Translational Pharmacogenomics at Mount Sinai and Beyond

Aniwaa Owusu Obeng, PharmD

Assistant Professor
The Charles Bronfman Institute for Personalized Medicine
Department of Medicine
Department of Genetics and Genomic Sciences
Icahn School of Medicine at Mount Sinai

Clinical Pharmacogenomics Coordinator
The Mount Sinai Hospital
Pharmacy Department

Outline

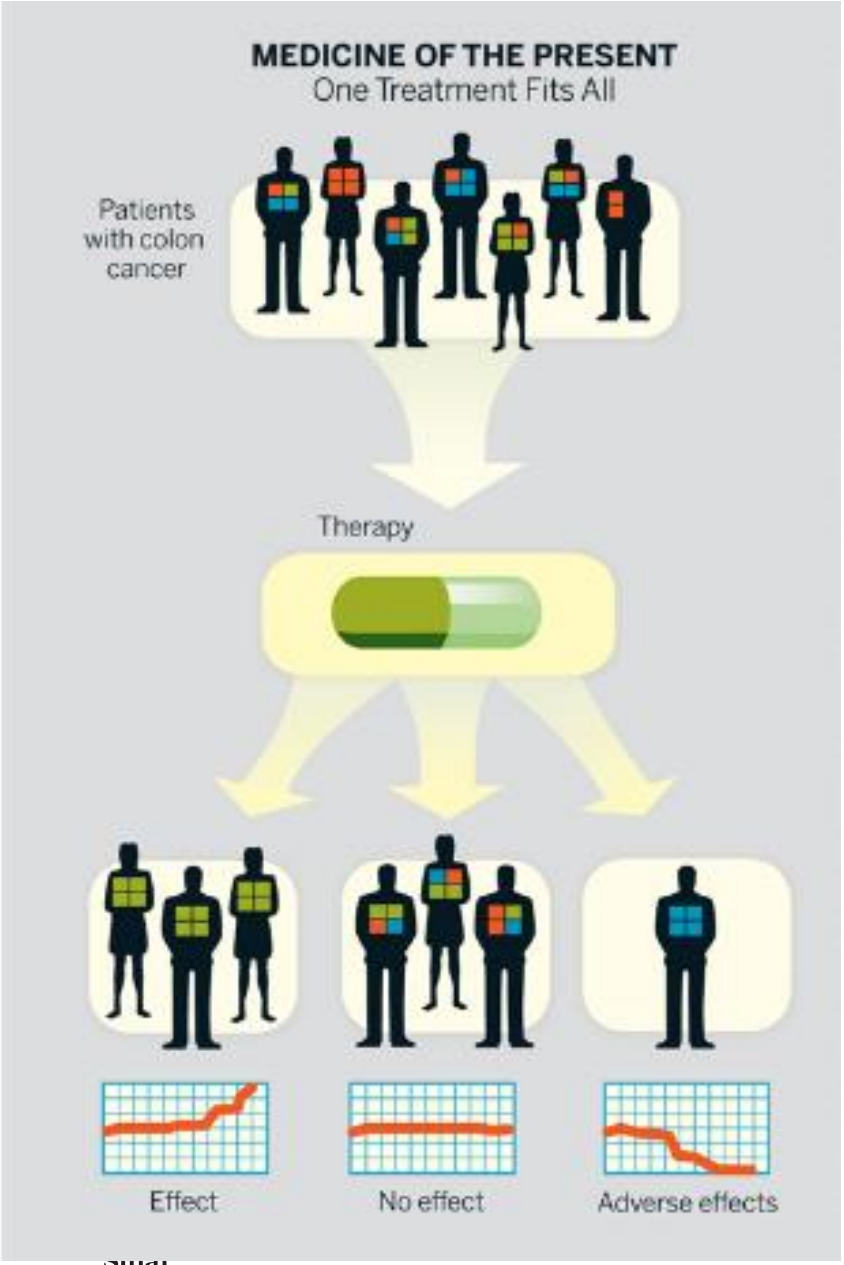
I. BACKGROUND
   A. Pharmacogenomics and its Potential Benefits

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

III. IMPLEMENTATION
   A. Warfarin Pharmacogenetics
   B. Multi-ethnic Dosing Strategy and Implementation

IV. LESSONS LEARNED / FUTURE DIRECTIONS

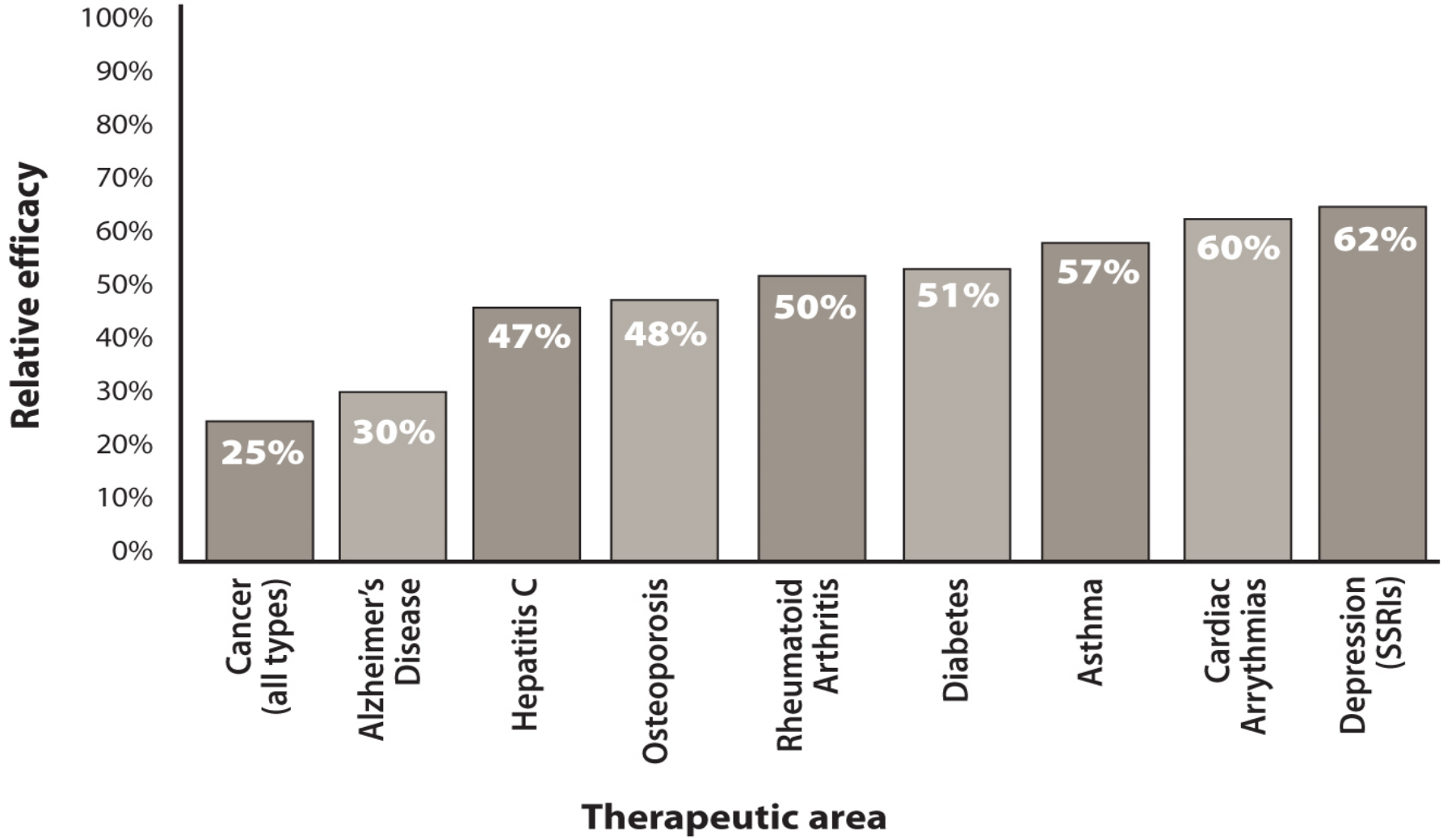
Medical Practice Status Quo



- After diagnosis, patients are prescribed therapy with no reference to the patient's genetic information
- Known as
  - "Trial and error"
  - "One size fits all"

Take it Personally. Accessed on June 16, 2017. [Internet]. Image Available from: http://www.5280.com/2015/12/take-it-personally/

One size does not fit all: Relative efficacy of drug and disease, according to Spear et al.



