analysis, Center researchers combined trials that occurred in the U.S. and trials that occurred outside the U.S. (see Figure 22). No meaningful difference in INR was found in the U.S. trials, but studies in other countries showed a marginally statistically significant reduction of 21% in the pharmacogenetically guided group compared to controls (RR, 0.79; 95% CI, 0.62 to 1.00; p = .05). The Chi^2 test for differences in subgroups was not statistically significant (p = .17). The forest plots for additional analyses are in Appendix E. None of these other subgroup analyses yielded findings that helped to explain the main effect: number of genes tested (Figure 27), race (Figure 28), sample size (Figure 29), length of follow-up (Figure 30), or risk of bias (Figure 31).

Overanticoagulation puts the patient at risk of bleeding.[43] There are likely to be "overshoots" during initiation of warfarin therapy, but with close monitoring, risks can be minimized.[43] A supratherapeutic INR that is less than 5.0 generally requires no action more aggressive than holding a dose or checking the INR again. Therefore, the clinical significance of the meta-analytic finding, even if it were statistically significant, is unclear.

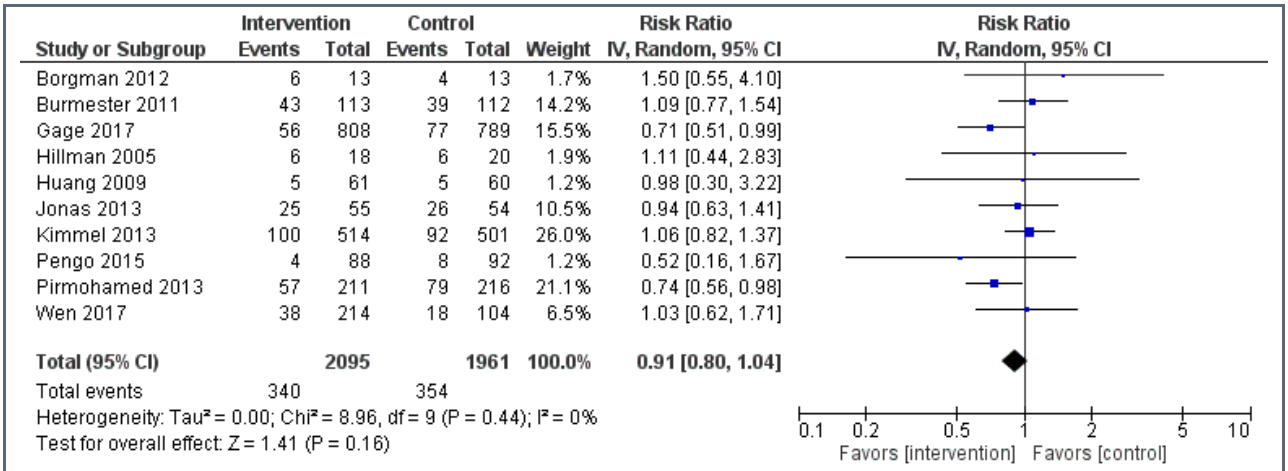


Figure 19. Meta-analysis of Pharmacogenetic Testing vs. Control for INR ≥ 4

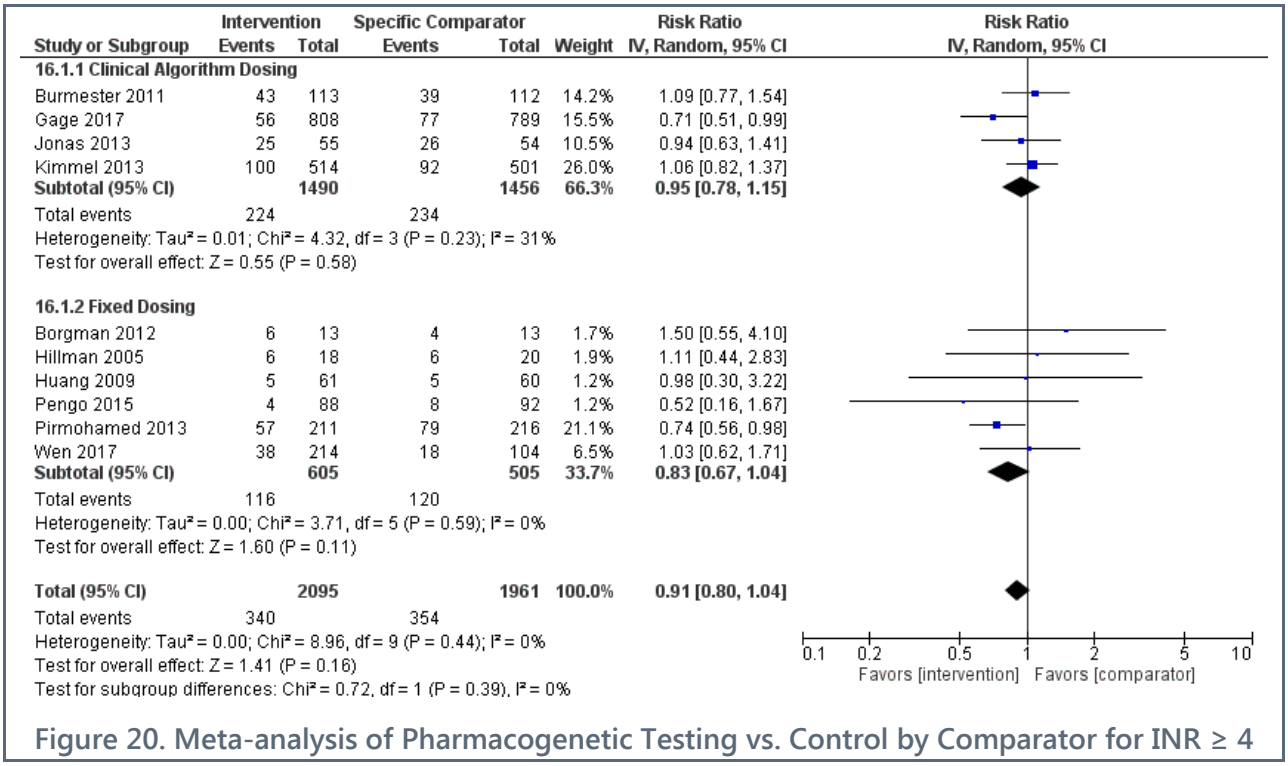


Figure 20. Meta-analysis of Pharmacogenetic Testing vs. Control by Comparator for INR ≥ 4

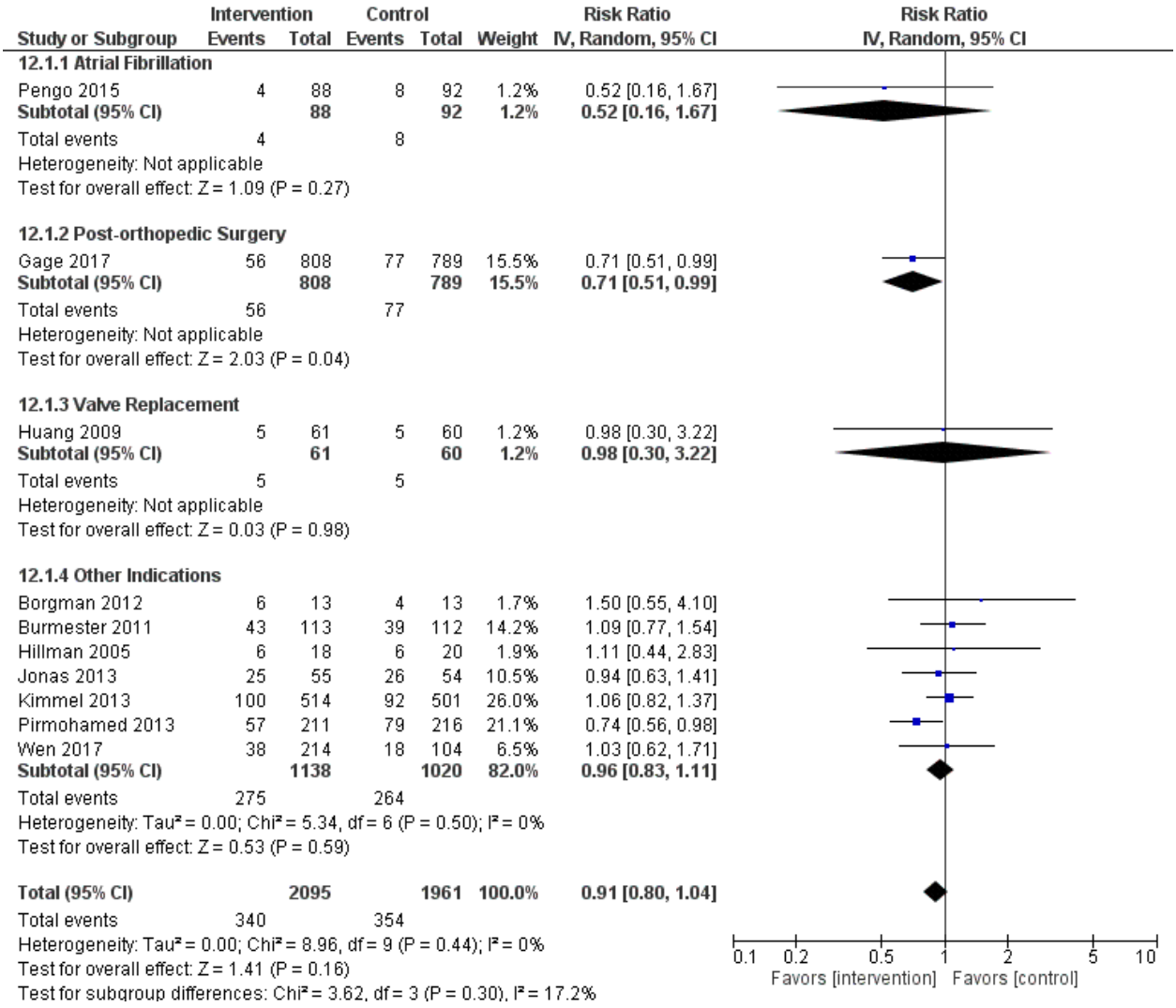


Figure 21. Meta-analysis of Pharmacogenetic Testing vs. Control by Indication for INR ≥ 4

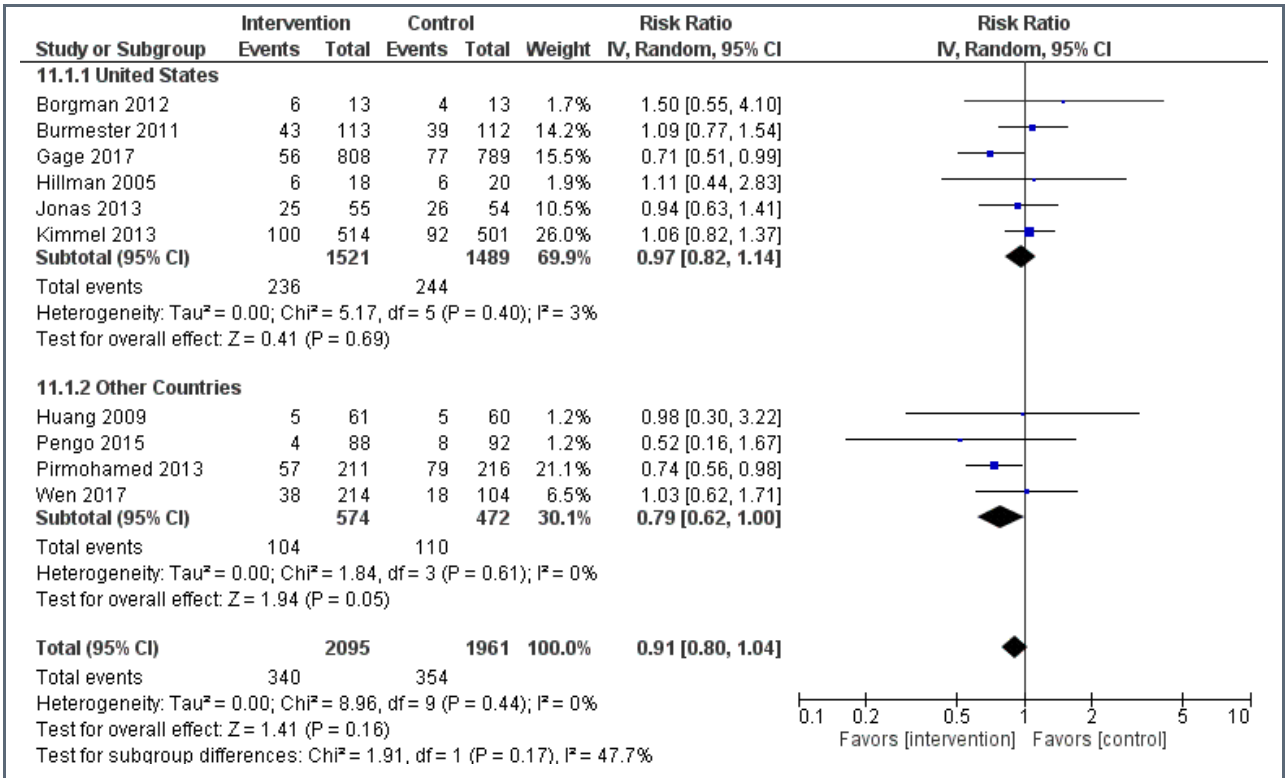


Figure 22. Meta-analysis of Pharmacogenetic Testing vs. Control by Country for INR ≥ 4

Additional Outcomes

In addition to the primary outcomes, Center researchers included 13 RCTs in the meta-analyses that also reported additional outcomes of interest. These other outcomes fell into 3 main categories: time to a stable INR or stable warfarin dose (reported in 7 RCTs), time to a therapeutic INR or proportion of patients reaching that goal by a certain timeframe (reported in 8 RCTs), and adverse events (reported in 7 RCTs). Although these outcomes were reported across many of the studies, they were not reported with enough uniformity to allow meaningful meta-analyses. Table 8 contains detailed information about the results of each study for these additional outcomes.

Time to stable INR or stable warfarin dose

Seven studies reported some measure of time to a stable INR or stable warfarin dose.[20,24-26,28-30] Studies reported time in days, although studies reported either mean [25,30] or median[26,28,29] days and 2 studies[20,24] did not specify which measure was used. The definition of "stable" also varied among studies and included having an INR of 1.8 to 3.2 for a minimum of 4 consecutive days;[20] the first of 3 INRs within a therapeutic range;[30] the first of 2 INR values within the therapeutic range, with INRs measured at least a week apart;[26,29] and the dose that led to an INR in the therapeutic range INR in at least 7 days.[25] Other studies did not specify the definition of stability. The number of days to reach these measures varied widely. For example, Pengo et al. (2015) reported that the pharmacogenetic group achieved a stable INR in a mean of 5.9 days (95% CI, 5.00 to 9.93) compared to 5.05 days (95% CI, 4.24 to 5.86; p = .28) in the fixed-dose comparator

group.[30] Pirmohamed et al. (2013) reported that the median days to a stable warfarin dose was 44 in the pharmacogenetic group versus 59 in the fixed-dose comparator group (HR, 1.40; 95% CI, 1.12 to 1.74; p = .003).[26] In summary, the pharmacogenetically guided groups generally had shorter times to attaining a stable INR, but no differences were statistically significant and comparison is limited because of different interventions, comparators, outcome measures, and measurement timeframes.

Time to a therapeutic INR

Similar to the outcome of time to a stable INR or stable warfarin dose, studies reported a variety of measures for the time to a therapeutic dose of warfarin. Although these 3 categories of outcomes are similar and obviously related, they differ in that the time to a therapeutic INR can be defined based on one measure only and the time to stability is usually longer. Two studies[20,27] defined the time to a therapeutic INR as the proportion of patients with a therapeutic INR on day 5 and reported that proportion on day 8. Anderson et al. (2007) reported that 69.7% in the pharmacogenetic group had a therapeutic INR on day 5 and 68.8% did on day 8, compared to 68.3% at day 5 and 63.0% at day 8 in the fixed dose comparison group.[27] At neither time period was the difference statistically significant. The substantially smaller pilot study by Borgman et al. (2012) that also used a fixed-dose comparator reported day 5 proportions of 69.2% versus 38.5% (p = .12) and day 8 proportions of 100% vs. 61.5% (p = .01). Jonas et al. (2013) reported the proportions with a therapeutic INR by day 30 (11% vs. 15%) and by day 90 (21% vs. 26%) for the pharmacogenetic and clinical algorithm groups, respectively.[22] At neither time period were the differences between the pharmacogenetic and clinical algorithm groups statistically significant.[22] Kimmel et al. (2013) reported that similar proportions of patients achieved a therapeutic INR by day 14 of 81% for the pharmacogenetic group versus 85% for the clinical algorithm group (HR, 0.94; 95% CI, 0.82 to 1.1).[21] Pengo et al. (2015) did not find a statistical difference in the proportions by day 19: 68.2% in the pharmacogenetic group versus 65.2% in the fixed-dose comparison group (p = .67).[30]

Three studies reported the number of days to a therapeutic INR. These ranged from less than a week in the Caraco et al. (2008)[24] study (4.8 ± 1.46 days in the pharmacogenetic group vs. 7.5 ± 3.06 days in the clinical algorithm group; p < .001) to more than 3 weeks in the Pirmohamed et al. (2013) study (21 days vs. 29 days; HR, 1.43; 95% CI, 1.17 to 1.76). In summary, the results for the outcome of time to a therapeutic INR were more mixed than the time to a stable INR; studies found no difference or some benefit to the pharmacogenetic dosing interventions. Comparison was also limited by differences in interventions, comparators, outcome measures, and measurement timeframes.

Adverse events

The outcomes of major bleeding and thromboembolic events were explored in the meta-analysis. Several studies reported additional or more detailed adverse events. Six[21,25-28,31] of the 7 studies that reported additional adverse events reported composites that included events such as major bleeding, VTE, and mortality that were analyzed independently in the meta-analysis. All

adverse events reported across studies were secondary outcomes, and the trials were likely underpowered to detect meaningful differences, so interpretation of any finding should be cautious. As with the definitions of other additional outcomes, the definitions of serious adverse events varied across studies.

In addition to the composite measures they reported, Gage et al. (2017) reported cardiovascular events of 3 types: myocardial infarction, stroke, and AFib. There were a small number of events overall and no statistical differences between the pharmacogenetically and clinically-guided dosing groups. No statistically significant differences existed between groups in either the incidence or location of infections. Subgroup analyses for the PTTR outcome by Gage et al. (2017) did find statistically significant differences based on the INR target (1.8 vs. 2.5): a 1 mg or greater difference in the predicted warfarin dose based on the 2 algorithms and race. The PTTR was statistically different for the INR target of 2.5, but not for 1.8 (mean PTTR difference, 5.8; 95% CI, 2.5 to 9.1; p = .001), but was not for the INR target of 1.8 (mean PTTR difference 1.1, 95% CI, -2.2 to 4.5). If the 2 algorithms predicted a 1 mg or greater difference in warfarin dose, there was a difference in PTTR between the groups (mean PTTR difference, 7.0; 95% CI, 3.4 to 10.6; p < .001), but there was no difference for a discrepancy of < 1 mg (mean PTTR difference, 0.9; 95% CI, -2.2 to 4.0; p = .57). No difference in the 2 dosing algorithms was observed for Black patients (mean PTTR difference, 0.2; 95% CI, -8.9 to 9.4; p = .96), but a difference was apparent for non-Black patients (mean PTTR difference, 3.7; 95% CI, 1.2 to 6.1; p = .003).

