


Agency medical director comments

Pharmacogenetic testing for patients being treated with oral anticoagulants


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## Oral Anticoagulation: a broad array of indications

<b>Prevention</b>	<b>Treatment</b>
<ul style="list-style-type: none"><li>• Atrial fibrillation</li><li>• DVT prophylaxis</li><li>• Congestive heart failure</li><li>• Prosthetic heart valves</li><li>• Stroke</li></ul>	<ul style="list-style-type: none"><li>• DVT</li><li>• Pulmonary embolus</li><li>• Inherited thrombophilia*</li><li>• Other thrombus</li><li>• Coronary artery disease</li></ul>


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## Anticoagulation with oral agents

- Achieving adequate anticoagulation therapy with vitamin K antagonists (warfarin) is often a balancing act
- Individual prescriber 'practice and experience' or clinical algorithms are used for initial dosing and adjustments
- Testing for genetic polymorphisms of 3 enzymes involved in the metabolism of warfarin are available
- Can testing improve patient centered outcomes by increasing the amount of time in the therapeutic range and minimizing undesired outcomes?

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## Agency medical director concerns

Safety = Low

Efficacy = High

Cost = Medium/High

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## Agency utilization and cost 2015-2017

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 A	36	61	26
Dollars Allowed by Total Treatments w	\$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 <sup>#</sup>	
PEBB/Medicare	\$156	\$63	
Medicaid HCA/MCO	\$143	\$80	

# Cannot be determined from claim.

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## Diagnosis and CPT codes


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 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

Dix: 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


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## Key questions

1. What is the clinical utility of genetic testing to inform treatment decisions for patients being treated with oral anticoagulants?
  - Does information obtained from the results of genetic testing change prescribing behavior?
  - Do decisions informed by genetic testing improve patient outcomes or reduce adverse events compared to usual care?
2. Are there any direct harms associated with genetic testing used to inform oral anticoagulation dosing?

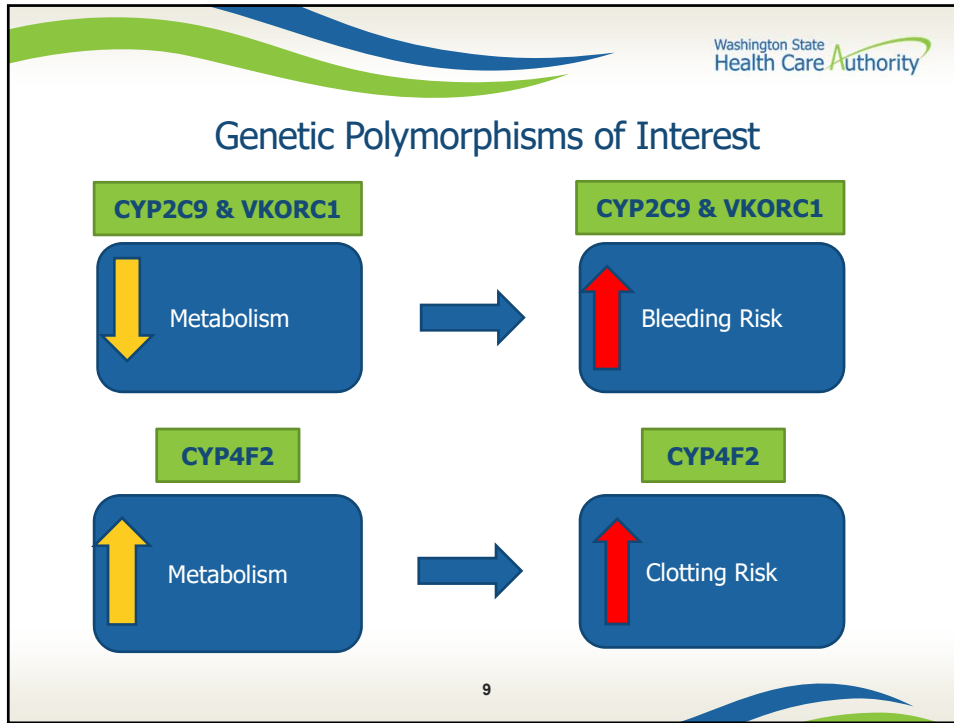
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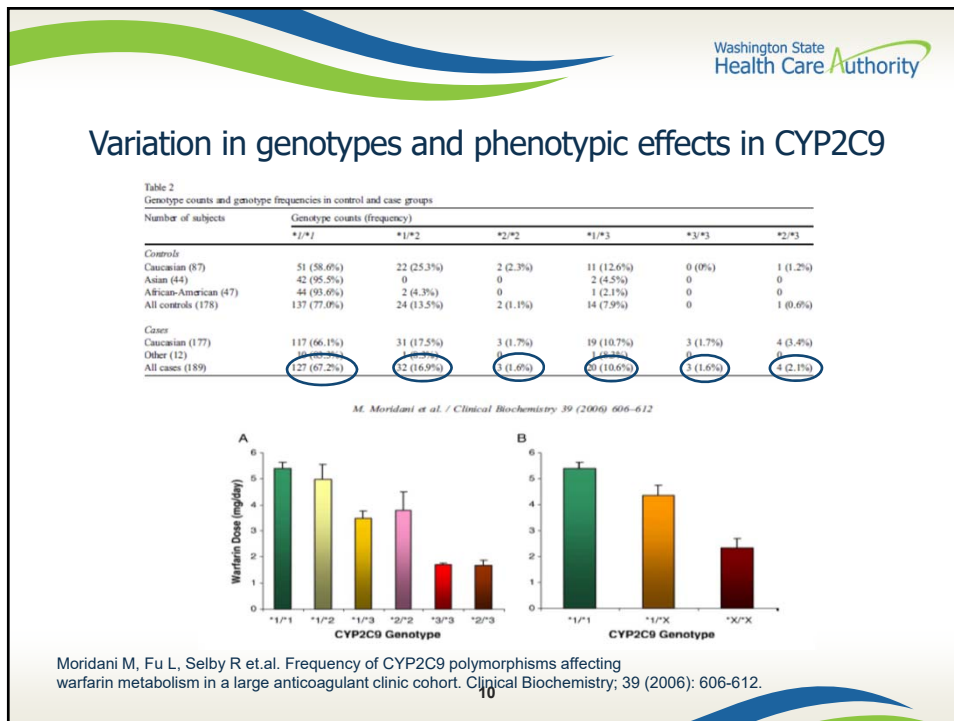
## Key questions

3. Are there differences in outcomes or harms across different patient populations?
  - a. Patient characteristics (e.g., such as age, sex or race)?
  - b. Clinical history (e.g., prior treatment, whether the diagnosis is initial or recurrent, duration of diagnosis, severity of illness, or concurrent medications)?
4. What are the costs and cost-effectiveness of genetic testing to guide the selection or dose of medications?

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## Dosing with and without genotyping

**Table 2. Distribution of Genotypes Across Study Groups**

Genetic Loci	Warfarin Dosing, No. (%)	
	Genotype-Guided (n = 808)	Clinically Guided (n = 789)
<b>CYP2C9*2 (430C&gt;T) rs1799853</b>		
CC	641 (79.3)	612 (77.6)
CT	151 (18.7)	169 (21.4)
TT	16 (2.0)	8 (1.0)
<b>CYP2C9*3 (1075A&gt;C) rs1057910</b>		
AA	5mg-11.5mg	677 (85.8)
AC		102 (12.9)
CC		10 (1.3)
<b>VKORC1*2 (-1639G&gt;A) rs9923231</b>		
GG	305 (37.8)	293 (37.1)
AG	371 (45.9)	352 (44.6)
AA	132 (16.3)	144 (18.3)
<b>CYP4F2*3 (1297G&gt;A) rs2108622</b>		
GG	379 (46.9)	397 (50.3)
AG	350 (43.3)	331 (42.0)
AA	79 (9.8)	61 (7.7)

**Required Patient Information**

Age: 65    Sex: Female    Ethnicity: Non-Hispanic

Race: White, Caucasian, or Middle Eastern

Weight: 160 lbs or 72.7 kgs    BSA 1.8

Height: (5 feet and 5 inches) or (165.1 cms)

Smokes: Yes    Liver Disease: No    **7.5 mg**

Indication: Deep venous thrombosis

Baseline INR: 1.2    Target INR: 2.5     Randomize & Blind

Amiodarone/Cordarone® Dose: 0 mg/day

Statin/HMG CoA Reductase Inhibitor: No statin

Any azole (eg. Fluconazole): No

Sulfamethoxazole/Sepra/Bactrim/Cotrim/Sulfatrim: No

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## Considerations in Evaluating Genetic Tests of Association

- Assess the risk for bias
  - Correct definition and accurate recording of phenotype with blinding
  - Have potential differences between diseased and non-diseased been considered? (ethnicity)
  - Measurement of the variants unbiased and accurate
  - Do the genotype proportions observe the Hardy-Weinberg equilibrium?
  - Have the inferences been adjusted for multiple comparisons?
  - Are the results consistent with other studies?
- How large and precise are the results?
- Can the results be applied to patient care?
 

- What are the absolute and relative effects?
  - Is the patient better off as a result?
  - Is the risk associated allele likely to be present in my patient?