Hua LV. May 2011. Research developments accelerate discovery, application of personalized medicine. Accessed on June 16, 2017. [Internet}. Available from: https://www.healio.com/optometry/retina-vitreous/news/print/primary-care-optometry-news/%7B6e941852-5b8c-418b-8c7e-b1ad83837a28%7D/research-developments-accelerate-discovery-application-of-personalized-medicine

Adverse Drug Reactions

- Over 2 million serious ADRs per year
- 106,000 deaths yearly
  - 20% of all injuries or death to hospitalized patients
- 4th leading cause of death
  - Ahead of pulmonary disease, diabetes, AIDS, pneumonia, accidents and automobile deaths
- $136 billion yearly
  - More than costs of care for CV and DM

Preventable Adverse Drug Reactions: A Focus on Drug Interactions. U.S. Food and Drug Administration. Updated: 6/18/2014. Accessed on 1/19/2016. [Internet]. Available from: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm110632.htm#

Adverse Drug Events

2007 – 2009 : pts ≥ 65 years
99,628 annual hospitalizations
166,174 annual ED visits

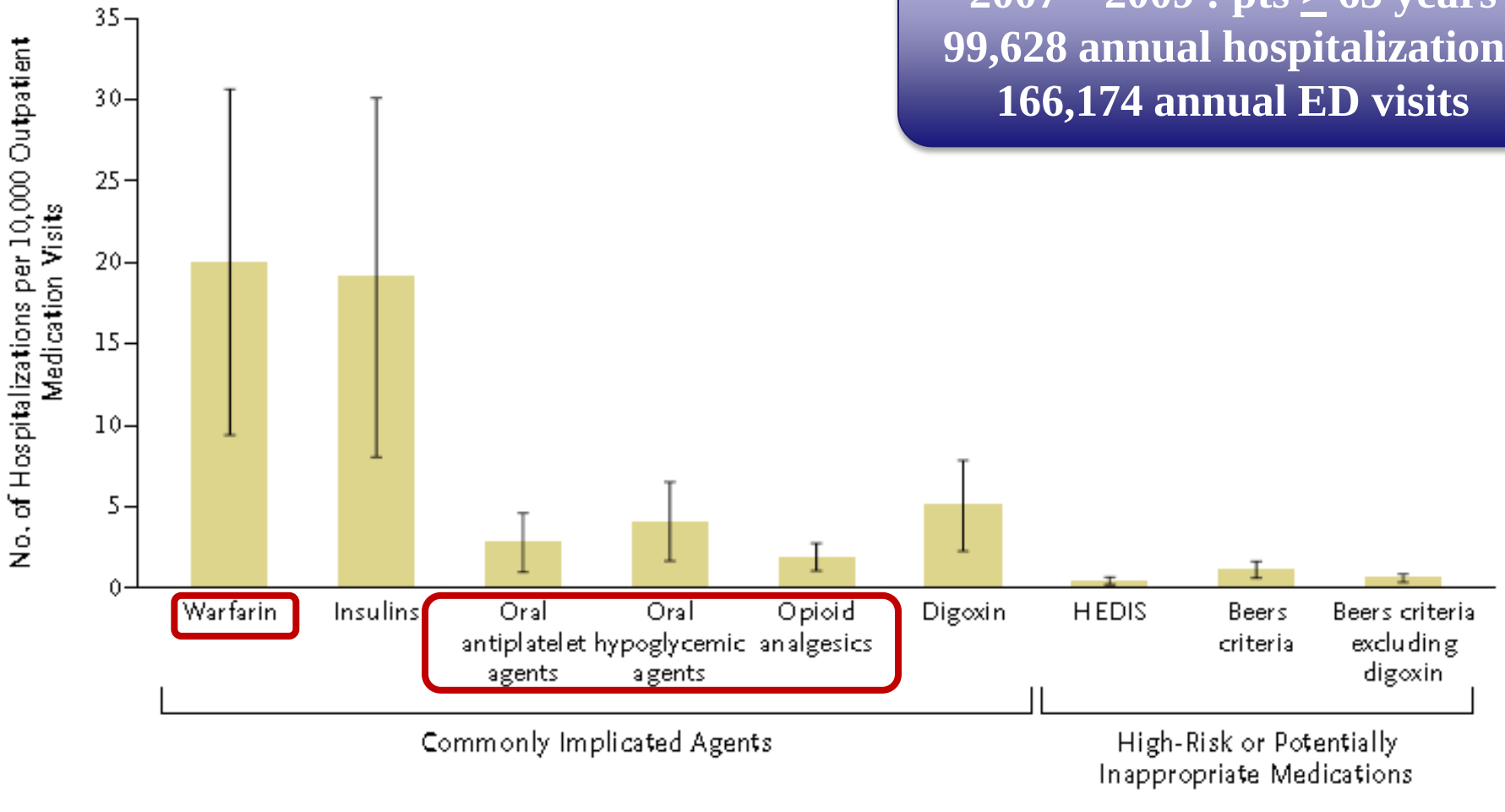


Figure 1. Estimated Rates of Emergency Hospitalizations for Adverse Drug Events in Older U.S. Adults, 2007–2009.

Budnitz DS, Lovegrove MC, Shehab N, et al. NEJM 2011; 365: 2002 - 2012

Drug Response is Multifactorial

Genetics

Ica of l Mount Sinai

Medicine

Pharmacogenomics (PGx)

- The study of how genes affect a person's response to medications.

- Pharmacology (the science of drugs) PLUS genomics (the study of genes and their functions)

- Potential benefits
  - Improve utility of existing therapies
  - Increase drug effectiveness
  - Improve drug safety

- Inform discovery and development of novel therapeutic agents

Pharmacogenomics (PGx)

