Implementation of Multi-ethnic Algorithm-Guided Warfarin Dosing

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Mount Sinai

OUTLINE

I. INTRODUCTION

A. Mount Sinai Health System
B. Mount Sinai Pre-emptive Pharmacogenomics Programs

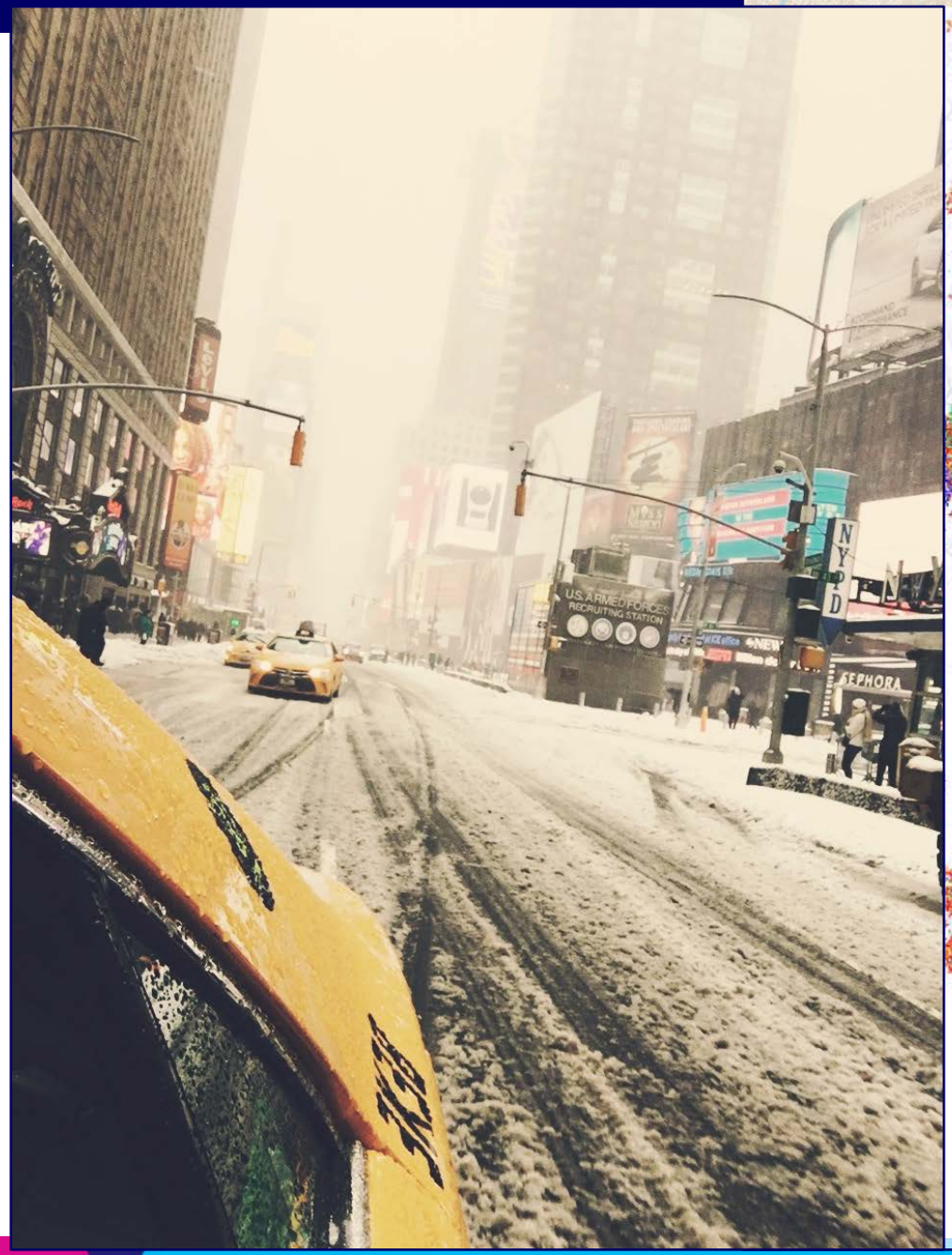
II. IMPLEMENTATION

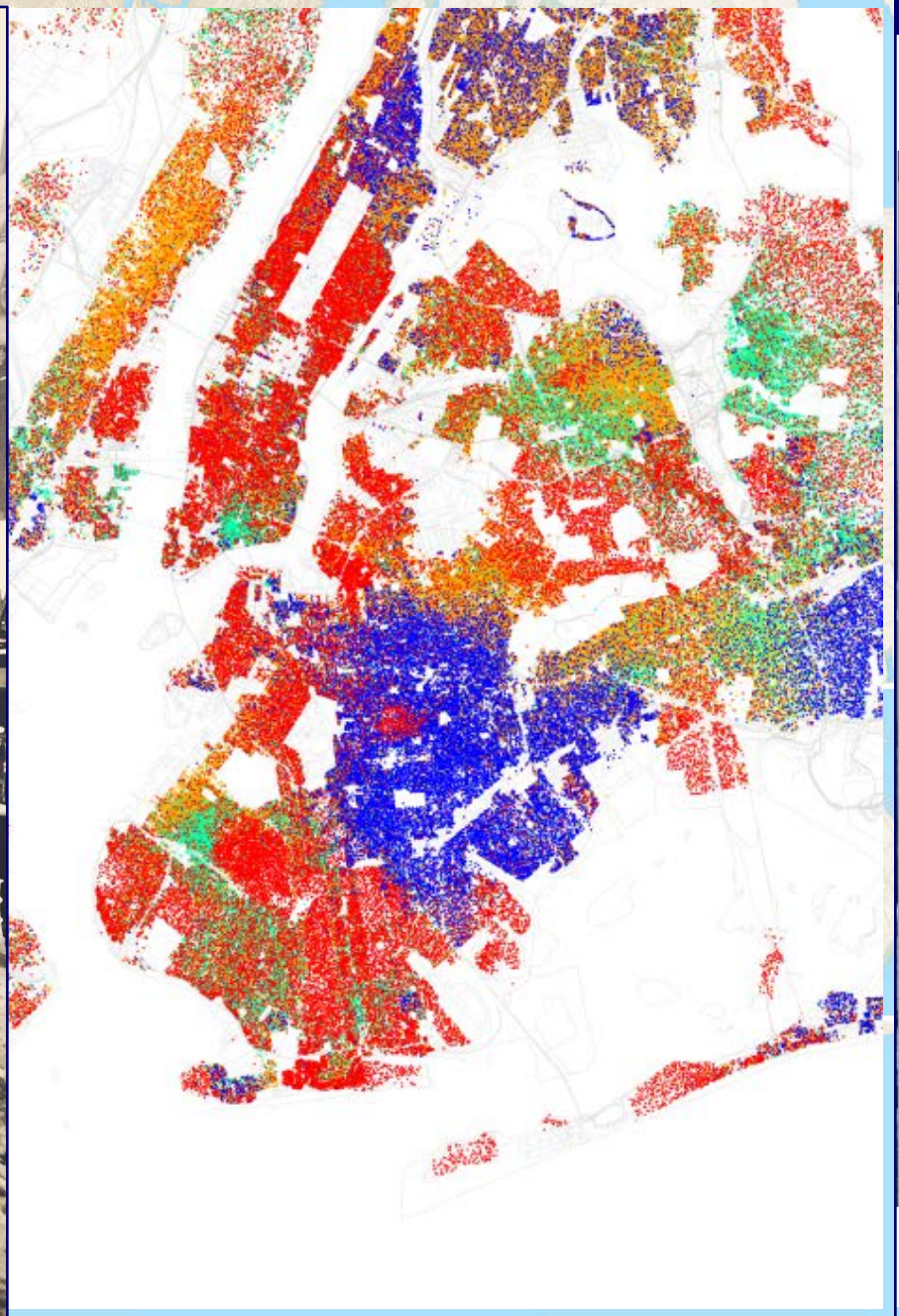
A. Warfarin Pharmacogenetics
B. Multi-ethnic Warfarin Dosing Strategy
C. Pilot Implementation Results

III. LESSONS LEARNED / FUTURE DIRECTIONS

MOUNT SINAI

Mount Sinai Health System at a Glance





Icahn School of Medicine at Mount Sinai

SCHOOL OPENED 1968

Freestanding medical school at the forefront of scientific training, biomedical research, and patient care

34
DEPARTMENTS

23+
CLINICAL AND RESEARCH INSTITUTES

5,600+ FACULTY MEMBERS

556 MEDICAL STUDENTS

258 PhD STUDENTS

2,000+ RESIDENTS AND FELLOWS

90 MD/PhD STUDENTS

240 MASTERS STUDENTS

600+ POSTDOCTORAL STUDENTS

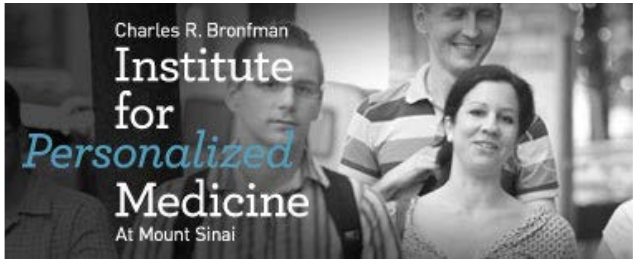
#4 IN RESEARCH DOLLARS PER PRINCIPAL INVESTIGATOR AMONG U.S. MEDICAL SCHOOLS

Icahn School of Medicine at Mount Sinai

For you. For life.