User's Guide to the Medical Literature: 3<sup>rd</sup> Edition

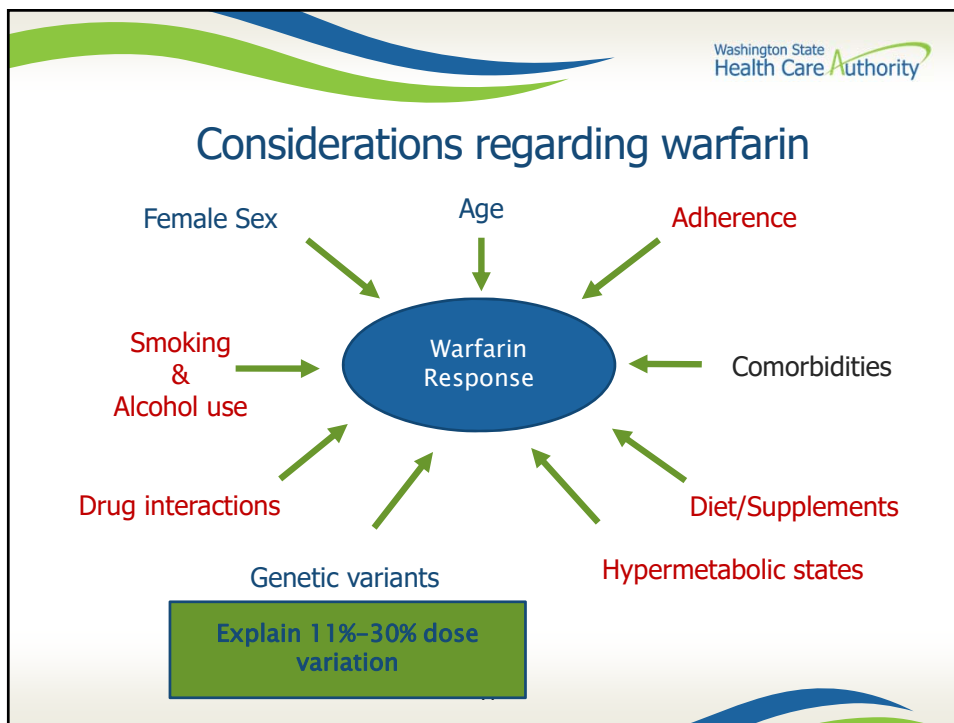
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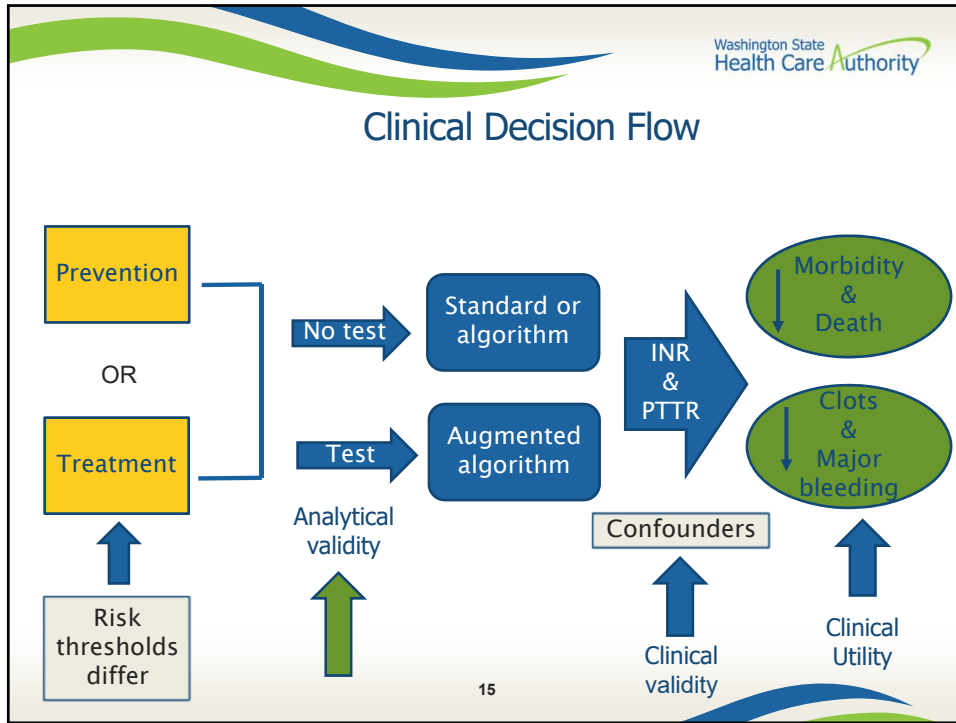
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## Drug metabolism is a multifactorial process

- Drug metabolism relates to:
  - Pharmacokinetics: the time course of absorption, distribution, metabolism and excretion
  - Pharmacodynamics: relationship between the drug concentration at the site of action and the resultant effect, including time, intensity of effect and adverse reactions
  - Other factors influencing drug effects are variations in:
    - Absorption
    - Distribution
    - Disease states
    - Drug Interactions
    - Ability to metabolize and eliminate (genetics)

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### Effectiveness

Question	Quality of evidence	Findings
Is there a dose or med change compared to no test?	NA	Built into algorithms, often only used for 1 <sup>st</sup> dose or for early dosing(1 <sup>st</sup> 2 weeks)
Is there an effect on PTTR?	Low	No statistical difference
Is there an effect on over-anticoagulation?	Low	No statistical difference
Is there an effect on thromboembolic events?	Moderate	No statistical difference
Is there an effect on major bleeding?	<b>Moderate</b>	~1 fewer event for every 100 persons tested

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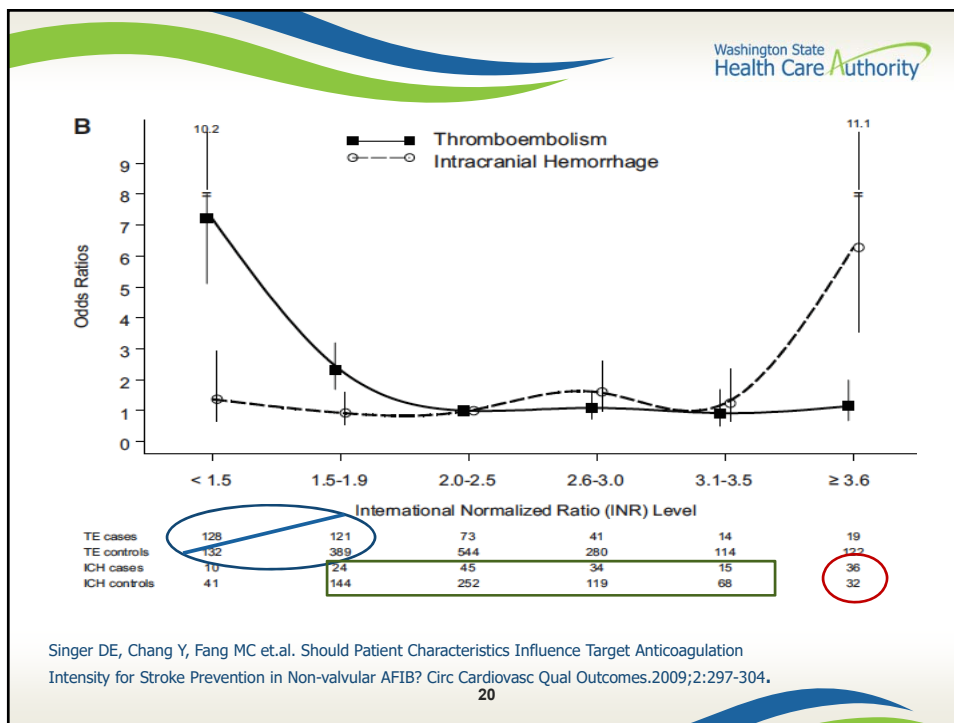
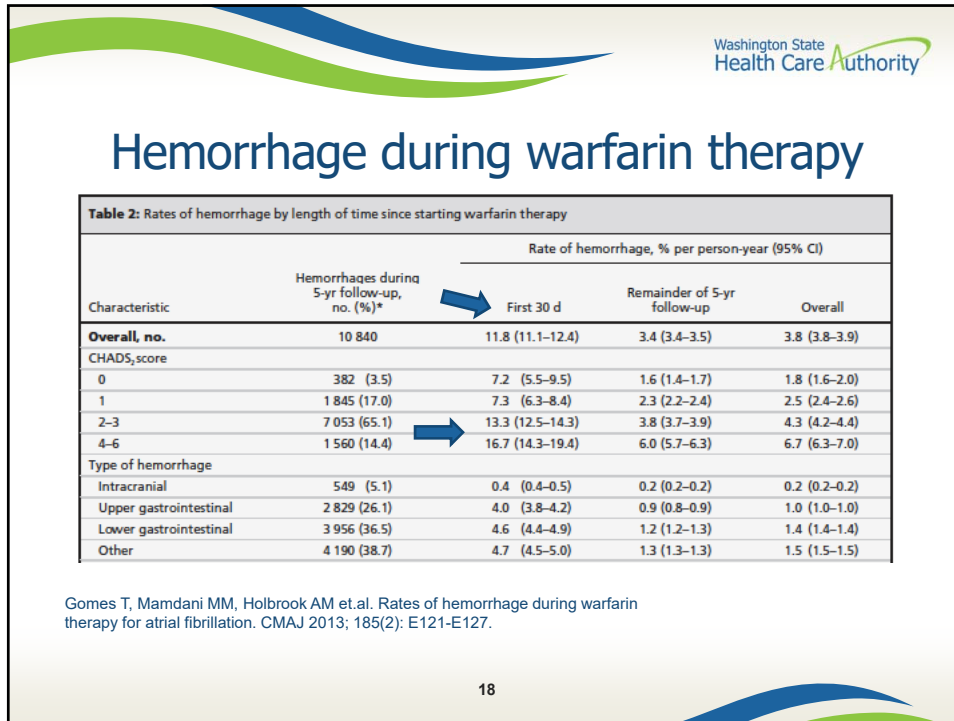



## Effectiveness

Question	Quality of evidence	Findings
Are there any direct harms?	NA	Harms from the therapy not the test
Sub group differences related to clinical history?	Exploratory	Detailed in presentation
Sub group differences related to patient characteristics?	Exploratory	Detailed in presentation
Cost comparison, effectiveness and utility studies?	Very Low	None cost effective at a US QALY threshold of <\$50,000

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- ## Who is at increased risk of bleeding?
- Age >65?
  - INR>4
  - Highly variable INRs
  - HTN
  - Prior stroke
  - Liver disease
  - Adherence
  - Large dietary variations
  - Serious heart disease
  - Anemia
  - Malignancy
  - Trauma
  - Renal insufficiency
  - Concomitant drugs
  - Acute illness
  - Exacerbations of CHF
  - **H/O GI Bleed\***
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## Bleeding occurs with elevated INRs

**Table 3. Components of the Composite Primary End Point<sup>a</sup>**

	Warfarin Dosing, No. (%)		Absolute Difference (95% CI), %	Relative Rate (95% CI)	P Value
	Genotype-Guided (n = 808)	Clinically Guided (n = 789)			
Met $\geq 1$ primary end point component <sup>b</sup>	87 (10.8)	116 (14.7)	3.9 (0.7 to 7.2)	0.73 (0.56 to 0.95) <sup>c</sup>	.02
<b>Primary End Point Components</b>					
Major bleeding on days 1-30	2 (0.2)	8 (1.0)	0.8 (-0.2 to 1.8)	0.24 (0.05 to 1.15)	.06
Plus INR <4	2 (0.2)	6 (0.8)	0.5 (-0.4 to 1.5)		
Plus INR $\geq 4$	0	2 (0.3)	0.3 (-0.4 to 1.0)		
INR $\geq 4$ on days 1-30	56 (6.9)	77 (9.8)	2.8 (0.1 to 5.6)	0.71 (0.51 to 0.99)	.04
Venous thromboembolism on days 1-60	33 (4.1)	38 (4.8)	0.7 (-1.3 to 2.8)	0.85 (0.54 to 1.34)	.48
PE or symptomatic DVT	10 (1.2)	15 (1.9)	0.7 (-0.7 to 2.1)		
PE	3 (0.4)	8 (1.0)	0.6 (-0.3 to 1.7)		
Death on days 1-30	0	0			

Abbreviations: DVT, deep vein thrombosis; INR, international normalized ratio; NA, not applicable; PE, pulmonary embolism.