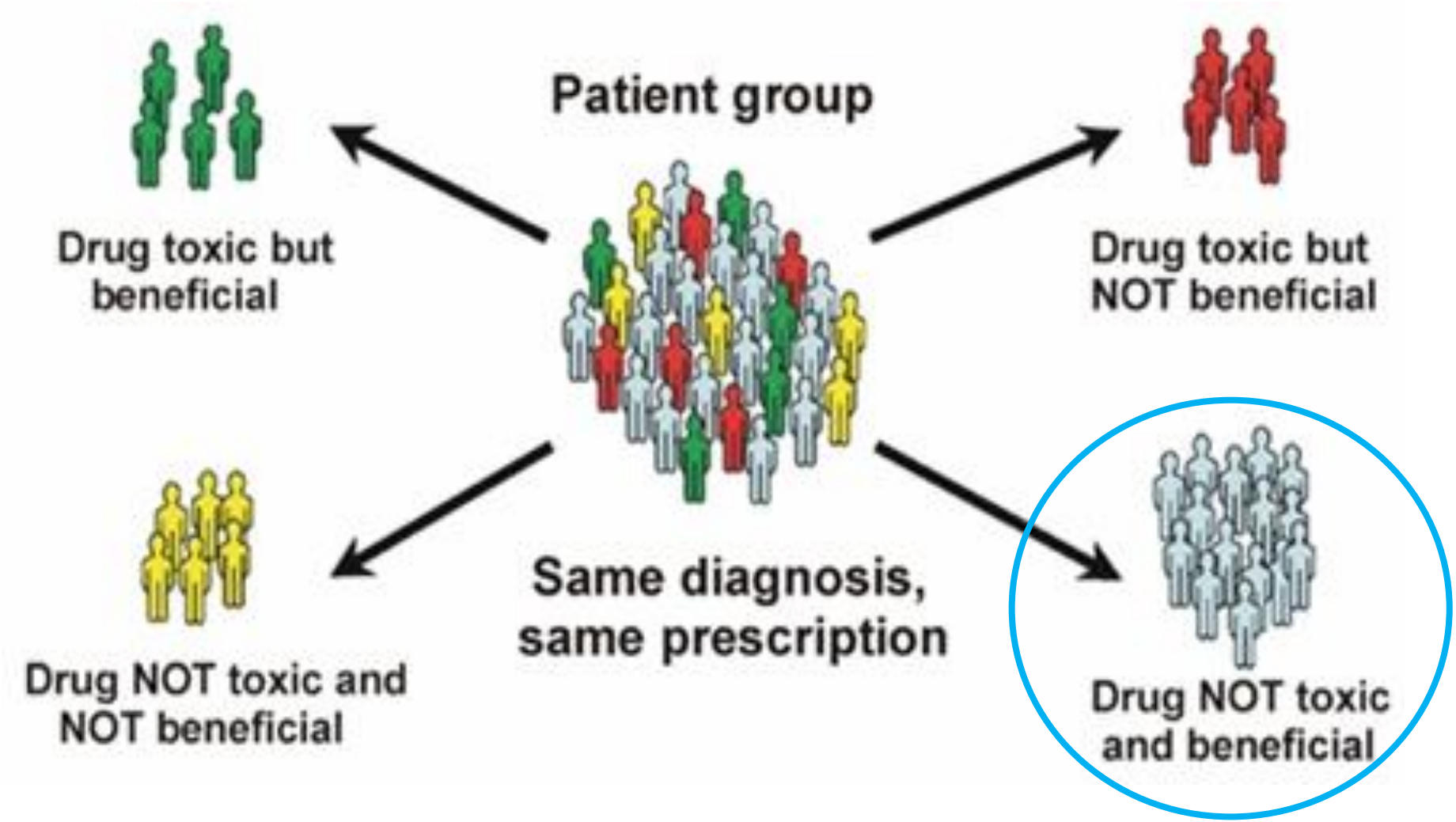
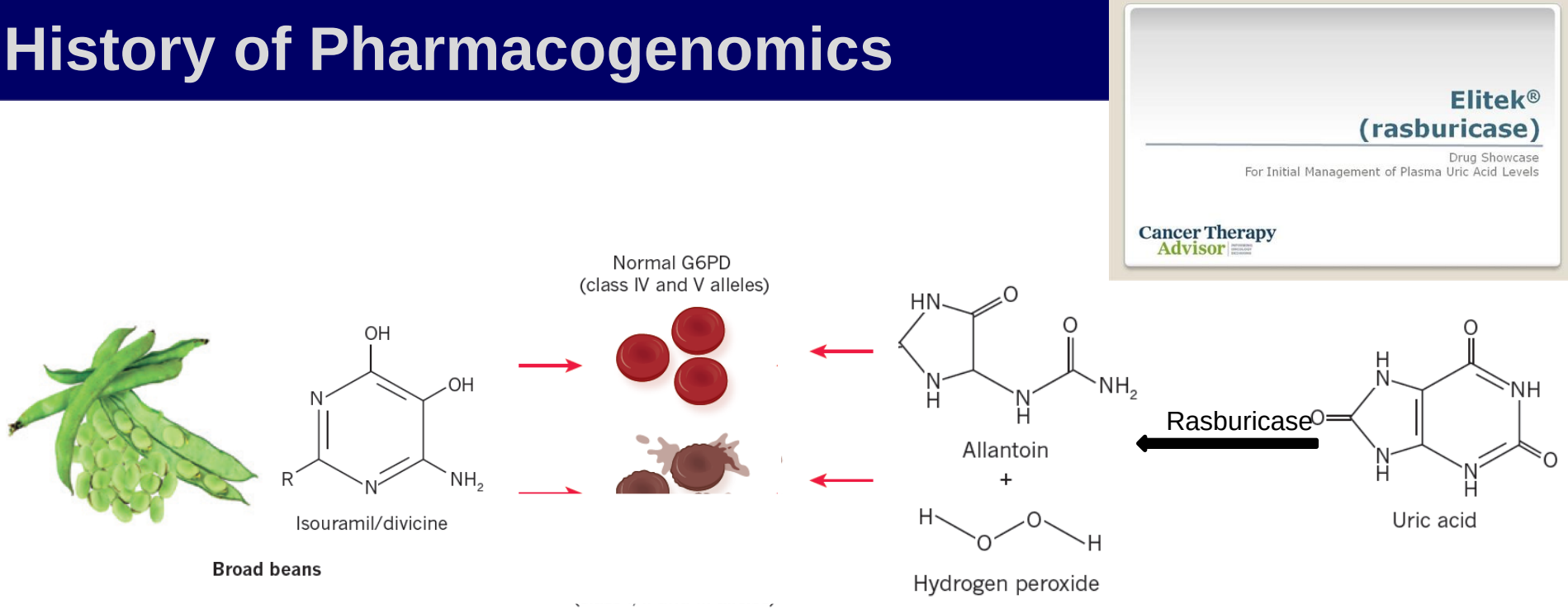


Image accessed from: http://mytorontocanadambastudentexperience.blogspot.com/2012/10/personalized-medicine-or-p4-medicine.html

History of Pharmacogenomics



- Pythagoras in 510 BC
- Broad beans (Vicia faba)
- Over 2000 years later attributed to glucose-6-phosphate dehydrogenase (G6PD)
- Hemolytic anemia

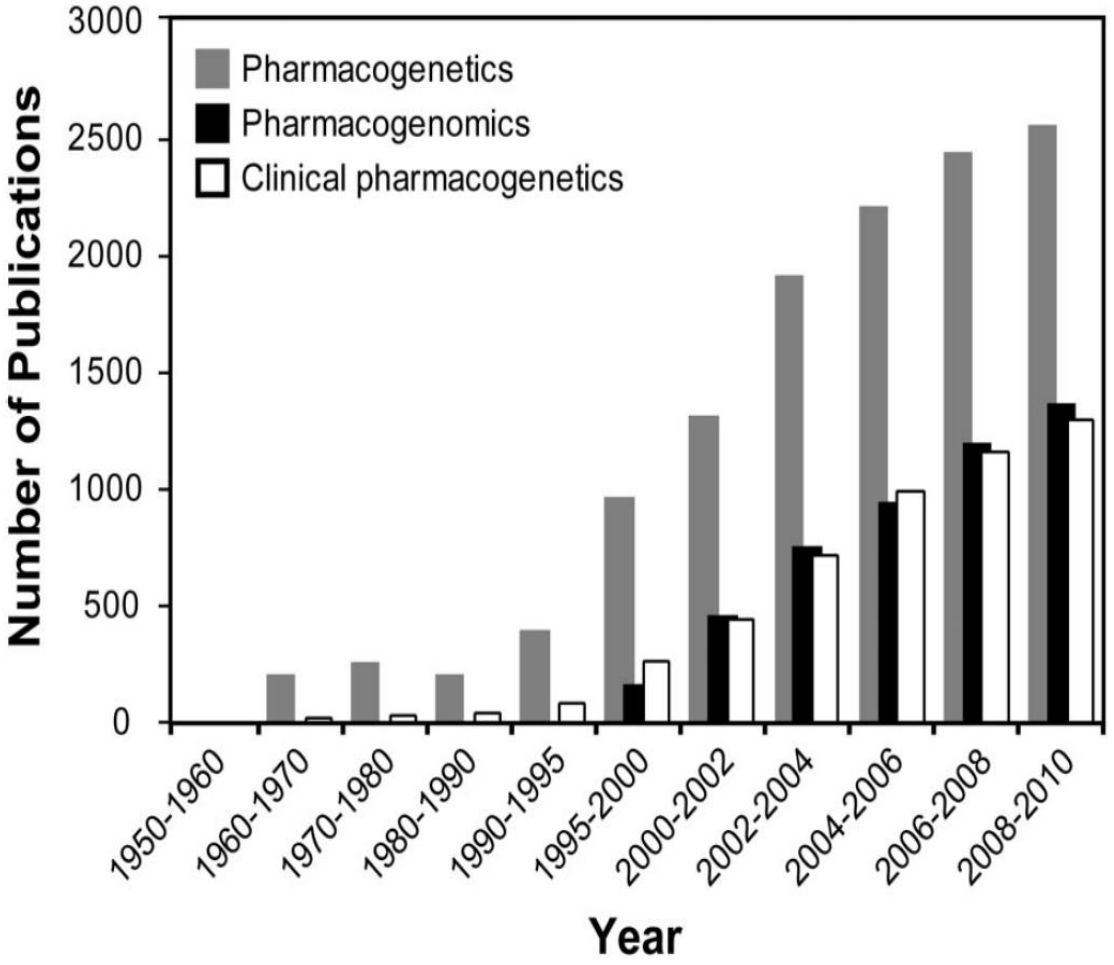
- Uric acid end-product (hydrogen peroxide)
- Primarily class II "Mediterranean" allele of G6PD
- RBCs of G6PD-deficient patients → insufficient NADPH
- Reduced protection from oxidative damage
- Rasburicase is contraindicated in G6PD –deficient individuals

Sinai

Relling MV, Evans WE. Pharmacogenomics in Clinic. Nature. Oct 15, 2015. 526: 343-350

Evolution of Pharmacogenomics

- **1930s** – early observations of unusual drug reactions.
- **1959** – Sir Friedrich Vogel coined the term "pharmacogenetics".
- **1962** – first textbook on this discipline.
- **2000s** – introduction of the term "pharmacogenomics".

