GIFT: Genetics Informatics Trial of Warfarin Therapy for Deep Venous Thrombosis Prevention

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The Problem: Warfarin works, but

WARNING: BLEEDING RISK

- **COUMADIN can cause major or fatal bleeding. (5.1)**
- **Perform regular monitoring of INR in all treated patients. (2.1)**

----------DOSAGE AND ADMINISTRATION ----------

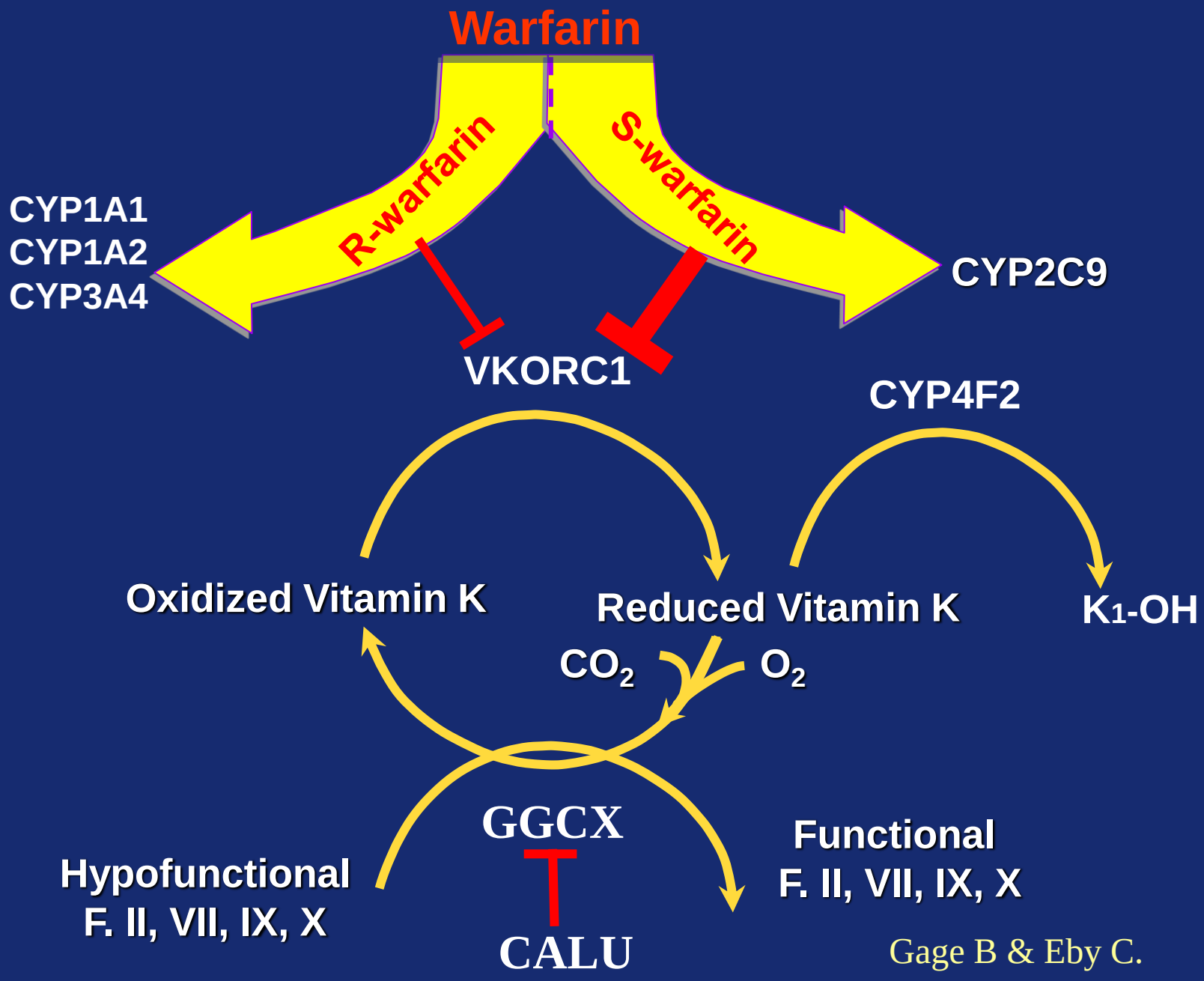
- Individualize dosing regimen for each patient, and adjust based on INR response.
- Knowledge of genotype can inform initial dose selection.