<sup>a</sup> There were 1597 patients who met criteria for a primary end point.

<sup>b</sup> Patients who met multiple end points were counted only once in the total.

<sup>c</sup> When using a mixed model with site as a random effect, the odds ratio was 0.70 (95% CI, 0.52-0.94), confirming a benefit with genotype-guided dosing of warfarin.

Gage BF et.al. The GIFT Randomized Controlled Trial.  
<https://www.ncbi.nlm.nih.gov/pubmed/28973620>


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## Current state agency policy

- PEBB (Regence) – Not covered, investigational**
- Medicaid FFS and Managed Care – Not covered; coverage-criteria not known**
- Labor and Industries – Not covered**
- Dept. of Corrections –**


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## Other Payers

- CMS: Not covered unless part of an RCT
- Noridian LCD: same as national coverage determination
- Aetna, Cigna: not covered


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## Agency Medical Directors Recommendations for Pharmacogenomics Testing to Guide Oral Anticoagulant Dosing

- Do Not Cover
  - There is currently not strong or consistent evidence that outcomes important to patients are improved.

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Questions?

**More Information:**

<http://xxxxx.xxx>

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**Order of Scheduled Presentations:**

**Pharmacogenetic testing for patients being treated with anticoagulants**

Name	
1	
2	
3	
4	
5	
6	

No requests to provide public comment on this technology review were received.





# Pharmacogenetic Testing for Patients Being Treated With Oral Anticoagulants

Washington State Health Care Authority  
Health Technology Clinical Committee  
May 18, 2018

Valerie J. King, MD, MPH



## Outline

- Background
- Methods and search results
- Included studies
- Meta-analyses by outcome
- GRADE summary
- Clinical practice guidelines
- Payer policies
- Overall summary



## Background

- Anticoagulant drugs (blood thinners) are used to prevent blood clots
- Common indications for anticoagulation include atrial fibrillation (AFib), deep venous thrombosis (DVT), pulmonary embolism (PE), and orthopedic surgery
- Warfarin (Coumadin) is the most commonly prescribed oral anticoagulant, although use of direct oral anticoagulants (DOACs) is increasing
- Clinical decisions about which of these agents to use depend on the indication for anticoagulation, medical comorbidities, and potential drug interactions

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## Background

- Risk of thrombosis weighed against risks of bleeding—warfarin has a narrow therapeutic window
- Wide variations in warfarin dose requirements, based on diet, comorbidities, drug interactions, indications, etc.
- Warfarin requires careful monitoring
  - International Normalized Ratio (INR) test measures time for blood to clot derived from the prothrombin time test
  - At initiation of therapy, INR tested frequently
  - After initial stabilization, testing usually done monthly

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## Background

- Two non-pharmacogenetic methods for initial dosing of warfarin:
  - Fixed dose (e.g., 5 or 10 mg per day)
  - Clinical algorithm dosing using patient's characteristics: age, sex, ethnicity, body surface area, comorbidities, and target INR
- Pharmacogenetic method for initial dosing:
  - Genotype information added to the algorithm calculation for initial warfarin dosing

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## Technology Description

- Genotypes that may be included in pharmacogenetic algorithms:
  - Cytochrome P450 2C9 (*CYP2C9*)
  - Vitamin K epoxide reductase (*VKORC1*)
  - Cytochrome P450 4F2 (*CYP4F2*)

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## Technology Description

- The *CYP2C9* enzyme metabolizes warfarin
  - Polymorphisms in *CYP2C9* reduce enzymatic activity, leading to lower required doses of warfarin
  - Up to 50% per allele
- Warfarin blocks *VKORC1* enzyme activity
  - Genetic variants in *VKORC1* result in the therapeutic dose of warfarin being reduced
  - Approximately 25% per variant allele
- The *CYP4F2* enzyme cleaves the phytal side chain of vitamin K, leading to inactive metabolites
  - Genetic polymorphism in *CYP4F2* can increase the warfarin therapeutic dose
  - Up to 12% per allele

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## Technology Description

- Among populations of European ancestry, common variants in *CYP2C9*, *VKORC1*, and *CYP4F2* account for up to 18%, 30%, and 11%, respectively, of the variance in stable warfarin dose
- Variants of these genes explain less of the dose variability among patients of other ancestries because of differing allele frequencies across populations
  - *CYP2C9*\*2 is almost absent in Asian populations
  - 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

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# Methods



## Scope: PICO

- **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

## Scope: PICO

### ▪ Outcomes

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

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## Scope: 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 to 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 to usual care without genetic testing?

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## Scope: Key Questions

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 to 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?

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## Eligible Studies

- Key Questions 1, 2, and 3:
  - Randomized controlled trials
  - Systematic reviews (with and without meta-analysis) of randomized controlled trials
- Key Question 4:
  - Cost-effectiveness studies and other comparative economic evaluations
  - Systematic reviews (with and without meta-analysis) of these types of studies

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## Evidence Sources

- Search of multiple databases:
  - Ovid MEDLINE
  - Cochrane Database of Systematic Reviews
  - Cochrane Central Register of Controlled Trials
- Additional evidence sources:
  - Agency for Healthcare Research and Quality (AHRQ)
  - U.K. National Institute for Health and Care Excellence (NICE)
  - Veterans Administration Evidence-based Synthesis Program
  - PharmGKB, Stanford University's online resource for information about genetic variation on drug responses
  - Reference lists of included studies

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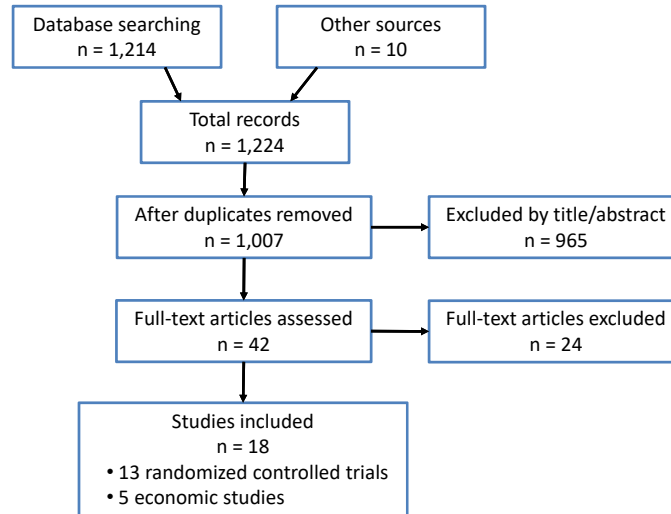
## Evidence Sources

- ClinicalTrials.gov database for ongoing and recently completed registered trials
- For clinical practice guidelines:
  - Evidence sources (e.g., MEDLINE)
  - AHRQ National Guideline Clearinghouse
- For payer policies:
  - Centers for Medicare & Medicaid Services (CMS) Medicare Coverage Database for National and Local Coverage Determinations applicable to Washington State
  - Private payers: Aetna, Cigna, and Regence websites

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## PRISMA Study Flow Diagram



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## Risk of Bias for Studies

- Two independent Center researchers evaluated studies for methodological risk of bias
- Each study assessed using Center instruments adapted from international standards and assessments
- A rating of high, moderate, or low risk of bias was assigned to each study based on adherence to recommended methods and potential for bias
- Risk-of-bias criteria are listed in Appendix B

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## Overall Quality of Evidence

- Center researchers assigned a summary judgment for the overall quality of evidence for each outcome
- Based on GRADE: Grading of Recommendations, Assessment, Development, and Evaluation
- The GRADE system defines the confidence that the estimate of the effect of the intervention on the outcome lies close to the true effect (listed on next slide)

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## GRADE Definitions of Quality of Evidence

High	<u>Very confident</u> that the estimate of the effect of the intervention on the outcome lies close to the true effect
Moderate	True effect is likely to be close to the estimate of the effect, but there is a <u>possibility that it is different</u>
Low	<u>Little confidence</u> in the estimate of the effect of the intervention on the outcome and the true effect may be substantially different from the estimate of the effect
Very Low	<u>No confidence</u> in the estimate of the effect of the intervention on the outcome and the true effect is likely to be substantially different from the estimate of effect

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## Meta-analysis Methodology

- Meta-analyses for 5 outcomes
  - Patient-important outcomes:
    - **Mortality** (binary, unique event)
    - **Major bleeding** (binary, unique event)
    - **Thromboembolic events** (binary, unique event)
  - Intermediate or surrogate outcomes:
    - Percentage of time in therapeutic range (**PTTR**) (continuous, as a percentage of follow-up time)
    - **Overanticoagulation**--INR greater than or equal to 4 (binary, unique event)

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## Meta-analysis Methodology

- Using RevMan 5.3, estimated pooled and subgroup mean differences for continuous outcomes and risk ratios for continuous and binary outcomes
  - Used the inverse variance statistical technique and random effects models for all outcomes
  - When there were sufficient numbers of studies and data, prespecified subgroup analyses were conducted

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## Prespecified Subgroup Analyses

- Control group comparator
  - Clinical algorithm-guided dosing; fixed dosing
- Risk of bias
  - High; moderate; low
- Sample size
  - $\geq 400$  or  $< 400$  total participants
- Number of genes in the pharmacogenetic algorithm
  - 3 genes; 2 genes; 1 gene

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## Prespecified Subgroup Analyses (continued)

- Country where the study was conducted
  - United States; other countries
- Clinical indication
  - AFib; cardiac valve or orthopedic surgery; other indications
- Race and ethnicity of participants
  - $\geq 90\%$  White participants;  $\geq 90\%$  Asian participants; or other combinations
- Follow-up period
  - $>30$  days or  $\leq 30$  days

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# Evidence Review



## RCTs Included for Meta-Analyses

Citation Country	Duration N Randomized	Indications	Genes Tested Comparator
Anderson et al. 2007 U.S.	3 months 206	Orthopedic surgery, VTE, AFib	<i>CYP2C9*2/*3, VKORC1</i> Standard dosing
Borgman et al. 2012 U.S.	12 weeks 34	VTE, AFib	<i>CYP2C9*2/*3, VKORC1</i> Standard dosing
Burmester et al. 2011 U.S.	60 days 230	AFib, VTE	<i>CYP2C9*2/*3, VKORC1, CYP4F2</i> Clinical algorithm
Caraco et al. 2008 Israel	1 month/ variable 283	VTE, AFib	<i>CYP2C9*2/*3</i> Clinical algorithm