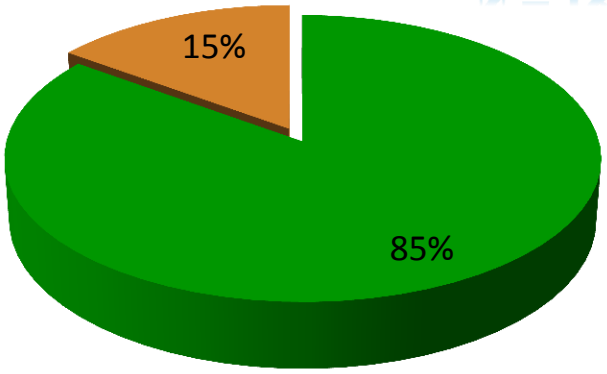


Scott SA. Personalizing medicine with clinical pharmacogenetics. Genet Med. 2011. 13 (12):987 – 995.

PGx and FDA-Approved Medications

FDA-approved medications n = 1200

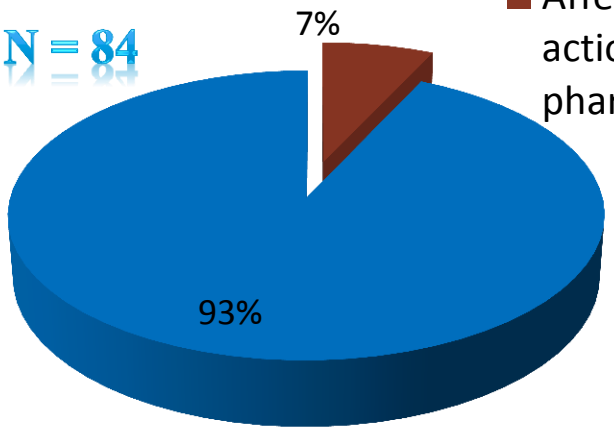
N = 180



PGx information in drug label

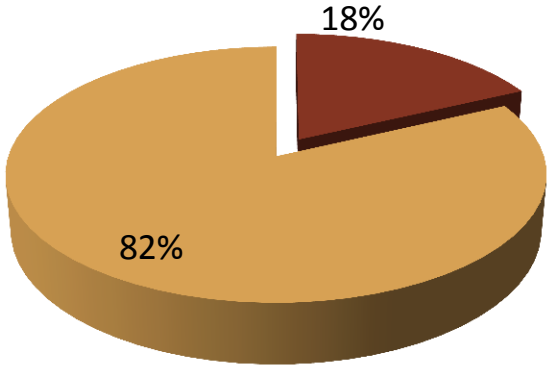
FDA-approved medications n = 1200

N = 84



Affected by actionable pharmacogenes

Prescriptions in the US n = 4 billion



Prescriptions for PGx high risk meds

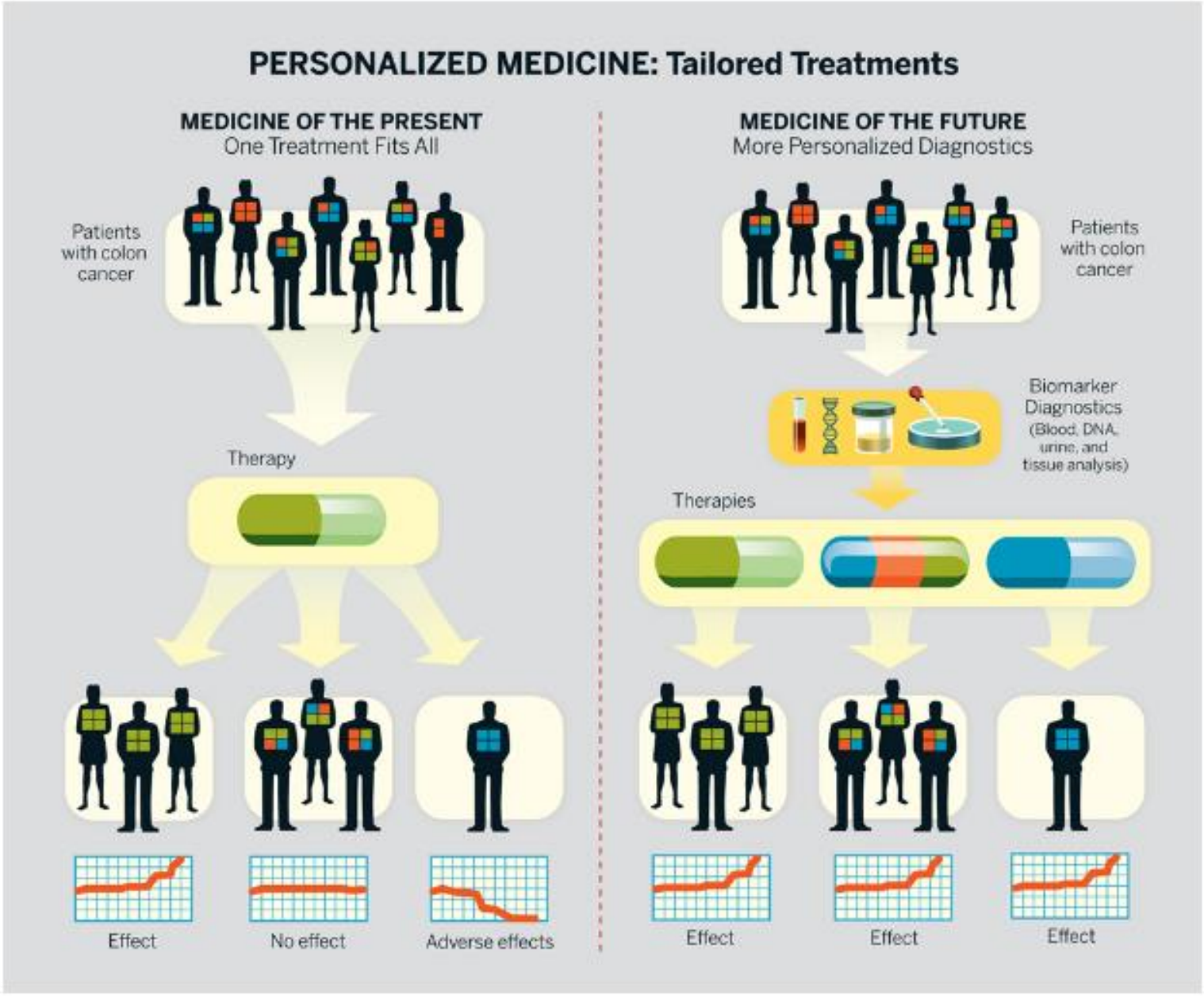
N = 720 MILLION

Icahn School of Medicine at Mount Sinai

The Charles Bronfman Institute for Personalized Medicine

Relling MV, Evans WE. Nature. 2015