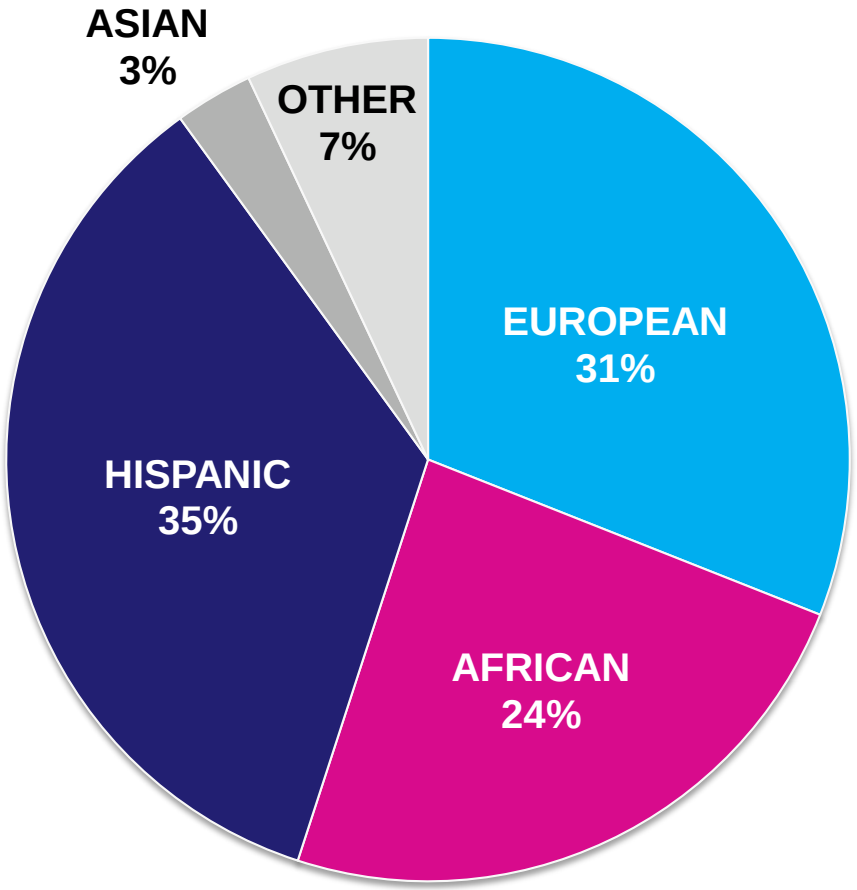
The Charles Bronfman Institute for Personalized Medicine (IPM): Bio*Me*™ Biobank

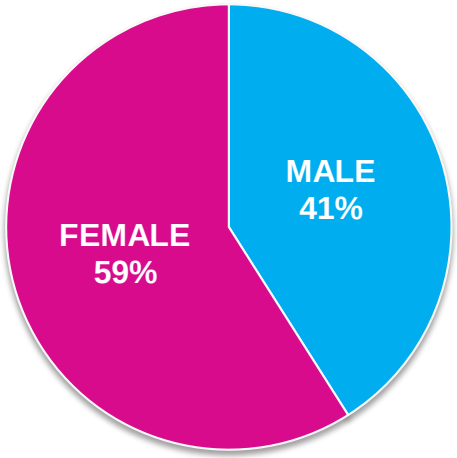
- **Prospective collection of DNA and plasma samples linked to EHR for genomic medicine research.**
- **DNA and plasma samples linked to de-identified EHR (Mount Sinai Data Warehouse).**
  - **Affymetrix, Illumina, panels, exomes**
- **Originally developed to enable genomic discovery, later evolved to facilitate clinical implementation.**
- **Permission to re-contact participants for future research.**



The Charles Bronfman Institute for Personalized Medicine (IPM): Bio*Me*™ Biobank

- **> 35,000 patients enrolled; 500 new subjects per month.**





CLINICAL PGX IMPLEMENTATION: TESTING

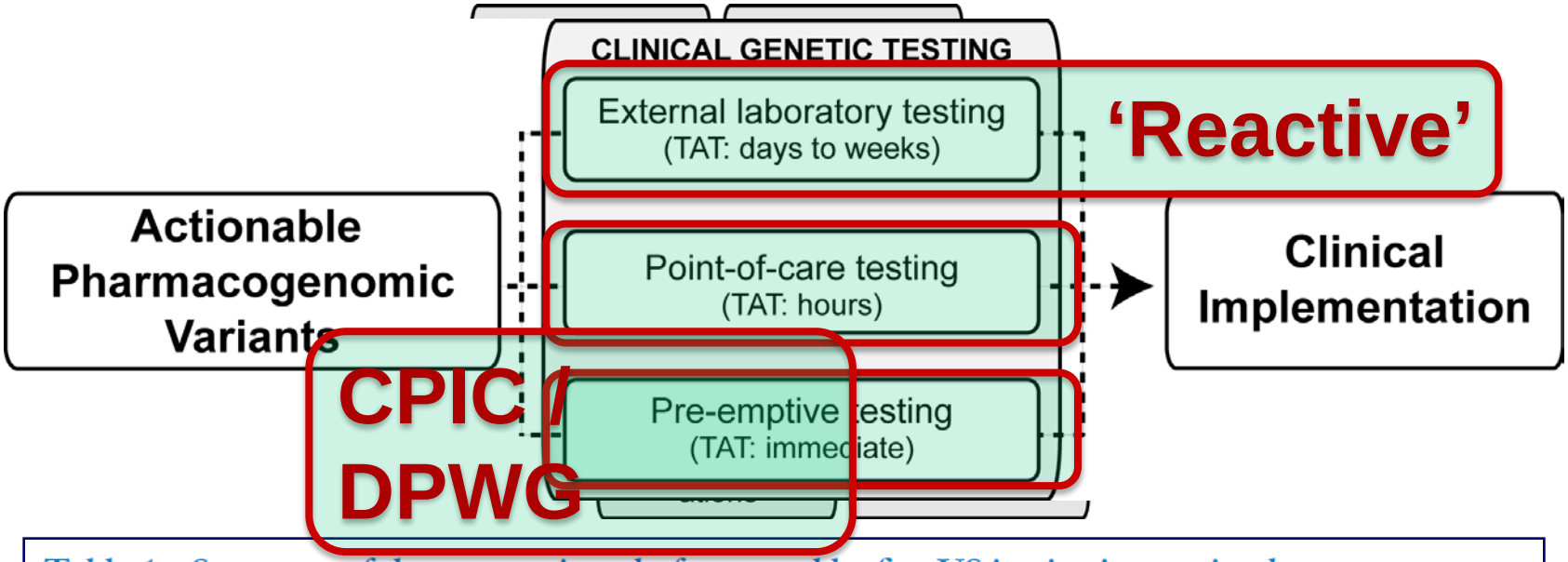


Table 1 Summary of the genotyping platform used by five US institutions to implement array-based, preemptive pharmacogenetic testing

Institution (reference)	Genotyping platform	Number of genes assayed
Mayo Clinic (43)	PGRNseq	84
Mount Sinai Medical Center (42)	Sequenom iPLEX ADME PGx	36
St. Jude Children's Research Hospital (65)	Affymetrix DMET Plus Array	230
University of Florida and Shands Hospital (35)	Life Technologies Quant Studio Open Array	120
Vanderbilt University Medical Center (69)	VeraCode ADME Core Panel	34

Scott SA. Genet Med, 2011; Scott SA. Clin Pharmacol Ther, 2013; Dunnenberger HM, et al. Annu Rev Pharmacol Toxicol, 2015.

IMPLEMENTATION: PRE-EMPTIVE PGX TESTING

IPM PGx

- 1000 Bio*Me* patients
- Internal Medicine Associates (IMA) clinic
- Genotyping (Agena)
- Providers are consented and surveyed
- Unlimited number of drug-gene pairs
- CLIPMERGE
- EHR data collection