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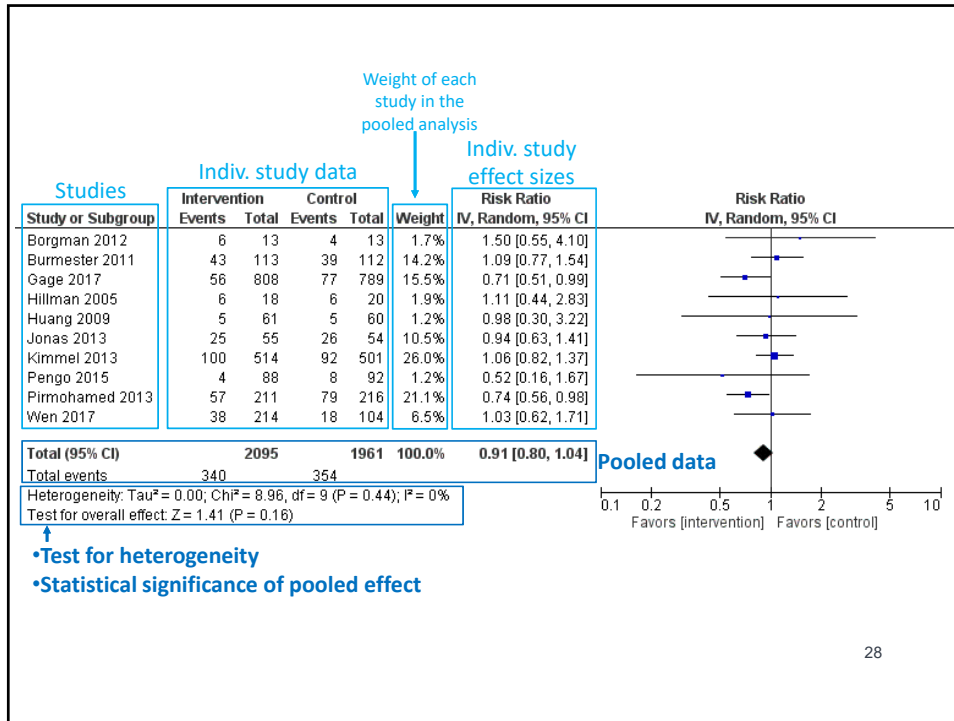
## RCTs Included for Meta-Analyses

Citation Country	Duration N Randomized	Indications	Genes Tested Comparator
Gage et al. 2017 <sup>31</sup> U.S.	90 days 1,650	Hip or knee arthroplasty	<i>CYP2C9*2/*3, VKORC1, CYP4F2</i> Clinical algorithm
Hillman et al. 2005 <sup>23</sup> U.S.	4 weeks 38	AFib, VTE, cardiac valve replacement, orthopedic surgery, other	<i>CYP2C9*2/*3</i> Standard dosing
Huang et al. 2009 <sup>28</sup> China	50 days 142	Cardiac valve replacement	<i>CYP2C9*2/*3, VKORC1</i> Standard dosing
Jonas et al. 2013 <sup>22</sup> U.S.	90 days 109	VTE, AFib, other	<i>CYP2C9*2/*3, VKORC1</i> Clinical algorithm

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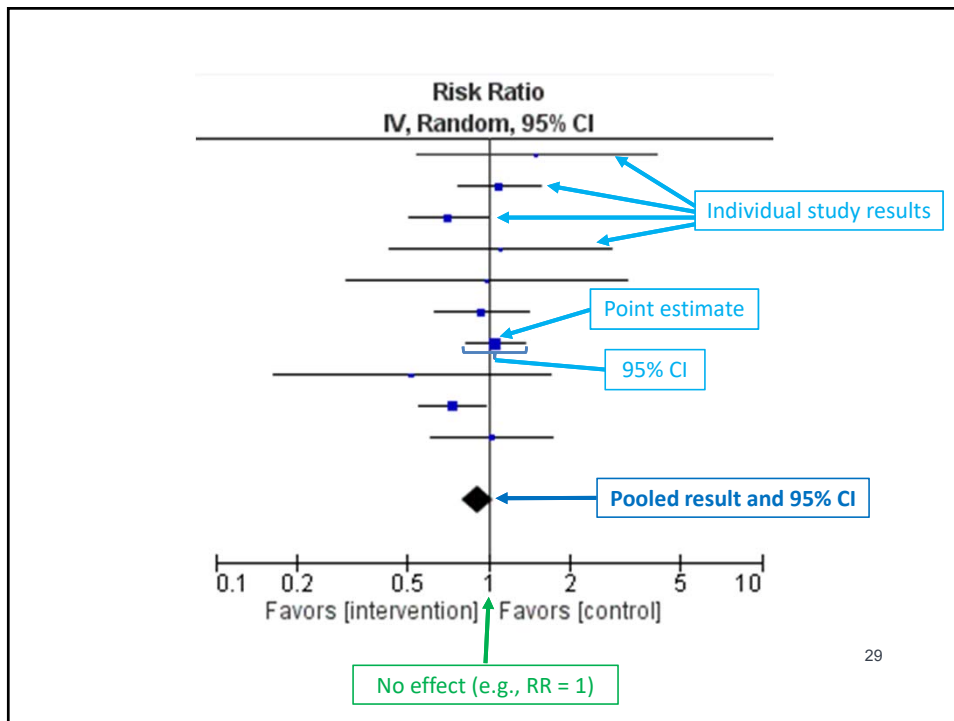
## RCTs Included for Meta-Analyses

Citation Country	Duration N Randomized	Indications	Genes Tested Comparator
Kimmel et al. 2013 <sup>21</sup> U.S.	6 months 1,015	VTE, AFib, other	<i>CYP2C9*2/*3, VKORC1</i> Clinical algorithm
Pengo et al. 2015 <sup>30</sup> Italy	30 days 200	AFib	<i>CYP2C9*2/*3, VKORC1, CYP4F2</i> Standard dosing
Pirmohamed et al. 2013 <sup>26</sup> UK, Sweden	12 weeks 455	AFib, VTE	<i>CYP2C9*2/*3, VKORC1</i> Clinical algorithm
Wang et al. 2012 <sup>25</sup> China	50 days 106	Cardiac valve replacement	<i>CYP2C9*2/*3, VKORC1</i> Standard dosing
Wen et al. 2017 <sup>29</sup> Taiwan	90 days 320	AFib, VTE, other	<i>CYP2C9*3, VKORC1; CYP2C9*2/*3, VKORC1</i> Clinical algorithm



- Test for heterogeneity
- Statistical significance of pooled effect

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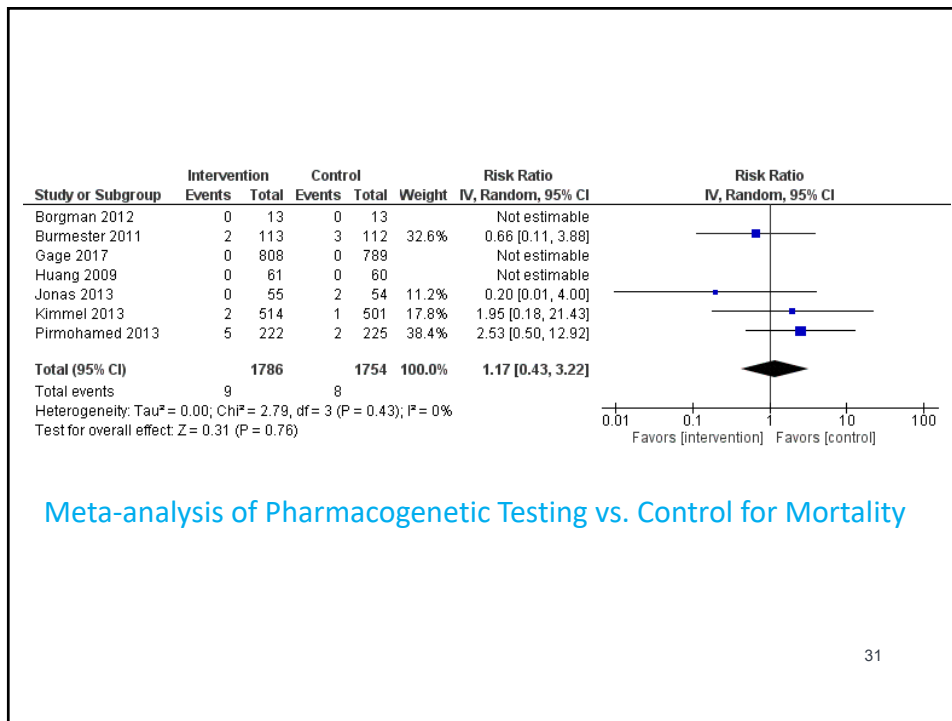
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## Meta-analyses: Mortality

7 RCTs reported mortality

- None reported deaths related to the dosing method
- 3 trials reported no deaths in either group
- Results
  - Pharmacogenetic: 9 deaths among 1,786 (0.50%)
  - Control: 8 deaths among 1,754 (0.46%)
  - Absolute risk difference: 0.48 fewer deaths per 1,000 people without pharmacogenetic testing (95% CI, -4.1 to 5.0)
  - RR 1.17 (95% CI, 0.43 to 3.22) in favor of the control group
- Meta-analysis was fairly unstable because of low numbers of events
  - Additional mortality events occurring in either group could modify the estimate of effect
- Overall quality of evidence: Low

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## Meta-analysis of Pharmacogenetic Testing vs. Control for Mortality

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## Meta-analyses: Major Bleeding