Warfarin causes more emergency department visits among the elderly than any other drug (N. Shehab **JAMA** 2016).

INR = International Normalized Ratio. Values > 3 or 4 predispose to bleeding

Genetics Informatics Trial (GIFT) of Warfarin Therapy for DVT Prevention

- Hypothesis: Pharmacogenetic dosing of warfarin therapy decreases the rate of adverse events vs. clinical-algorithm dosing

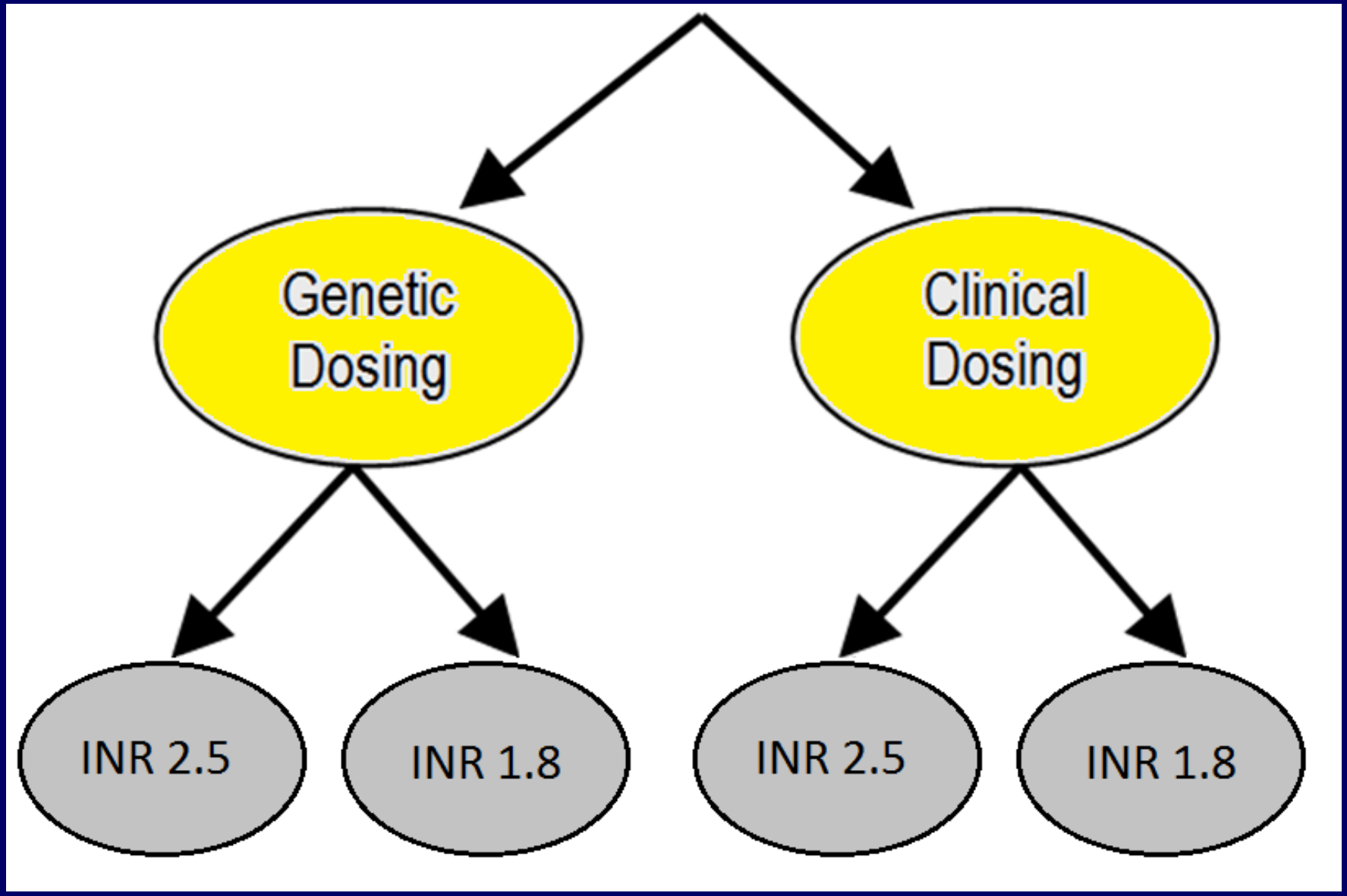


Gage B & Eby C.
Pharmacogenomics J. 2004

Warfarin Pharmacogenetics

- Cytochrome P450 2C9 *(*CYP2C9) SNPs slow S-warfarin metabolism
- VKORC1-1639 G>A Vitamin K epoxide reductase increases warfarin sensitivity
- CYP4F2 V433M reduces vitamin K clearance

2 x 2 Factorial Design