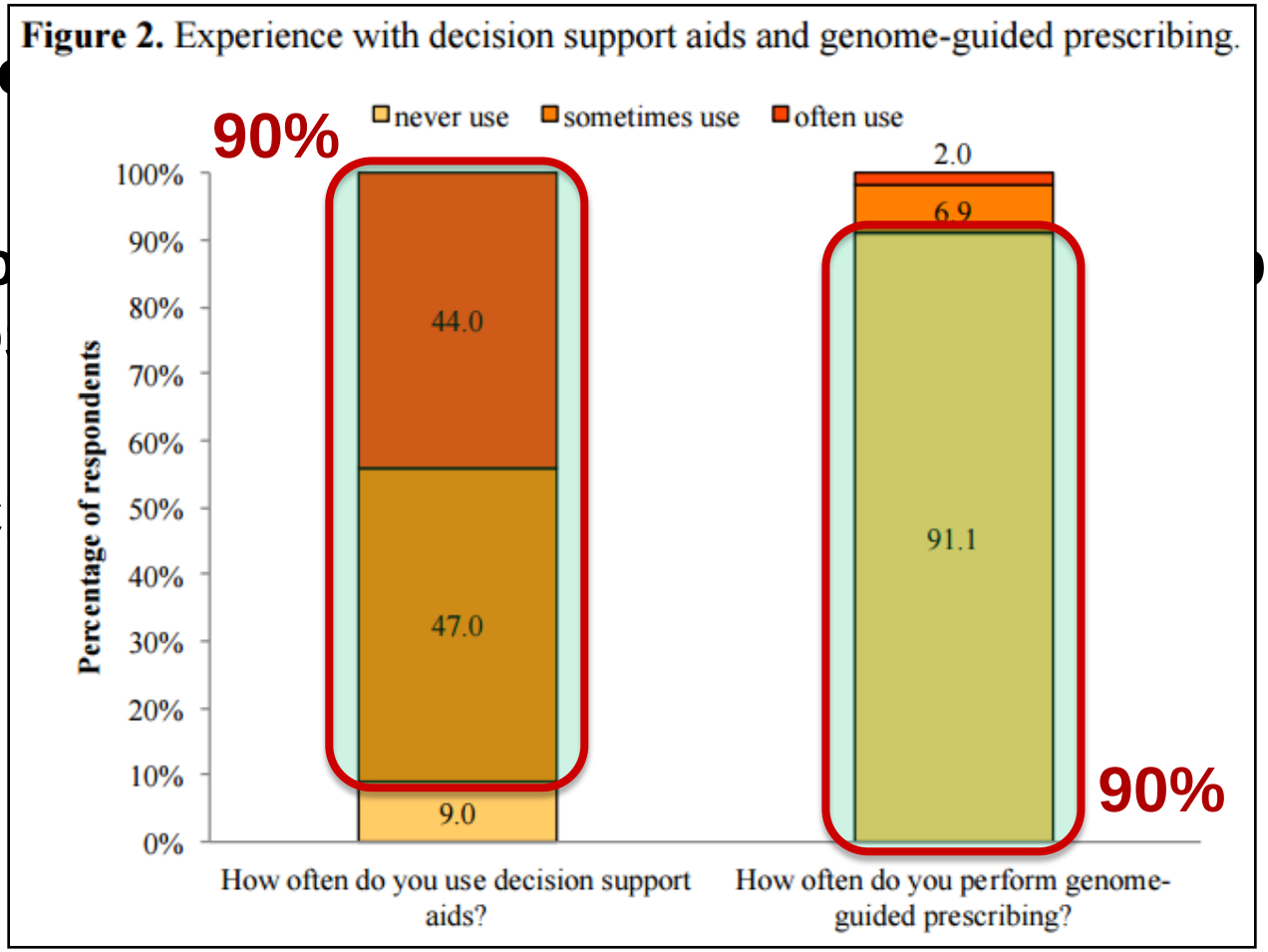
eMERGE PGx

- 663 Bio*Me* and non-Bio*Me* patients
- Faculty Practice Associates (FPA) clinic
- Sequencing (PGRNseq) and genotyping (Agena)
- Providers are co-investigators
- CDS for simvastatin, clopidogrel and warfarin
- CLIPMERGE
- EHR data collection

- ***Objective:*** **Develop process best-practices for implementation of personalized medicine.**
  - **Focus on providers**
  - **eMERGE PGx also enables discovery**

IMPLEMENTATION: PRE-EMPTIVE PGX TESTING

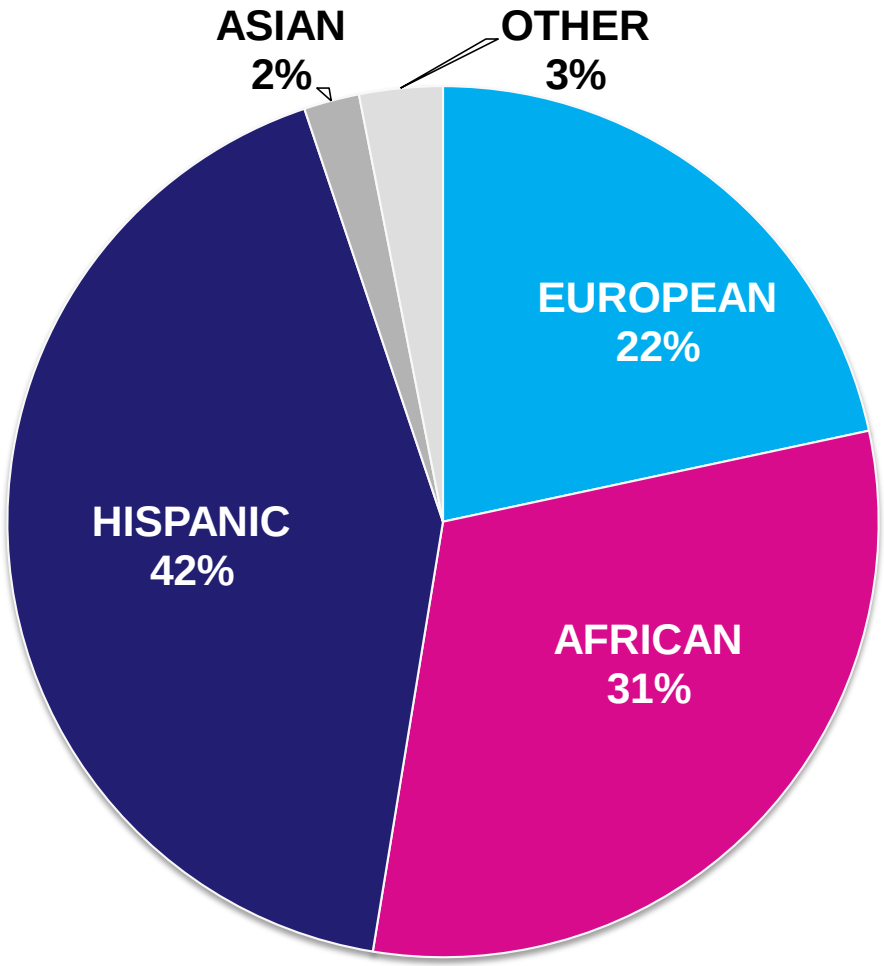
- **One hour training session, online video available.**
  - **Only ~40% of surveyed providers felt knowledgeable about genomic testing.**
- **Compl**
- **Additio** **edded in the CD**
- **Post-C**

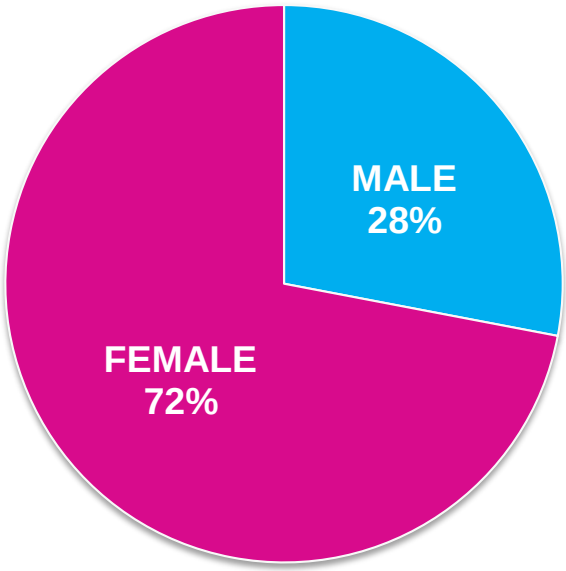


Overby CL, et al. J Pers Med. 2014.

IMPLEMENTATION: PRE-EMPTIVE PGX TESTING

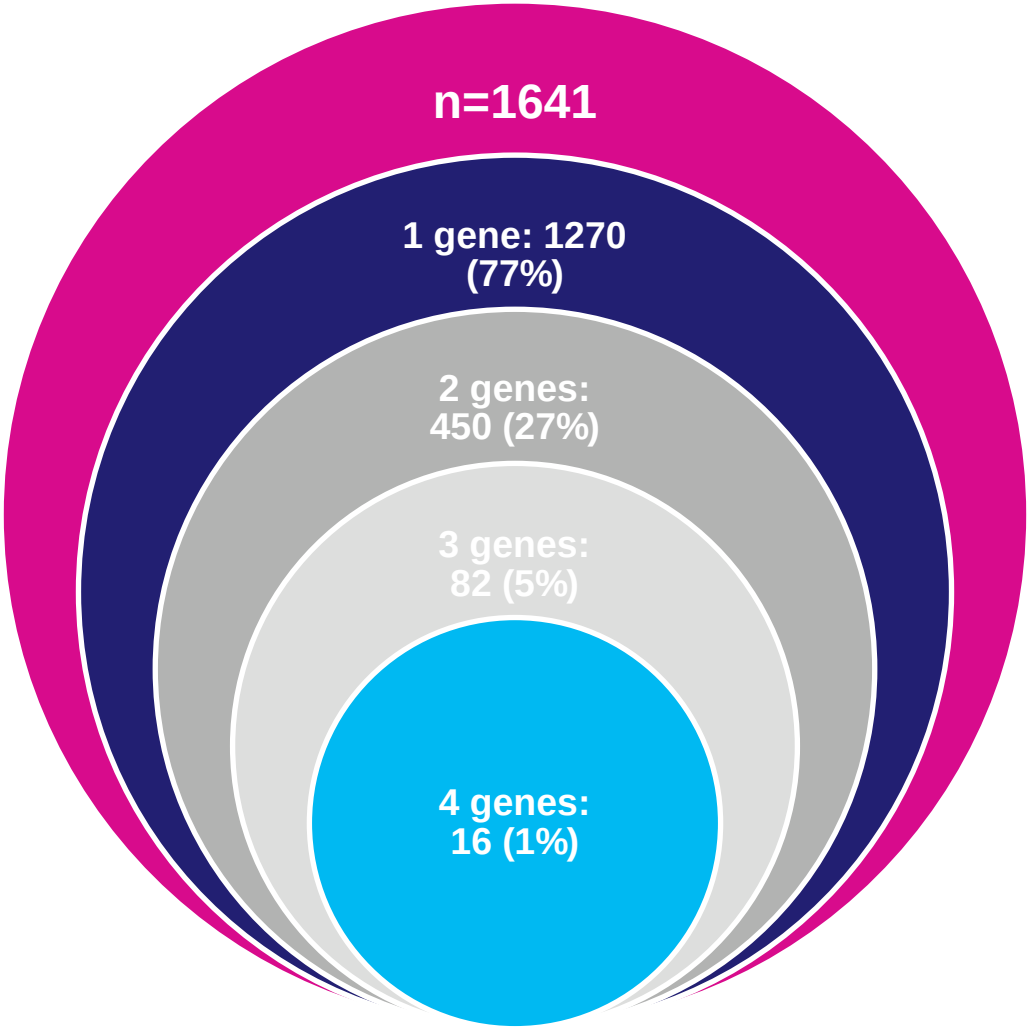
- **Mount Sinai IPM PGx programs (n=1641):**
  - **Clopidogrel: *CYP2C19*; Simvastatin: *SLCO1B1*; Warfarin: *CYP2C9 / VKORC1*; Tramadol: *CYP2D6*; Codeine: *CYP2D6***