Key Question 2: Harms

Harms outcomes are reflected in several items described under Key Question 1. Mortality, major bleeding, and VTE are all adverse outcomes and occurred with pharmacogenetically guided warfarin dosing and all comparators, including clinically guided and fixed-dose warfarin initiation. Other adverse events reported are also described in the additional outcomes subsection under Key Question 1. Patients with an indication for oral anticoagulation to prevent VTE have increased risk of thrombosis if they are not sufficiently anticoagulated and, on the other hand, increased risks of bleeding if they are sufficiently anticoagulated. These are not harms, per se, of pharmacogenetic testing, but represent known risks of both anticoagulation and the patient's underlying indication and comorbid health factors.

Major bleeding, VTE events, overanticoagulation, and PTTR all had point estimates indicating benefit for pharmacogenetic dosing. However, none of these differences was statistically significant, with the exception of major bleeding. There was a 57% lower risk of bleeding in the pharmacogenetically guided groups overall, although the total number of events was small (29 of 2,054 in the control groups vs. 12 of 2,187 in the pharmacogenetic groups). The quality of evidence for the outcome was moderate and future research could affect knowledge about the effect compared to standardized algorithm dosing.

Key Question 3: Subpopulations

Three subgroup analyses, by clinical indication and by race, for the major bleeding, PTTR and overanticoagulation outcomes are relevant to this question. These subgroup analyses were not

performed for the other outcomes because the number of studies and outcome events were more limited. The subgroup analyses by race should be considered exploratory because of the inability to conduct individual patient meta-analysis and the limited racial information included in most studies. In addition, the RCT by Caraco et al.[24] did not report race or ethnicity as a participant characteristic, and was therefore not included in these analyses. Racial composition of individual studies is detailed in Table 6 of Appendix C. There were no statistically significant subgroup differences by race (White vs. Asian vs. racially and ethnically mixed study populations) for either PTTR or overanticoagulation. For both outcomes, the point estimates favored the pharmacogenetic intervention for White participants (PTTR: mean difference 2.3%; 95% CI, -0.46 to 5.23; I^2 = 51%, and INR ≥ 4; RR, 0.84; 95% CI, 0.68 to 1.04; I^2 = 21%). For the subgroup analysis of major bleeding by race, the risk, although favoring the intervention, was not statistically significantly different for White or Asian subgroups. However, for the two studies with other race combinations,[21,22] the difference was statistically significant in favor of the intervention (RR, 0.35; 95% CI, 0.13 to 0.97; I^2 = 0%).

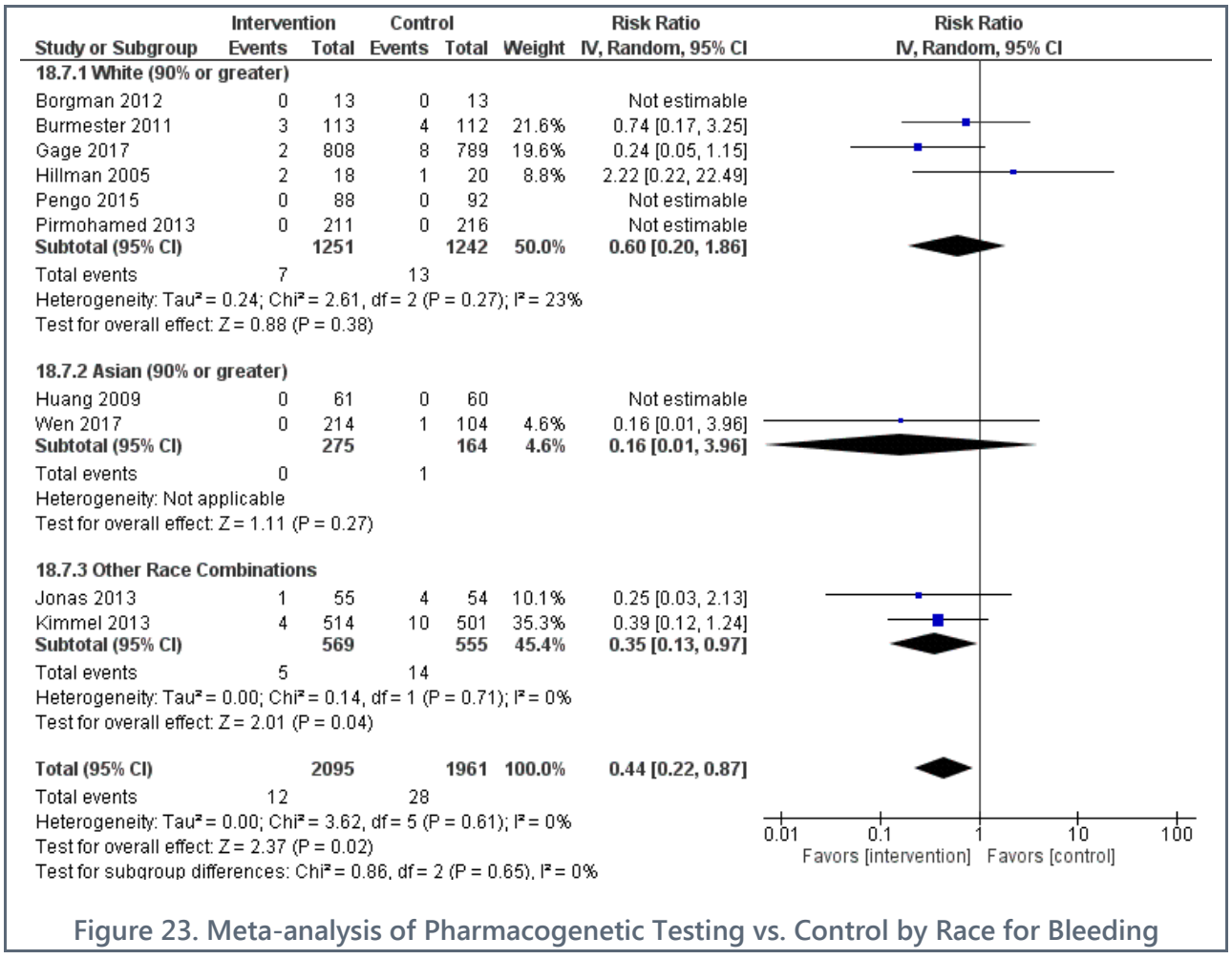


Figure 23. Meta-analysis of Pharmacogenetic Testing vs. Control by Race for Bleeding

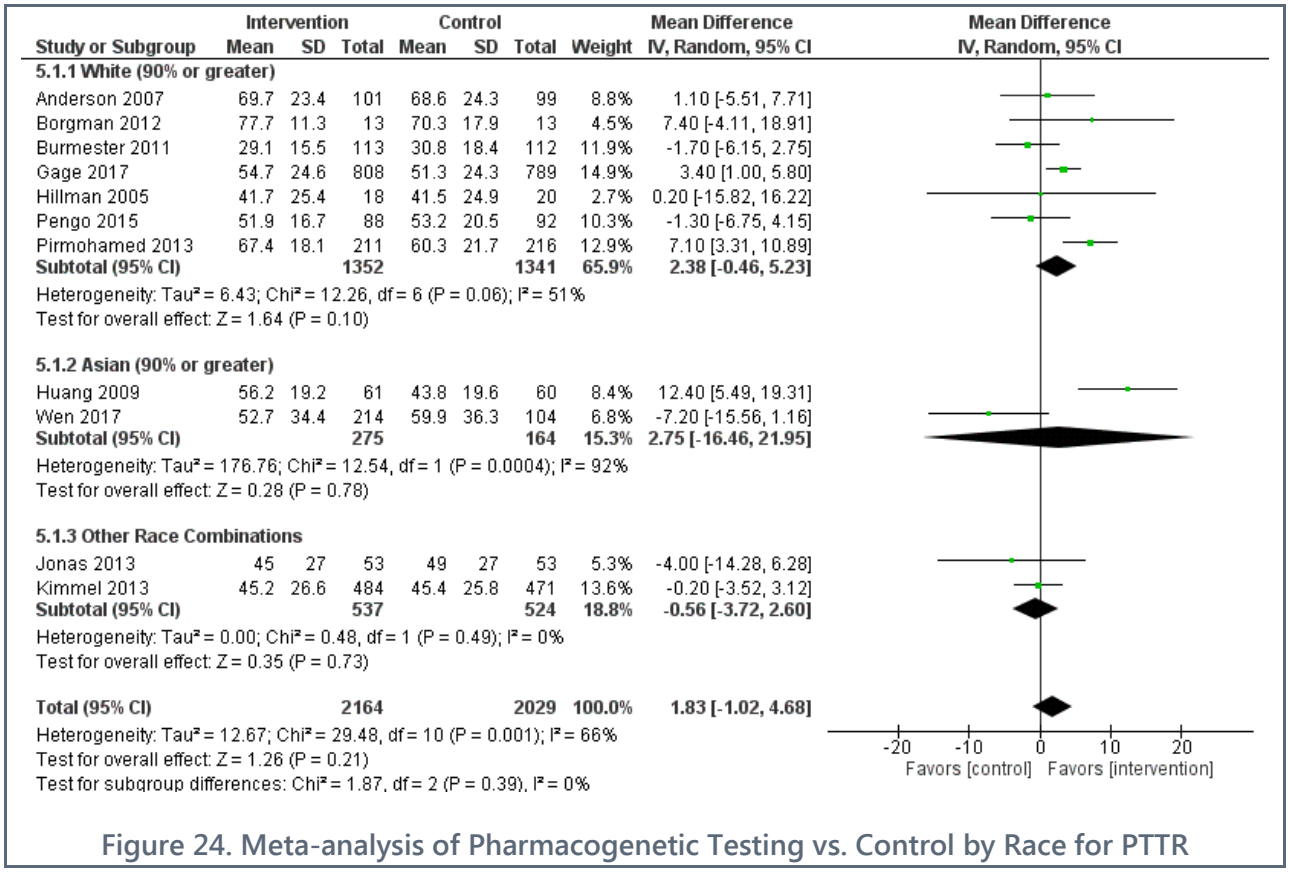


Figure 24. Meta-analysis of Pharmacogenetic Testing vs. Control by Race for PTTR

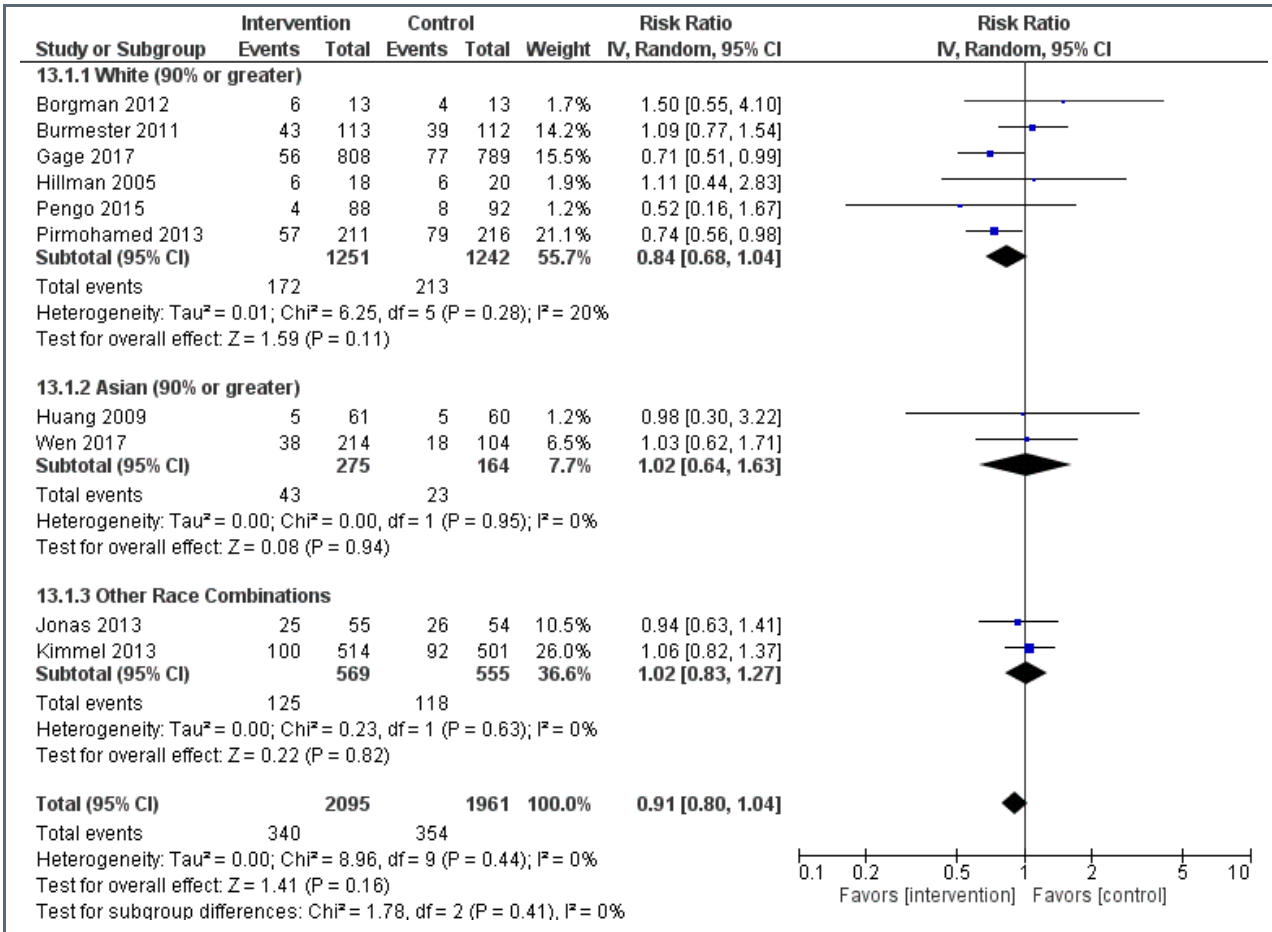


Figure 25. Meta-analysis of Pharmacogenetic Testing vs. Control by Race for INR ≥ 4

The subgroup analysis for major bleeding by indication did not demonstrate a statistically significant difference for any of the indications that could be analyzed (orthopedic surgery or a broad group of studies with other and mixed indications). However, both subgroups had point estimates that favored the pharmacogenetic intervention (orthopedic surgery: RR, 0.24; 95% CI, 0.05 to 1.15; and other indications: RR, 0.49; 95% CI, 0.23 to 1.04; I^2 = 0%). Subgroup analyses for AFib and cardiac valve replacement were not possible because there were no events in either study group.

The subgroup analyses of PTTR according to the indication for anticoagulation (AFib, orthopedic surgery for hip or knee replacement, heart valve replacement, and mixed other indications) demonstrated a benefit for the pharmacogenetic intervention for orthopedic surgery (mean difference, 3.4%; 95% CI, 1.00 to 5.80) and valve replacement (mean difference, 12.40; 95% CI, 5.49 to 19.31). However, for the orthopedic surgery subgroup, the 95% CI touched 1.0, and was very similar to the overall point estimate from the main analysis. The point estimate for the valve replacement subgroup was about 3 times higher than the main effect estimate, which might indicate a true effect in that clinical setting, but could also be due in part to differences in the comparator employed, country of study, participants' age and race, and length of follow up.

Both estimates were based on only 1 study each, Gage et al. (2017) for orthopedic surgery and Huang et al. (2009) for valve replacement. Although Center researchers rated the Gage et al. (2017) study as having a low risk of bias and it was adequately powered, the Huang et al. (2009) study was small and rated as having a high risk of bias.

In the subgroup analyses of overanticoagulation by indication, a difference in favor of the pharmacogenetic intervention was noted for the orthopedic surgery subgroup, but for no other subgroups (RR, 0.71, 95% CI, 0.51 to 0.99). Again, only Gage et al. (2017) contributed data to this subgroup. Because of reporting of race by the various RCTs, a subgroup meta-analysis of any outcome for Black patients could not be performed. However, Gage et al. (2017) did report the PTTR for Black patients compared to all other races enrolled in the RCT. They found a statistically significant effect only for the group of patients of other races (91% of the study participants were White and 6.4% were Black). For participants of other races, the mean difference for PTTR was 3.7%, 95% CI, 1.2 to 6.1, p = .003), and for Black participants there was no difference from the pharmacogenetic intervention (mean difference 0.2%, 95% CI, -8.9 to 9.4, p = .96). This finding might reflect the lack of prevalence of *CYP2C9* alleles *2 and *3 in African American populations. The Kimmel et al. (2013) study, conducted among patients largely with indications of AFib and VTE, reported that clinically guided dosing resulted in improved PTTR among Black patients compared to the pharmacogenetic intervention.

Key Question 4: Cost and Cost-Effectiveness

Five economic modeling studies, published between 2009 and 2017, were identified.[32-34,44,45] Center researchers rated 2 studies[34,45] as having a high risk of bias and 3[32,33,44] a moderate risk of bias. The economic modeling studies were generally older than larger and more recent RCTs. Each incorporated effectiveness estimates based on 1 to 3 older RCTs. All 5 studies assumed a hypothetical population of patients initiating warfarin therapy for AFib and did not consider other clinical indications for anticoagulation.[32-34,44,45] The mean ages of these populations ranged from 65 to 72.5, and 1 study limited the population to males. Three studies[33,34,45] assumed a U.S. perspective (either societal or third-party payer), 1[32] assumed a UK health service perspective, and 1[44] was conducted with estimates for the UK and Swedish health system perspectives. All 5 studies reported costs per quality-adjusted life-year (QALY), and some studies reported other economic outcomes as well. Full details about these 5 studies are in Table 9. The cost/QALY estimate and the key assumptions for each study are in Table 2. Cost/QALY ranged from $60,725 to $171,800 in 2007 U.S. dollars. More recent estimates applicable to the U.S. setting were not found. Cost/QALY pertaining to the UK NHS ranged from £6,702 (2014 £) to £13,266 (2011 £). Given dates of publication, no economic study could make use of more recently published RCTs, and most studies derived clinical outcome base-case assumptions from 1 to 3 RCTs, as listed in Table 2. When one of the modeling studies stated specific assumptions about incorporating PTTR, the estimate was higher and more in favor of pharmacogenetically guiding dosing than in the meta-analysis in this report, which found a mean difference of 3.11% (95% CI, -0.28 to 6.50), with the exception of the Meckley et al. (2010) study.[45] The cost of testing among U.S. perspective studies ranged from $175 to $475 in 2007 U.S. dollars.