Genotyping Strategy

- Initially: Genotyping at clinical sites with retrospective confirmation and DNA banking by Central Laboratory
- Later: Central laboratory provided pre-surgery genotyping for all clinical sites
- Genotype Method: Predominantly GenMarkDx eSensor instrument and reagents

Randomization & Double Blinding

- Randomized 1:1 to genetic vs. clinical dosing
  - stratified by arthroplasty site, self-identified race, and center: HSS, Intermountain Healthcare, Rush, University of Utah, UT Southwestern, and WUSTL
- Participants and study personnel were blind to study arm and genotype, but not to warfarin dose

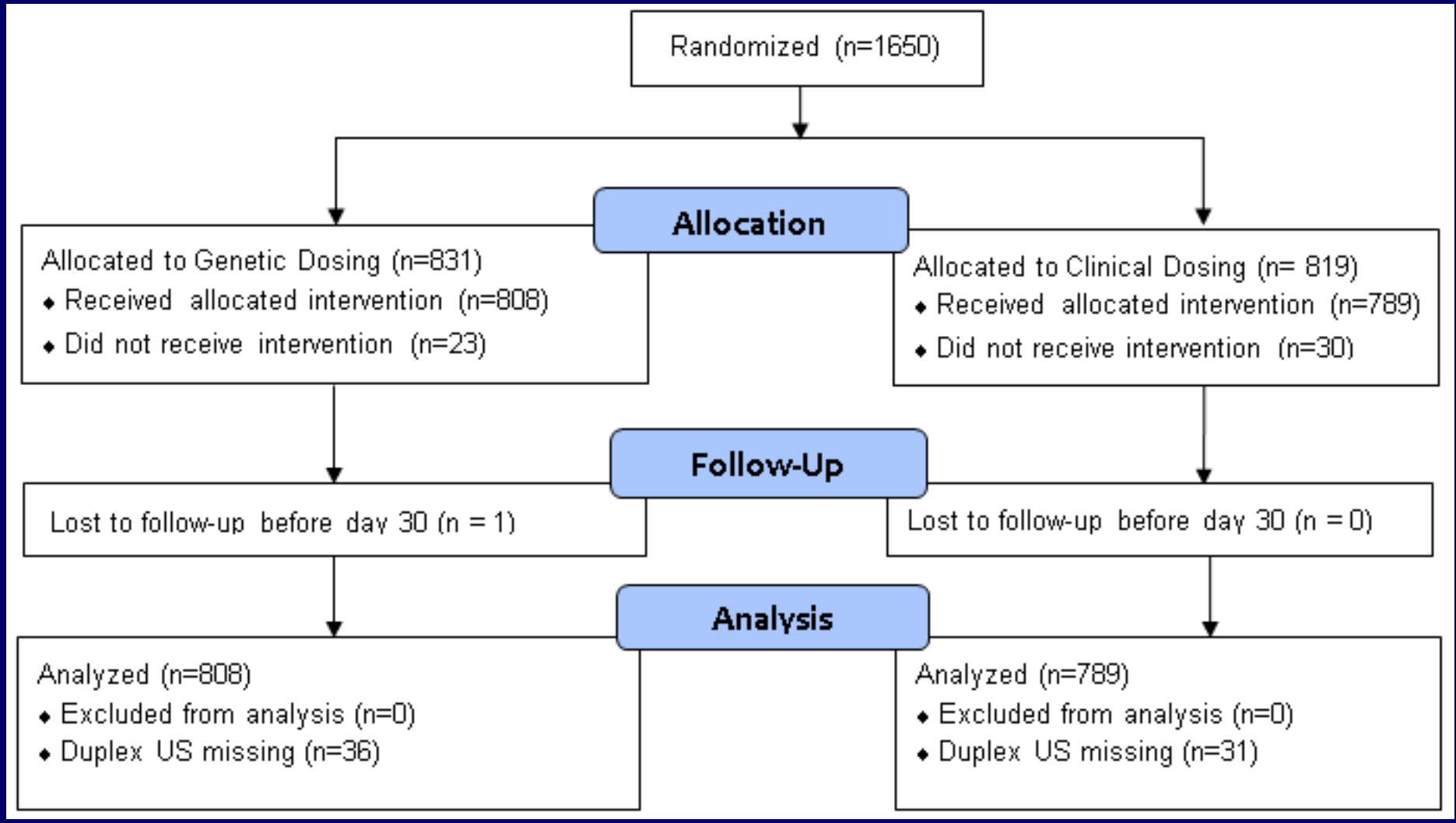
Primary Outcome Was a Composite of:

- Major bleeding within 30 days,
- INR ≥ 4 within 30 days,
- Death within 30 days, and
- Venous thromboembolism (VTE) confirmed by objective testing within 60 days of arthroplasty
  - Patients were screened for DVT using Duplex US

Statistical Analyses

- Modified intention-to-treat basis
  - included all randomized participants who received 1+ doses of warfarin.
- A priori high-risk subgroup:
  - Participants whose clinical and genetic predicted doses (on day 1) differed by $\geq$ 1.0 mg/day.
- Two-sided alpha of 0.05, partitioned:
  - 0.044 alpha required in total cohort
  - Remaining alpha in high-risk subgroup
- 1600 participants provided 80% power

GIFT CONSORT Diagram

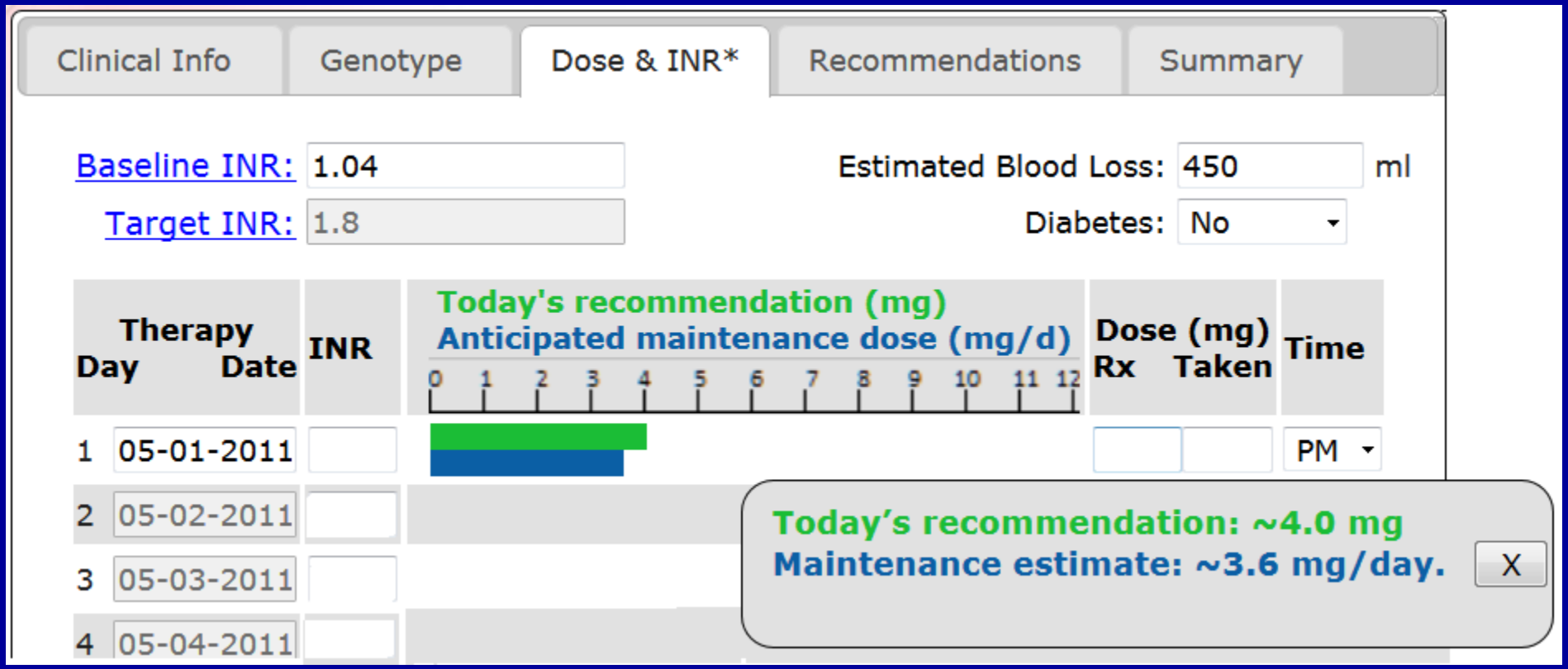


GIFT Participants

Variable	Genetic N=808	Clinical N=789
Age, years: mean (SD)	72.2 (5.3)	72.0 (5.5)
Indication: N (%)		
Hip Replacement	207 (25.6)	199 (25.2)
Knee Replacement	601 (74.4)	590 (74.8)
Female: N (%)	522 (64.6)	496 (62.9)
Race: N (%)		
African American	52 (6.4)	50 (6.3)
American Indians or Native	1 (0.1)	0 (0.0)
Asian or Indian Subcontinent	16 (2.0)	13 (1.7)
Caucasian	735 (91.0)	719 (91.1)
Statin†: N (%)	365 (45.2)	402 (51.0)
Diabetes: N (%)	116 (14.4)	105 (13.3)

† P = 0.02.