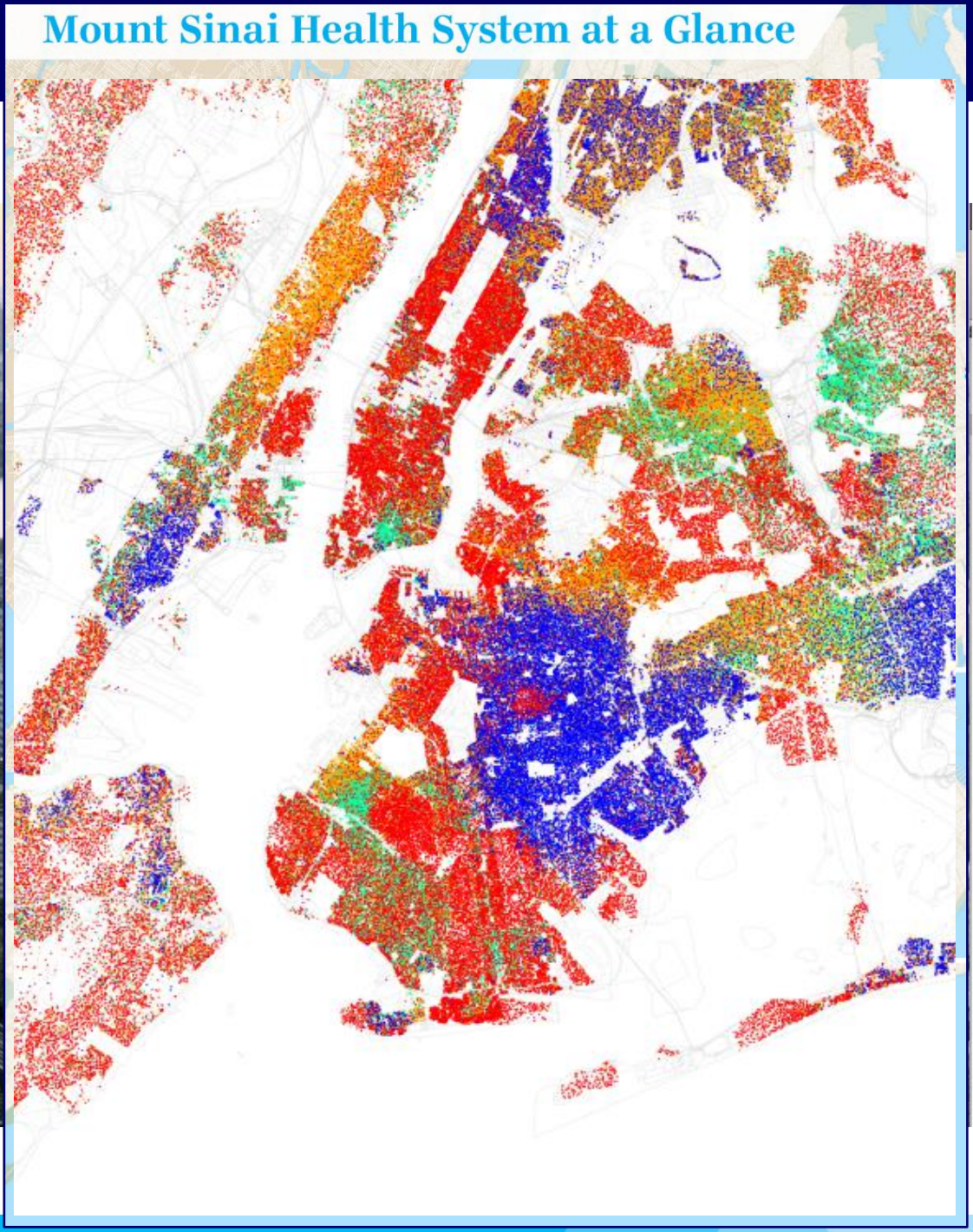
Shifting the Status Quo



Take it Personally. Accessed on June 16, 2017. [Internet]. Image Available from: http://www.5280.com/2015/12/take-it-personally/

PGx at Mount Sinai

Mount Sinai



Icahn School of Medicine at **Mount Sinai**

The Charles Bronfman Institute for Personalized Medicine

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

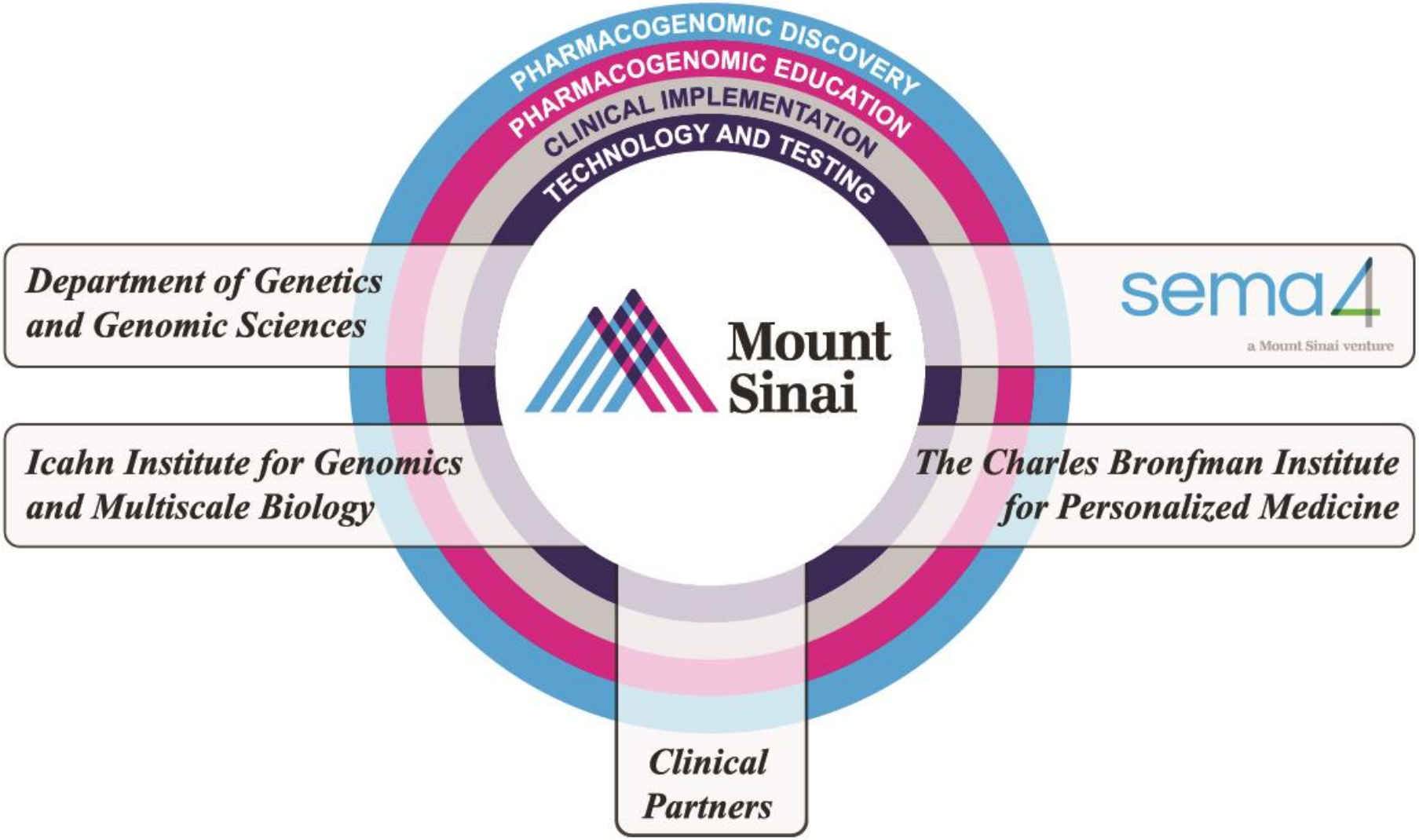
Icahn School of Medicine at Mount Sinai

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.**

Translational PGx at Mount Sinai



Icahn School of Medicine at Mount Sinai

The Charles Bronfman Institute for Personalized Medicine

Scott SA, Owusu Obeng A, Botton MR, et al. Pharmacogenomics, 2017.