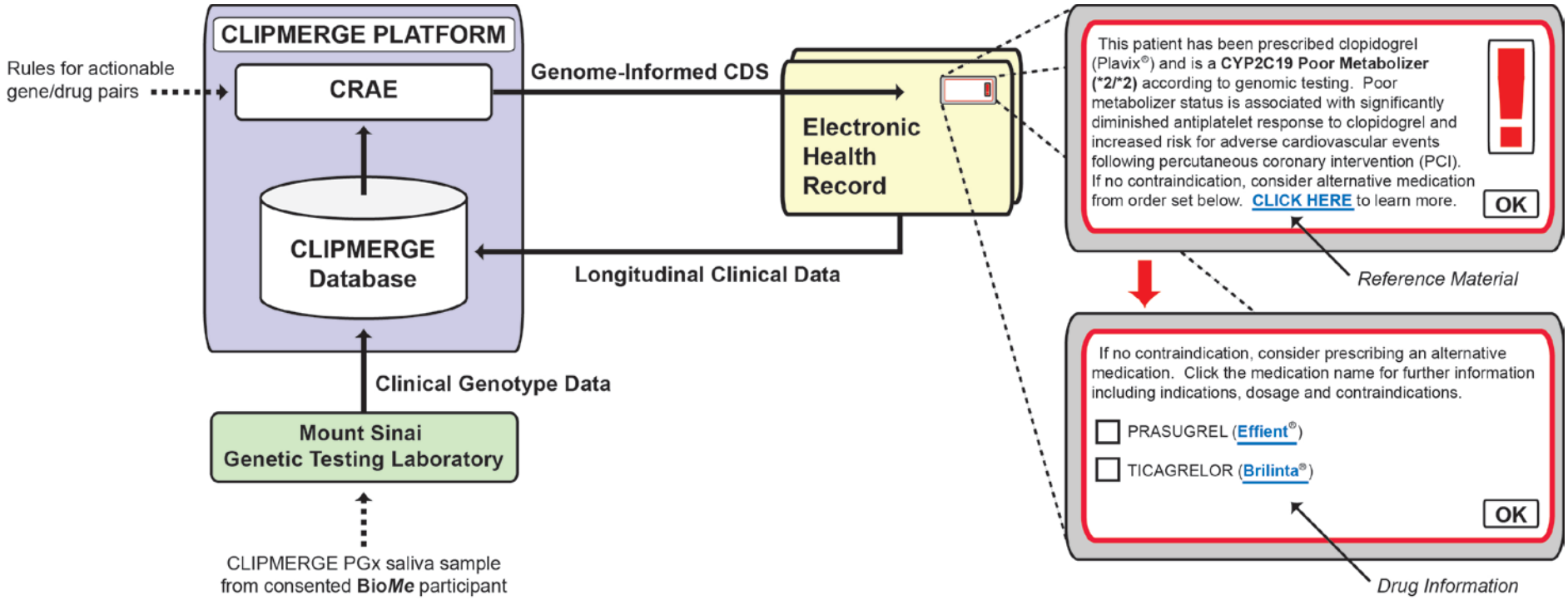
IMPLEMENTATION: PRE-EMPTIVE PGX TESTING

- **~77% of patients have at least one 'actionable' variant in *CYP2C19*, *SLCO1B1*, *CYP2C9*, and/or *VKORC1*.**



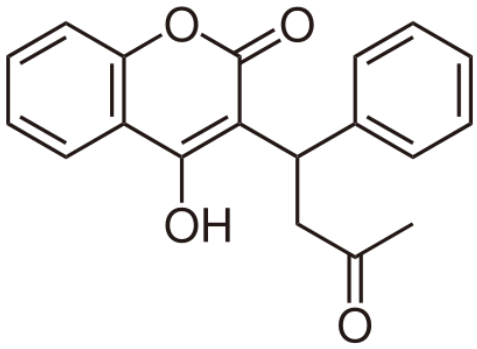
IMPLEMENTATION: PRE-EMPTIVE PGX TESTING

- **Implementation is enabled by CLIPMERGE:**
  - **Advanced data management system that is external to, but communicates with Epic.**
  - **Clinical decision support (CDS) in real-time at the point-of-care.**



Gottesman O, et al. Clin Pharmacol Ther, 2013.

Warfarin Pharmacogenetics



WARFARIN PHARMACOGENETICS: BACKGROUND

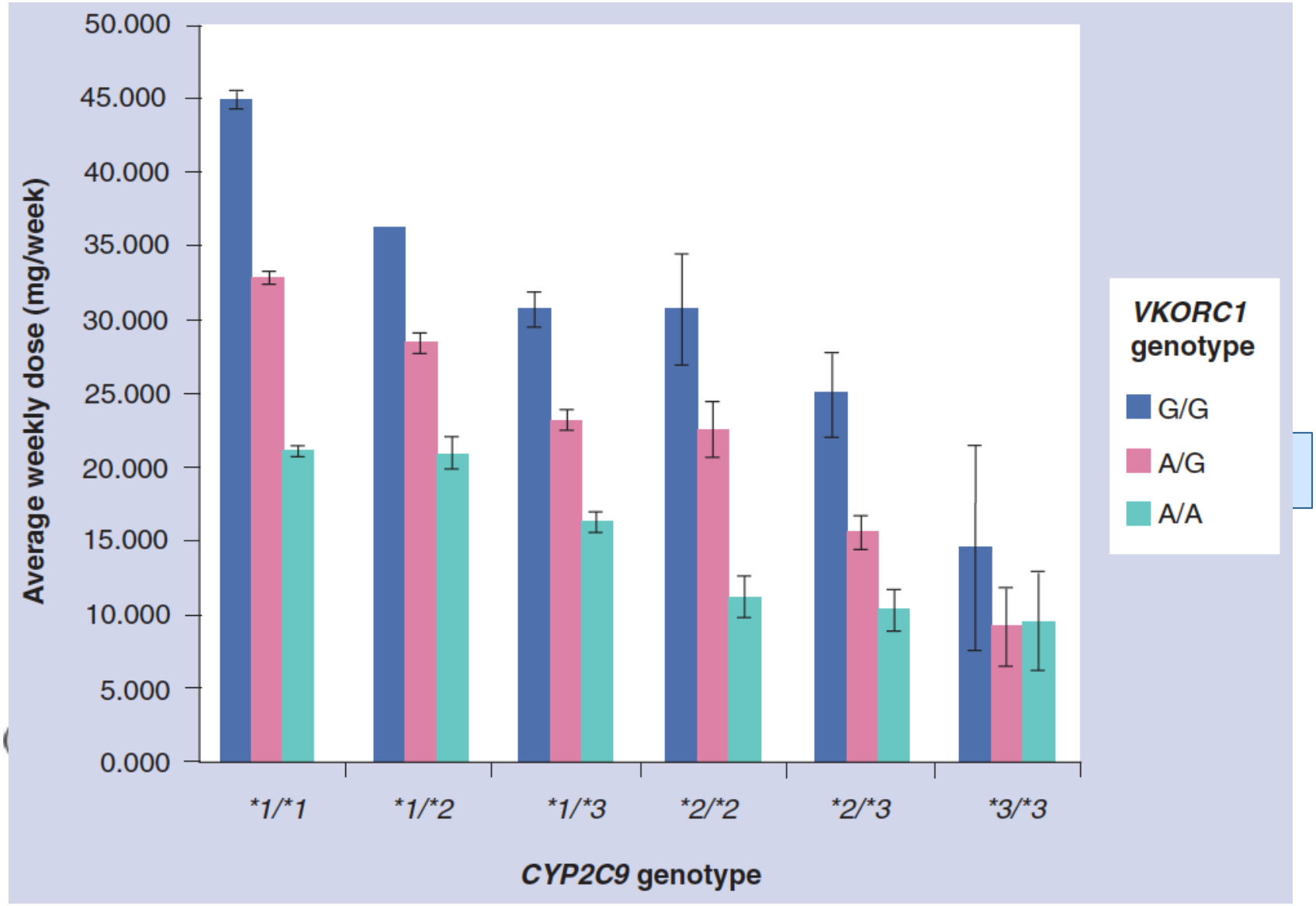
- **Widely used oral anticoagulant for prevention of thrombosis and embolism.**
  - **AF, DVT, PE, MV**

- **Wide interindividual differences in drug response:**
  - **Narrow therapeutic range**
  - **High risk of bleeding or stroke**