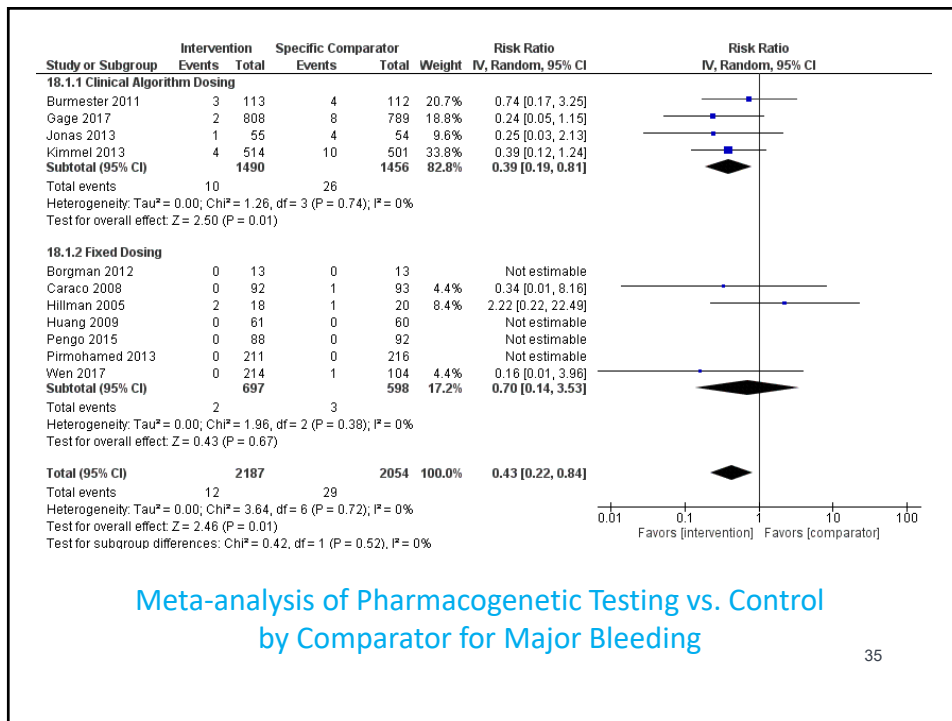
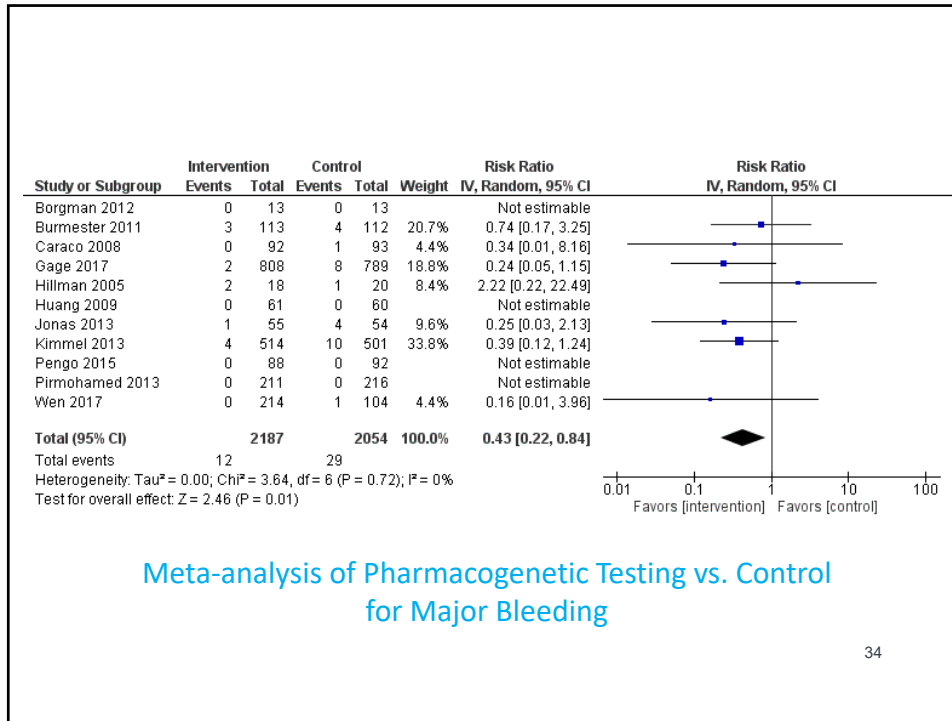
- 11 RCTs reported major bleeding as an outcome
- RCT authors' definition of major bleeding varied, generally included bleeding necessitating hospitalization or requiring interventions such as blood transfusion
- 4 RCTs without any major bleeding in either group
- Results
  - Pharmacogenetic: 12 events among 2,187 (0.55%)
  - Control: 29 events among 2,054 (1.4%)
  - Absolute difference: 8.6 fewer events per 1,000 people with pharmacogenetic testing (95% CI, 2.7 to 14.4)
  - RR 0.43 (95% CI, 0.22 to 0.84; p = .01)
- Overall quality of evidence: Moderate

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## Meta-analyses: Major Bleeding

- The major bleeding benefit of pharmacogenetically guided warfarin dosing cannot be explained by whether the control group was dosed according to a clinical algorithm or 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

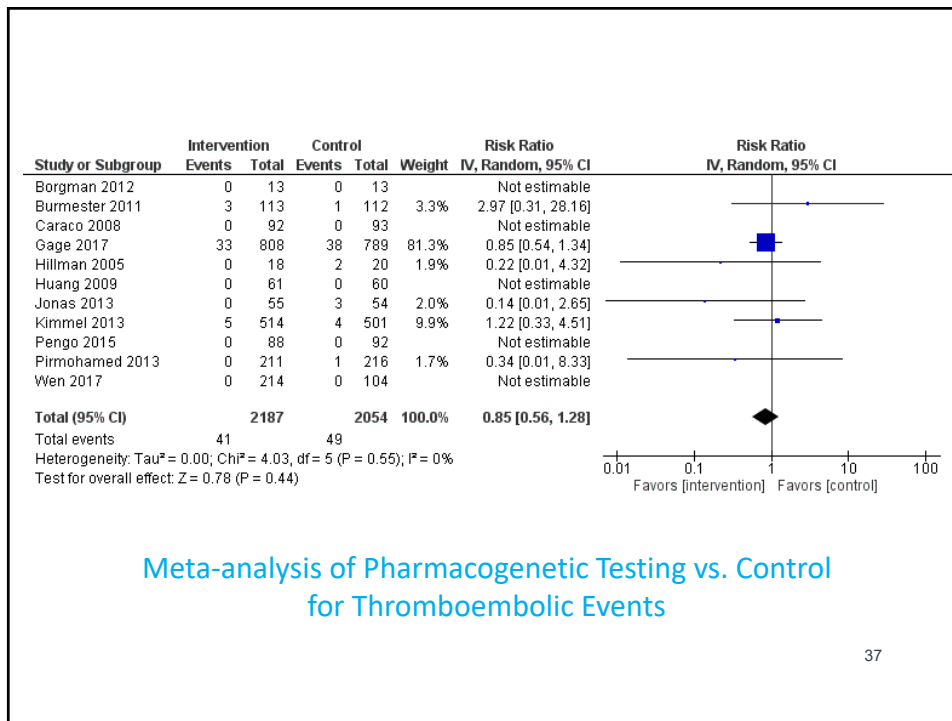
33



## Meta-analyses: Thromboembolic Events

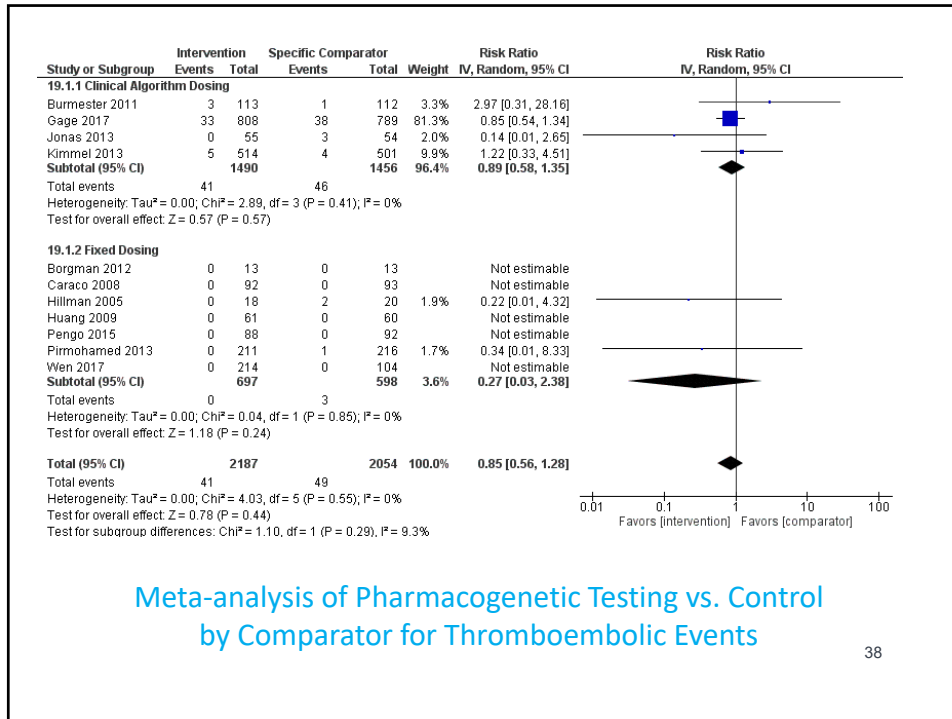
- 11 RCTs reported thromboembolic events
- 5 trials reported no events in either group
- Results
  - Pharmacogenetic: 41 events among 2,187 (1.9%)
  - Control: 49 events among 2,054 (2.4%)
  - Absolute difference: 5.1 fewer events per 1,000 people with pharmacogenetic testing (95% CI, -3.6 to 13.8)
  - RR 0.85 (95% CI, 0.56 to 1.28; p = .44)
- Results heavily weighted by Gage RCT (81%)
- Subgroup analysis by comparator, no statistically significant difference
- Overall quality of evidence: Moderate