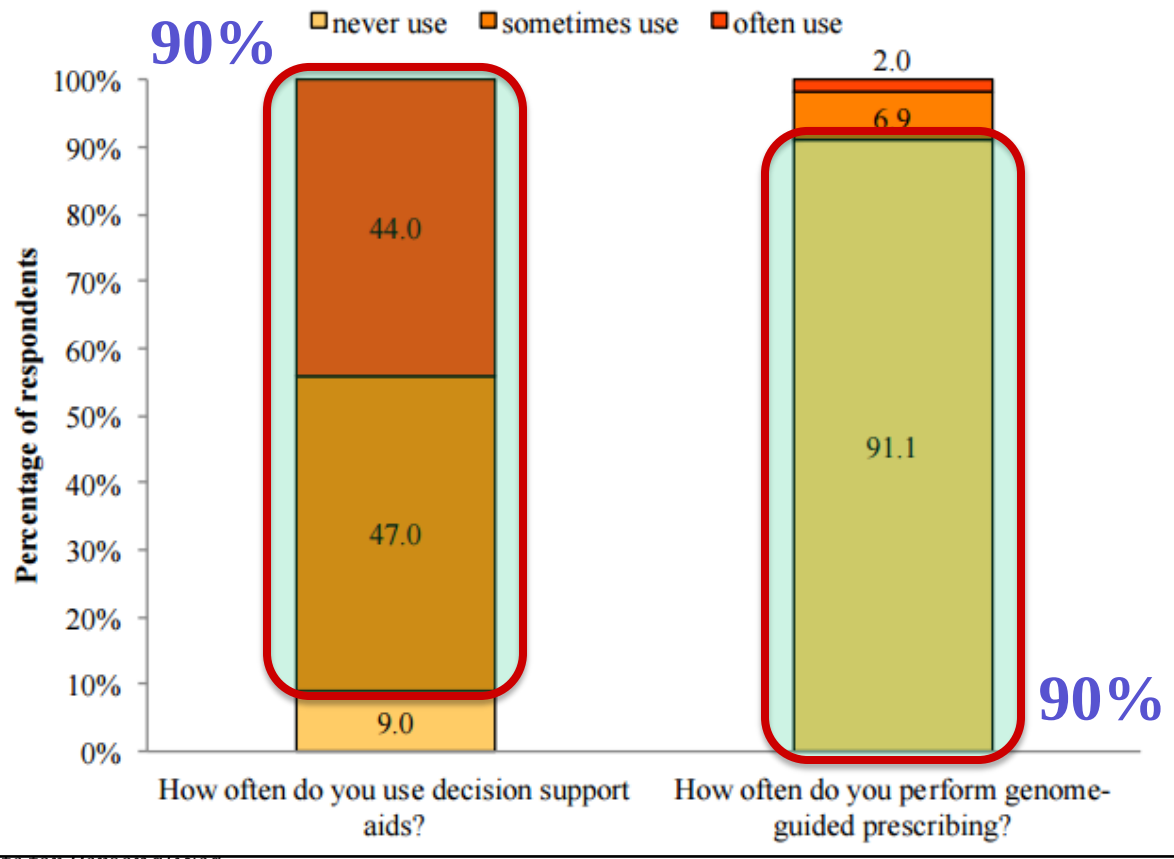
Threefold Aims of PGx at Mount Sinai

- Educational Initiatives
  - Patients
    - Brochures, videos, social media memes
  - Providers
    - Six week long rotation for pharmacy students / residents
    - Pharmacogenomics Journal Club Meetings
    - Presentations
    - Summer volunteer opportunities for students and trainees
- Clinical pharmacogenomics
- Translational Research

Implementation: Provider Education

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

Figure 2. Experience with decision support aids and genome-guided prescribing.



the CDS.

Icahn School of Medicine at Mount Sinai

The Institute for Personalized Medicine

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

Implementation: Patient Education

At Mount Sinai, we believe that:

100% of patients should receive medications that **work for them.**

100% of patients should receive medications that are **safe for them.**

Because when it comes to your health,

One size does not fit all.

****

As a *patient* in the Mount Sinai Health System, *Your* doctor may order a genetics test to help select the **right** medication at the **right** dose for *YOU*!

****

Contact Us to Schedule a Pharmacogenetics Consultation

Translational Initiatives in Pharmacogenomics
The Charles Bronfman Institute for Personalized Medicine

Tel: 212-241-7371
Email: CLIPMERGETEAM@mssm.edu

1468 Madison Ave
Annenberg Building, 18th Floor
Room 18-16
New York, NY 10029

The Charles Bronfman Institute for Personalized Medicine

Your Guide to

Pharmacogenetics Testing

Mount Sinai

Threefold Aims of PGx at Mount Sinai

- Educational Initiatives
- Clinical pharmacogenomics
  - Ongoing projects: IPM PGx and eMERGE PGx
  - Implementation of PGx across the Mount Sinai Health system
- Translational Research
  - Expand the evidence base for drug-gene pairs
  - Develop and successfully implement best practice for clinical PGx

Pharmacogenomics Implementation Programs

IPM PGx

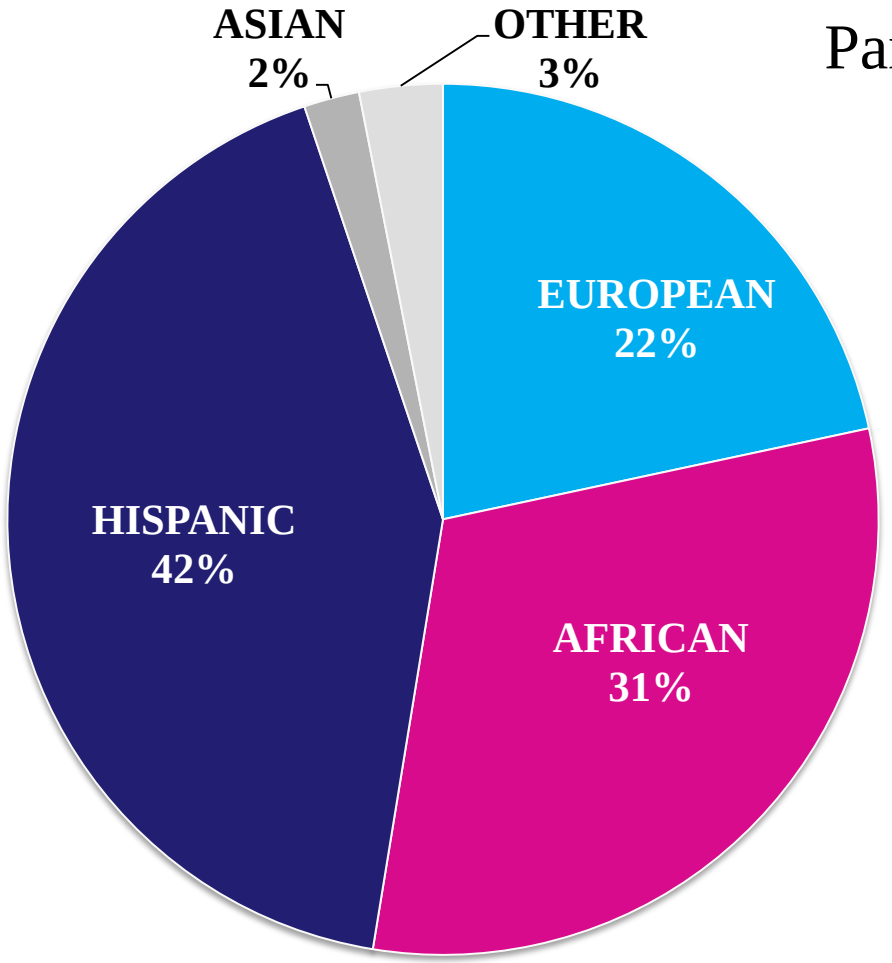
- 1500 BioMe patients
- IMA clinic
- Pre-emptive genotyping
- Providers are consented and surveyed
- Unlimited number of drug-gene pairs
- CLIPMERGE
- EHR data collection

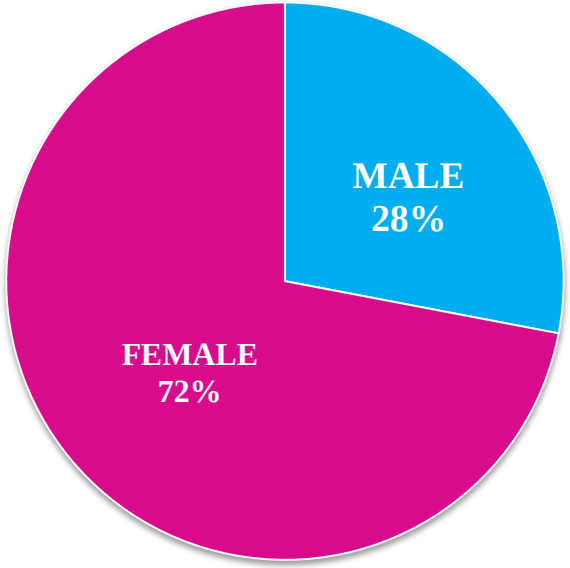
eMERGE PGx

- 663 BioMe and non-BioMe patients
- FPA clinic
- Pre-emptively sequenced
- Providers are co-investigators
- CDS for simvastatin, clopidogrel and warfarin
- CLIPMERGE
- EHR data collection