- **Requires frequent monitoring by INR (typical target 2-3).**

- **Warfarin dosing variability is due to many factors:**
  - **Age, gender, drug interactions, diet (vitamin K), alcohol, smoking, pharmacogenetics (PK and PD)**

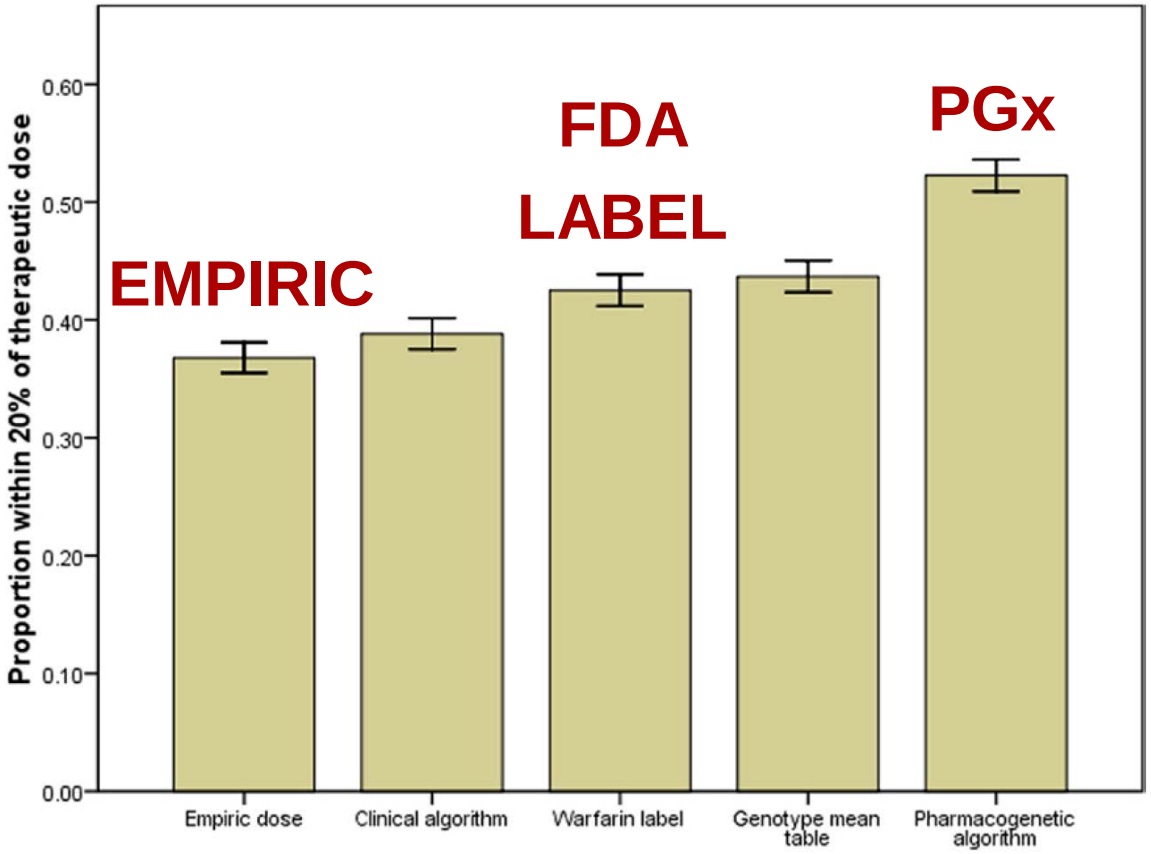
WARFARIN PHARMACOGENETICS: BACKGROUND



Scott SA and Desnick RJ, 2014; Kurnik D, et al. Pharmacogenomics, 2009.

WARFARIN PHARMACOGENETICS: TRIALS

- **Warfarin PGx dosing algorithms have been tested retrospectively and in clinical trials.**
  - **Warfarindosing.org; IWPC: *CYP2C9*2, *3, VKORC1* -1639G>A**



Finkelman BS, et al. JACC, 2011.

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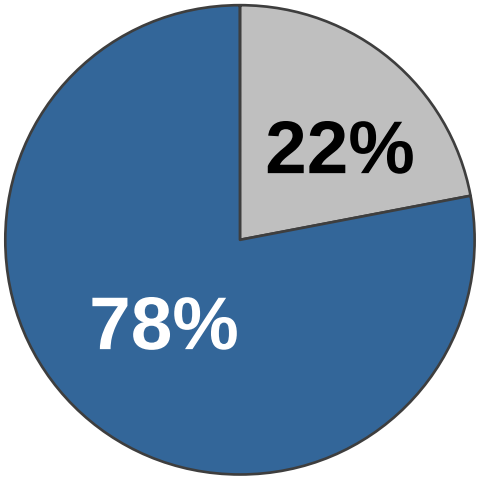
WPGx Trial	Year	Design	n	Comparison Arm	Primary End point	Result
CoumaGen	**2007**	**RCT**	206	**Standard dosing**	Out of range (OOR) INRs	**1. PGx more accurate** **2. No difference in OOR INR**
Medco-Mayo	**2010**	**CE**	896/ 2688	**Standard dosing** (concurrent+historical)	Incident event rate	**Hospitalizations: HR 0.69** **Bleeding/thrombo: HR 0.72**
Marshfield	**2011**	**RCT**	230	**Clinical algorithm**	1. Prediction error 2. PTTR	**1. PGx more accurate** **2. No difference in PTTR**
CoumaGen-II	**2012**	**CE**	504/ 1866	**Standard dosing** (historical)	1. OOR INRs 2. PTTR	**1. Fewer OOR INRs** **2. Greater PTTR** **3. Fewer events**
EUPACT	**2013**	**RCT**	455	**Standard dosing**	PTTR	**1. Greater PTTR** **2. Fewer INR>4** **3. Less time to INR**
COAG	**2013**	**RCT**	1015	**Clinical algorithm**	PTTR	**1. No difference in PTTR** **2. No difference time to INR** **3. No difference in > or < INR**
GIFT	**2015**	**RCT**	1600	**Clinical algorithm**	Composite thrombo, bleeding, INR >4, death	**2017**

Scott SA and Lubitz SA. Pharmacogenomics, 2014.

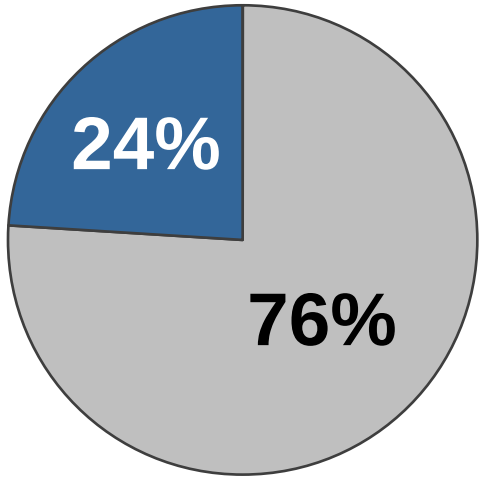
WARFARIN PGX: COAG vs EUPACT

- **Common warfarin PGx dosing algorithms do not perform well in non-Caucasian populations.**
  - **Particularly among African-Americans**
  - **COAG: 27% self-reported black**
- **NYC-Mount Sinai multi-ethnic *CYP2C9* (**2* and **3*) + *VKORC1* (-1639G>A) allele frequencies:**

Caucasian



African-American



Wild-type (*CYP2C9* and *VKORC1*)

Variant carriers (*CYP2C9* and/or *VKORC1*)

Scott SA, et al. Pharmacogenomics, 2010.