In sensitivity analyses, these economic modeling studies also explored the ranges of various model parameters, including time in or out of therapeutic range and clinical outcomes such as the risk of stroke or bleeding. Eckman et al. (2009) concluded that pharmacogenetically guided dosing was only cost-effective at a conventional threshold of $50,000/QALY if it was restricted to patients at high risk for hemorrhage, prevented more than a third of major bleeding events, and cost less than $200.[34] Meckley et al. (2010) estimated that the pharmacogenetic approach would result in a cost/QALY of less than $50,000 in only 46% of simulations.[45] According to Patrick et al. (2009), the intervention was cost-effective at the $50,000 threshold only when the pharmacogenetic algorithm resulted in a mean PTTR difference compared to standard care of 9% or greater.[33] Based on meta-analysis in this report, assuming that pharmacogenetically guided dosing resulted in a 3.11% increase in time, the cost/QALY found by Meckley et al. (2010) would be approximately $190,000.[45] In sensitivity analysis, Pink et al. (2013) estimated that the cost/QALY decreased to £10,946.[32] Verhoef et al. (2016) reported that model results were sensitive to estimates of PTTR, stroke risk, and cost of the test.[44] In multiple Monte Carlo simulations, Verhoef et al. (2016) reported that the cost/QALY was below a £20,000 threshold 93% of the time and below a SEK500,000 threshold 67% of the time.[44]

Table 2. Cost-Effectiveness Estimates of Cost/QALY for Pharmacogenetic Warfarin Dosing

Citation Study Risk of Bias	Cost/QALY	Key Assumptions
Eckman et al. 2009[34] High	$171,800	2007 U.S. dollars, societal perspective, lifetime horizon, 3%/year discount rate, 69-year-old men with AFib, test cost $400, PTTR assumption not stated, but assumed percentage time below therapeutic range 7.5% in standard fixed-dose arm and 4.8% in pharmacogenetic arm using Hillman et al. 2005,[23] Anderson et al. 2007,[27] and Caraco et al. 2008[24] RCTs to populate effectiveness and outcomes base-case assumptions
Meckley et al. 2010[45] High	$60,725	2007 U.S. dollars, U.S. third-party payer perspective, lifetime horizon, 3%/year discount rate, 69-year-old men with AFib, test cost $175, assumed time below/in/over therapeutic range based on Anderson et al. 2007[27] study (PTTR mean difference 1.10%, but reanalyzed by Meckley et al. 2010 authors by genotype and modeled to include time above and below therapeutic range as well) and used assumptions from Caraco et al. 2008[24] (PTTR mean difference 17%) in sensitivity analysis
Patrick et al. 2009[33] Moderate	> $100,000	2007 U.S. dollars, societal perspective, lifetime horizon, 3%/year discount rate, 70-year-olds with AFib, test cost $475, model varied cost/QALY based on how testing changed the percentage time spent in therapeutic range from 0% to 30%, base-case PTTR based on Anderson et al. 2007[27] and Caraco et al. 2008,[24] cost/QALY listed is for

Citation Study Risk of Bias	Cost/QALY	Key Assumptions
		increase of PTTR of < 5%, although was modeled for 9% as well with cost/QALY of < $50,000
Pink et al. 2013[32] Moderate	£13,266	2011 GBP (£), UK NHS perspective, lifetime horizon, 3.5%/year discount rate, population with average profile of people in the UK with AFib (mean age 72.5 years), test cost, simulation assumed that PTTR would increase with pharmacogenetic testing by about 11-12% in months 1 and 2, with assumptions based on results of Anderson et al. 2012[77] (excluded from this review because it was a comparison of 2 pharmacogenetic algorithms and did not include a non-pharmacogenetic comparator)
Verhoef et al. 2016[44] Moderate	£6,702 SEK 253,848	2014 GBP (£) and Swedish krona (SEK), lifetime horizon, 3.5%/year discount rate for UK, 3%/year for Sweden, mean age 70.9 years for UK and 72.5 for Sweden, test cost £35.03 for UK and SEK440, used clinical assumptions from the EU-PACT study,[26] which set base-case PTTR at 7%

Abbreviations. AFib: atrial fibrillation; PTTR: percentage of time in therapeutic range; QALY: quality-adjusted life-years.

Summary

Thirteen RCTs and 5 economic modeling studies contributed data to this summary of the clinical and economic impact of pharmacogenetic testing compared to other dosing strategies for the initiation of warfarin anticoagulation. Table 3 presents a summary of the quantity of data, quality of evidence, and relative and anticipated absolute effects of pharmacogenetic dosing initiation of warfarin compared to alternative dosing methods.

Nearly all studies had some limitations, and the overall quality of evidence rating was low for 3 clinical outcomes (i.e., mortality, PTTR, and INR ≥ 4) and moderate for 2 others (i.e., major bleeding and thromboembolic events). The 2 outcomes (PTTR and overanticoagulation) that were reported most robustly across studies, and for which the data estimates are therefore most stable, are intermediate outcomes. The outcome of thromboembolic events showed a small, not statistically significant difference in favor of pharmacogenetic testing. Conversely, overall mortality showed a small, not statistically significant, difference in favor of other dosing initiation strategies. Major bleeding was the only clinical outcome with a significant difference, although this was only seen in the clinical algorithm comparator subgroup. The overall anticipated effect of pharmacogenetically guided warfarin initiation is 8.6 fewer episodes of major bleeding per 1,000 people. Among the subgroup of studies with a clinical algorithm comparator, the anticipated effect of pharmacogenetically guided warfarin initiation is 11.1 (95% CI, 3.2 to 19.1) fewer bleeding episodes per 1,000 people; among the subgroup of fixed-dose comparator studies, the anticipated difference is 2.1 (95% CI, -4.8 to 9.1) fewer episodes per 1,000 people, although the CI on this estimate is not statistically significant. Overall, the subgroup analysis indicates that the major bleeding benefit of pharmacogenetically guided warfarin dosing seen in

the main analysis cannot be explained by whether the control group was dosed according to a clinical algorithm or with a fixed-dose approach. However, the maximum allowed initial doses under clinical algorithms were higher (10 to 12 mg) among the 3 studies that contributed the most events within this subgroup.[7,21,31] In general, clinical practice guidelines recommend starting doses between 5 mg and 10 mg and being more cautious for patients with higher risks of bleeding such as the elderly, and those with impaired nutrition, liver disease, congestive heart failure, recent cardiopulmonary bypass, use of antiplatelet therapy, or other risk factors.[38]

There is possibly more value for pharmacogenetic testing among certain subgroups, including patients undergoing scheduled hip or knee replacement or heart valve replacement. White patients might derive more benefit from testing based on the prevalence of particular genetic variants in that racial subgroup.

These conclusions should be evaluated in light of several limitations. RCTs were not powered to detect patient-important outcomes like mortality, and there were few events for death, major bleeding, and thromboembolism, which contributed to statistical imprecision. PTTR and overanticoagulation were reported more robustly and most RCTs were powered to detect a difference in PTTR. Although these outcomes can be validly measured, they are relatively poor surrogates for patient-important outcomes. Although there was a statistically significant difference of 3.11% in the mean difference of time in the therapeutic INR range favoring pharmacogenetic testing, this finding was statistically heterogeneous. The finding is also of questionable clinical significance, and nearly all of the observed benefit could be explained when studies were analyzed by the type of comparator used. When a clinical algorithm was used, there was essentially no difference compared to use of a pharmacogenetic algorithm. A similar trend was seen with the outcome of overanticoagulation, although the effect was not as pronounced.

Other limitations to interpretation of these RCTs are the differences in outcome definitions across studies, the follow-up period for each outcome, and variation in clinical indications. The baseline risk of outcomes such as thromboembolism and bleeding likely varied across populations, which may limit generalizability of meta-analytic estimates. Studies were also conducted in a variety of health systems, both domestic and international, which further contributes to clinical heterogeneity: some outcomes such as PTTR had markedly different results between U.S.- and non-U.S. based studies. These limitations contribute to both lower quality of evidence ratings and the ability to widely generalize findings.

Cost-effectiveness analyses were also limited by a lack of recent RCT data to inform model parameters, as well as more basic issues with adherence to best practices in cost-effectiveness study methodology. Center researchers rated the overall quality of evidence as very low. The 3 modeling studies that were U.S. based are 8 to 9 years old, and therefore could not have incorporated the growing body of literature about pharmacogenetic testing for warfarin therapy initiation. Costs of genetic tests might also be quite different than the estimates incorporated into the models because costs of genetic tests have generally tended to decrease over time.[46]

None of the 3 U.S. based studies found pharmacogenetic testing to be cost-effective at a threshold of $50,000, and 2 found pharmacogenetic testing to not be cost-effective at a threshold of $100,000. The overall quality of economic study evidence was rated as very low.

Table 3. GRADE Summary of Evidence

Outcome	Number of Participants Studies	Quality of Evidence	Estimated Effect Size (95% CI)	Anticipated Absolute Effects	
				Risk with and without Pharmacogenetic Testing and 95% CI (per 1,000 people)	Risk Difference and 95% CI (per 1,000 people)
Clinical utility—Mortality	n = 3,540 k = 7	Low ●●○○	RR 1.17, (95% CI, 0.43 to 3.22)	5.0 (2.5 to 9.7) 4.6 (2.1 to 9.1)	0.48 (-4.1 to 5.0) fewer deaths without pharmacogenetic testing
Clinical utility—Major Bleeding	n = 4,241 k = 11	Moderate ●●●○	RR 0.43, (95% CI, 0.22 to 0.84)	5.5 (3.0 to 9.7) 14.1 (9.8 to 20.3)	8.6 (2.7 to 14.6) fewer episodes of major bleeding with pharmacogenetic testing
Clinical utility—Thromboembolic Events	n = 4,241 k = 11	Moderate ●●●○	RR 0.85, (95% CI, 0.56 to 1.28)	18.8 (13.8 to 25.4) 23.9 (18.0 to 31.5)	5.1 (-3.6 to 13.8) fewer thromboembolic events with pharmacogenetic testing
Clinical utility—Time in Therapeutic Range	n = 4,378 k = 12 <u>Subgroups</u> Clinical dosing algorithm comparator n = 2,883 k = 4	Low ●●○○	Mean difference, 3.11 (95% CI, -0.28 to 6.50) <u>Subgroups</u> Clinical dosing algorithm comparator Mean difference, 0.54 (95% CI, -2.44 to 3.52)	Not applicable	Not applicable

Outcome	Number of Participants Studies	Quality of Evidence	Estimated Effect Size (95% CI)	Anticipated Absolute Effects	
				Risk with and without Pharmacogenetic Testing and 95% CI (per 1,000 people)	Risk Difference and 95% CI (per 1,000 people)
	Fixed-dose comparator n = 1,495 k = 8		Fixed-dose comparator Mean difference, 4.97 (95% CI, -0.50 to 6.50)		
Clinical utility—INR > 4	n = 3,056 k = 10	Low ●●○○	RR 0.90, (95% CI, 0.79 to 1.03)	162.3 (147.1 to 178.7) 180.5 (164.1 to 198.2)	18.2 (-5.0 to 41.5) people per 1,000 had lower risk of over-anticoagulation with pharmacogenetic testing

Clinical Practice Guidelines

Center researchers identified 8 clinical practice guidelines that have been published since 2012. The American Society of Hematology anticipates publishing guidelines on the optimal management of anticoagulation therapy in 2018.[78] Three of the identified guidelines include recommendations against the use of pharmacogenetic testing for anticoagulant therapy. The American College of Chest Physicians 2012 guideline *Evidence-Based Management of Anticoagulant Therapy* includes a strong recommendation against the routine use of pharmacogenetic testing for guiding doses of vitamin K antagonist therapy, such as warfarin.[36] The 2013 guidelines on antithrombotics indications and management from the Scottish Intercollegiate Guidelines Network (SIGN) include a Grade A recommendation against pharmacogenetic testing before the initiation of therapy with a vitamin K antagonist, such as warfarin.[37] The Australasian Society of Thrombosis and Haemostasis's 2013 update to the guidelines for warfarin reversal conclude that pharmacogenetic testing to guide warfarin dosing is not necessary.[50] This is a strong recommendation with moderate-quality evidence.[50] Center researchers assessed the SIGN guidelines and the guidelines from the American College of Chest Physicians as having good methodological quality, and the Australasian Society of Thrombosis and Haemostasis guideline as having poor methodological quality.

Two guidelines include recommendations for the use of pharmacogenetic testing for warfarin dosing. The Clinical Pharmacogenetics Implementation Consortium (CPIC) 2017 update to the guidelines on pharmacogenetics-guided warfarin dosing recommend that warfarin maintenance dosage for adults be based on genetic information.[8] These guidelines recommend that pharmacogenetically guided dosing use a validated published algorithm (e.g., algorithms by IWPC,[51] Gage et al.,[52] EU-PACT,[26] and Lenzini et al.[53]). The recommendations for pediatric patients state that there is strong evidence for the use of *CYP2C9**2 and *3 and *CYP2C9*-1639G>A genotype testing to guide warfarin dosing in children of European ancestry using a validated published pediatric pharmacogenetic algorithm (e.g., algorithms by Hamberg et al.[79] and Biss et al.[80]). The guidelines conclude that studies in Japanese pediatric individuals are conflicting, and for other ethnicities, there is no evidence documenting that *CYP2C9* and *CYP2C9* are important.[8] Center researchers assessed the CPIC guidelines as having poor methodological quality.

The Canadian Pharmacogenomics Network for Drug Safety published guidelines on genetic testing of *CYP2C9* and *CYP2C9* for warfarin therapy in 2015.[54] These guidelines have a moderate-strength recommendation that testing of all warfarin-naive patients (children and adults) for *CYP2C9 (21639G.A), CYP2C9*2,* and *CYP2C9*3* should be considered before initiation of therapy and within the first 2 weeks of therapy.[54] In addition, such pharmacogenetic testing should be considered for all patients who are at increased risk of bleeding complications, who consistently show out-of-range INRs, or who experience adverse events while receiving warfarin.[54] Genetic testing *for CYP2C9*5*, *6, *8, or *11 and *CYP4F2 V433M* is not recommended.[54] Center researchers assessed these guidelines as having poor methodological quality.

Three of the identified guidelines do not mention pharmacogenetic testing:

- American College of Cardiology, American Heart Association Task Force on Practice Guidelines, and the Heart Rhythm Society 2014 guidelines on AFib[48]
- American College of Cardiology and American Heart Association Task Force on Clinical Practice Guidelines 2017 update to the guidelines on valvular heart disease[49]
- Canadian Agency for Drugs and Technologies in Health (CADTH) 2012 guidelines on antithrombotic agents for patients with AFib[47]

Center researchers assessed the CADTH guidelines as having good methodological quality and the other 2 guidelines as having poor methodological quality.

Of the 8 identified guidelines, 3[36,37,50] of them include recommendations on the initial dose of warfarin when not using pharmacogenetic testing. The American College of Chest Physicians guideline *Evidence-Based Management of Anticoagulant Therapy* suggests initiating warfarin at 10 mg daily for the first 2 days for patients sufficiently healthy to be treated as outpatients.[36] Another guideline by the American College of Chest Physicians, *Oral Anticoagulant Therapy*, discusses flexibility in determining the starting dose of warfarin.[38] These guidelines suggest that initial doses between 5 and 10 mg are effective, with appropriate dosing varying by inpatient or outpatient status, age, concomitant treatments, and comorbidities.[38] An initial dose of 2 to 3 mg may be appropriate for patients who have undergone heart valve replacement.[38]

The SIGN guidelines state that the initial treatment dose for acute thromboembolism is generally 10 mg warfarin, but includes recommendations to vary the initial dose based on age, body weight, comorbidities, and other factors.[37] The Australasian Society of Thrombosis and Haemostasis guidelines recommend avoiding high loading doses of warfarin and starting at 5 mg daily or even lower in elderly patients.[50]

Selected Payer Coverage Determinations

Medicare

One Medicare NCD was identified for pharmacogenetic testing of patients using oral anticoagulants.[55] This NCD does not provide coverage for pharmacogenetic testing, unless the beneficiary is enrolled in an RCT of anticoagulation therapy with warfarin.[55] The beneficiaries enrolled in such a study must have not been previously tested for *CYP2C9* or *CYP2C9* alleles and must have received fewer than 5 days of warfarin in the anticoagulation regimen for which the testing is ordered.[55] Additional requirements from the NCD for a qualifying RCT are listed in Appendix H. This NCD includes a statement that it has been or is currently being reviewed under the NCD process.[55]

Center researchers identified one Medicare LCD by Noridian that applies to Washington on pharmacogenetic testing of patients using oral anticoagulants.[56] This LCD includes the same coverage determination as the NCD above[55] for testing of the *CYP2C9* or *CYP2C9* alleles.[56] The LCD states that all other coverage for genetic testing for *CYP2C9* and *CYP2C9* is considered investigational at this time.[56]

Private Payers

The Aetna policy on pharmacogenetic and pharmacodynamic testing, last reviewed on 9/22/2017, considers genotyping for *CYP2C9* to inform dosing of coumarin derivatives to be experimental and investigational.[57] This policy considers genotyping for *CYP2C9* polymorphism to test for reduced or enhanced effects or severe side effects of drugs metabolized by the vitamin K epoxide reductase complex subunit (including warfarin) to be experimental and investigational.[57] The Cigna policy on pharmacogenetic testing, effective 1/15/2017, does not cover genotyping for *CYP2C9* or *CYP2C9*.[59] The Regence policy on CYP450 genotyping states that *CYP2C9* and *CYP2C9* genotyping for the purpose of warfarin dose management is considered investigational.[58]

Conclusions

The goal of anticoagulant therapy is to prevent thromboembolism while minimizing the risk of bleeding. Warfarin management is complex because of its narrow therapeutic range and the large number of variables that can influence anticoagulation. Among these variables are age, body surface area, medical comorbidities, diet, drug interactions, and genetic factors. This systematic review and meta-analysis was conducted to inform policy decisions in the state of Washington regarding whether pharmacogenetic testing for the initiation of warfarin therapy has clinical utility and cost-effectiveness compared to other management strategies.

Three meta-analytic outcomes represent end outcomes of importance to patients: mortality, thromboembolic events, and major bleeding. This meta-analysis found a 17% lower risk of death when conventional dosing strategies were employed, although the difference was not statistically significant and the overall confidence in this finding is based on low quality of evidence. There were 15% fewer thromboembolic events in the pharmacogenetic testing group meta-analysis, although this was also not statistically significant; confidence in this finding was moderate based on the quality of evidence. Major bleeding was 57% less likely with the pharmacogenetic intervention compared to dosing by a clinical algorithm. This finding was statistically significant, but had a moderate quality of evidence.

None of the studies reported deaths directly related to the pharmacogenetic or comparator dosing method; most studies reported all-cause mortality and did not attribute deaths to the intervention. The small number of events overall make this outcome somewhat unstable. The meta-analysis for thromboembolic events was heavily influenced by the Gage et al. (2017) RCT,[31] which included an additional outcome assessment for asymptomatic lower extremity DVT with the use of duplex ultrasound approximately 1 month after surgery. No other study screened for asymptomatic cases of thromboembolism, and the size of the trial[31] meant that this RCT was heavily weighted in the meta-analysis, such that the meta-analysis likely overstates any advantage of pharmacogenetic testing.

Major bleeding was the 1 outcome that favored pharmacogenetic testing, but there are caveats to this finding as well. Four of the 11 RCTs had no major bleeding events in either study group, and 2 additional RCTs had only 1 event each. The addition of these RCTs to the meta-analysis is

recommended to improve the overall precision of results, but also creates a situation in which outlier studies might have more influence, particularly with a small overall number of events. These studies all had slightly different definitions of major bleeding and different lengths of follow-up during which the outcome could be detected. The Kimmel et al. (2013) study, which accounted for one-third of the weight in the meta-analysis, had a broad definition of major bleeding and a 4-week follow-up period.[21] The Gage et al. (2017) RCT, accounting for about 19% of the meta-analytic weight for this outcome, had a more narrow definition of major bleeding and collected outcomes in the first month of treatment, but was conducted only among patients having lower extremity arthroplasty surgery for which bleeding might reasonably be expected to be more likely overall.[31] The much smaller RCT by Burmester et al. (2011)[7] contributed nearly 21% of the meta-analytic weight to the outcome of major bleeding. Burmester et al. (2011) collected outcomes in the first 14 days of therapy and reported major bleeding in several ways: events adjudicated by the study's Data Safety Monitoring Board or events defined as either "significant" or "life-threatening."[7] Center researchers used the adjudicated events for the meta-analysis, but noted that the other 2 definitions had more bleeding episodes within the pharmacogenetically tested group.