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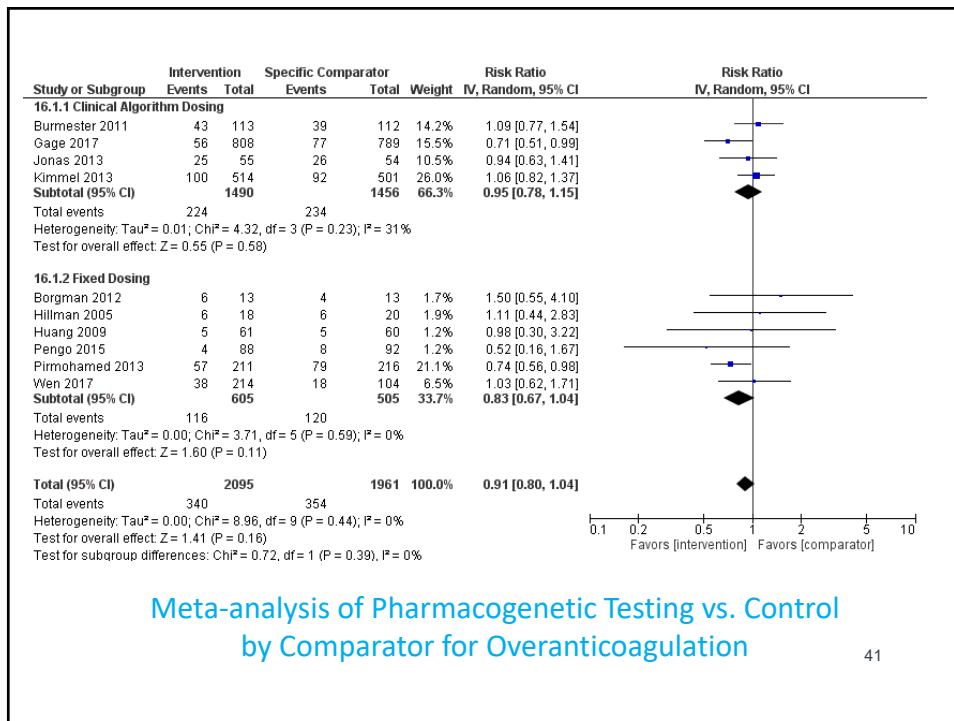
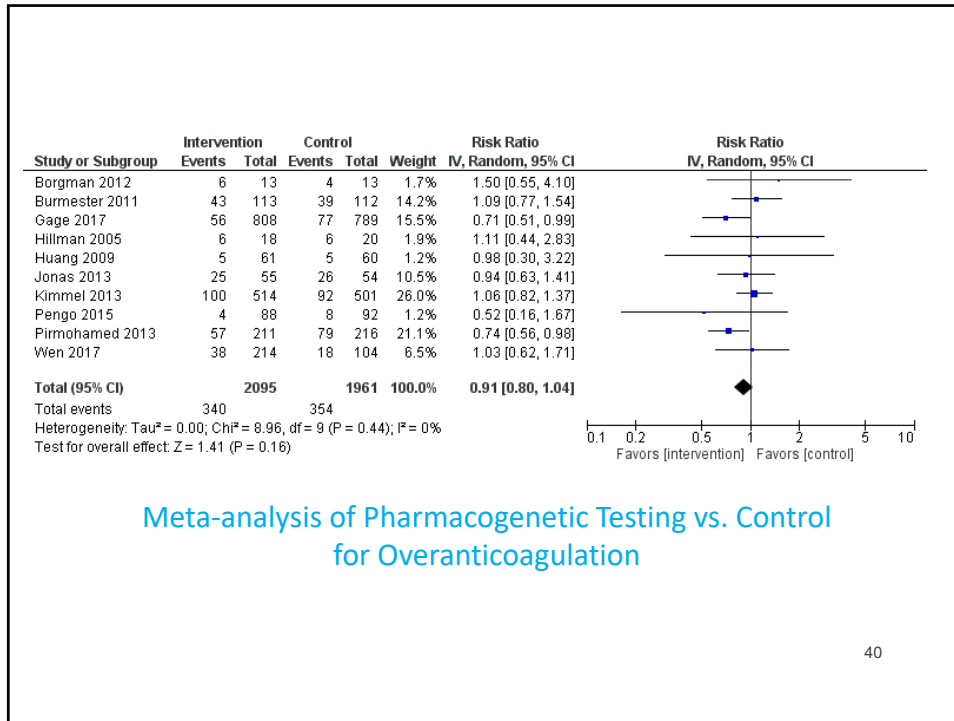
### Meta-analysis of Pharmacogenetic Testing vs. Control for Thromboembolic Events

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## Meta-analyses: Overanticoagulation (INR ≥ 4)

- 9 RCTs reported INR ≥ 4, and 1 RCT reported INR > 3.5
- Trials reported INR in different time periods, ranging from 28 days to 3 months
- Results
  - Pharmacogenetic: 340 events among 2,095 (16.2%)
  - Control: 354 events among 1,961 (18.1%)
  - Absolute difference: 18.2 fewer people with overanticoagulation per 1,000 people with pharmacogenetic testing (95% CI, -5 to 41.5)
  - RR 0.91 (95% CI, 0.80 to 1.04; p = .16)
- Overall quality of evidence: Low



## Meta-analyses: PTTR

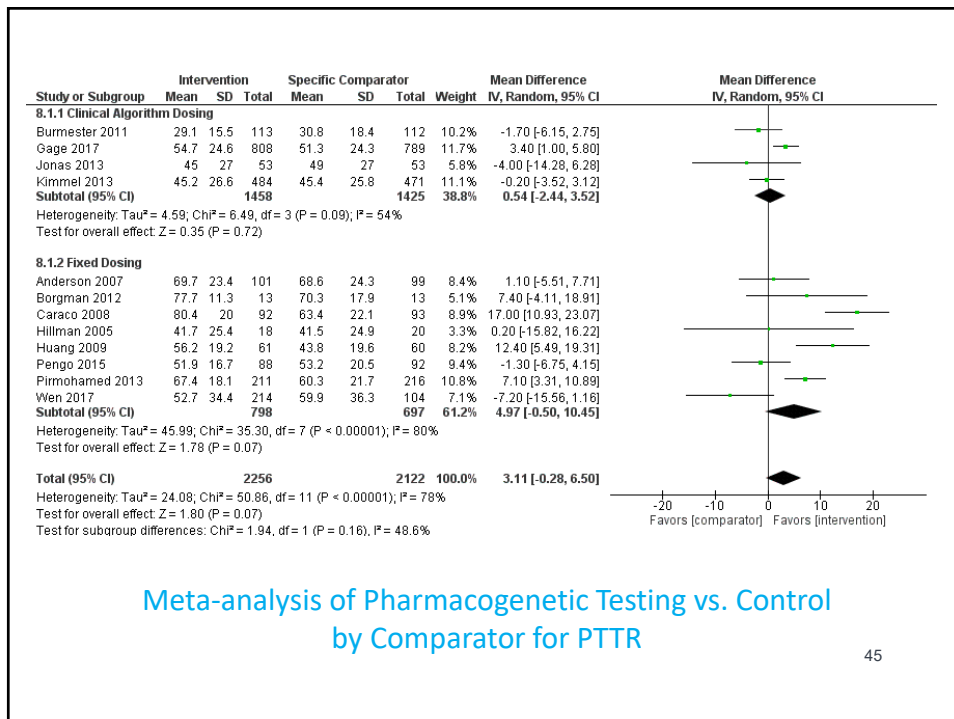
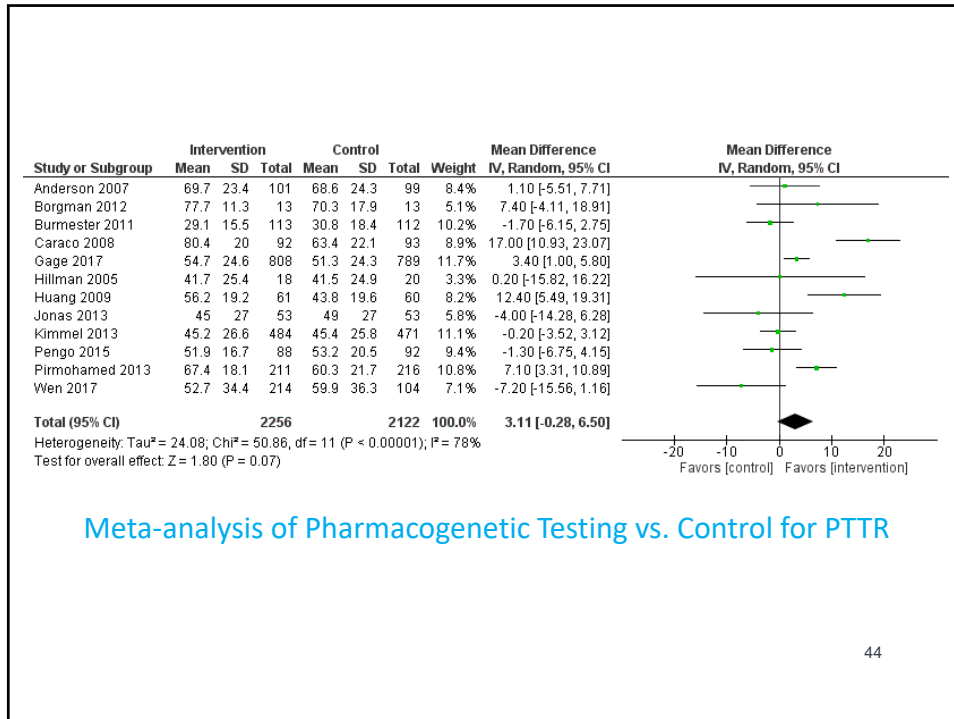
- 12 of the 13 RCTs reported PTTR
- Definitions and therapeutic range varied (e.g., 1.8 to 3.2, 2 to 3.5)
- Length of follow-up varied from 14 to 90 days
- No statistically significant difference between groups
- Pharmacogenetic group had 3.1 percentage points more time within the therapeutic range compared to control group (95% CI, -0.28 to 6.50;  $p = .07$ )
- There was substantial statistical heterogeneity ( $I^2 = 78\%$ )
- Overall quality of evidence: Low

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## Meta-analyses: PTTR

- Results of subgroup analysis by comparator
  - Pharmacogenetic group compared to clinical algorithm mean difference 0.54% (95% CI, -2.44 to 3.52;  $p = .72$ )
  - Pharmacogenetic group compared to fixed-dose mean difference, 4.97% (95% CI, -0.50 to 10.45;  $p = .07$ )
- Overall PTTR difference with pharmacogenetic testing largely explained by use of a fixed-dose warfarin initiation rather than a clinical algorithm

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### GRADE Table for Effectiveness Outcomes

Outcome	# of Participants Studies	Quality of Evidence	Estimated Effect Size (95% CI)	Anticipated Absolute Effects	
				Risk w/ and w/o PG Testing (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

### GRADE Table for Effectiveness Outcomes

Outcome	# of Participants Studies	Quality of Evidence	Estimated Effect Size (95% CI)	Anticipated Absolute Effects	
				Risk w/ and w/o PG Testing (per 1,000 people)	Risk Difference and 95% CI (per 1,000 people)
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 PG testing
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-anti-coagulation with PG testing



### GRADE Table for Effectiveness Outcomes

Outcome	Number of Participants Studies	Quality of Evidence	Estimated Effect Size (95% CI)
Clinical Utility—Time in Therapeutic Range	n = 4,378 k = 12	Low ●●○○	Mean difference, 3.11 (95% CI, -0.28 to 6.50)
	Subgroups Clinical dosing algorithm comparator n = 2,883 k = 4		Subgroups Clinical dosing algorithm comparator Mean difference, 0.54 (95% CI, -2.44 to 3.52)
	Fixed-dose comparator n = 1,495 k = 8		Fixed-dose comparator Mean difference, 4.97 (95% CI, -0.50 to 6.50)