WARFARIN PGx: AFRICAN ANCESTRY VARIANTS

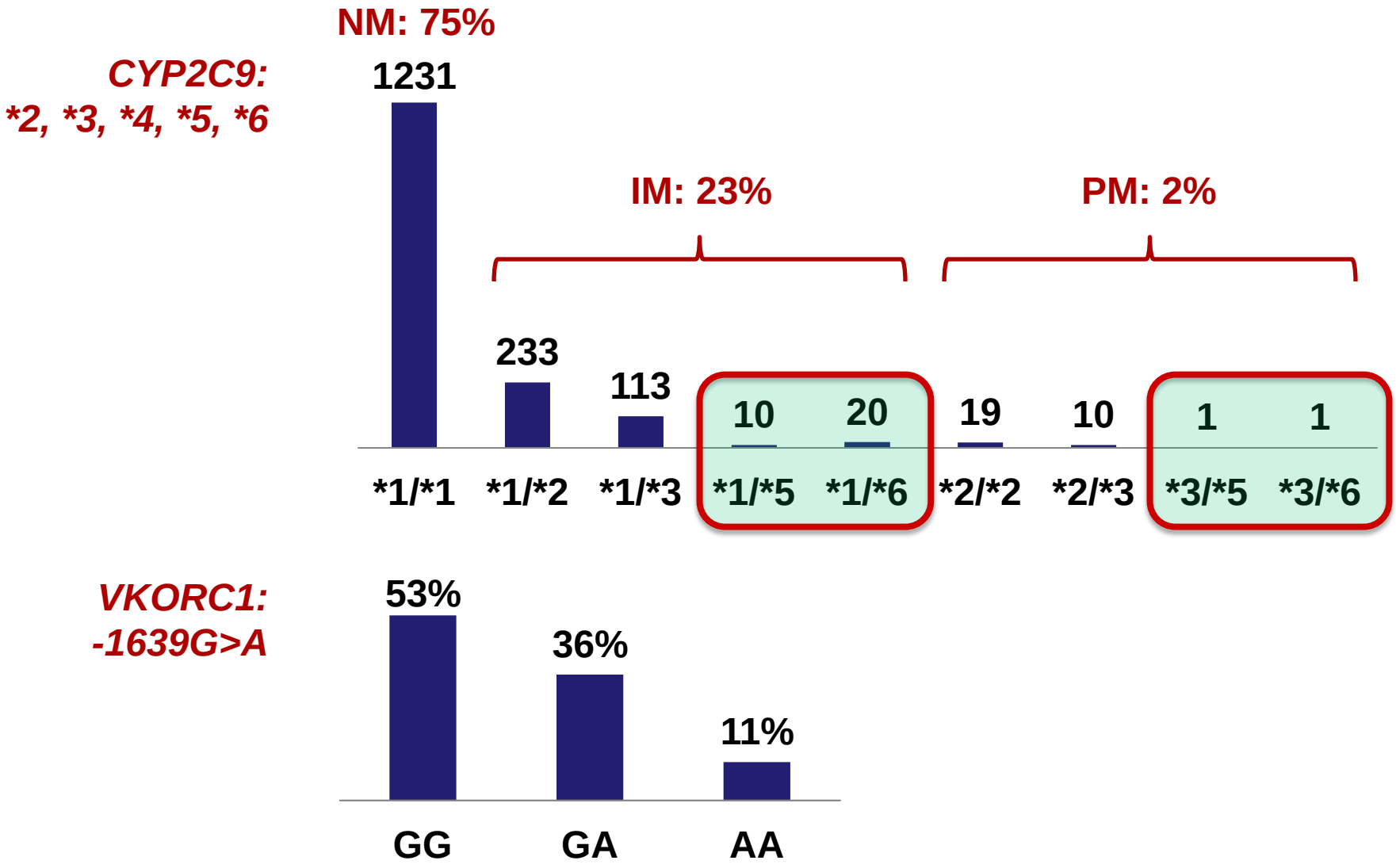
- ***DISCOVERY:*** **Novel variants in the African-American population (IWPC-GWAS).**
  - ***CYP2C* region: rs12777823 ($p=0.5x10^{-12}$); AA MAF: 25%**
  - **Explains ~5% of dosing variability in AA population.**
  - ***Perera MA, et al. Lancet, 2013.***

- ***ALGORITHMS:*** **Improvements in African-Americans.**
  - ***CYP2C9*5, *6, *8, *11*; and rs12777823**
  - **Inclusion of these variants improved prediction for both WD and IWPC algorithms.**
  - ***Drozda K, et al. Pharmacogenet Genomics, 2015.***

- ***ALGORITHMS:*** **Improvements in African-Americans.**
  - **Race-specific pharmacogenetic algorithms, rather than race-adjusted algorithms, should be used to guide warfarin dosing.**
  - ***Limdi NA, et al. Blood, 2015.***

WARFARIN PGx: *CYP2C9* and *VKORC1*

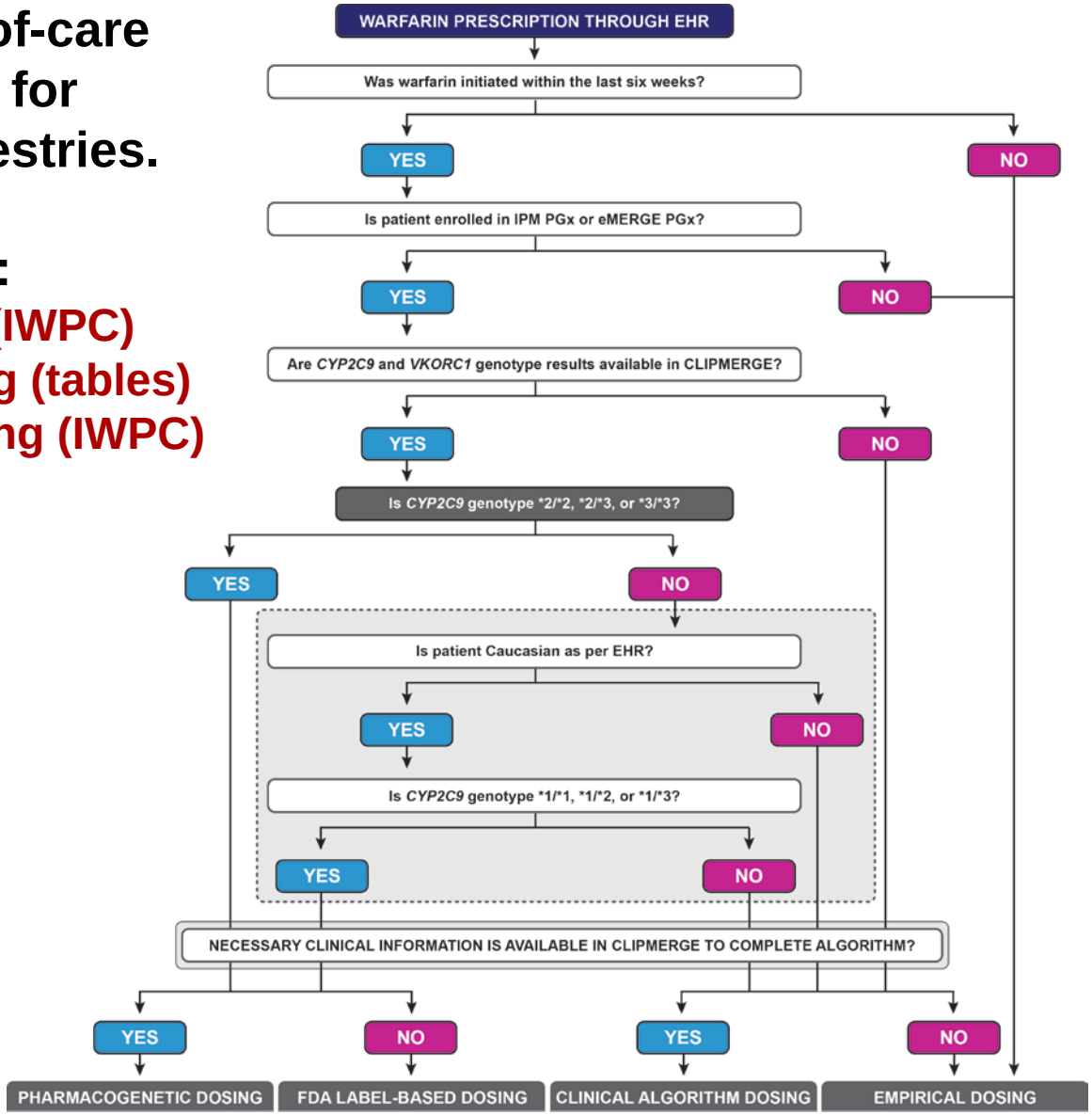
- **Sinai IPM PGx / eMERGE PGx Cohort (n=1641):**



WARFARIN PGx: IMPLEMENTATION STRATEGY

- ***Objective:*** **enable point-of-care warfarin dose prediction for patients of different ancestries.**

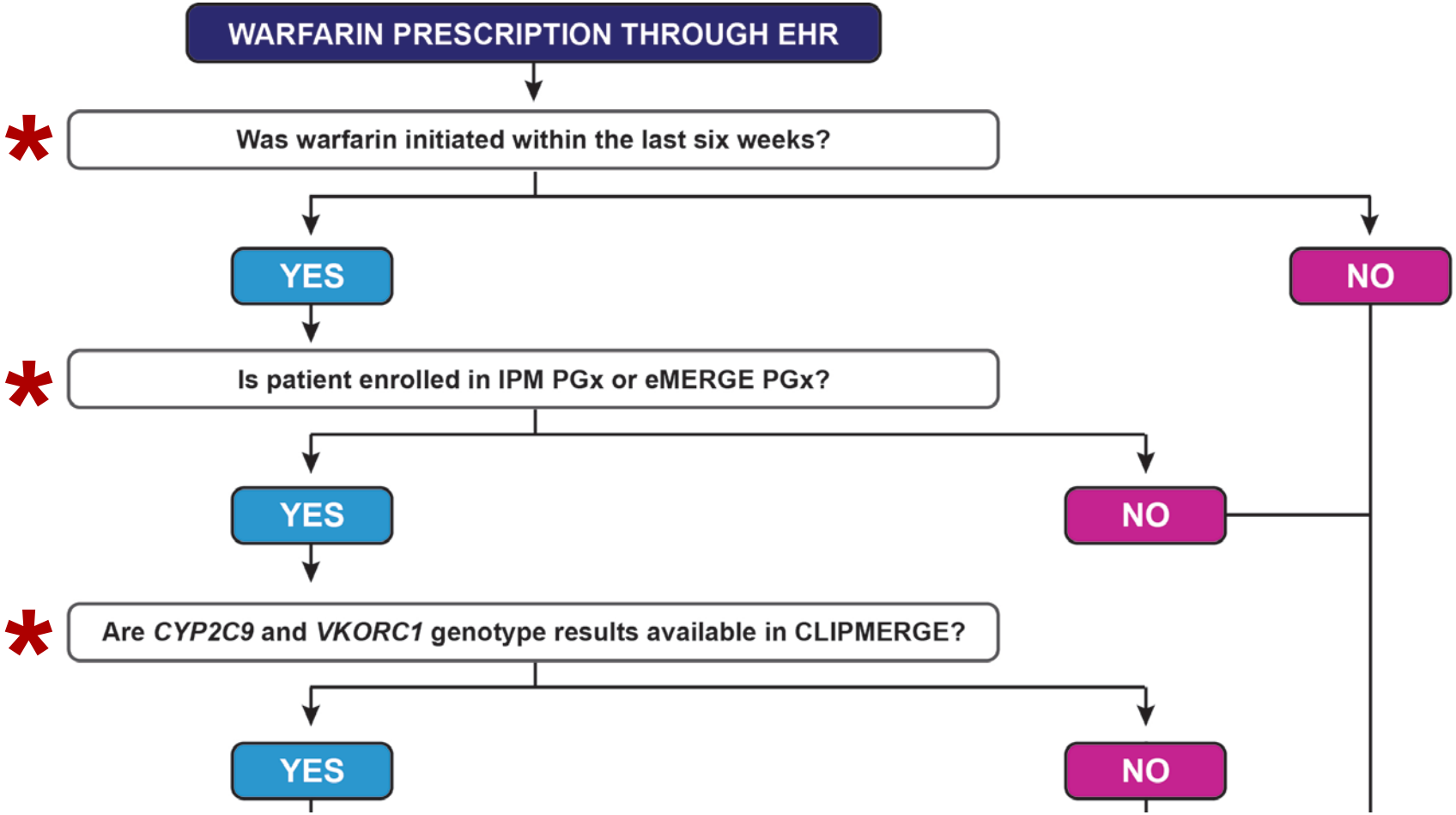
- **Four possible outcomes:**
  1. **PGx algorithm dosing (IWPC)**
  2. **FDA label-based dosing (tables)**
  3. **Clinical algorithm dosing (IWPC)**
  4. **Empiric dosing**