Two meta-analytic outcomes are intermediate outcomes: PTTR and overanticoagulation. These 2 outcomes were more robustly reported across RCTs, and therefore more amenable to subgroup analyses. The risk of overanticoagulation was 10% lower and the PTTR 3.11% higher in the pharmacogenetic testing intervention groups. Neither of these estimates was statistically significant, and Center researchers had low confidence in both findings based on the quality of evidence.

Overanticoagulation puts the patient at risk of bleeding.[43] There are likely to be "overshoots" during initiation of warfarin therapy, but with close monitoring, risks can be minimized.[43] A supratherapeutic INR that is less than 5.0 generally requires no action more aggressive than holding a dose or checking the INR again. Therefore, the clinical significance of the meta-analytic finding, even if it was statistically significant, is not clear. A PTTR of greater than 60%, and preferably 75%, is associated with improved outcomes for patients, including mortality, major bleeding, stroke, and heart attack.[41] However, many factors influence the PTTR, from individual patient characteristics to the frequency of INR measurement and the organization and effectiveness of anticoagulation services.[42] Center researchers were unable to ascertain a minimal clinically significant level for differences in PTTR and noted that 8[7,21-23,28-31] of 12 RCTs in this meta-analysis did not have PTTR results in either group that met the 60% threshold. It is, therefore, difficult to gauge the significance of the 3.11 percentage point difference in PTTR found in this meta-analysis. The pharmacogenetically guided algorithms used in the RCTs in this systematic review all included clinical factors in addition to genetic variant data. Subgroup meta-analysis determined that the PTTR advantage seen in the pharmacogenetic testing groups could be explained by the use of fixed-dose warfarin initiation rather than a clinical algorithm in the comparator group. When the RCT used a clinical algorithm, there was no longer any advantage to the addition of pharmacogenetic testing.

There were 5[32-34,44,45] modeling studies to contribute to evaluating the cost-effectiveness of pharmacogenetic testing for warfarin therapy in the setting of AFib. All of these studies had limitations, and the overall quality of evidence was very low. Only 3 of the studies were conducted using a U.S. perspective. All 3 assumed a higher PTTR than was found in the meta-analysis, and despite this did not find the intervention cost-effective in 2007 U.S. dollars at a conventional threshold of $50,000.

Center researchers identified 8 relevant clinical practice guidelines.[8,36,37,47-50,54] Of these, 3 guidelines, including the American College of Chest Physicians 2012 guideline *Evidence-Based Management of Anticoagulant Therapy,*[36] recommend against the use of pharmacogenetic testing to initiate warfarin therapy, 2 guidelines recommend its use,[8,54] and 3 have no recommendation.[47-49] Neither the Medicare NCD nor the Noridian LCD provide coverage for pharmacogenetic testing except for enrollees participating in RCTs of warfarin treatment, and no relevant private payers cover the testing. In summary, the evidence on pharmacogenetic testing for warfarin therapy is limited, with only some evidence that it might decrease episodes of major bleeding. Neither good-quality practice guidelines nor payer coverage policies support its use.

Center researchers did not identify studies involving oral anticoagulants other than warfarin that were eligible for inclusion. The trials registry site www.ClinicalTrials.gov lists ongoing studies that involve pharmacogenetic testing and direct-acting oral anticoagulants (see Appendix G).

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Appendix A. Search Strategy

Databases:

- Ovid MEDLINE <1946 to December Week 4 2017>
- Ovid MEDLINE In-Process & Other Non-Indexed Citations <January 3, 2018>
- EBM Reviews—Cochrane Central Register of Controlled Trials <November 2017>
- EBM Reviews—Cochrane Database of Systematic Reviews <2005 to December 28, 2017>

1 (Warfarin or Coumadin or Jantoven or dabigatran or pradaxa or Rivaroxaban or Xarelto or Apixaban or Eliquis or Edoxaban or Savaysa or Betrixaban or Bevyxxa or Otamixaban or (oral* adj2 (anticoagul* or anti-coagul*))).mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, sy, sh, kw, tx, ct]

2 exp Anticoagulants/ad, ae, ct, tu, to [Administration & Dosage, Adverse Effects, Contraindications, Therapeutic Use, Toxicity]

3 exp Administration, Oral/

4 2 and 3

5 1 or 4

6 exp Prothrombin/ai [Antagonists & Inhibitors]

7 exp Factor Xa Inhibitors/

8 exp Vitamin K/ai [Antagonists & Inhibitors]

9 6 or 7 or 8

10 (((factor adj (II or xa)) or vitamin k or prothrombin) adj3 (antagon* or inhibit* or block* or interfer*)).mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, sy, sh, kw, tx, ct]

11 5 or 9 or 10

12 exp Pharmacogenetics/ or pharmacogene*.mp. or pharmacogenom*.mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, sy, sh, kw, tx, ct]

13 11 and 12

14 exp Genetic Variation/

15 exp Metabolism/

16 14 and 15

17 11 and 16

18 exp Pharmacogenomic Variants/

19 11 and 18

20 exp Precision Medicine/

21 11 and 20

22 (pharmacogenet* or pharmacogenom*).mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, sy, sh, kw, tx, ct]

23 11 and 22

24 exp genetic testing/ or genetic test*.mp.

25 11 and 24

26 13 or 17 or 19 or 21 or 23 or 25

27 limit 26 to humans [Limit not valid in CCTR,CDSR; records were retained]

28 remove duplicates from 27

29 limit 28 to (meta analysis or systematic reviews) [Limit not valid in CCTR,CDSR; records were retained]

30 limit 28 to randomized controlled trial [Limit not valid in CDSR; records were retained]

31 limit 28 to controlled clinical trial [Limit not valid in CDSR; records were retained]

32 limit 28 to pragmatic clinical trial [Limit not valid in CCTR,CDSR; records were retained]

33 limit 28 to clinical trial, all [Limit not valid in CCTR,CDSR; records were retained]

34 limit 28 to comparative study [Limit not valid in CDSR; records were retained]

35 30 not 29

36 31 not (29 or 30)

37 32 not (29 or 30 or 31)

38 33 not (29 or 30 or 31 or 32)

39 34 not (29 or 30 or 31 or 32 or 33)

40 29 or 30 or 31 or 32 or 33 or 34

41 exp epidemiologic studies/

42 28 and 41

43 42 not 40

44 28 not (40 or 42)

45 exp Economics/

46 ec.fs.

47 (cost or costs or econom* or financ* or dollar*).ti.

48 45 or 46 or 47

49 28 and 48

Appendix B. Additional Methods

Risk of Bias Assessment: Randomized Controlled Trials

Domain	Domain Elements The elements included in each domain are assessed and rated as *Yes*, *No*, *Unclear*, or *Not Applicable* based on performance and documentation of the individual elements in each domain. The overall risk of bias for the study is assessed as *High*, *Moderate,* or *Low* based on assessment of how well the overall study methods and processes were performed to limit bias and ensure validity.
Randomization	• An appropriate method of randomization is used to allocate participants or clusters to groups, such as a computer random number generator • Baseline characteristics between groups or clusters are similar
Allocation Concealment	• An adequate concealment method is used to prevent investigators and participants from influencing enrollment or intervention allocation
Intervention	• Intervention and comparator intervention applied equally to groups • Co-interventions appropriate and applied equally to groups • Control selected is an appropriate intervention
Outcomes	• Outcomes are measured using valid and reliable measures • Investigators use single outcome measures and do not rely on composite outcomes, or the outcome of interest can be calculated from the composite outcome • The trial has an appropriate length of follow-up and groups are assessed at the same time points • Outcome reporting of entire group or subgroups is not selective
Masking (Blinding) of Investigators and Participants	• Investigators and participants are unaware (masked or blinded) of intervention status
Masking (Blinding) of Outcome Assessors	• Outcome assessors are unaware (masked or blinded) of intervention status
Intention to Treat Analysis	• Participants are analyzed based on random assignment (intention-to-treat analysis)
Statistical Analysis	• Participants lost to follow-up unlikely to significantly bias the results (i.e., complete follow-up of ≥ 80% of the participants overall and nondifferential, ≤ 10% difference between groups) • The most appropriate summary estimate (e.g., risk ratio, hazard ratio) is used • Paired or conditional analysis used for crossover RCT • Clustering appropriately accounted for in a cluster-randomized trial (e.g., use of an intraclass correlation coefficient)
Other Biases (as appropriate)	List others in table footnote and describe, such as: • Sample size adequacy

Domain	Domain Elements The elements included in each domain are assessed and rated as *Yes*, *No*, *Unclear*, or *Not Applicable* based on performance and documentation of the individual elements in each domain. The overall risk of bias for the study is assessed as *High*, *Moderate,* or *Low* based on assessment of how well the overall study methods and processes were performed to limit bias and ensure validity.
	• Interim analysis or early stopping • Recruitment bias, including run-in period used inappropriately • Use of unsuitable crossover intervention in a crossover RCT
Interest Disclosure	• Disclosures of interest are provided for authors/funders/commissioners of the study • Interests are unlikely to significantly affect study validity
Funding	• There is a description of source(s) of funding • Funding source is unlikely to have a significant impact on study validity

Risk of Bias Assessment: Economic Studies

Domain	Domain Elements **The elements included in each domain are assessed and rated as *Yes*, *No*, *Unclear*, or *Not Applicable* based on performance and documentation of the individual elements in each domain. The overall risk of bias for the study is assessed as *High*, *Moderate,* or *Low* based on assessment of how well the overall study methods and processes were performed to limit bias and ensure validity.**
Target Population	• Target population and care setting described • Describe and justify basis for any target population stratification, identify any a priori identifiable subgroups • If no subgroup analyses were performed, justify why they were not required
Perspective	• State and justify the analytic perspective (e.g., societal, payer, etc.)
Time Horizon	• Describe and justify the time horizon(s) used in the analysis
Discount Rate	• State and justify the discount rate used for costs and outcomes
Comparators	• Describe and justify selected comparators • Competing alternatives appropriate and clearly described
Modelling	• Model structure (e.g., scope, assumptions made) is described and justified • Model diagram provided, if appropriate • Model validation is described (may involve validation of different aspects such as structure, data, assumptions, and coding and different validation models such as comparison with other models) • Data sources listed and assumptions for use justified • Statistical analyses are described
Effectiveness	• Estimates of efficacy/effectiveness of interventions are described and justified • The factors that are likely to have an impact on effectiveness (e.g., adherence, diagnostic accuracy, values, and preferences) are described and an explanation of how they were factored into the analysis is included • The quality of evidence for the relationship between the intervention and outcomes, and any necessary links, is described
Outcomes	• All relevant outcomes are identified, measured, and valued appropriately (including harms/adverse events) for each intervention, and the justification for information/assumptions is given • Any quality of life measures used in modelling are described and their use justified • Any other outcomes that were considered, but rejected, are described with the rationale for rejection • Ethical and equity-related outcomes are considered and included when appropriate

Domain	Domain Elements The elements included in each domain are assessed and rated as *Yes*, *No*, *Unclear*, or *Not Applicable* based on performance and documentation of the individual elements in each domain. The overall risk of bias for the study is assessed as *High*, *Moderate,* or *Low* based on assessment of how well the overall study methods and processes were performed to limit bias and ensure validity.
Resource Use/Costs	• All resources used are identified, valued appropriately, and included in the analyses • Methods for costing are reporting (e.g., patient level) • Resource quantities and unit costs are both reported • Methods for costing time (e.g., lost time, productivity losses) are appropriate and a justification is provided if time costs are not considered
Uncertainty	• Sources of uncertainty in the analyses are identified and justification for probability distributions used in probabilistic analyses are given • For scenario analyses, the values and assumptions tested are provided and justified
Results	• All results are presented in a disaggregated fashion, by component, in addition to an aggregated manner • All results are presented with undiscounted totals prior to discounting and aggregation • Natural units are presented along with alternative units (e.g., QALYs) • The components of the incremental cost-effectiveness ratio (ICER) are shown (e.g., mean costs of each intervention in numerator and mean outcomes of each intervention in denominator) • Results of scenario analyses, including variability in factors such as practice patterns and costs, are reported and described in relation to the reference (base) case
Interest Disclosure	• Disclosures of interest are provided for authors/funders/commissioners of the study • Interests are unlikely to significantly affect study validity
Funding Source	• There is a description of source(s) of funding • Funding source is unlikely to have a significant impact on study validity

Risk of Bias Assessment: Clinical Practice Guidelines

Domain	Domain Elements Assessment indicates how well the guideline methodology and development process were performed to limit bias and ensure validity for elements in domain (each domain rated as *Good*, *Fair*, or *Poor* overall based on performance and documentation of elements)
Scope and Purpose	• Objectives specifically described • Health question(s) specifically described • Population (patients, public, etc.) specified
Rigor of Evidence Development	• Systematic literature search • Study selection criteria clearly described • Strengths and limitations of individual studies and overall quality of the body of evidence assessed
Rigor of Recommendations Development	• Methods for developing recommendations clearly described • Explicit link between recommendations and supporting evidence and includes strengths/limitations • Balance of benefits and harms (side effects, risks) considered • External review conducted • Updating procedure specified
Stakeholder Involvement	• Relevant professional groups are represented • Views and preferences of target population sought • Target users defined
Clarity and Presentation	• Recommendations specific, unambiguous • Different management options clearly presented • Key recommendations easily identifiable
Applicability and Implementation	• Provides advice and/or tools on how the recommendations can be put into practice • Description of facilitators and barriers to application • Potential resource implications considered • Monitoring/audit/review criteria presented
Editorial Independence	• Views of funding body have not influenced the content of the guideline • Competing interests of members have been recorded, monitored, and addressed appropriately

Appendix C. Evidence Tables

Abbreviations Used in Evidence Tables

ACC: American College of Cardiology

AFib: atrial fibrillation

AHA: American Heart Association

aOR: adjusted odds ratio

BSA: body surface area

CI: confidence interval

HR: hazard ratio

INR: international normalized ratio

MD: mean difference

NR: not reported

OR: odds ratio

QALY: quality-adjusted life-years

RR: risk ratio

SD: standard deviation

UK: United Kingdom

U.S.: United States

Table 4. Study Characteristics

Citation	Country	Total randomized	Total analyzed	Treatment analyzed	Control analyzed	Genotypes tested	Duration	Treatment dosing	Control dosing
Anderson et al. 2007[27]	U.S.	206	200	101	99	*CYP2C9*2/*3, VKORC1*	3 months	Regression equation based on authors' previous study with twice the predicted dose given on days 1 and 2; then doses adjusted based on INR	10 mg of warfarin on days 1 and 2; 5 mg on days 3 and 4; then doses adjusted based on the day 5 INR
Borgman et al. 2012[20]	U.S.	34	26	13	13	*CYP2C9*2/*3, VKORC1*	12 weeks	Generally 5 mg on day 1; then doses according to PerMIT algorithm	Generally started at 5 mg per day, but clinician discretion allowed; dose adjustments based on warfarin induction algorithm during first week; then doses adjusted based on INR
Burmester et al. 2011[7]	U.S.	230	225	113	112	*CYP2C9*2/*3, VKORC1, CYP4F2*	60 days	Marshfield pharmacogenetic model on days 1 and 2; then adjustments based on guidelines from ACC and AHA	Marshfield pharmacologic model on days 1 and 2, which allowed doses up to 10 mg; then adjustments based on guidelines from ACC and AHA
Caraco et al. 2008[24]	Israel	283	185	92	93	*CYP2C9*2/*3*	1 month /variable	Algorithm designed by authors for first 8 days; then adjustments based on guidelines from ACC and AHA	Algorithm by Ageno et al.[35] that generally started at 5 mg, for first 8 days; then adjustments based on guidelines from ACC and AHA

Citation	Country	Total randomized	Total analyzed	Treatment analyzed	Control analyzed	Genotypes tested	Duration	Treatment dosing	Control dosing
Gage et al. 2017[31]	U.S.	1,650	1,597	808	789	*CYP2C9*2/*3, VKORC1, CYP4F2*	90 days	Pharmacogenetic algorithm at WarfarinDosing.org for first 11 days	Clinical dosing algorithm at WarfarinDosing.org for first 11 days. Algorithm would allow for doses of 10 mg per day, but the average or range of starting doses was not reported.
Hillman et al. 2005[23]	U.S.	38	38	18	20	*CYP2C9*2/*3*	4 weeks	Multivariable model by authors	5 mg on the first day; then doses adjusted based on INR
Huang et al. 2009[28]	China	142	121	61	60	*CYP2C9*2/*3, VKORC1*	50 days	Algorithm designed by authors; then doses adjusted based on INR	2.5 mg/day for the first 3 days; then doses adjusted based on INR
Jonas et al. 2013[22]	U.S.	109	109	55	54	*CYP2C9*2/*3, VKORC1*	90 days	Washington University School of Medicine algorithm with clinical variables and genotype; then adjustments based on guidelines from ACC and AHA	Washington University School of Medicine algorithm with only clinical variables (algorithm allows for doses of 10 mg per day, but specific starting doses were not reported); then adjustments based on guidelines from ACC and AHA
Kimmel et al. 2013[21]	U.S.	1,015	955	514	501	*CYP2C9*2/*3, VKORC1*	6 months	Pharmacogenetic algorithm for first 3 days; dose-revision algorithm (included genotype) for days 4 or 5; then	Clinical algorithm for first 3 days with doses ranging from about 2 to 12 mg; dose-revision algorithm for days 4 or 5; then

Citation	Country	Total randomized	Total analyzed	Treatment analyzed	Control analyzed	Genotypes tested	Duration	Treatment dosing	Control dosing
								algorithm-predicted dose adjustments based on INR	algorithm-predicted dose adjustments based on INR
Pengo et al. 2015[30]	Italy	200	180	88	92	*CYP2C9*2/*3, VKORC1, CYP4F2*	30 days	Pharmacogenetic algorithm by Zambon et al. for first 6 days; then clinician-determined doses using PARMA software	5 mg/day for 4 days; clinical prediction model using day 5 INR for days 5 and 6; then clinician-determined doses using PARMA software
Pirmohamed et al. 2013[26]	UK, Sweden	455	427	211	216	*CYP2C9*2/*3, VKORC1*	12 weeks	Slightly modified version of IWPC algorithm for first 3 days; algorithm using day 4 INR for days 4 and 5; then doses adjusted based on INR	Dose based on age for first 3 days (over 75 years: 5 mg per day; 75 years and younger: 10 mg, 5 mg, 5 mg for days 1, 2, and 3, respectively); then doses adjusted based on INR
Wang et al. 2012[25]	China	106	101	50	51	*CYP2C9*2/*3, VKORC1*	50 days	Algorithm by Huang et al. for first 3 days; then dose adjustments based on INR	2.5 mg/day for first 3 days; then dose adjustments based on INR
Wen et al. 2017[29] Taiwan algorithm IWPC algorithm	Taiwan	320	318	107 107	104	*CYP2C9*3, VKORC1* *CYP2C9*2/*3, VKORC1*	90 days	Taiwan algorithm for first 3 days; then dose adjustments based on INR International Warfarin Pharmacogenetic Consortium algorithm for first 3 days; then dose adjustments based on INR	5 mg per day for first 3 days; then dose adjustments based on INR

Abbreviations. AFib: atrial fibrillation; VTE: venous thromboembolism; INR: international normalized ratio; ACC: American College of Cardiology; AHA: American Heart Association.