### Key Question 1: Summary

- All studies had limitations
- Surrogate outcomes, PTTR and INR  $\geq 4$ , had most data
- Overall quality of evidence rating
  - Low: mortality, PTTR, and INR  $\geq 4$
  - Moderate: major bleeding and thromboembolic events
- Major bleeding is only clinical outcome with a statistically significant difference
  - Absolute differences are small
  - Limitations diminish the confidence in the internal and external validity of this finding
- Statistically significant difference for mean PTTR favoring pharmacogenetic testing explained by use of fixed-dose comparator

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## Key Question 2: Harms

- Harms outcomes are reflected in the meta-analyses: mortality, major bleeding, and thromboembolic events
- Other adverse events reported in the RCTs are described in report (Table 8 in Appendix C) including:
  - Cardiovascular events (e.g., stroke, myocardial infarction)
  - Serious infection
  - INR > 4 or INR not in therapeutic range
  - Composite measures of adverse events
- No pattern for other adverse outcomes related to pharmacogenetic testing

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## Key Question 3: Special Populations

- 3 subgroup analyses by race: major bleeding, PTTR and overanticoagulation
  - Not performed for the other outcomes because of limited number of studies and outcome events
  - Consider subgroup analyses by race exploratory because of inability to conduct individual patient meta-analysis and lack of information reported by most studies
  - Racial and ethnic composition of individual studies is detailed in Table 6 of Appendix C

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### Key Question 3: Special Populations

- Major bleeding by race
  - Not statistically significantly different for White or Asian subgroups
  - For studies with mixed race combinations, the difference was statistically significant in favor of the intervention
    - RR, 0.35; 95% CI, 0.13 to 0.97
- For PTTR and overanticoagulation, no statistically significant subgroup differences by race

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### Key Question 3: Special Populations

- Major bleeding by indication subgroup analysis did not demonstrate statistically significant differences
- Subgroups by indication:
  - Orthopedic surgery: RR, 0.24; 95% CI, 0.05 to 1.15
  - Other/mixed indications: RR, 0.49; 95% CI, 0.23 to 1.04

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### Key Question 3: Special Populations

- Subgroup analysis of PTTR by indication:
  - Orthopedic surgery: mean difference, 3.4%; 95% CI, 1.00 to 5.80
  - Valve replacement: mean difference, 12.40; 95% CI, 5.49 to 19.31
- Subgroup analysis of overanticoagulation, by indication:
  - Orthopedic surgery (RR, 0.71; 95% CI, 0.51 to 0.99)

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### Key Question 4: Economic Outcomes

- 5 economic modeling studies published between 2009 and 2017: 2 studies rated as having a high risk of bias and 3 as having a moderate risk of bias
- All 5 studies assumed a hypothetical population of patients initiating warfarin therapy for AFib
- 3 studies assumed a U.S. perspective (either societal or third-party payer), 1 assumed a UK health service perspective, and 1 was conducted with estimates for the UK and Swedish health system perspectives

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## Key Question 4: Economic Outcomes

Citation Study Risk of Bias	Cost/QALY	Key Assumptions
Eckman et al. 2009 High	\$171,800	2007 U.S. dollars, societal perspective, lifetime horizon, 69-year-old men with AFib
Meckley et al. 2010 High	\$60,725	2007 U.S. dollars, U.S. third-party payer perspective, lifetime horizon, 69-year-old men with AFib
Patrick et al. 2009 Moderate	> \$100,000	2007 U.S. dollars, societal perspective, lifetime horizon, 70-year-olds with AFib
Pink et al. 2013 Moderate	£13,266	2011 GBP (£), UK NHS perspective, lifetime horizon, population with average profile of people in the UK with AFib (mean age 72.5 years)
Verhoef et al. 2016 Moderate	£6,702 SEK 253,848	2014 GBP (£) and Swedish krona (SEK), lifetime horizon, mean age 70.9 years for UK and 72.5 for Sweden

# Guidelines and Policies



## Clinical Practice Guidelines

- 8 clinical practice guidelines published since 2012
- 3 include recommendations against the use of pharmacogenetic testing for anticoagulant therapy
  - American College of Chest Physicians 2012 guideline *Evidence-Based Management of Anticoagulant Therapy*
  - Scottish Intercollegiate Guidelines Network (SIGN) 2013 guidelines on antithrombotics indications and management
  - Australasian Society of Thrombosis and Haemostasis's 2013 guideline

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## Clinical Practice Guidelines

- 2 guidelines recommend the use of pharmacogenetic testing for anticoagulant therapy
  - Clinical Pharmacogenetics Implementation Consortium (CPIC) 2017 updated guideline
  - Canadian Pharmacogenomics Network for Drug Safety 2015 guideline
- 3 guidelines did not contain any recommendation about pharmacogenetic tests
  - Canadian Agency for Drugs and Technologies in Health (CADTH) 2013 guidelines on atrial fibrillation
  - American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society 2014 guidelines on atrial fibrillation
  - American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines 2017 guidelines on valvular heart disease

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## Payer Policies

- Medicare
  - 1 Medicare National Coverage Determination (2009) identified, does not provide coverage for pharmacogenetic testing unless the beneficiary is enrolled in an RCT of anticoagulation therapy with warfarin
  - 1 Medicare Local Coverage Determination (2015) by Noridian that applies to Washington, which includes the same coverage determination as the National Coverage Determination
- Private Payers
  - Aetna, Cigna, and Regence do not cover genotyping for *CYP2C9* or *VKORC1* polymorphisms to inform warfarin dosing

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# Overall Summary



## Limitations

- Small overall number of events for patient-important outcomes creates statistical instability
- Heterogeneity among studies, including:
  - Study populations
  - Indications for treatment
  - Comparators used
  - Definitions and assessment of outcomes
  - System in which study was conducted
- Study differences should be carefully considered when interpreting conclusions

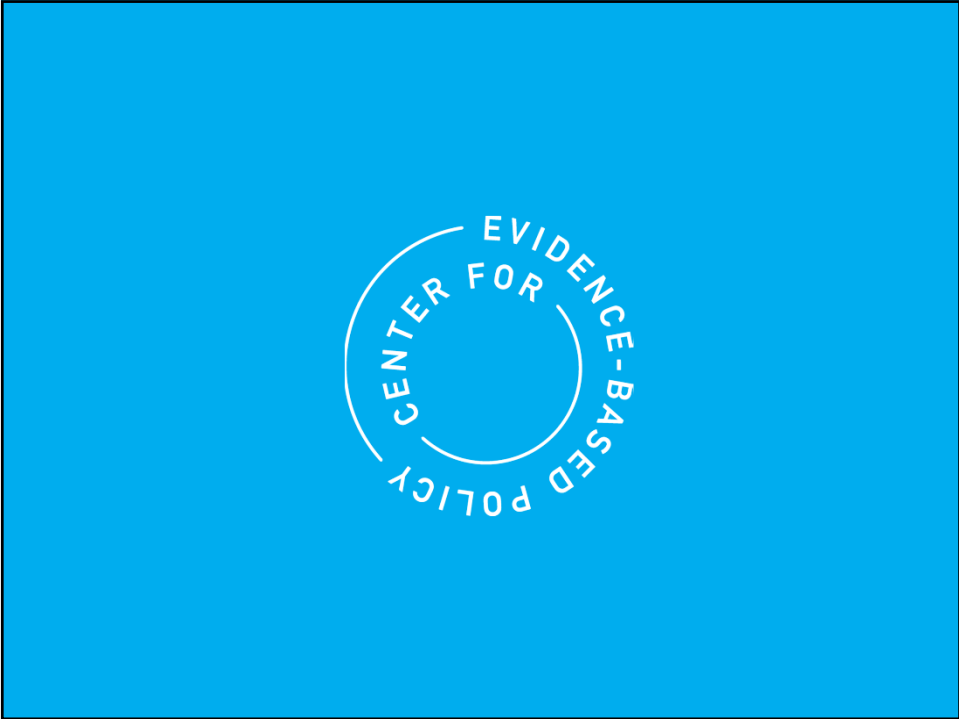
62

## Overall Summary

- Pharmacogenetic testing was associated with a slight, not statistically significant increased risk of mortality
- Pharmacogenetic testing associated with decreased but not statistically significant risks for thromboembolic events and overanticoagulation
- Pharmacogenetic testing was associated with a small, not statistically significant increase in PTTR
  - Difference limited to fixed-dose comparator studies
- Pharmacogenetic testing associated with a small, but statistically significant reduction in major bleeding events

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# HTCC Coverage and Reimbursement Determination Analytic Tool

HTA's goal is to achieve *better health care outcomes* for enrollees and beneficiaries of state programs by paying for proven health *technologies that work*.

To find best outcomes and value for the state and the patient, the HTA program focuses on three questions:

1. Is it safe?
2. Is it effective?
3. Does it provide value (improve health outcome)?

The principles HTCC uses to review evidence and make determinations are:

## Principle One: Determinations are evidence-based

HTCC requires scientific evidence that a health technology is safe, effective and cost-effective<sup>1</sup> as expressed by the following standards<sup>2</sup>:

- Persons will experience better health outcomes than if the health technology was not covered and that the benefits outweigh the harms.
- The HTCC emphasizes evidence that directly links the technology with health outcomes. Indirect evidence may be sufficient if it supports the principal links in the analytic framework.
- Although the HTCC acknowledges that subjective judgments do enter into the evaluation of evidence and the weighing of benefits and harms, its recommendations are not based largely on opinion.
- The HTCC is explicit about the scientific evidence relied upon for its determinations.

## Principle Two: Determinations result in health benefit

The outcomes critical to HTCC in making coverage and reimbursement determinations are health benefits and harms<sup>3</sup>:

- In considering potential benefits, the HTCC focuses on absolute reductions in the risk of outcomes that people can feel or care about.
- In considering potential harms, the HTCC examines harms of all types, including physical, psychological, and non-medical harms that may occur sooner or later as a result of the use of the technology.
- Where possible, the HTCC considers the feasibility of future widespread implementation of the technology in making recommendations.
- The HTCC generally takes a population perspective in weighing the magnitude of benefits against the magnitude of harms. In some situations, it may make a determination for a technology with a large potential benefit for a small proportion of the population.
- In assessing net benefits, the HTCC subjectively estimates the indicated population's value for each benefit and harm. When the HTCC judges that the balance of benefits and harms is likely to vary substantially within the population, coverage or reimbursement determinations may be more selective based on the variation.
- The HTCC considers the economic costs of the health technology in making determinations, but costs are the lowest priority.

<sup>1</sup>Based on Legislative mandate: See RCW 70.14.100(2).