PGx Implementation: Patient Demographics

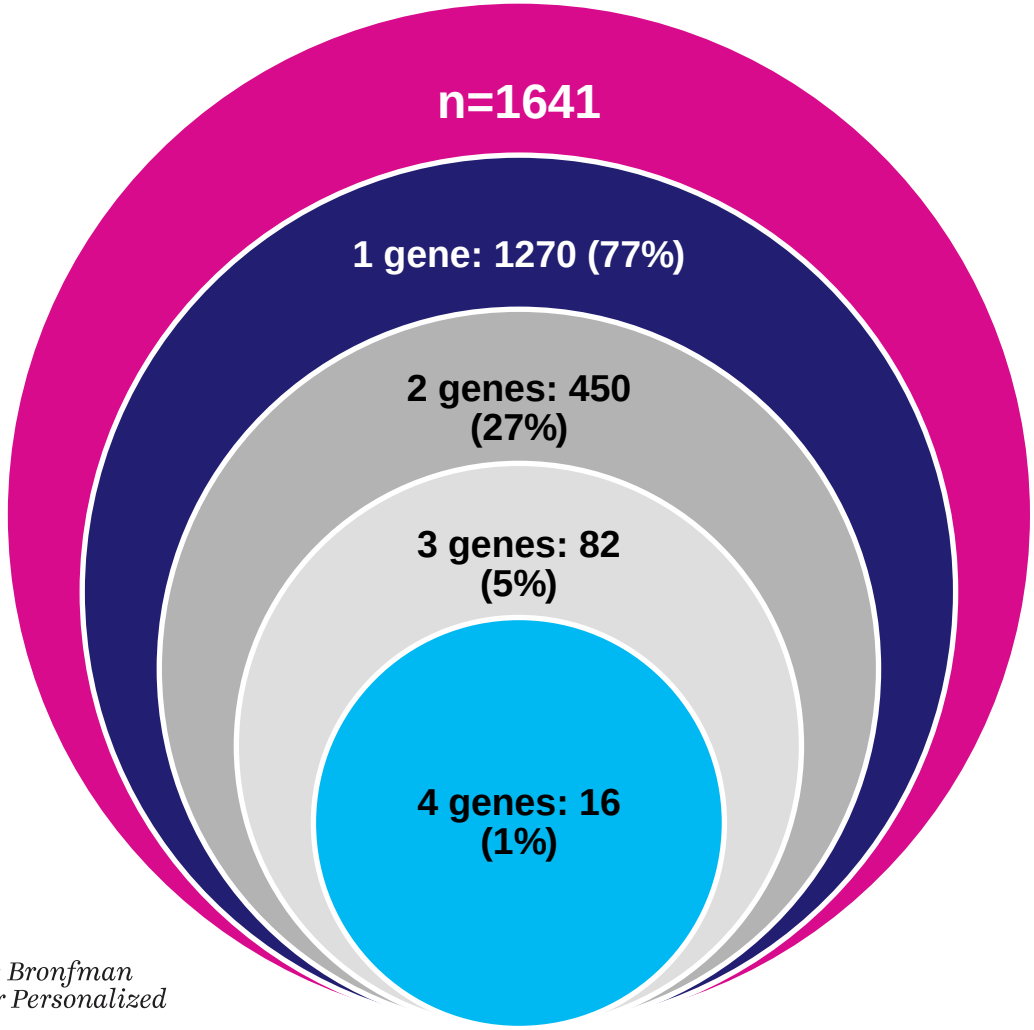
Patients Enrolled: 1641
Participating Physicians: 420





Implementation: Pre-emptive PGx Testing

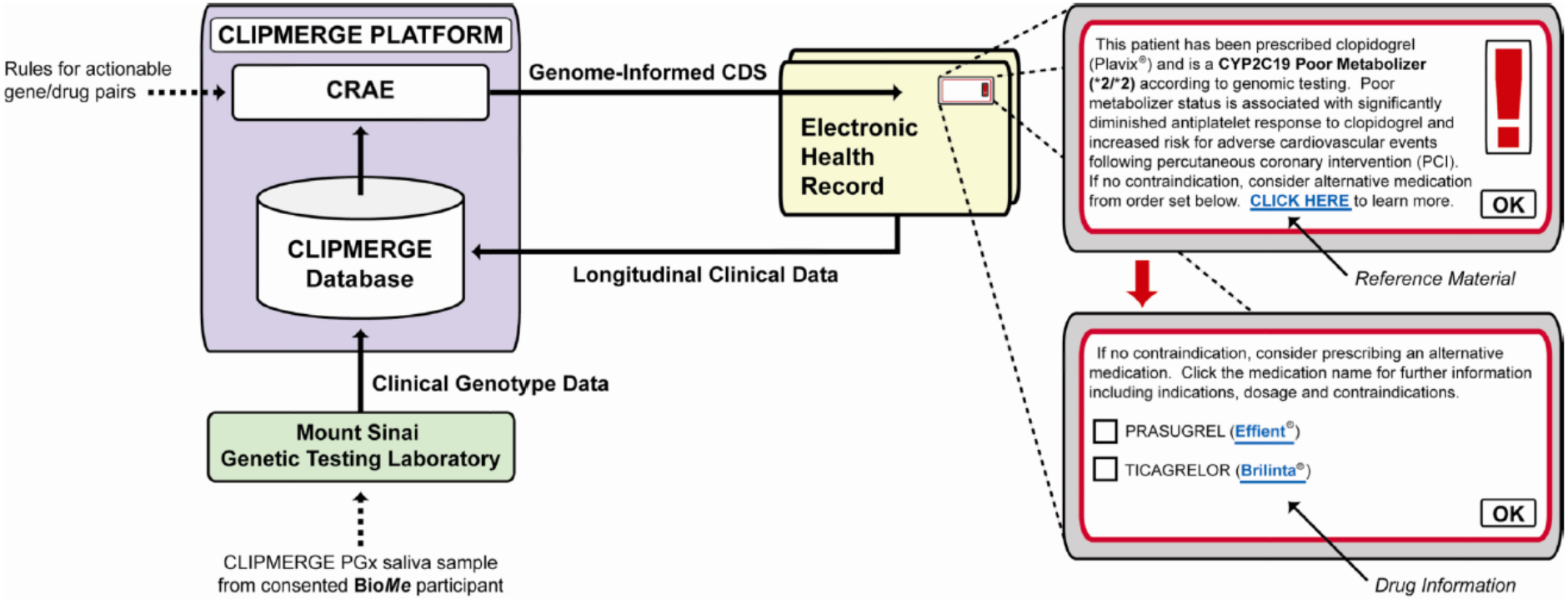
- **~77% of patients have <u>at least</u> one 'actionable' variant in *CYP2C19*, *SLCO1B1*, *CYP2C9*, and/or *VKORC1*.**



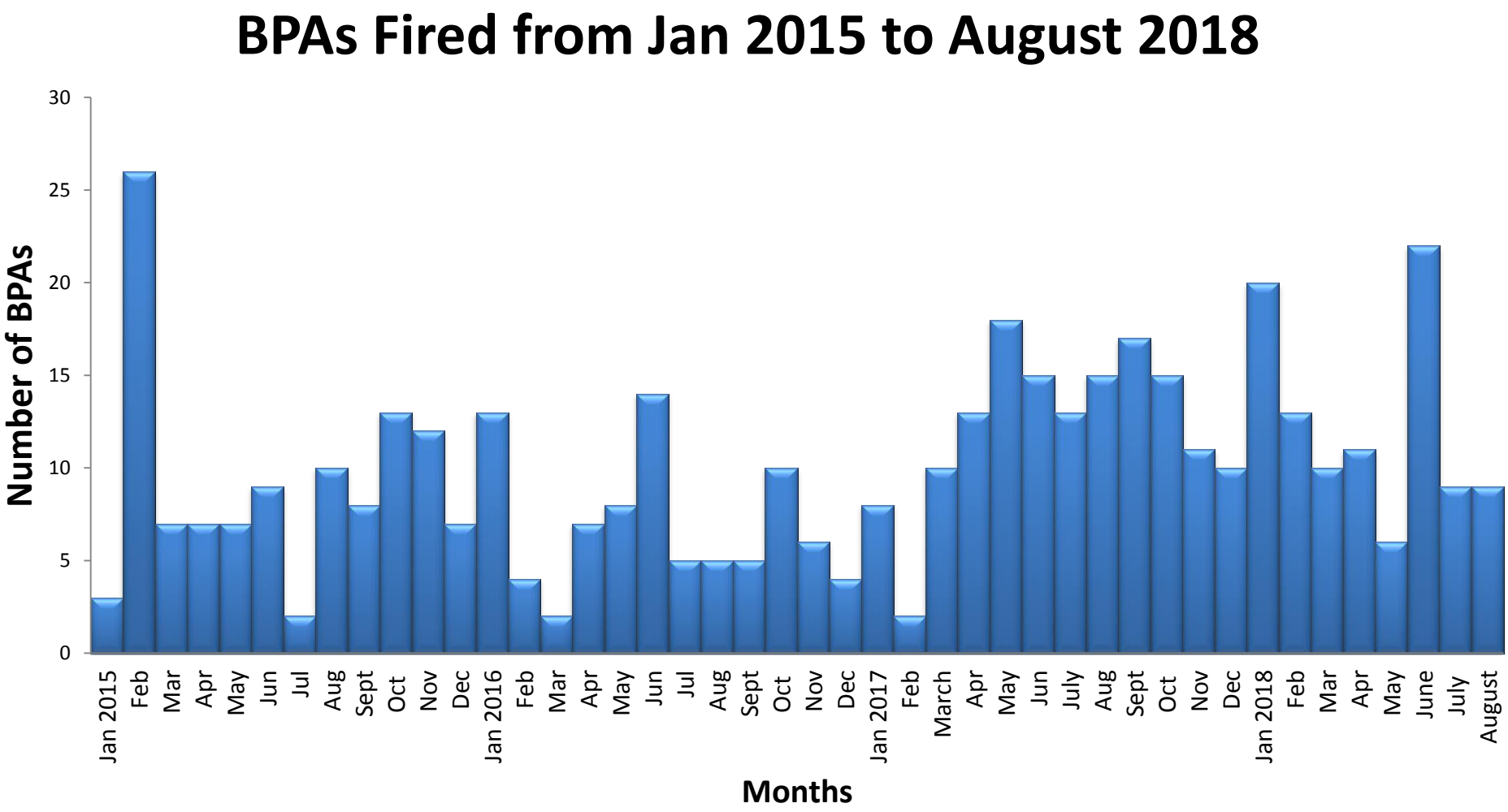
Delivering PGx to Physicians: CLIPMERGE

Clinical **I**mplementation of **P**ersonalized **M**edicine through **E**lectronic Health **R**ecords and **Ge**nomics