Table 5. Participant Demographic Characteristics

	Age (years)		Men (%)		White (%)		Black (%)		Asian (%)		Smoking (%)		BSA (m^2)	
Citation	Treat	Control	Treat	Control	Treat	Control	Treat	Control	Treat	Control	Treat	Control	Treat	Control
Anderson et al. 2007[27]	63.2	58.9	49.5	56.6	94.1	94.9	NR	NR	NR	NR	6.9	5.1	NR	NR
Borgman et al. 2012[20]	59	45	54	54	100	85	NR	NR	NR	NR	NR	NR	NR	NR
Burmester et al. 2011[7]	67.4	69.2	57	61	100	100	0	0	0	0	NR	NR	1.96	1.98
Caraco et al. 2008[24]	57.6	59.7	48.4	43.8	NR	NR	NR	NR	NR	NR	22	20	NR	NR
Gage et al. 2017[31]	72.2	72	35.4	37.1	91	91.1	6.4	6.3	2	1.6	2.6	4.2	1.92	1.92
Hillman et al. 2005[23]	68.8	70.5	44	45	100	100	0	0	0	0	17	15	2	2
Huang et al. 2009[28]	41.6	43	32.7	30	0	0	0	0	100	100	NR	NR	1.45	1.45
Jonas et al. 2013[22]	59	55.3	43.6	50	80	64.8	20	35.2	0	0	9.1	13	1.98	2.04
Kimmel et al. 2013[21]	59	57	53	49	NR	NR	27	27	11	11	15	14	2.01	2.03
Pengo et al. 2015[30]	71	75	65.9	65.2	100	100	0	0	0	0	9.1	10.8	1.97	1.88
Pirmohamed et al. 2013[26]	67.6	67.3	65.4	58.8	98.6	98.6	0.9	0.9	0.5	0.5	9.5	12.6	NR	NR
Wang et al. 2012[25]	41.9	42.8	30	31.3	0	0	0	0	100	100	NR	NR	1.57	1.59
Wen et al. 2017[29]	67; 67	66	55; 54	61	0; 0	0	0; 0	0	100; 100	100	17; 14	16	1.76; 1.69	1.78

Note. Treat: Treatment group; NR: Not reported.

Table 6. Participant Characteristics by Indication

	Indications									
	AFib/Flutter (%)		Venous thromboembolism (%)		Post-orthopedic surgery (%)		Valve (%)		Other (%)	
Citation	Treat	Control	Treat	Control	Treat	Control	Treat	Control	Treat	Control
Anderson et al. 2007[27]	13	15	19	28	65	55	NR	NR	3	2
Borgman et al. 2012[20]	38	31	54	38	NR	NR	NR	NR	NR	NR
Burmester et al. 2011[7]	43	49	38	38	0	0	21	17	0	0
Caraco et al. 2008[24]	37	31	63	69	0	0	0	0	0	0
Gage et al. 2017[31]	0	0	0	0	100	100	0	0	0	0
Hillman et al. 2005[23]	17	45	33	15	17	15	22	20	11	5
Huang et al. 2009[28]	0	0	0	0	0	0	100	100	0	0
Jonas et al. 2013[22]	42	26	47	57	NR	NR	4	0	7	17
Kimmel et al. 2013[21]	23	21	59	63	NR	NR	NR	NR	21*	19*
Pengo et al. 2015[30]	100	100	0	0	0	0	0	0	0	0
Pirmohamed et al. 2013[26]	72	73	28	27	0	0	0	0	0	0
Wang et al. 2012[25]	0	0	0	0	0	0	100	100	0	0
Wen et al. 2017[29]	58; 66	64	36; 26	26	NR	NR	NR	NR	6; 8	10

Note. NR: Not reported; Treat: treatment group.

**Figures include multiple indications and other indications.*

Table 7. Evidence Table for Outcomes Used in Meta-analysis

Citation	Time in therapeutic range	Major bleeding	Thromboembolic event	INR ≥ 4 at any point	Death
Anderson et al. 2007[27]	*Proportion of time within the therapeutic INR range (1.8 to 3.2) in the first 90 days (SD):* Treatment: 69.7% ± 23.4 vs. Control: 68.6% ± 24.3 (p = .53) Note: these data used in meta-analysis *Proportion of time within the therapeutic INR range (2 to 3) in the first 90 days (SD):* Treatment: 49.8% ± 24.6% vs. Control: 51.9% ± 24.5% (p = .54)	Outcome not reported	Outcome not reported	Outcome not reported	Outcome not reported
Borgman et al. 2012[20]	*Proportion of time within the therapeutic INR range (1.8 to 3.2) in 60-day period:* Treatment: 77.7% ± 11.3 vs. Control: 70.3% ± 17.9 (p = .441) Note: these data used in meta-analysis *Proportion of time within the therapeutic INR range (1.8 to 3.2) in the first 25 days of therapy (SD):* Treatment: 63.4% ± 15.8 vs.	No serious adverse events reported for any participants	No serious adverse events reported for any participants	*INR ≥ 4:* Treatment: 5/13 (38%) vs. Control: 5/13 (38%)	No serious adverse events reported for any participants

Citation	Time in therapeutic range	Major bleeding	Thromboembolic event	INR ≥ 4 at any point	Death
	Control: 55.3% ± 16.6 (p = .1805)				
Burmester et al. 2011[7]	*Proportion of time within the therapeutic INR range (2 to 3.5) during the first 14 days (SD):* Treatment: 29.1% ± 15.5 vs. Control: 30.8% ± 18.4 (p = .564)	*Bleeding that met Data Safety Monitoring Board criteria (serious events and other unanticipated health events):* Treatment: 3/113 (2.7%) vs. Control: 4/112 (3.5%)	*Thromboembolic event that met Data Safety Monitoring Board criteria (serious events and other unanticipated health events):* Treatment: 3/113 (2.7%) vs. Control: 1/112 (0.9%)	*INR exceeded 4.0:* Treatment: 43/113 (38%) vs. Control: 39/112 (35%)	*Deaths from any cause:* *Treatment: 2/113 (1.8%) vs. Control: 3/112(2.7%)*
Caraco et al. 2008[24]	*Proportion of time within the therapeutic INR range from initiation through stable anticoagulation (SD):* Treatment: 80.4 ± 20.0 vs. Control: 63.4 ± 22.1 (p < .001) Note: these data used in meta-analysis *Proportion of time within the therapeutic INR range (2 to 3) during initiation period of the first 8 days (SD):* Treatment: 45.4% ± 17.2 vs. Control: 24.5 ± 16.9 (p < .001)	*Major bleeding (drop in hemoglobin requiring hospitalization and transfusion of blood):* Treatment: 0/92 (0%) vs. Control 1/93 (1.1%)	*New thromboembolic event:* 0/92(0%) vs. 0/93 (0%)	Outcome not reported	Outcome not reported

Citation	Time in therapeutic range	Major bleeding	Thromboembolic event	INR ≥ 4 at any point	Death
Gage et al. 2017[31]	*Proportion of time within the therapeutic INR range (2.0 to 3.0 for patients with target INR of 2.5 and 1.5 to 2.1 for patients with a target INR of 1.8) during first 30 days:* Treatment: 54.7% (95% CI, 53.0% to 56.4%) vs. Control: 51.3% (95% CI, 49.6% to 53.0%) (MD, 3.4%, 95% CI, 1.1% to 5.8%; p = .004) SD back-calculated from CIs: 24.6 (intervention); 24.3 (control) Among Black patients: Treatment: 50.9% (95% CI, 44.8% to 57.0%) vs. Control: 50.7% (95% CI, 44.1% to 57.4%) (p = .96) Among non-Black patients: Treatment: 55.0% (95% CI, 53.3% to 56.7%) vs. Control: 51.3% (95% CI, 49.6% to 53.0%) (p = .003)	*Major bleeding in first 30 days:* Treatment: 2/808 (0.2%) vs. Control: 8/789 (1.0%) (RR, 0.24; 95% CI, 0.05 to 1.15; p = .06) Major bleeding included (1) bleeding into a critical area (intracranial, epidural, intraocular, pericardial, or retroperitoneal), (2) overt bleeding that resulted in death, (3) a hematoma requiring a return to the operating room, (4) a decrease in hemoglobin level of 2 g/dL or greater, (5) a transfusion of 2 or more units of blood, or (6) hemodynamic changes requiring a transfusion of 1 or more units of blood.	*Symptomatic or asymptomatic venous thromboembolism confirmed by objective testing in first 60 days:* Treatment: 33/808 (4.1%) vs. Control: 38/789 (4.8%) (RR, 0.85; 95% CI, 0.54 to 1.34; p = .48)	*INR ≥ 4 in first 30 days:* Treatment: 56/808 (6.9%) vs. Control: 77/789 (9.8%) (RR, 0.71; 95% CI, 0.51 to 0.99; p = .04)	*Death from any cause in first 30 days:* Treatment: 0/808 (0%) vs. Control: 0/789 (0%)

Citation	Time in therapeutic range	Major bleeding	Thromboembolic event	INR ≥ 4 at any point	Death
Hillman et al. 2005[23]	*Proportion of time within the therapeutic INR range (not reported) during first 4 weeks (SD):* Treatment: 41.7% ± 25.4% vs. Control: 41.5% ± 24.9%	*Major or minor hemorrhagic adverse event:* Treatment: 2/18 (11.1%) vs. Control: 4/20 (20%) For meta-analysis, major bleeding defined as gastrointestinal bleeding: Treatment: 2/18 (11%) vs. Control: 1/20 (5%)	*Thromboembolic event (deep venous thrombosis or pulmonary embolism)* Treatment: 0/18 (0%) vs. Control: 2/20 (10%)	*INR > 4.0:* Treatment: 6/18 (33.0%) vs. Control: 6/20 (30.0%)	Outcome not reported
Huang et al. 2009[28]	*Days within the therapeutic INR range (1.8 to 3.0) during first 50 days (SD):* Treatment: 28.1 ± 9.3 vs. Control: 22.1 ± 9.8; (p = .003) Calculated as proportion of time in therapeutic range for meta-analysis: Treatment: 56.2% ± 19.2% vs. Control: 43.8% ± 19.6%	No major adverse events reported for any participants	No major adverse events reported for any participants	*INR > 3.5:* Treatment: 5/61 (8.2%) vs. Control: 5/60 (8.3%)	No major adverse events reported for any participants

Citation	Time in therapeutic range	Major bleeding	Thromboembolic event	INR ≥ 4 at any point	Death
Jonas et al. 2013[22]	*Proportion of time within the therapeutic INR range (1.8 to 3.2 for patients with target range of 2 to 3 and 2.3 to 3.7 for patients with target range of 2.5-3.5) during first 90 days:* Treatment: 45% ± 27% vs. Control: 49% ± 27% (p = .59) In this analysis, n = 53 for treatment and n= 53 for control	*Major hemorrhagic events (bleeding requiring hospitalization or transfusion):* Treatment: 1/55 (1.8%) vs. Control: 4/54 (7.4%) (p = .17)	*Thrombotic events (DVT, pulmonary emboli, or thromboembolic strokes that developed or progressed after warfarin initiation):* Treatment: 0/55 (0.0%) vs. Control: 3/54 (5.6%) (p = .08)	*INR > 4:* Treatment: 25/55 (44.6%) vs. Control: 26/54 (49.1%) (p = .65)	*Deaths from any cause:* Treatment: 0/55 (0.0%) vs. Control: 2/54 (3.7%) (p = .15)
Kimmel et al. 2013[21]	*Proportion of time within the therapeutic INR range (2 to 3) during first 4 weeks (SD)*: Treatment: 45.2% ± 26.6 vs. Control: 45.4% ± 25.8 (AMD, −0.2; 95% CI, −3.4 to 3.1; p = .91) In this analysis, n = 484 for treatment and n = 471 for control Among Black patients: Treatment: 35.2% vs. Control: 43.5% (AMD, −8.3%; p = .01). Among non-Black patients: Treatment: 48.8% vs. Control: 46.1%	*Major bleeding in first 4 weeks*: Treatment: 4/514 (0.8%) vs. Control: 10/501 (2.0%) (HR, 0.41; 95% CI, 0.13 to 1.31; p = .013) HR adjusted for race and clinical center Major bleeding: fatal hemorrhage, intracranial bleeding, or symptomatic bleeding requiring overnight hospitalization or	*Thromboembolism (DVT, pulmonary embolism, or embolic stroke) in first 4 weeks:* Treatment: 5/514 (1.0%) vs. Control: 4/501 (0.8%) (HR, 1.27; 95% CI, 0.34 to 4.73; p = .72) HR adjusted for race and clinical center	*INR ≥ 4 in first 4 weeks*: Treatment: 100/514 (19.5%) vs. Control: 92/501 (18.4%) (HR, 1.08; 95% CI, 0.81 to 1.44; p = .59) HR adjusted for race and clinical center	*Death from any cause in first 4 weeks:* Treatment: 2/514 (0.4%) vs. Control: 1/501 (0.2%) (HR, 2.09; 95% CI, 0.19 to 23.22; p = .55) HR adjusted for race and clinical center

Citation	Time in therapeutic range	Major bleeding	Thromboembolic event	INR ≥ 4 at any point	Death
	(AMD, 2.8%; p = .15) *From day 4 or 5 to day 14 (SD):* Treatment: 40.3 ± 28.3 vs. Control: 40.3 ± 27.3 (MD, 0.1; 95% CI, −3.4 to 3.6; p = .96) *From day 15 to day 28 (SD):* Treatment: 59.9 ± 36.6 vs. Control: 59.9 ± 36.3 (MD, 0.0; 95% CI, -4.8 to 4.7; p = .99)	major therapeutic intervention			
Pengo et al. 2015[30]	*Proportion of time within the therapeutic INR range (2 to 3) during first 19 days:* Treatment: 51.9% (95% CI, 48.4% to 55.5%) vs. Control: 53.2% (95% CI, 48.9% to 57.4%) (p = .71) SD back-calculated from CIs: 16.7 (intervention); 20.5 (control)	No major/minor bleeding complications occurred	No major/minor thromboembolic complications occurred	*INR > 4:* Treatment: 4/88 (4.5%; 95% CI, 1.3 % to 11.2%) vs. Control: 8/92 (8.7%; 95% CI, 3.8% to 16.4%) (p = NR)	Outcome not reported
Pirmohamed et al. 2013[26]	*Proportion of time within the therapeutic INR range (2.0 to 3.0) during first 12 weeks (SD):* Treatment: 67.4% ±18.1% vs. Control: 60.3% ±21.7%	*Major bleeding:* Treatment: 0/211 (0.0%) vs. Control: 0/216 (0.0%)	*Thromboembolic event (indicating therapeutic failure):* Treatment: 0/211 (0%) vs. Control: 1/216 (0.5%)	*INR ≥ 4:* Treatment: 57/211 (27.0%) vs. Control: 79/216 (36.6%) (OR, 0.63; 95% CI, .41 to 0.97; p = .03)	*Death from any cause:* Treatment: 5/222 (2.3%) vs. Control: 2/225 (0.9%)

Citation	Time in therapeutic range	Major bleeding	Thromboembolic event	INR ≥ 4 at any point	Death
	(adjusted difference, 7.0%; 95% CI, 3.3 to 10.6; p < .001) Difference adjusted for center and indication (AFib or venous thromboembolism) Note: these data used in meta-analysis *Proportion of time within the therapeutic INR range (2.0 to 3.0) during first 4 weeks (SD):* Treatment: 54.6% ± 23.0% vs. Control: 45.7% ± 24.3% (adjusted difference, 8.8%; 95% CI, 4.4 to 13.1; p < .001)	Major bleeding: •Clinically overt bleeding associated with a drop in hemoglobin of ≥20g/l (≥2g/dl) •Clinically overt blood loss needing transfusion of ≥2 units of whole blood or erythrocytes •Bleeding involving critical anatomical sites: intracranial, intraspinal, intramuscular with compartment syndrome, intraocular, retroperitoneal, pericardial, and atraumatic intra-articular bleeding •Fatal bleeding			
Wang et al. 2012[25]	Outcome not reported	Outcome not reported	Outcome not reported	Outcome not reported	Outcome not reported

Citation	Time in therapeutic range	Major bleeding	Thromboembolic event	INR ≥ 4 at any point	Death
Wen et al. 2017[29]	*Proportion of time within the therapeutic INR range (2.0 to 3.0) during weeks 5 to 9 (SD):* Treatment (Taiwan algorithm): 53.0% ± 33.8% vs. Treatment (IWPC algorithm): 52.4% ± 35.0% vs. Control: 59.9% ± 36.3% (p = .24)	*Major bleeding:* Treatment (Taiwan algorithm): 0/107 (0%) vs. Treatment (IWPC algorithm): 0/107 (0%) vs. Control: 1/104 (1%) (p = .33) Major bleeding defined as • Clinically overt bleeding associated with a drop in hemoglobin of ≥20g/l • Clinically overt blood loss needing transfusion of ≥2 units of whole blood or erythrocytes • Bleeding involving critical anatomical sites: intracranial, intraspinal, intramuscular with compartment syndrome, intraocular, retroperitoneal, pericardial, and atraumatic intra-articular bleeding • Fatal bleeding	*Thromboembolism:* Treatment (Taiwan algorithm): 0/107 (0%) vs. Treatment (IWPC algorithm): 0/107 (0%) vs. Control: 0/104 (0%)	*INR ≥ 4:* Treatment (Taiwan algorithm): 20/107 (18.7%) vs. Treatment (IWPC algorithm): 18/107 (16.8%) vs. Control: 18/104 (17.3%) (p = .93)	Outcome not reported

Table 8. Evidence Table for Additional Outcomes (not included in meta-analysis)

Citation	Adverse events	Days to stable INR or dose	Days to therapeutic INR or dose	Other outcomes
Anderson et al. 2007[27]	*Serious adverse clinical events:* Treatment: 4/101 (4.0%) vs. Control: 5/99 (5.1%) (OR, 0.78; 95% CI, 0.20 to 2.98; p = .71) *Serious adverse clinical events or INR ≥ 4:* Treatment: 34/101 (34.7%) vs. Control: 42/99 (42.4%) (OR, 0.72; 95% CI, 0.41 to 1.28; p = .26) Serious adverse clinical events included use of vitamin K, major bleeding events (after the Thrombolysis in Myocardial Infarction and Columbus Investigators), thromboembolic events, stroke (all cause), myocardial infarction, and death (all cause).	Not reported	*Percentage of patients reaching therapeutic INR on day 5:* Treatment: 69.7% vs. Control: 68.3% (OR, 1.07; 95% CI, 0.56 to 2.04; p = .85) *Percentage of patients reaching therapeutic INR on day 8:* Treatment: 68.8% vs. Control: 63.0% (OR, 1.29; 95% CI, 0.71 to 2.36; p = .41)	Not reported
Borgman et al. 2012[20]	Not reported	*Days to first stable therapeutic INR (INR remains within acceptable range (INR 1.8 to 3.2) for a minimum of 4 consecutive days:* Treatment: 4.7 (95% CI, 3.5 to 8) vs. Control: 8.3 (95% CI, 3.5 to 17.5; p = .0152)	*Percentage of patients reaching therapeutic INR by day 5:* Treatment: 69.2% vs. Control: 38.5% (p = .1156) *Percentage of patients reaching therapeutic INR by day 8:*	Not reported

Citation	Adverse events	Days to stable INR or dose	Days to therapeutic INR or dose	Other outcomes
			Treatment: 100% vs. Control: 61.5% (p = .0128)	
Burmester et al. 2011[7]	Not reported	*Median days to stable dose in therapeutic range:* Treatment: 29 (95% CI, 23 to 36) vs. Control: 31 (95% CI, 24 to 36) (p = .90)	Not reported	*Proportion of time within the therapeutic INR range during the first 14 days, interpolated INR between 2 consecutive tests and weighted proportionately by how close the INR was to target (SD):* Treatment: 1.21 ± 0.12 vs. Control: 1.20 ± 0.15 (p = .891)
Caraco et al. 2008[24]	Not reported	*Mean days required to reach stable anticoagulation:* Treatment: 22.1 ± 6.9 vs. Control: 40.2 ± 21.1 (HR, 4.23; 95% CI, 2.95 to 6.07; p < .001)	*Mean days required to reach the therapeutic INR range (i.e., first INR > 2) (SD):* Treatment: 4.80 ± 1.46 vs. Control: 7.53 ± 3.06 (p < .001)	Not reported