<sup>2</sup>The principles and standards are based on USPSTF Principles at: <http://www.ahrq.gov/clinic/ajpmsuppl/harris3.htm>

<sup>3</sup>The principles and standards are based on USPSTF Principles at: <http://www.ahrq.gov/clinic/ajpmsuppl/harris3.htm>

## Using evidence as the basis for a coverage decision

Arrive at the coverage decision by identifying for Safety, Effectiveness, and Cost whether (1) evidence is available, (2) the confidence in the evidence, and (3) applicability to decision.

### 1. *Availability of Evidence:*

Committee members identify the factors, often referred to as outcomes of interest, that are at issue around safety, effectiveness, and cost. Those deemed key factors are ones that impact the question of whether the particular technology improves health outcomes. Committee members then identify whether and what evidence is available related to each of the key factors.

### 2. *Sufficiency of the Evidence:*

Committee members discuss and assess the evidence available and its relevance to the key factors by discussion of the type, quality, and relevance of the evidence<sup>4</sup> using characteristics such as:

- Type of evidence as reported in the technology assessment or other evidence presented to committee (randomized trials, observational studies, case series, expert opinion);
- The amount of evidence (sparse to many number of evidence or events or individuals studied);
- Consistency of evidence (results vary or largely similar);
- Recency (timeliness of information);
- Directness of evidence (link between technology and outcome);
- Relevance of evidence (applicability to agency program and clients);
- Bias (likelihood of conflict of interest or lack of safeguards).

Sufficiency or insufficiency of the evidence is a judgment of each clinical committee member and correlates closely to the GRADE confidence decision.

Not Confident	Confident
Appreciable uncertainty exists. Further information is needed or further information is likely to change confidence.	Very certain of evidentiary support. Further information is unlikely to change confidence

### 3. *Factors for Consideration - Importance*

At the end of discussion a vote is taken on whether sufficient evidence exists regarding the technology's safety, effectiveness, and cost. The committee must weigh the degree of importance that each particular key factor and the evidence that supports it has to the policy and coverage decision. Valuing the level of importance is factor or outcome specific but most often include, for areas of safety, effectiveness, and cost:

- Risk of event occurring;
- The degree of harm associated with risk;
- The number of risks; the burden of the condition;
- Burden untreated or treated with alternatives;

<sup>4</sup> Based on GRADE recommendation: <http://www.gradeworkinggroup.org/FAQ/index.htm>

- The importance of the outcome (e.g. treatment prevents death vs. relief of symptom);
- The degree of effect (e.g. relief of all, none, or some symptom, duration, etc.);
- Value variation based on patient preference.

## **Clinical Committee Findings and Decisions**

### **Efficacy Considerations**

- What is the evidence that use of the technology results in more beneficial, important health outcomes? Consider:
  - Direct outcome or surrogate measure
  - Short term or long term effect
  - Magnitude of effect
  - Impact on pain, functional restoration, quality of life
  - Disease management
- What is the evidence confirming that use of the technology results in a more beneficial outcome, compared to no treatment or placebo treatment?
- What is the evidence confirming that use of the technology results in a more beneficial outcome, compared to alternative treatment?
- What is the evidence of the magnitude of the benefit or the incremental value?
- Does the scientific evidence confirm that use of the technology can effectively replace other technologies or is this additive?
- For diagnostic tests, what is the evidence of a diagnostic tests' accuracy?
  - Does the use of the technology more accurately identify both those with the condition being evaluated and those without the condition being evaluated?
- Does the use of the technology result in better sensitivity and better specificity?
- Is there a tradeoff in sensitivity and specificity that on balance the diagnostic technology is thought to be more accurate than current diagnostic testing?
- Does use of the test change treatment choices?

### **Safety**

- What is the evidence of the effect of using the technology on significant morbidity?
  - Frequent adverse effect on health, but unlikely to result in lasting harm or be life-threatening, or;
  - Adverse effect on health that can result in lasting harm or can be life-threatening?
- Other morbidity concerns?
- Short term or direct complication versus long term complications?
- What is the evidence of using the technology on mortality – does it result in fewer adverse non-fatal outcomes?

### **Cost Impact**

- Do the cost analyses show that use of the new technology will result in costs that are greater, equivalent or lower than management without use of the technology?

## **Overall**

- What is the evidence about alternatives and comparisons to the alternatives?
- Does scientific evidence confirm that use of the technology results in better health outcomes than management without use of the technology?
- 

### **Next Step: Cover or No Cover**

If not covered, or covered unconditionally, the Chair will instruct staff to write a proposed findings and decision document for review and final adoption at the following meeting.

### **Next Step: Cover with Conditions**

If covered with conditions, the Committee will continue discussion.

- 1) Does the committee have enough information to identify conditions or criteria?
  - Refer to evidence identification document and discussion.
  - Chair will facilitate discussion, and if enough members agree, conditions and/or criteria will be identified and listed.
  - Chair will instruct staff to write a proposed findings and decision document for review and final adoption at next meeting.
- 2) If not enough or appropriate information, then Chair will facilitate a discussion on the following:
  - What are the known conditions/criteria and evidence state
  - What issues need to be addressed and evidence state

The chair will delegate investigation and return to group based on information and issues identified. Information known but not available or assembled can be gathered by staff ; additional clinical questions may need further research by evidence center or may need ad hoc advisory group; information on agency utilization, similar coverage decisions may need agency or other health plan input; information on current practice in community or beneficiary preference may need further public input. Delegation should include specific instructions on the task, assignment or issue; include a time frame; provide direction on membership or input if a group is to be convened.

## **Clinical Committee Evidence Votes**

### **First Voting Question**

The HTCC has reviewed and considered the technology assessment and information provided by the administrator, reports and/or testimony from an advisory group, and submissions or comments from the public. The committee has given greatest weight to the evidence it determined, based on objective factors, to be the most valid and reliable.

**Discussion Document:** What are the key factors and health outcomes and what evidence is there?  
 (Applies to the population in the PICO for this review.)

<b>Safety Outcomes</b>	<b>Importance of Outcome</b>	<b>Safety Evidence/Confidence in Evidence</b>
Harms associated with testing		
Cardiovascular events (e.g., stroke, myocardial infarction)		
Serious infection		

<b>Efficacy – Effectiveness Outcomes</b>	<b>Importance of Outcome</b>	<b>Efficacy / Effectiveness Evidence</b>
Mortality		
Major bleeding		
Thromboembolic events		
Overanticoagulation		
Time in therapeutic range		

<b>Cost Outcomes</b>	<b>Importance of Outcome</b>	<b>Cost Evidence</b>
Cost effectiveness		
Direct cost		

<b>Special Population Considerations/ Outcomes</b>	<b>Importance of Outcome</b>	<b>Special Populations Considerations/ Evidence</b>
Race/ethnicity		
Gender		
Age		
Clinical history		
Comorbidities		

**For Safety:** Is there sufficient evidence, under some or all situations, that the technology is safe for the indications considered?

Unproven (no)	Less (yes)	Equivalent (yes)	More in some (yes)	More in all

**For Efficacy/Effectiveness:** Is there sufficient evidence, under some or all situations, that the technology has a meaningful impact on patients and patient care?

Unproven (no)	Unproven (no)	Unproven (no)	Unproven (no)	Unproven (no)

**For Cost Outcomes/Cost-Effectiveness:** Is there sufficient evidence, under some or all situations, that the technology is cost-effective for the indications considered?

Unproven (no)	Unproven (no)	Unproven (no)	Unproven (no)	Unproven (no)

**Discussion**

Based on the evidence vote, the committee may be ready to take a vote on coverage or further discussion may be warranted to understand the differences of opinions or to discuss the implications of the vote on a final coverage decision.

- Evidence is insufficient to make a conclusion about whether the health technology is safe, efficacious, and cost-effective;
- Evidence is sufficient to conclude that the health technology is unsafe, ineffectual, or not cost-effective
- Evidence is sufficient to conclude that the health technology is safe, efficacious, and cost-effective for all indicated conditions;
- Evidence is sufficient to conclude that the health technology is safe, efficacious, and cost-effective for some conditions or in some situations

A straw vote may be taken to determine whether, and in what area, further discussion is necessary.

**Second Vote**

Based on the evidence about the technologies’ safety, efficacy, and cost-effectiveness, it is

\_\_\_\_\_ Not Covered \_\_\_\_\_ Covered Unconditionally \_\_\_\_\_ Covered Under Certain Conditions



## Discussion Item

Is the determination consistent with identified Medicare decisions and expert guidelines, and if not, what evidence is relied upon.

## Next Step: Proposed Findings and Decision and Public Comment

At the next public meeting the committee will review the proposed findings and decision and consider any public comments as appropriate prior to a vote for final adoption of the determination.

- 1) Based on public comment was evidence overlooked in the process that should be considered?
- 2) Does the proposed findings and decision document clearly convey the intended coverage determination based on review and consideration of the evidence

## Next Step: Final Determination

Following review of the proposed findings and decision document and public comments:

## Final Vote

Does the committee approve the Findings and Decisions document with any changes noted in discussion?

If yes, the process is concluded.

If no, or an unclear (i.e., tie) outcome Chair will lead discussion to determine next steps.

## Medicare

[From page 24 of the Final Evidence Report]

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. 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. This NCD includes a statement that it has been or is currently being reviewed under the NCD process. Center researchers identified 1 Medicare LCD by Noridian that applies to Washington. This LCD includes the same coverage determination as the 1 identified NCD.

## Guidelines

[From pages 23-24 of the Final evidence Report]

## 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.<sup>47-49</sup> 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.<sup>36</sup> 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.<sup>37</sup> 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.<sup>50</sup>

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.<sup>8</sup> These guidelines recommend that pharmacogenetically guided dosing use a validated published algorithm (e.g., algorithms by IWPC,<sup>51</sup> Gage et al.,<sup>52</sup> EU-PACT,<sup>26</sup> and Lenzini et al.<sup>53</sup>).

The Canadian Pharmacogenomics Network for Drug Safety published a guideline on genetic testing of *CYP2C9* and *VKORC1* for warfarin therapy in 2015.<sup>54</sup> This guideline, also rated as having poor methodological quality, has a moderate-strength recommendation that testing of all warfarin-naïve 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.<sup>54</sup> 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.<sup>54</sup>

Of the 8 identified guidelines, 3 of them<sup>36,37,50</sup> 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.<sup>36</sup> Another guideline by the American College of Chest Physicians, *Oral Anticoagulant Therapy*, discusses flexibility in determining the starting dose of warfarin.<sup>38</sup> 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.<sup>38</sup>

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.<sup>37</sup> 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.<sup>50</sup>