Owusu Obeng A, et al. Clin Pharmacol Ther, 2016.

WARFARIN PGx: IMPLEMENTATION STRATEGY

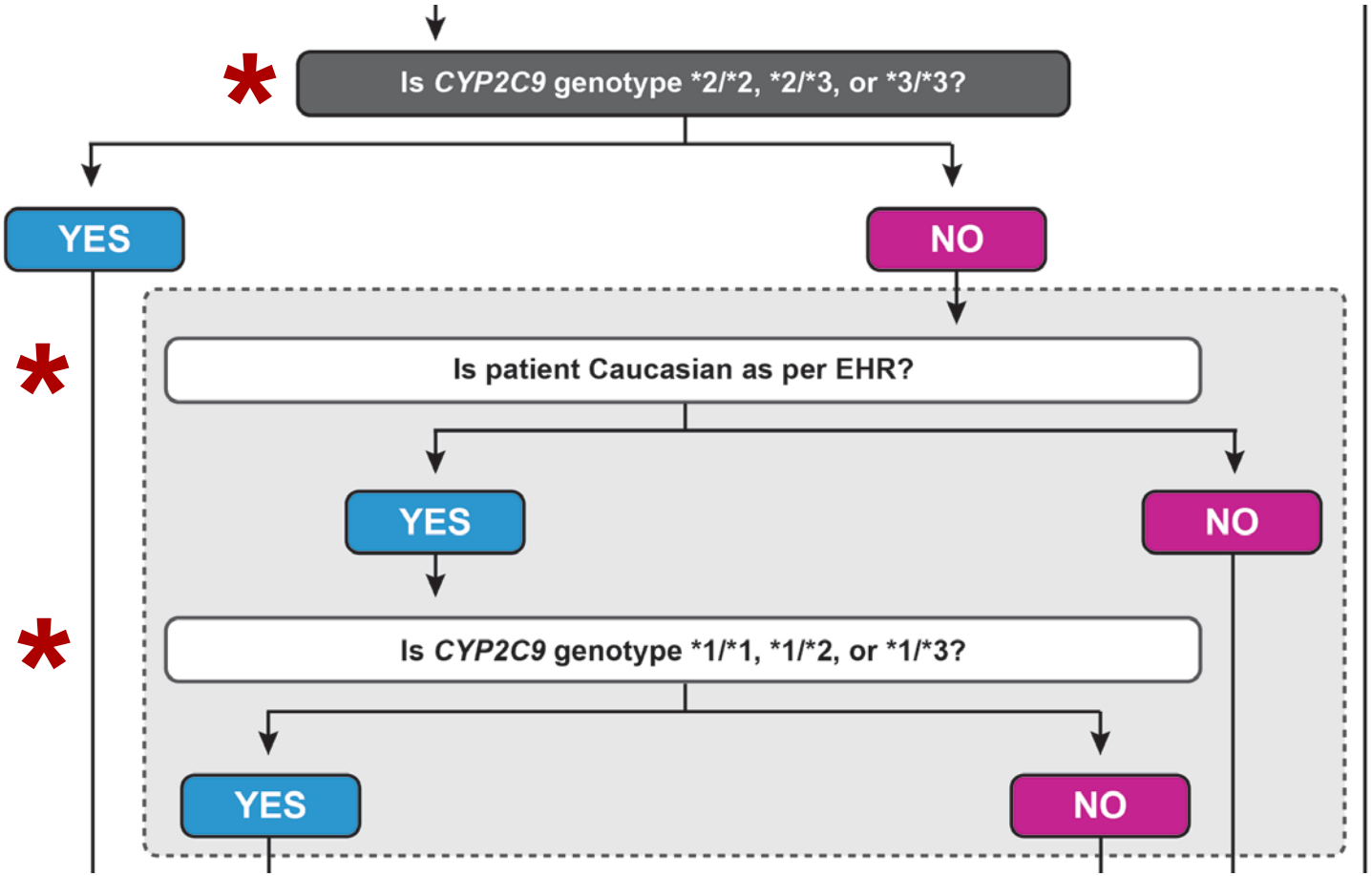
- ***Stage 1:***



Owusu Obeng A, et al. Clin Pharmacol Ther, 2016.

WARFARIN PGx: IMPLEMENTATION STRATEGY

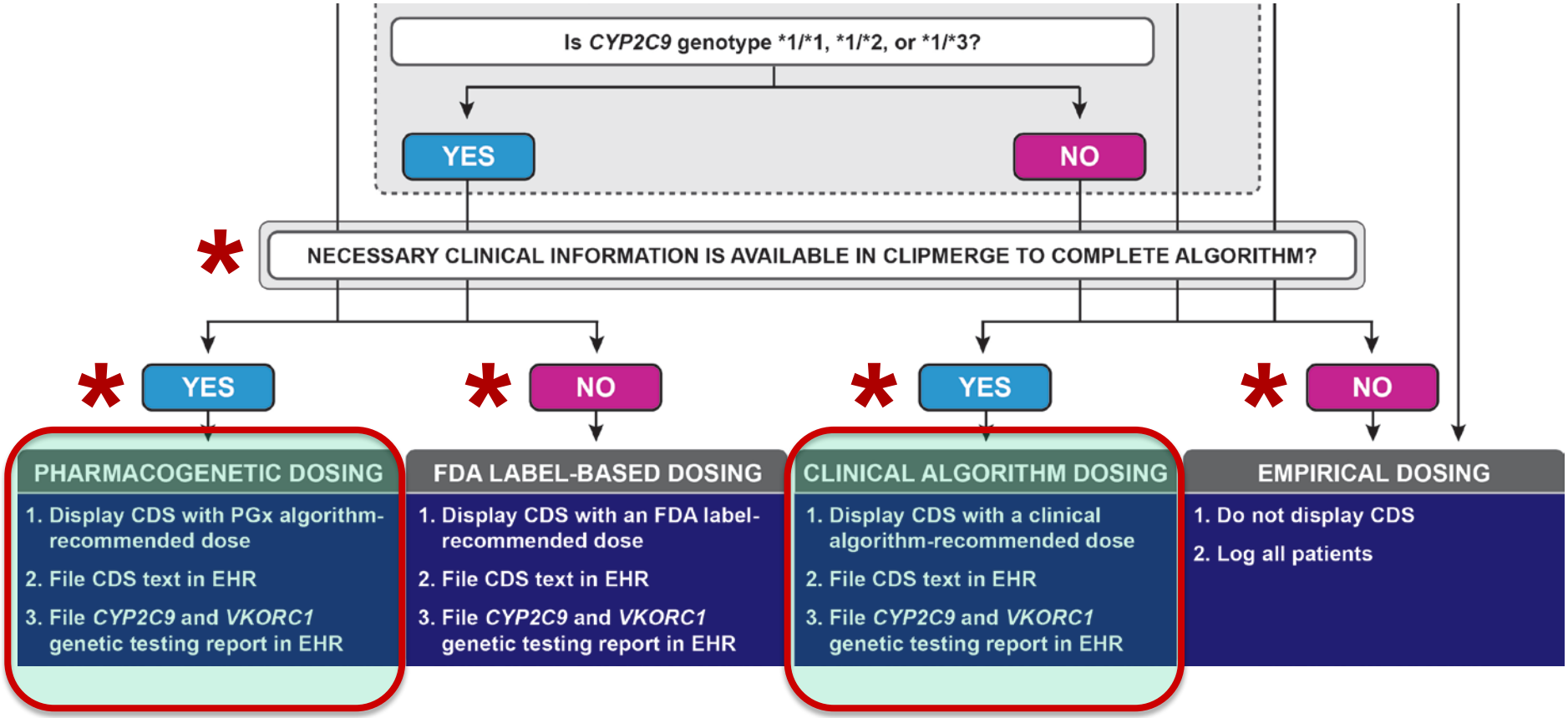
- ***Stage 2:***



Owusu Obeng A, et al. Clin Pharmacol Ther, 2016.