From Days 1-11, WarfarinDosing.org Provided Guidance; Clinicians Did the Dosing



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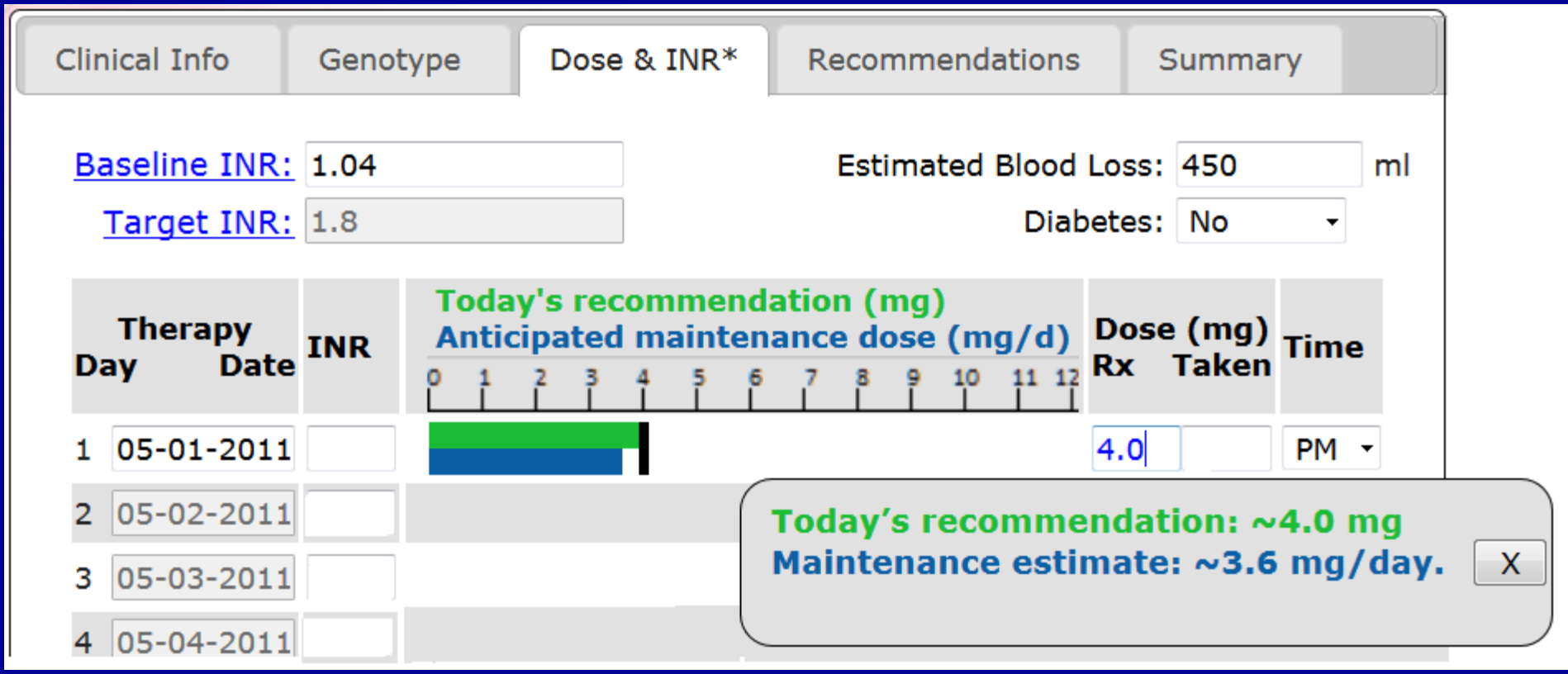

Primary Results (N = 1597)

Endpoint	Genotype Group, N = 808, % (N)	Clinical Group, N = 789, % (N)	P-value
Major bleed (days 1-30)	**0.25% (2)**	**1.01% (8)**	**0.062**
INR ≥ 4 (days 1-30)	**6.9% (56)**	**9.8% (77)**	**0.041**
VTE (days 1-60)	**4.1% (33)**	**4.8% (38)**	**0.48**
Death (days 1-30)	**0.0% (0)**	**0.0% (0)**	**1.00**
Total	10.8% (87)	14.7% (116)	0.018

Genetic dosing reduced the relative risk of adverse outcomes by 27% (RR=0.73; 95% CI: 0.56 – 0.95).

Benefit of Genetic Dosing Was Consistent:

- There was no significant interaction in any of these subgroups
  - African-Americans
  - *CYP2C9* genotype
  - Target INR 2.5 vs. 1.8
  - Hip vs. knee arthroplasty

Secondary Outcome: Percentage of Time in the Therapeutic Range (PTTR) During Days 4-28 of Warfarin Therapy

Analyses	Genotype-Group		Clinical Group		Mean Difference	
	N	PTTR	N	PTTR	(95% CI)	P Value
Overall	803	54.7	785	51.3	3.4 (1.1, 5.8)	0.004
High-risk	321	55.5	333	48.4	7.0 (3.4, 10.6)	0.0002
Stratified by Target INR						
Target 2.5 (2.0-3.0)	399	56.2	389	50.4	5.8 (2.5, 9.1)	0.0006
Target 1.8 (1.5-2.1)	404	53.3	396	52.1	1.1 (-2.2, 4.5)	0.51

GIFT Conclusions

- Algorithm-assisted warfarin dosing is safe
  - Dosing algorithms from WarfarinDosing.org should be integrated into EMRs
- Genotype-guided dosing reduced the relative risk of adverse outcomes by 27%
  - Improved INR control, especially among high-risk subgroup.

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