Gage et al. 2017[31]	*Composite outcome of major bleeding, INR ≥ 4, venous thromboembolism, or death within 30 days:* Treatment: 87/808 (10.8%) vs. Control: 116/789 (14.7%) (absolute difference, 3.9%; 95% CI, 0.7% to 7.2%; p = .02; RR, 0.73; 95% CI, 0.56 to 0.95) In the high-risk subgroup (n = 658; 41.2% of participants): Treatment: 11.5% vs. Control: 15.2% (absolute difference of 3.76% (95% CI, –9.0% to 1.5%; p = .16) No significant interaction in any of the subgroups examined on the composite outcome: High-risk subgroup-patients whose clinically guided vs genotype-predicted warfarin doses differed by 1.0mg/d or greater (p = .88) Black race (p = .74) CYP2C9 genotype (p = .16) Target INR of 1.8 vs. 2.5 (p = .70) Hip vs. knee arthroplasty (p = .36)	Not reported	Not reported	Not reported

Citation	Adverse events	Days to stable INR or dose	Days to therapeutic INR or dose	Other outcomes
	Composite outcome of major bleeding, INR ≥ 4, venous thromboembolism, or death within 90 days: Treatment: 90/808 (11.1%) vs. Control: 119/789 (14.1%) (absolute difference, 3.9%; 95% CI, 0.6% to 7.3%; p = .02) *Risk of an INR exceeding target INR by 1.5 or greater:* *(HR, 0.78; 95% CI, 0.59 to 1.03; log-rank test p = .08)* *Cardiovascular event (Myocardial infarction, stroke, AFib):* Treatment: 10/808 (1.2%) vs. Control: 13/789 (1.6%) (p = .49) *Serious infection:* Treatment: 15/808 (1.9%) vs. Control: 12/789 (1.5%) (p = .93)			
Hillman et al. 2005[23]	Not reported	Not reported	Not reported	Not reported

Citation	Adverse events	Days to stable INR or dose	Days to therapeutic INR or dose	Other outcomes
Huang et al. 2009[28]	*Adverse outcome (INR > 3.5, bleeding, or venous thrombosis):* Treatment: 7/61 (11.5%) vs. Control: 8/60 (13.3%) (p = .757)	*Median days to reach stable warfarin dose:* Treatment: 24 vs. Control: 35 (p = .001)	Not reported	Not reported
Jonas et al. 2013[22]	Not reported	Not reported	*Proportion of patients reaching therapeutic INR by day 30 (SD):* Treatment: 11% ± 20.0% vs. Control: 15% ± 27.8% (p = .34) *Proportion of patients reaching therapeutic INR by day 90 (SD):* Treatment: 21% ± 38.2 vs. Control: 26% ± 48.2% (p = .3) *Mean days to therapeutic dose (SD):* Treatment: 34.7 ± 24.8 vs. Control: 35.9 ± 28.1 (p = .87)	Not reported
Kimmel et al. 2013[21]	*INR ≥ 4, major bleeding, or thromboembolism in the first 4 weeks:* Treatment: 154/514 (30%) vs. Control: 170/501 (34%) (HR, 0.91; 95% CI, 0.73 to 1.1; p = .42)	Not reported	*Proportion of patients to first therapeutic INR within 14 days:* Treatment: 0.81 (95% CI, 0.77 to 0.84) vs. Control: 0.85 (95% CI, 0.81 to 0.88) (HR, 0.94; 95% CI, 0.82 to 1.1; p = .36)	Not reported

Citation	Adverse events	Days to stable INR or dose	Days to therapeutic INR or dose	Other outcomes
Pengo et al. 2015[30]	*Proportion of time spent at INR > 4.0:* Treatment: 0.7% vs. Control: 1.8% (p = .02) *Proportion of out-of-range INRs (<2.0 or >3.0) in first 19 days:* Treatment: 45.1% (95% CI, 40.4% to 49.7%) vs. Control: 43.6% (95% CI, 38.7% to 48.6%) (p = .79)	*Mean days to stable anticoagulation (first INR in a series of 3 INR within the therapeutic range):* Treatment: 5.96 (95% CI, 5.00 to 9.93) vs. Control: 5.05 (95% CI, 4.24 to 5.86) (p = .28)	*Proportion of patients reaching therapeutic INR by day 19:* Treatment: 60/88 (68.2%) vs. Control: 60/92 (65.2%) (p = .67)	Not reported
Pirmohamed et al. 2013[26]	*Any serious adverse event:* Treatment: 15/222 (6.8%) vs. Control: 23/225 (10.2%)	*Median days to stable dose:* Treatment: 44 vs. Control: 59 (HR, 1.40; 95% CI, 1.12 to 1.74; p = .003)	*Median days to reach therapeutic INR:* Treatment: 21 vs. Control: 29 (HR, 1.43 95% CI, 1.17 to 1.76; p < .001)	*Proportion of time within the therapeutic INR range (2.0 to 3.0) during weeks 9 to 12 (SD):* Treatment: 74.5% ± 25.2% vs. Control: 72.9% ± 29.8% (adjusted difference, 1.4%; 95% CI, –3.8 to 6.6; p = .61)

Citation	Adverse events	Days to stable INR or dose	Days to therapeutic INR or dose	Other outcomes
Wang et al. 2012[25]	*Adverse events (bleeding, venous thrombosis, or INR over 3.5) during 50-day follow-up:* Treatment: 10.0% vs. Control: 15.7% (p = .55)	*Mean days to stable warfarin maintenance dose (dose that led to the patient's INR values within the therapeutic range measured at least 7 days) (SD):* Treatment: 27.5 ± 1.8 vs. Control: 34.7 ± 1.8 (p < .001) *Median days to stable warfarin maintenance dose:* Treatment: 24.0 ± 1.7 vs. Control: 33.0 ± 4.5 (p < .001)	Not reported	Not reported
Wen et al. 2017[29]	Not reported	*Median days to stable therapeutic dose (days to first of 2 consecutive INRs in the therapeutic range without dose adjustment, measured at least 1 week apart):* Treatment (Taiwan algorithm):14 vs. Treatment (IWPC algorithm): 14 vs. Control: 11 (p = .03); significant difference between the International Warfarin Pharmacogenetic Consortium group and the standard dose group	*Median days to reach therapeutic INR (days to reach first of 2 INR value ranges that were measured at least 1 week apart within the target range):* Treatment (Taiwan algorithm): 17 vs. Treatment (IWPC algorithm): 17 vs. Control: 11 (p = .35)	Not reported

Table 9. Evidence Table for Economic Outcomes

Citation Test	Design Comparators	Population Analytic assumptions	Main findings
Eckman et al. 2009[34] *CYP2C9*2, CYP2C9*3, and/or VKORC1*	*Design:* Cost-effectiveness analysis using Markov state transition decision model *Comparator:* Standard induction of warfarin therapy	*Population:* Men age 69 years with newly diagnosed nonvalvular AFib requiring initiation of warfarin therapy and having no contraindications to warfarin therapy *Analytic assumptions:* • Societal perspective • Lifetime time horizon • Costs in 2007 U.S. dollars • Annual discount rate 3% • RR for major bleeding in pharmacogenetic group 0.68 compared to standard dosing group, only during the first month of warfarin induction • Patients in pharmacogenetic group reached therapeutic INR an average of 2.7 days earlier (4.8 days vs. 7.5 days) • Cost of testing $400 • 3-day delay in initiating warfarin after pharmacogenetic testing • Medical costs from average Medicare reimbursement for the corresponding CPT or DRG	*Incremental cost-effectiveness ratio of pharmacogenetic testing:* $171,800 per QALY 10% chance that genotype-guided dosing is likely to be cost-effective (< $50,000 per QALY) Marginal cost-effectiveness ratio of pharmacogenetic testing decreases to $116,000 per QALY if no delay in initiating treatment, compared to the assumption of a 3-day delay For genetic testing to cost less than $50,000 per QALY, it would have to be either restricted to patients at high risk for hemorrhage, or testing must prevent greater than 32% of major bleeding events, be available within 24 hours, and cost less than $200
Meckley et al. 2010[45]	*Design:* Decision-analytic Markov model using Tree-Age software *Comparator:* Usual care with standard dosing	*Population:* 65-year-old AFib patients newly initiated on long-term warfarin therapy *Analytic assumptions:* • US third-party payer perspective • Lifetime time horizon • Costs in 2007 U.S. dollars • Assumptions derived from 1 trial • Annual discount rate 3%	*Incremental cost-effectiveness ratio of pharmacogenetic testing:* $60,725 per QALY In sensitivity analysis, cost per QALY ranged from testing dominating to standard care dominating, and the incremental cost-effectiveness ratio was < $50,000 per QALY in 46% of simulations

Citation Test	Design Comparators	Population Analytic assumptions	Main findings
		• Probability of moving from a no-event state to adverse event based on the percentage of time spent above, below, and within therapeutic INR range and genotype • Genotyping costs based on publicly available tests with a base case of $175 • Medical costs for warfarin pills, anticoagulation clinic management, and INR tests based on Intermountain Healthcare (Salt Lake City, UT) costs • Cost of treating adverse events obtained from the 2005 Healthcare Cost and Utilization Project database	
Patrick et al. 2009[33] *CYP2C9, VKORC1*	*Design:* Threshold analysis to assess test characteristics under which pharmacogenetic test would be cost-effective, using state transition Markov model *Comparator:* Usual care with standard dosing	*Population:* 70-year-old patients with newly diagnosed AFib *Analytic assumptions:* • Societal perspective • Costs in 2007 U.S. dollars • Annual discount rate 3% • Model varied increased time in target INR range for pharmacogenetic group vs. standard dosing from 0% to 30% • Pharmacogenetic testing increased the time spent in the target INR range during the first 3 months, but not subsequently • Patients assumed to have major bleeding events at rates predicted by their INRs, based on previous studies • Cost of testing $475, plus $100 for phlebotomy and recordkeeping • Hospitalization costs calculated from the Nationwide Inpatient Sample; physician service	If pharmacogenetic testing increases time spent in target INR range by < 5 percentage points, incremental cost-effectiveness ratio was greater than $100,000 per QALY If pharmacogenetic testing increases time spent in target INR range by 9 percentage points, incremental cost-effectiveness ratio was below $50,000 per QALY

Citation Test	Design Comparators	Population Analytic assumptions	Main findings
		costs were estimated from payment rates from the Medicare Physician Fee Schedule	
Pink et al. 2003[32]	*Design:* Cost-effectiveness analysis from a discrete-event simulation model *Comparator:* Standard clinical algorithms	*Population:* Patients with nonvalvular AFib; baseline characteristics assumed to follow the average profile of the UK AFib population *Analytic assumptions:* • Perspective of UK National Health Service • Lifetime time horizon • Costs in 2011 Great Britain Pound • Annual discount rate 3.5% • Pharmacogenetic testing increased the time spent in the target INR range during the first 3 months, but not subsequently • Costs based on National Health Service reference costs	*Incremental cost-effectiveness ratio for pharmacogenetic testing:* £13,226 per QALY Incremental cost-effectiveness ratios most sensitive to changes in stroke rates, vascular death rates, and the duration of treatment benefits
Verhoef et al. 2016[44]	*Design:* Cost-effectiveness analysis using Markov model using Microsoft Excel *Comparator:* Usual care with standard dosing	*Population:* Hypothetical cohort of patients with AFib initiating warfarin treatment with mean age 70.9 years for UK and 72.5 for Sweden *Analytic assumptions:* • Perspectives of the National Health Service in the UK and health-care sector in Sweden • Costs in 2014 GBP (£) and Swedish krona (SEK) • Lifetime time horizon • Annual discount rate 3.5% for UK and 3% for Sweden (in accordance with national guidelines) • Test cost £35.03 for UK and SEK440 for Sweden • Clinical assumptions from the EU-PACT study,[26] which set base-case PTTR at 7%	*Incremental cost-effectiveness ratio of pharmacogenetic testing:* £6,702 per QALY and 253,848 SEK per QALY Incremental cost-effectiveness ratio was below the willingness-to-pay threshold of £20,000 per QALY gained in 93% of the simulations in UK and below 500,000 SEK per QALY in 67% of the simulations in Sweden

Appendix D. Risk of Bias Assessments

Table 10. Risk of Bias: Randomized Controlled Trials

Citation	Randomization	Allocation concealment	Intervention	Outcomes	Masking of investigators and participants	Masking of outcome assessors	Intention to treat analysis	Statistical analysis	Other biases	Interest disclosure	Funding source	Overall risk of bias assessment Comments
Anderson et al. 2007[27]	Y	N	Y	Y	Y	Unclear	Y	Unclear	--	Y	Y	Moderate Inadequate allocation concealment Unclear masking of outcome assessment Unclear description of the statistical analysis.
Borgman et al. 2012[20]	Unclear	N	Y	Y	N	Unclear	Unclear	N	N*	N	Y	High Some authors with equity interest in the test provider Unclear randomization Inadequate allocation concealment Lack of masking Inadequate statistical analysis
Burmester et al. 2011[7]	Y	Y	Y	Y	Y	Y	Y	N	--	N	Unclear	Moderate Partial funding from a test manufacturer Authors were patent holders for technology involved in the genomic test Inadequate statistical analysis description

Citation	Randomization	Allocation concealment	Intervention	Outcomes	Masking of investigators and participants	Masking of outcome assessors	Intention to treat analysis	Statistical analysis	Other biases	Interest disclosure	Funding source	Overall risk of bias assessment Comments
Caraco et al. 2008[24]	N	N	Unclear	Y	Y	N	Unclear	N	--	Y	Y	High Using pseudo-randomization Inadequate allocation concealment and statistical analysis description Lack of outcome assessor masking
Gage et al. 2017[31]	Y	Y	Y	Y	Y	Y	Y	Y	--	N	Y	Low Several authors had commercial research funding and other income GenMarkDx loaned genotyping platform to the central laboratory involved in the study
Hillman et al. 2005[23]	Unclear	Unclear	Y	Y	N	N	N	Y	N*	Unclear	Y	High No interest disclosure Unclear randomization and allocation concealment Lack of masking Midstudy protocol changes

Citation	Randomization	Allocation concealment	Intervention	Outcomes	Masking of investigators and participants	Masking of outcome assessors	Intention to treat analysis	Statistical analysis	Other biases	Interest disclosure	Funding source	Overall risk of bias assessment Comments
Huang et al. 2009[28]	Unclear	Unclear	Unclear	Y	N	N	N	Y	--	Unclear	Y	High No interest disclosure Unclear randomization and allocation concealment Inadequate detail about the genetic dosing protocol Lack of masking
Jonas et al. 2013[22]	Y	Y	Y	Y	Y	Y	Y	Y	--	Y	Y	Low
Kimmel et al. 2013[21]	Y	Y	Y	Y	Y	Y	Y	Y	--	N	Y	Low Several authors had research grants, consulting contracts or equity interests with commercial entities
Pengo et al. 2015[30]	Y	Unclear	Y	Y	N	N	Y	Y	--	Y	Y	Moderate Unclear allocation concealment Lack of masking
Pirmohamed et al. 2013[26]	Y	Unclear	Y	Y	N	N	Y	Y	--	?	Y	Moderate Unclear allocation concealment Lack of masking

Citation	Randomization	Allocation concealment	Intervention	Outcomes	Masking of investigators and participants	Masking of outcome assessors	Intention to treat analysis	Statistical analysis	Other biases	Interest disclosure	Funding source	Overall risk of bias assessment Comments
Wang et al. 2012[25]	Y	Unclear	Y	Y	N	N	Y	Y	--	Y	Unclear	High No interest disclosure Unclear allocation concealment Lack of masking
Wen et al. 2017[29]	Y	Unclear	Y	Y	N	N	Y	Y	--	N	Y	High One author holds European patent for a *CYP2C9* gene test Unclear allocation concealment Inadequate detail about the genetic dosing protocol Lack of masking

Table 11. Risk of Bias: Economic Studies

Part 1

Citation	Target population	Perspective	Time horizon	Discount rate	Comparators	Modeling	Effectiveness
Eckman et al. 2009[34]	N	Y	Y	Y	Y	Y	Unclear
Meckley et al.2010[45]	N	Y	Y	Y	Y	Y	Unclear
Patrick et al. 2009[33]	N	Y	Y	Y	Y	Y	Unclear
Pink et al. 2013[32]	Y	Y	Y	Y	Y	Y	Unclear
Verhoef et al. 2016[44]	Y	Y	Y	Y	Y	Unclear	Unclear

Part 2

Citation	Outcomes	Resource use/costs	Uncertainty	Results	Interest disclosure	Funding source	Overall risk of bias assessment Comments
Eckman et al. 2009	N	N	Y	N	Y	Y	High One author had consultancy with Bristol-Myers Squibb Inadequate evidence base for model assumptions Model used base case of 69-year-old man with newly diagnosed AFib
Meckley et al. 2010	Unclear	Y	Y	Unclear	Y	Y	High Inadequate evidence base for model assumptions Model used base case of 65-year-old man with newly initiated warfarin therapy

Citation	Outcomes	Resource use/costs	Uncertainty	Results	Interest disclosure	Funding source	Overall risk of bias assessment Comments
Patrick et al. 2009	Unclear	Y	Y	Unclear	Y	Y	Moderate Inadequate evidence base for model assumptions Model used base case of 70-year-old man with newly diagnosed AFib
Pink et al. 2013	Y	Unclear	Y	N	Y	Y	Moderate Inadequate evidence base for model assumptions Costing was performed from the perspective of the UK National Health Service
Verhoef et al. 2016	Unclear	Unclear	Y	Unclear	Y	Y	Moderate Inadequate evidence base for model assumptions

Table 12. Risk of Bias: Guidelines

Citation	Scope and purpose	Rigor of evidence development	Rigor of recommendations development	Stakeholder involvement	Clarity and presentation	Applicability and implementation	Editorial independence	Overall assessment
CADTH 2013[47]	Good	Good	Good	Fair	Good	Good	Good	Good
Holbrook et al. 2012[36]	Good	Good	Good	Fair	Good	Good	Fair	Good
January et al. 2014[48]	Fair	Poor	Poor	Fair	Fair	Good	Fair	Poor
Johnson et al. 2017[8]	Fair	Poor	Poor	Poor	Fair	Fair	Poor	Poor
Nishimura et al. 2017[49]	Fair	Poor	Fair	Fair	Fair	Fair	Fair	Poor
SIGN 2013[37]	Good	Good	Good	Good	Good	Good	Fair	Good
Shaw et al. 2015[54]	Good	Fair	Poor	Good	Fair	Fair	Good	Poor
Tran et al. 2014[50]	Good	Poor	Poor	Fair	Fair	Fair	Poor	Poor