WARFARIN PGx: IMPLEMENTATION STRATEGY

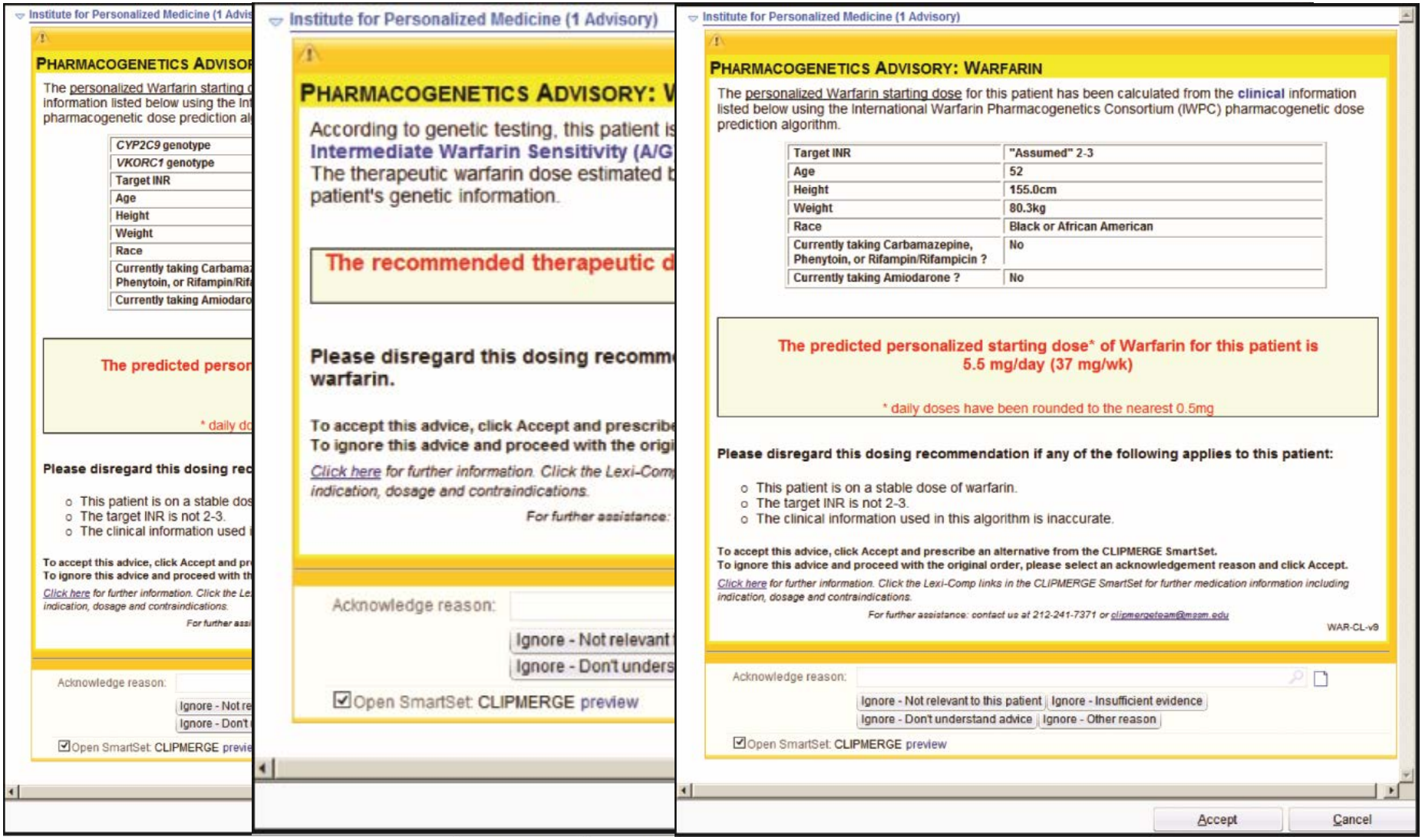
- ***Stage 3:***



Owusu Obeng A, et al. Clin Pharmacol Ther, 2016.

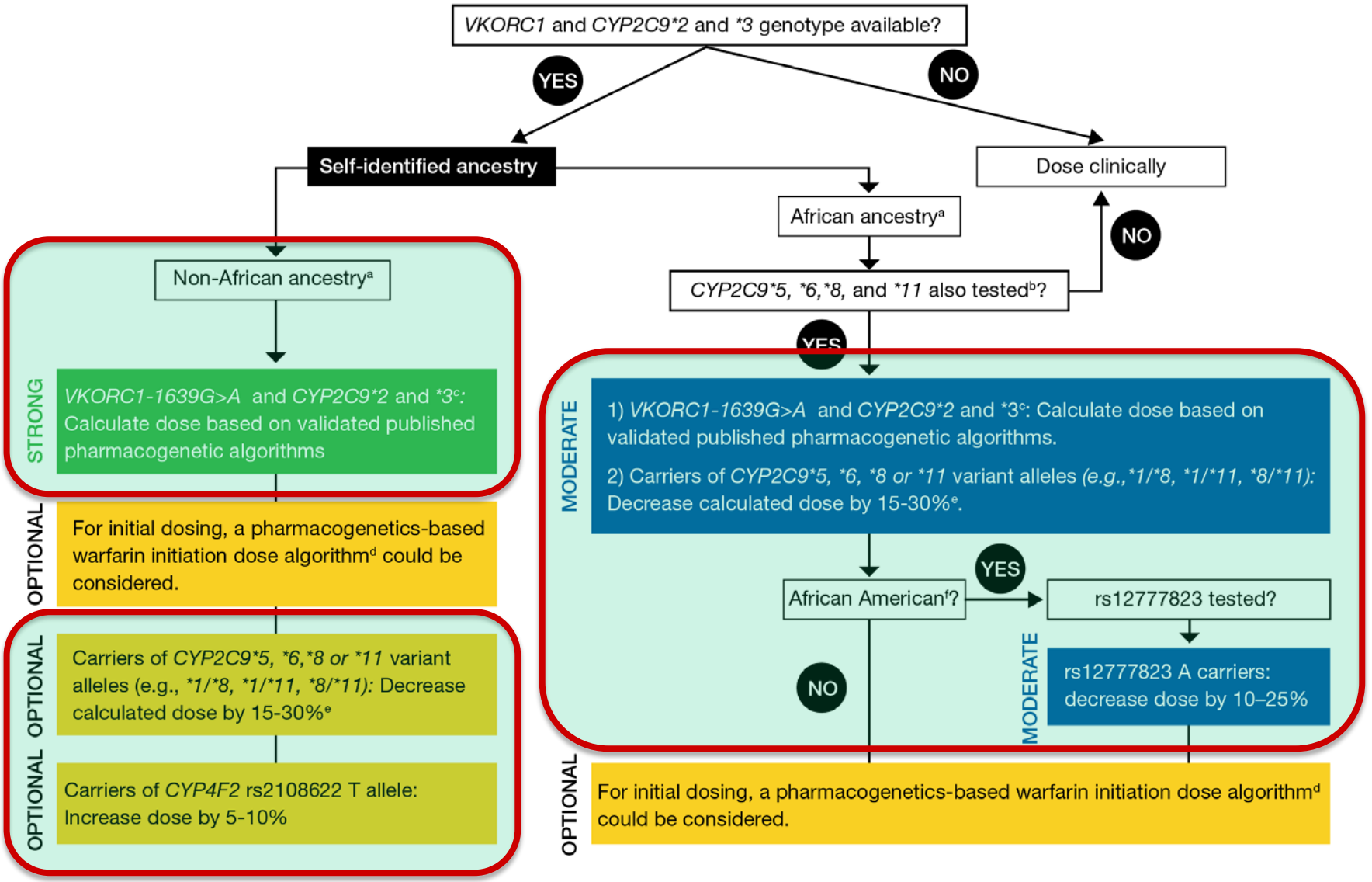
WARFARIN PGx: POINT-OF-CARE CDS

- **Clinical Decision Support:**



Owusu Obeng A, et al. Clin Pharmacol Ther, 2016.

WARFARIN PGx: ISMMS and CPIC 2017



Johnson JA, et al. Clin Pharmacol Ther, 2017.

WARFARIN PGx: IMPLEMENTATION RESULTS

- **How often are the dosing recommendations accepted and how accurate are they?**

- **A subset of providers (~10-20%) switched to novel oral anticoagulant (NOAC) after initiating warfarin.**
  - **Patients that were difficult to reach INR.**

- **Provider ACCEPTANCE manually determined by chart review of warfarin dosing patterns during initiation.**
  - **'Therapeutic' defined by stable dose over 3 consecutive INRs.**

- **Algorithm-based doses ACCEPTED by providers: 56%**

- **Majority of algorithm-guided CDS was triggered for clinical algorithm dosing (~85%).**

WARFARIN PGx: IMPLEMENTATION RESULTS

- How often are the dosing recommendations accepted and how **accurate** are they?

Algorithm **PREDICTED** dose accuracy	Within +/- 1 mg of daily therapeutic dose	78%

LESSONS LEARNED and FUTURE DIRECTIONS

1. **Warfarin is still commonly prescribed and managed in IMA clinic.**
   - **Provider education is critical.**
   - **Target Coumadin clinics.**

2. **Ancestry informed algorithm-based point-of-care warfarin dosing is accepted by majority of exposed providers.**
   - **Enabled more accurate prescribing than empirical dosing.**

3. **Clinical algorithm-based warfarin dosing is an option for implementation in non-Caucasian patient populations.**
   - **Additional *CYP2C9* star (*) alleles and African-American variants are included in the forthcoming comprehensive MGTL PGx panel.**

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Thank you.

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