Appendix E. Additional Meta-analysis Figures

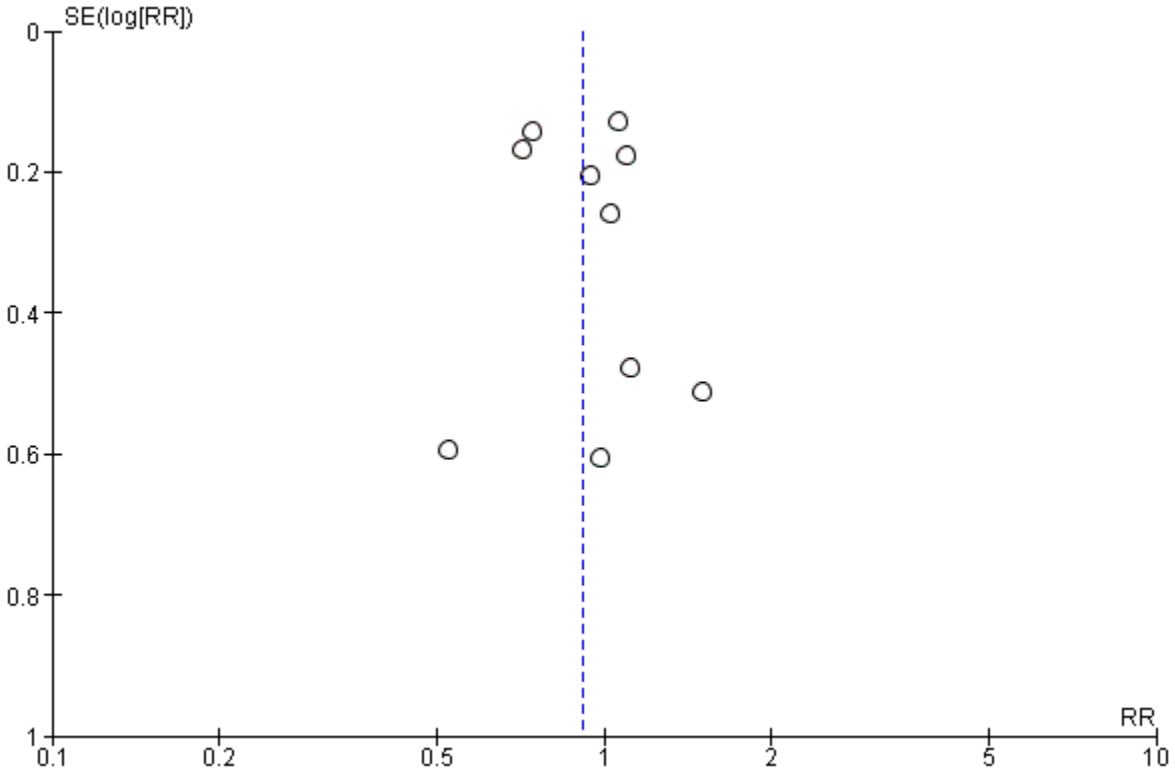

Figure 26. Funnel Plot of Eligible Randomized Controlled Trials for INR ≥ 4

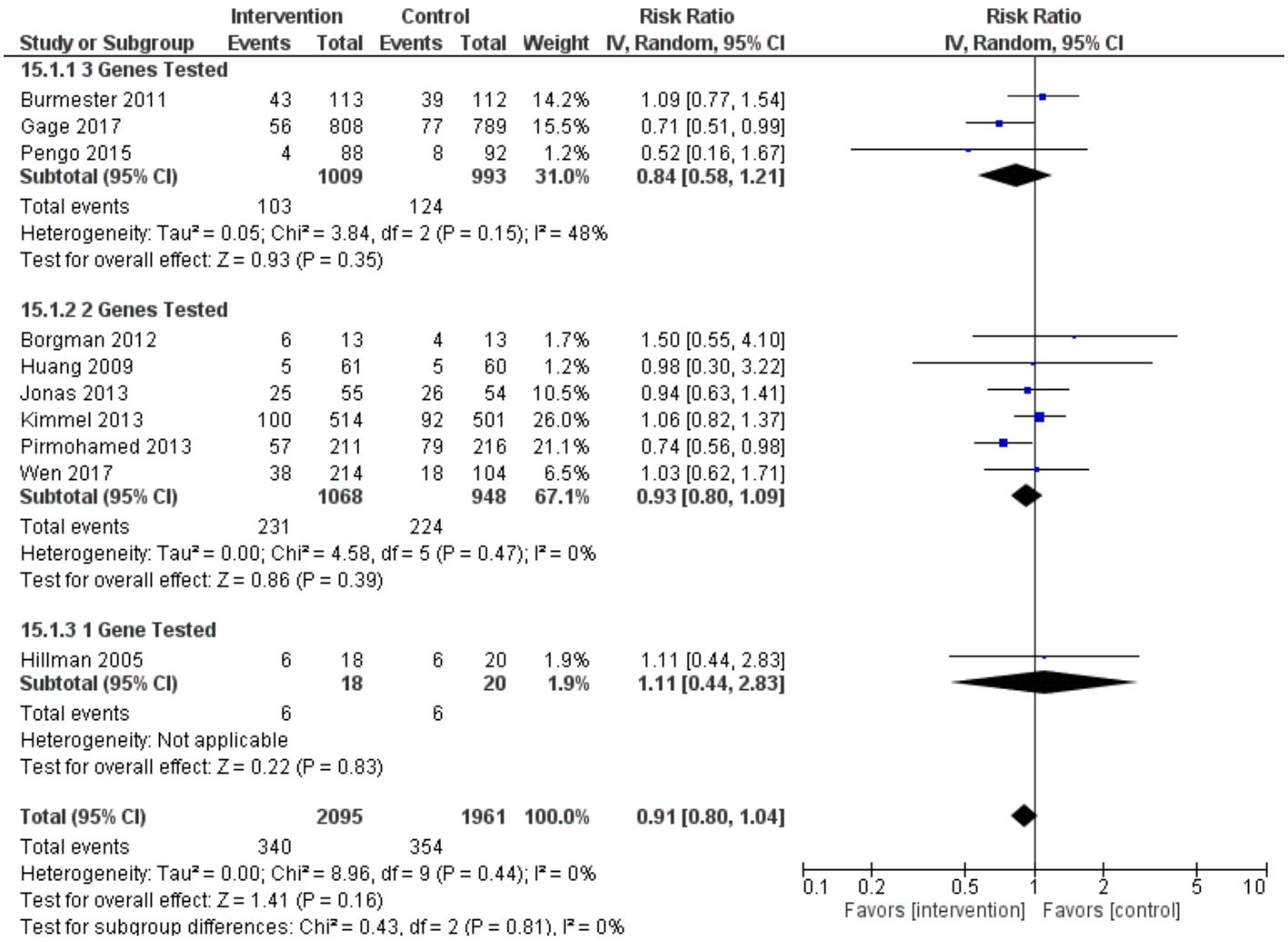

Figure 27. Meta-analysis of Pharmacogenetic Testing vs. Control by Number of Genes for INR ≥ 4

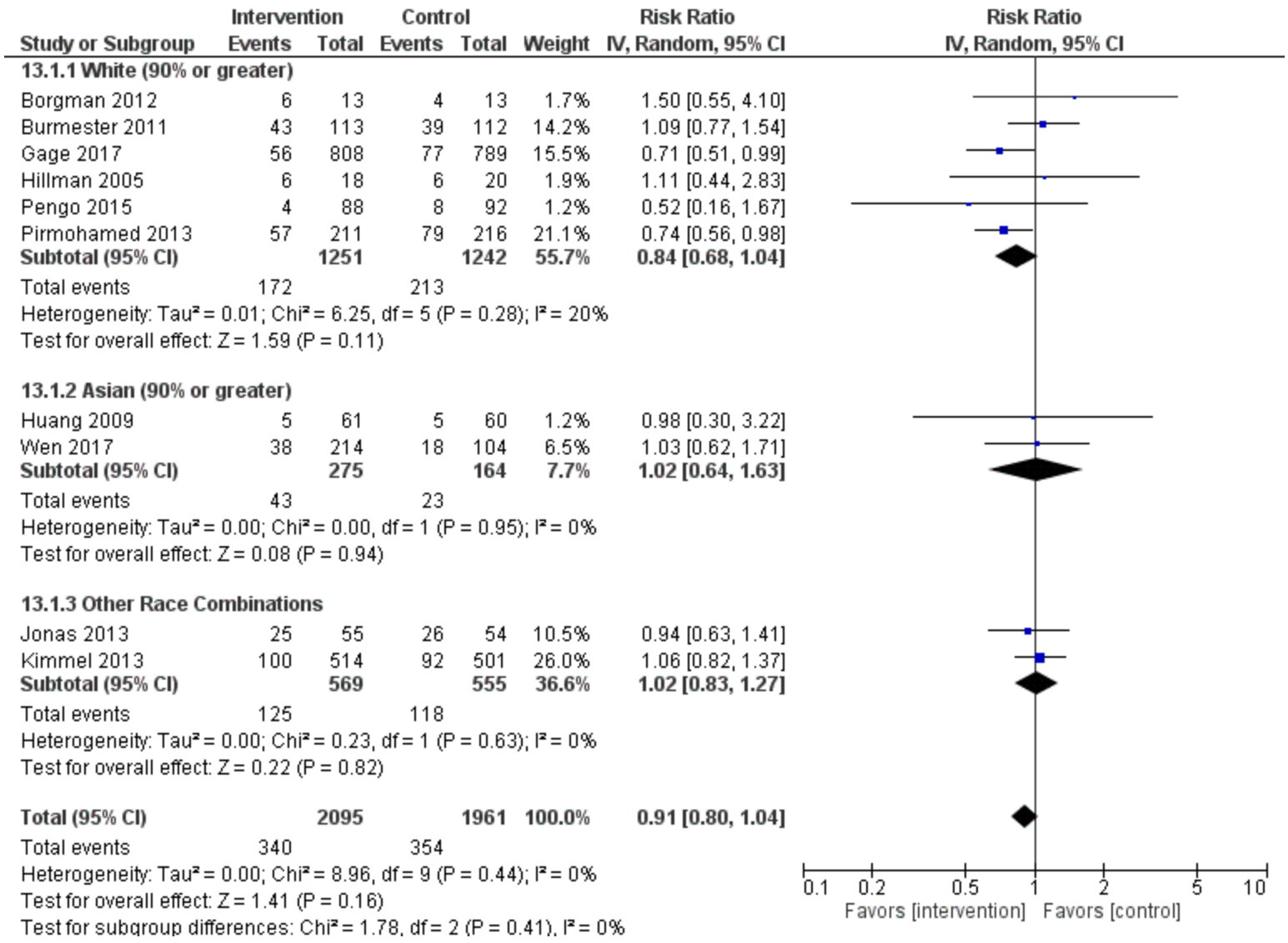

Figure 28. Meta-analysis of Pharmacogenetic Testing vs. Control by Race for INR ≥ 4

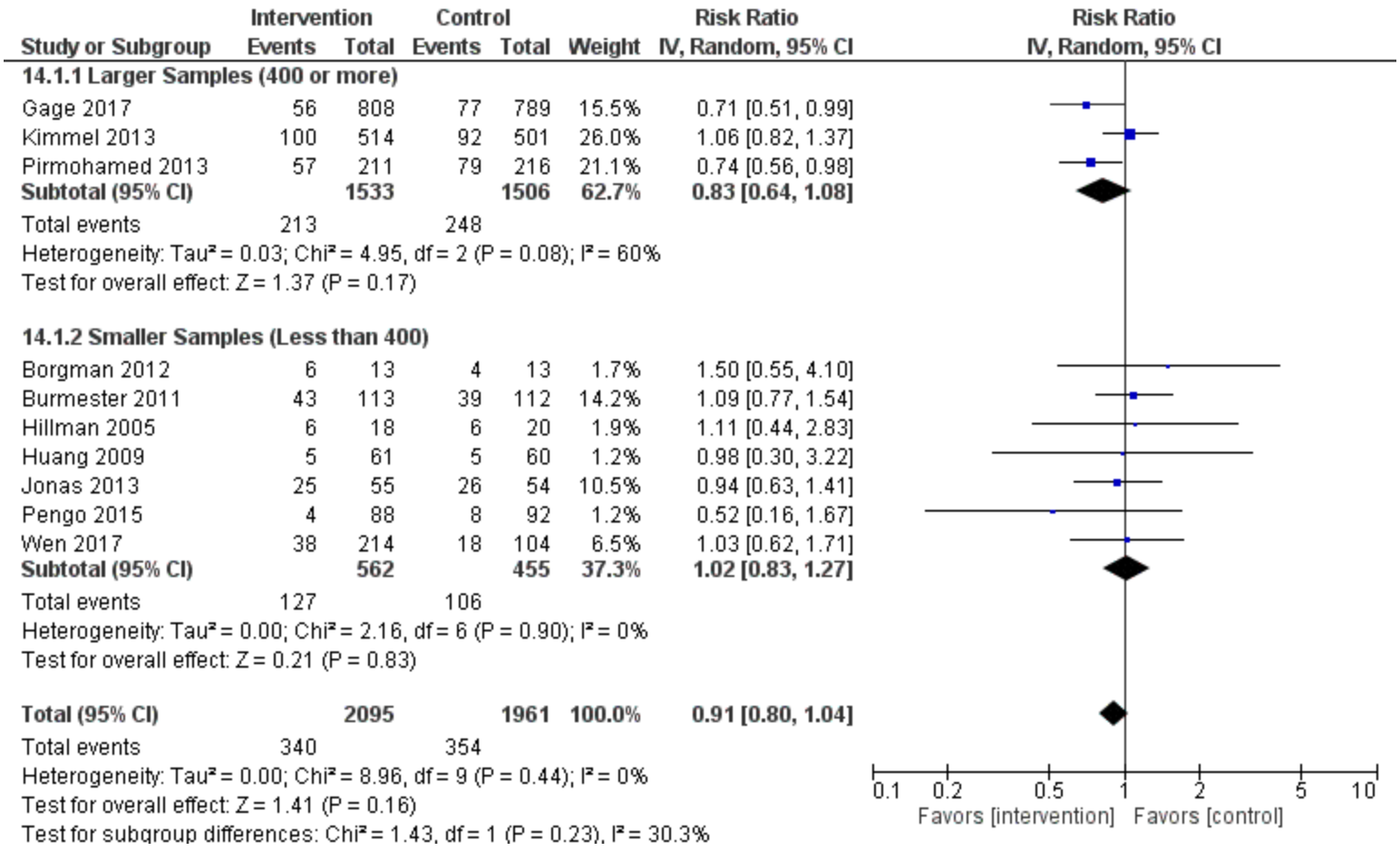

Figure 29. Meta-analysis of Pharmacogenetic Testing vs. Control by Sample Size for INR ≥ 4

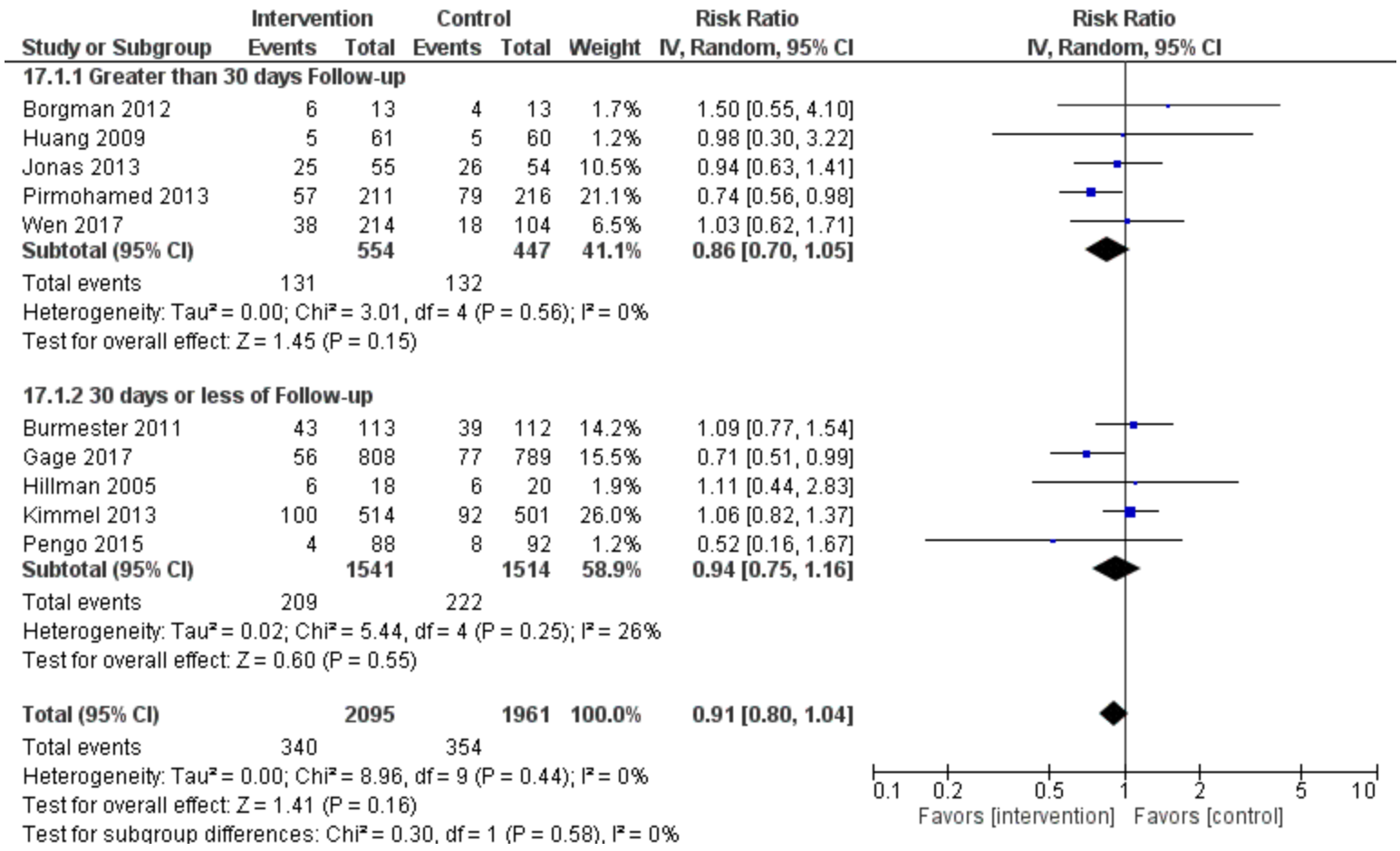

Figure 30. Meta-analysis of Pharmacogenetic Testing vs. Control by Follow-up for INR ≥ 4

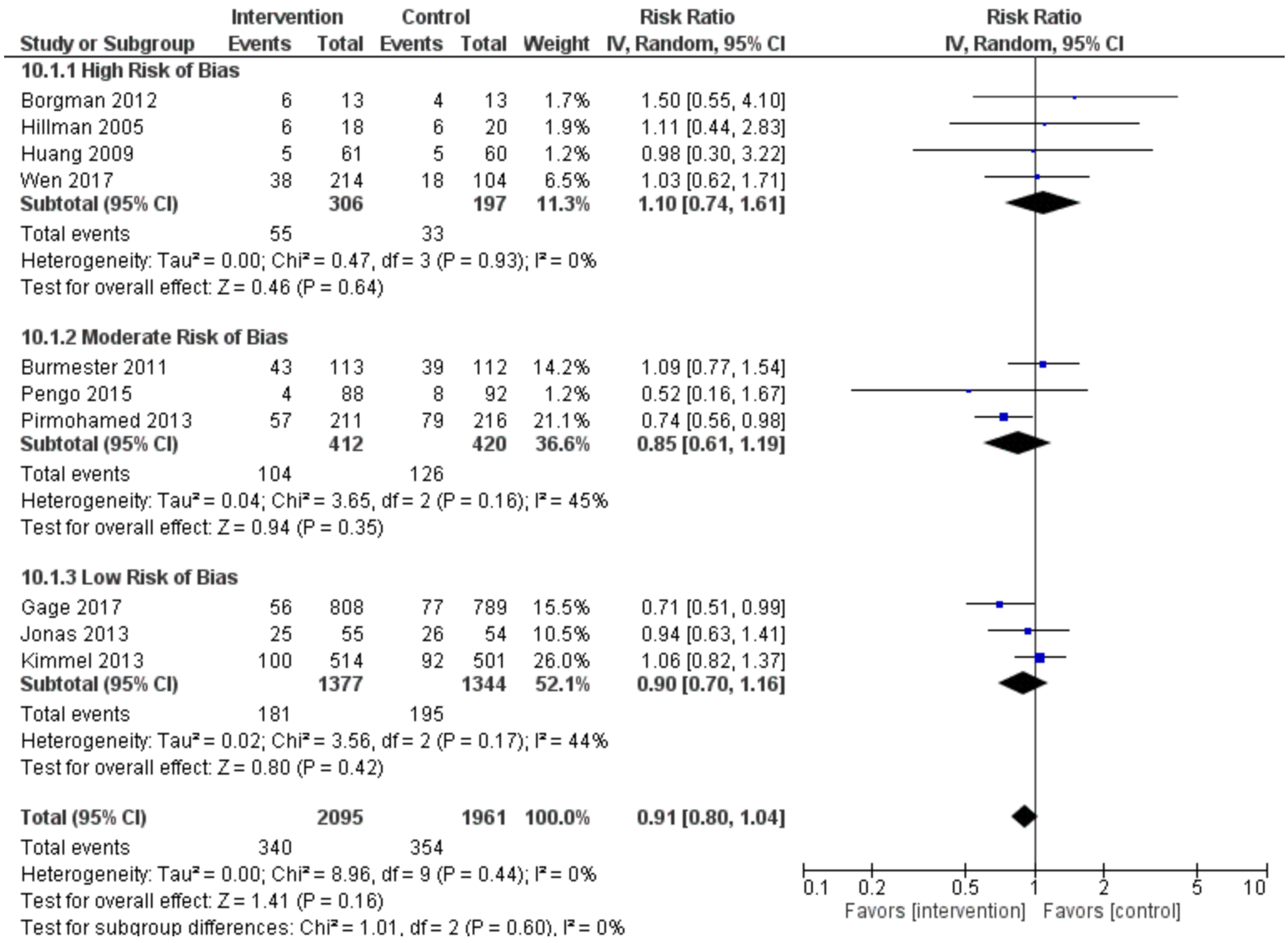

Figure 31. Meta-analysis of Pharmacogenetic Testing vs. Control by Risk of Bias for INR ≥ 4

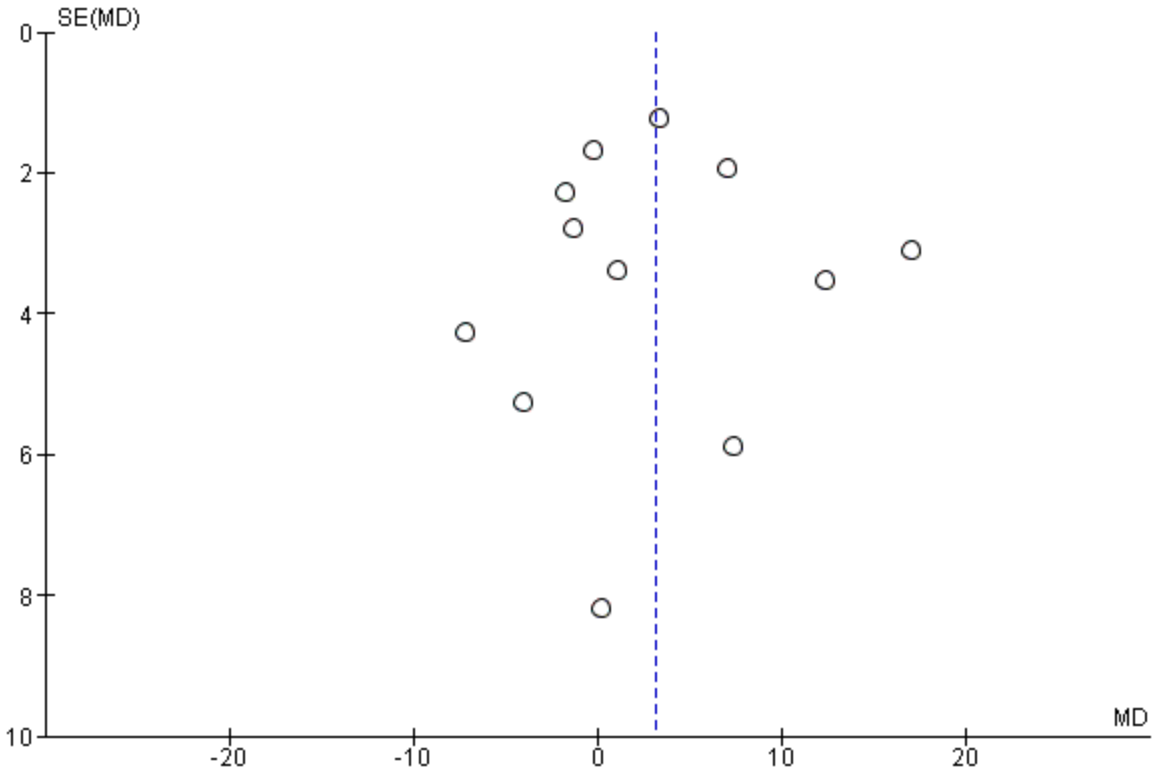

Figure 32. Funnel Plot of Eligible Randomized Controlled Trials for PTTR

Appendix F. GRADE Quality of Evidence

Number of Studies	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Comments	Overall Quality of Evidence Rating
Outcome: Clinical Utility—Mortality							
7 RCTs (4 with events)	Low	-1	0	-1	0	Overall analysis has wide CI that includes effect and no effect; subgroup analysis by comparator has opposite effects, indicating clinical heterogeneity	Low ●●○○
Outcome: Clinical Utility—Major Bleeding							
11 RCTs (7 with events)	Low	0	0	-1	0	Relatively wide confidence intervals of individual studies with subgroup analysis by comparator, indicating no statistically significant effect of fixed-dose strategy and pharmacogenetically guided dosing results in 61% fewer bleeding events compared to clinical algorithm	Moderate ●●●○
Outcome: Clinical Utility—Thromboembolic Events							
11 RCTs (6 with events)	Low	0	-1	0	0	Large weight of Gage et al. (81%) for pooled estimate; indirectness because of heterogeneity in outcome assessment	Moderate ●●●○
Outcome: Clinical Utility—INR ≥ 4							
10 RCTs	Low	0	-2	0	0	Outcome is indirect measure of harm and differing	Low ●●○○

Number of Studies	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Comments	Overall Quality of Evidence Rating
						definitions and differing follow-up time periods	
Outcome: Clinical Utility—Time in Therapeutic Range							
12 RCTs	Low	-1	-1	0	0	Outcome is indirect measure of harm; inconsistency from clinical heterogeneity because of different comparators and varying lengths of follow-up	Low ●●○○
Outcome: Cost-Effectiveness and Economic Outcomes							
5 modeling studies	Moderate	-1	-2	0	0	Cost/QALY estimates are both above and below generally accepted thresholds; U.S.- and non-U.S.-based models differ in results; models do not include estimates of efficacy from recent RCTs; older U.S.-based studies lack applicability to present-day costs of inputs and outcomes	Very low ●○○○

Appendix G. Studies Registered at ClinicalTrials.gov

Registered clinical trial number	Title of study	Study completion date (from https://clinicaltrials.gov/	Status of publications and whether study eligible for possible inclusion in systematic review
NCT00247702 (Taiwan)	The Association of Warfarin Dosage and Plasma Enantiomer Concentration With the Gene Polymorphisms of CYP and VKOR	June 2006	No published study; no outcome of interest and no comparator
NCT00377143 (U.S.)	PRospective Evaluation Comparing Initiation of Warfarin StrategiEs (PRECISE): Pharmacogenetic-guided Versus Usual Care	August 2006	Withdrawn (due to similar large study planned by NHLBI)
NCT00334464 (U.S.)	A Pharmacogenetic Study of Warfarin Dosing, "The COUMA-GEN Study"	November 2007	Published study included in review[27]
NCT00484640 (U.S.)	Modeling Genotype and Other Factors to Enhance the Safety of Coumadin Prescribing	May 2008	Published study included in review[7]
NCT00634907 (U.S.)	Prospective Genotyping For Total Hip or Knee Replacement Patients Receiving Warfarin (Coumadin)	October 2008	Published study excluded from review due to not being an RCT[81]
NCT00511173 (U.S.)	Comparison of Warfarin Dosing Using Decision Model Versus Pharmacogenetic Algorithm	November 2008	No published study; RCT would likely be included in review
NCT00830570 (U.S.)	The Clinical and Economic Impact of Pharmacogenomic Testing of Warfarin Therapy in Typical Community Practice Settings (MHSMayoWarf1)	January 2010	Published study excluded from review due to not pertaining to an intervention of interest[82]
NCT01178502 (South Korea)	PGx Study to Develop and Validate the Predictive Warfarin Dosing Algorithm for Personalized Warfarin Pharmacotherapy	April 2010	No published study; not an RCT

Registered clinical trial number	Title of study	Study completion date (from https://clinicaltrials.gov/	Status of publications and whether study eligible for possible inclusion in systematic review
NCT00993200 (U.S.)	PerMIT: Warfarin : A Prospective Randomized Controlled Trial Comparing Usual Care Warfarin Initiation to PerMIT Pharmacogenetic Guided Warfarin Therapy	December 2010	Published study included in review[20]
NCT01520402 (U.S.)	Genetic Response to Warfarin in Healthy Subjects	May 2011	Published study excluded from review due to not including an intervention of interest[83]
NCT00927862 (U.S.)	Applying Pharmacogenetic Algorithms to Individualize Dosing of Warfarin (Coumagen-II)	June 2011	Published study excluded from review due to lack of comparator[77]
NCT00654823 (Israel)	Pharmacogenetic Study of Warfarin Dose-Response: a Prospective Trial (PGxWarfarin)	June 2011	No published study; not an RCT and no outcome of interest
NCT00904293 (U.S.)	Genotype-Guided Warfarin Therapy Trial (WARFPGX)	January 2012	Published study included in review[22]
NCT01178034 (Italy)	Early Identification of Warfarin Maintenance Dosage	October 2012	Published study included in review[30]
NCT00970892 (Turkey)	VKORC1 and CYP2C9 Gene Polymorphisms and Warfarin Management	December 2012	No published study; not an RCT
NCT00839657 (U.S.)	Clarification of Optimal Anticoagulation Through Genetics (COAG)	April 2013	Published study included in review[21]
NCT01119274 (Germany)	EUropean Pharmacogenetics of AntiCoagulant Therapy - Phenprocoumon (EU-PACT)	April 2013	Published studies excluded from review due to no intervention of interest[84,85]
NCT01447511 (U.S.)	Pharmacogenetics of Warfarin Induction and Inhibition	June 2013	No published study; not an RCT and no comparator

Registered clinical trial number	Title of study	Study completion date (from https://clinicaltrials.gov/	Status of publications and whether study eligible for possible inclusion in systematic review
NCT01119261 (Germany)	EUropean Pharmacogenetics of AntiCoagulant Therapy - Acenocoumarol (EU-PACT)	June 2013	Two published studies excluded from review because drug not approved for use in the U.S.[84,85]
NCT01119300 (Germany)	EUropean Pharmacogenetics of AntiCoagulant Therapy - Warfarin (EU-PACT)	October 2013	Published study included in review[26]
NCT03015025 (Bolivia)	Creation and Validation of a Pharmacogenetic Dosage Algorithm for Acenocoumarol in Patients With Venous Thromboembolic Disease, Atrial Fibrillation and/or Mechanical Valvular Heart Prosthesis	October 2013	No published study; pharmacologic testing for a drug not approved for use in the U.S. and not an RCT
NCT02065388 (Taiwan)	Pharmacogenetic Dosing of Warfarin	December 2013	Published study included in review[29]
NCT01855737 (China)	The Study of Warfarin Maintenance Dose in Chinese Patients (WADCH)	January 2014	No published study; no outcome of interest
NCT01318057 (Puerto Rico)	Pharmacogenetics of Warfarin in Puerto Ricans	July 2014	No published study; not an RCT
NCT01610141 (China)	Applying Pharmacogenetics to Warfarin Dosing in Chinese Patients	June 2015	Published study excluded from review due to no outcome of interest[86]
NCT01305148 (U.S.)	Warfarin Adverse Event Reduction For Adults Receiving Genetic Testing at Therapy INitiation (WARFARIN) (WARFARIN)	December 2015 Suspended (Sponsor is raising funds for the remainder of the study)	No published study; RCT would likely be included in review
NCT02710747 (China)	The Pharmacogenetics of Optimal Warfarin Therapy in Chinese Patients After Heart Valve Replacement (POWAT)	July 2016	No published study; RCT would likely be included in review

Registered clinical trial number	Title of study	Study completion date (from https://clinicaltrials.gov/	Status of publications and whether study eligible for possible inclusion in systematic review
NCT01633957 (China)	A Trial of Genotype-based Warfarin Initiation in Patients With Mechanical Prosthetic Heart Valve (SYSU-WARFA)	August 2016	No published study; RCT would likely be included in review
NCT01006733 (U.S.)	Genetics Informatics Trial (GIFT) of Warfarin to Prevent DVT (GIFT)	November 2016	Published study included in review[31]
NCT02211326 (China)	Genotype-guided Warfarin Individualized Treatment	May 2017	No published study; RCT would likely be included in review
NCT00700895 (Singapore)	Assessing the Clinical Benefits of a Pharmacogenetics-Guided Dosing Regimen for Calculating Warfarin Maintenance Dose	August 2017	No published study; no outcome of interest
NCT02297126 (U.S.)	A Prospective Trial to Assess Cost and Clinical Outcomes of a Clinical Pharmacogenomic Program (INGenious)	June 2018	No published study; RCT and economic study might be eligible for inclusion in review
NCT02069132 (Italy)	Validation of International Warfarin Pharmacogenetics Consortium (IWPC) Algorithm in Elderly Patients With Comorbidity (VIALE)	June 2018	No published study; not an RCT
NCT03161496 (China)	A Research in Pharmacogenomics and Accurate Medication of Novel Oral Anticoagulants	December 2018	No study published; no comparator, and not an RCT
NCT03112525 (Switzerland)	DAPHNE Study: Real-Life Observational Study to Evaluate the Impact of the CYP3A4/5/7 and P-gp Pharmacogenetics and Phenotypic Activity on the Pharmacokinetic Profile of the Direct Oral Anticoagulants Rivaroxaban and Apixaban in Hospitalised Patients	April 2019	No study published; not an RCT
NCT02345356 (Puerto Rico)	A Genomic Approach to Warfarin Dose Prescription in Admixed Caribbean Hispanics	July 2019	No published study; not an RCT

Registered clinical trial number	Title of study	Study completion date (from https://clinicaltrials.gov/	Status of publications and whether study eligible for possible inclusion in systematic review
NCT02972385 (U.S.)	Pharmacogenomics of Warfarin in Hispanics and Latinos	September 2019	No published study; no outcome of interest
NCT02592980 (Brazil)	Evaluation of a Pharmacogenetic-based Warfarin Dosing Algorithm in Patients	December 2019	No published study; RCT would likely be included in review
NCT03225820 (U.S.)	Implementation of Point-of-Care Pharmacogenomic Decision Support Accounting for Minority Disparities	September 2020	No published study; RCT would likely be included in review

Appendix H. Detailed Payer Policies

Excerpt from the Medicare National Coverage Determination on Pharmacogenomic Testing for Warfarin Response[55]

Effective August 3, 2009, the Centers for Medicare & Medicaid Services (CMS) believes that the available evidence supports that coverage with evidence development (CED) under §1862(a)(1)(E) of the Social Security Act (the Act) is appropriate for pharmacogenomic testing of *CYP2C9* or *CYP2C9* alleles to predict warfarin responsiveness by any method, and is therefore covered only when provided to Medicare beneficiaries who are candidates for anticoagulation therapy with warfarin who:

1. Have not been previously tested for *CYP2C9* or *CYP2C9* alleles; and
2. Have received fewer than five days of warfarin in the anticoagulation regimen for which the testing is ordered; and
3. Are enrolled in a prospective, randomized, controlled clinical study when that study meets the following standards.

A clinical study seeking Medicare payment for pharmacogenomic testing of *CYP2C9* or *CYP2C9* alleles to predict warfarin responsiveness provided to the Medicare beneficiary who is a candidate for anticoagulation therapy with warfarin pursuant to CED must address one or more aspects of the following question:

Prospectively, in Medicare-aged subjects whose warfarin therapy management includes pharmacogenomic testing of *CYP2C9* or *CYP2C9* alleles to predict warfarin response, what is the frequency and severity of the following outcomes, compared to subjects whose warfarin therapy management does not include pharmacogenomic testing?

- Major hemorrhage
- Minor hemorrhage
- Thromboembolism related to the primary indication for anticoagulation
- Other thromboembolic event
- Mortality

The study must adhere to the following standards of scientific integrity and relevance to the Medicare population:

a. The principal purpose of the research study is to test whether a particular intervention potentially improves the participants' health outcomes.
b. The research study is well-supported by available scientific and medical information or it is intended to clarify or establish the health outcomes of interventions already in common clinical use.
c. The research study does not unjustifiably duplicate existing studies.
d. The research study design is appropriate to answer the research question being asked in the study.

e. The research study is sponsored by an organization or individual capable of executing the proposed study successfully.
f. The research study is in compliance with all applicable Federal regulations concerning the protection of human subjects found in the Code of Federal Regulations (CFR) at 45 CFR Part 46. If a study is regulated by the FDA, it also must be in compliance with 21 CFR Parts 50 and 56.
g. All aspects of the research study are conducted according to the appropriate standards of scientific integrity.
h. The research study has a written protocol that clearly addresses, or incorporates by reference, the Medicare standards.
i. The clinical research study is not designed to exclusively test toxicity or disease pathophysiology in healthy individuals. Trials of all medical technologies measuring therapeutic outcomes as one of the objectives meet this standard only if the disease or condition being studied is life-threatening as defined in 21 CFR § 312.81(a) and the patient has no other viable treatment options.
j. The clinical research study is registered on the www.ClinicalTrials.gov website by the principal sponsor/investigator prior to the enrollment of the first study subject.
k. The research study protocol specifies the method and timing of public release of all pre-specified outcomes to be measured including release of outcomes if outcomes are negative or study is terminated early. The results must be made public within 24 months of the end of data collection. If a report is planned to be published in a peer-reviewed journal, then that initial release may be an abstract that meets the requirements of the International Committee of Medical Journal Editors. However, a full report of the outcomes must be made public no later than 3 years after the end of data collection.
l. The research study protocol must explicitly discuss subpopulations affected by the treatment under investigation, particularly traditionally underrepresented groups in clinical studies, how the inclusion and exclusion criteria affect enrollment of these populations, and a plan for the retention and reporting of said populations on the trial. If the inclusion and exclusion criteria are expected to have a negative effect on the recruitment or retention of underrepresented populations, the protocol must discuss why these criteria are necessary.
m. The research study protocol explicitly discusses how the results are or are not expected to be generalizable to the Medicare population to infer whether Medicare patients may benefit from the intervention. Separate discussions in the protocol may be necessary for populations eligible for Medicare due to age, disability or Medicaid eligibility.

Consistent with section 1142 of the Act, the Agency for Healthcare Research and Quality (AHRQ) supports clinical research studies that CMS determines meet the above-listed standards and address the above-listed research questions.

Appendix I. See Attachment for Excluded Studies