Gottesman et al. Page 6



IPM PGx: Alerts Fired Thus Far



441 alerts so far!
10 BPAs per month on average

IPM Pharmacogenomics Clinical Implementation Dashboard – June 2018

IPM Drug-gene Evaluation

Potential Drug-Genes for Clinical Implementation

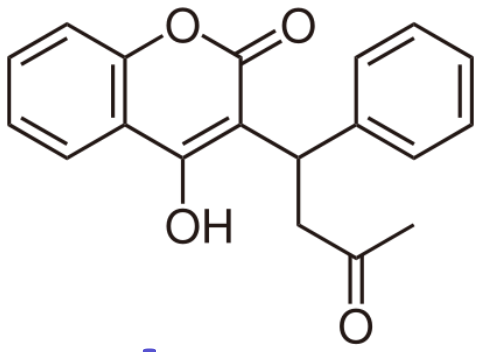
Pre-Clinical Implementation Workup

- Overview
- NYS CLIA & Decision Table
- Recommendations
- CLIPMERGE CDS Development
- PGx Implementation Group Approval

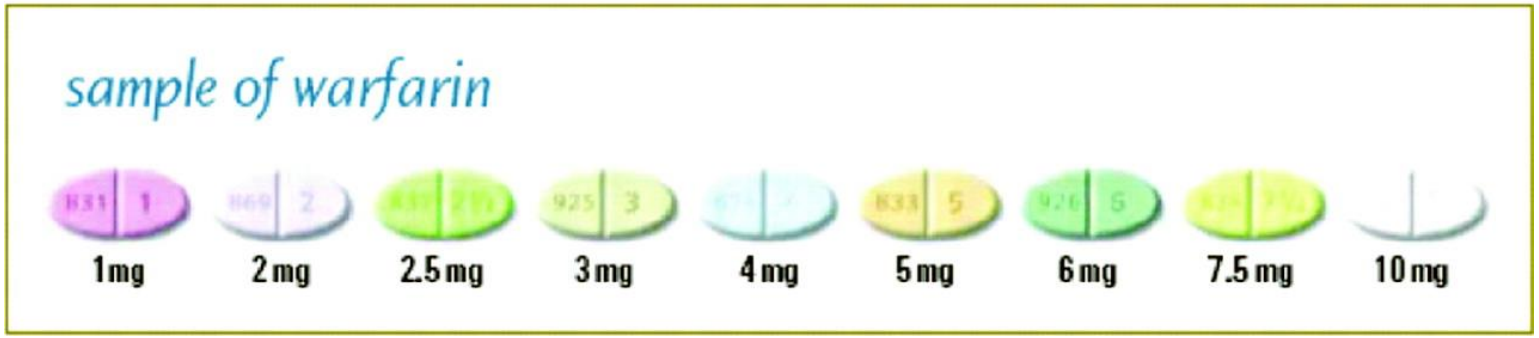
Post Implementation Evaluation

Feedback, continued review & revision

- Clopidogrel
- Simvastatin
- Warfarin
- Codeine
- Tramadol
- Nortriptyline
- SSRIs – Citalopram, Escitalopram, Sertraline, Paroxetine
- Phenytoin
- Proton pump inhibitors
- Amitriptyline, Imipramine, aripiprazole, clozapine, etc.
- Clobazam
- Azathioprine, Mercaptopurine
- Ondansetron
- Carbamazepine



Warfarin Pharmacogenetics



Warfarin Pharmacogenetics: Background

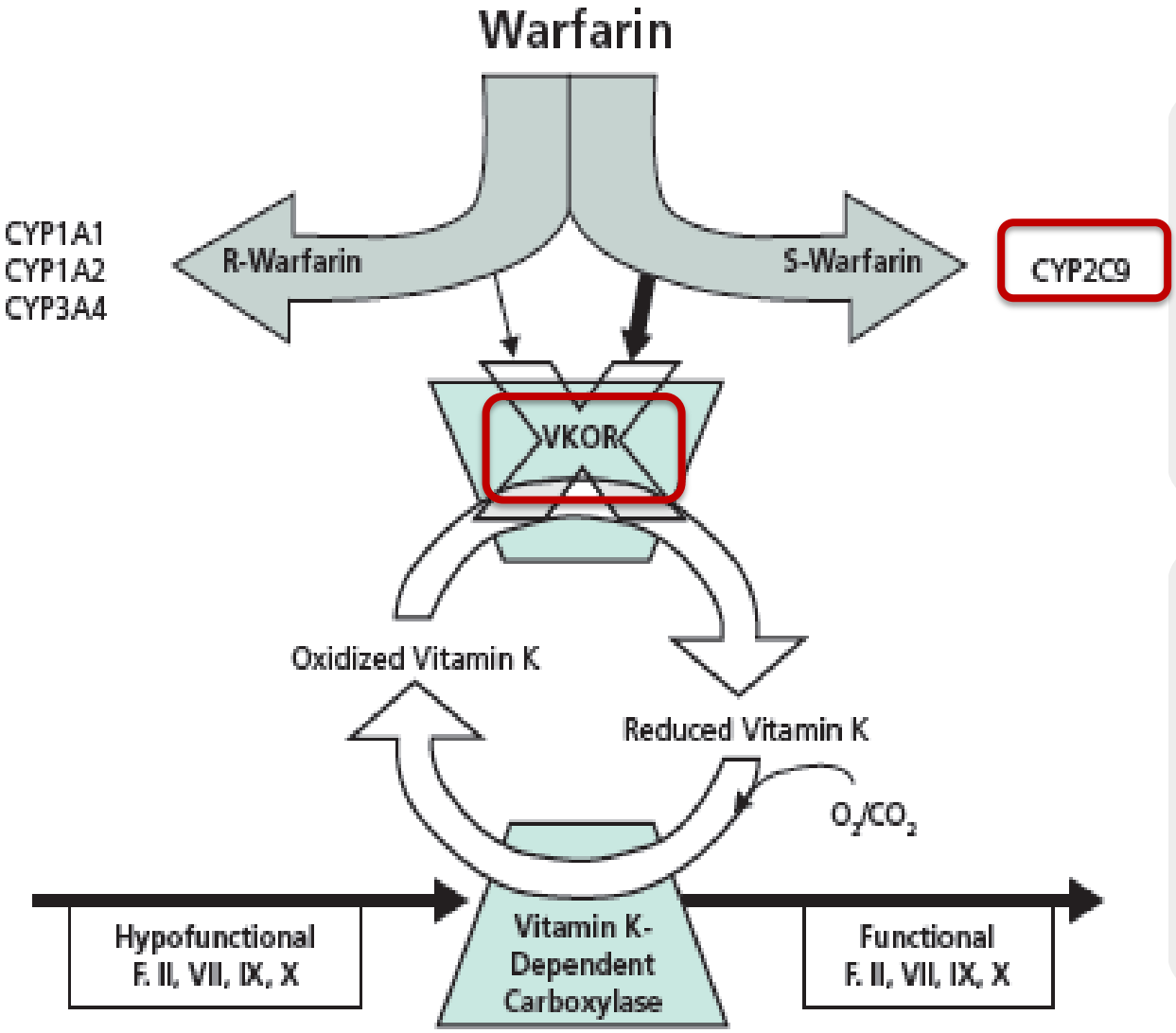
- **Widely used oral anticoagulant for prevention of thrombosis and embolism.**
  - **AF, DVT, PE, MV**

- **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)**

Pharmacogenomics of Warfarin



CYP2C9

Variant alleles (or SNPs) associated with **increased sensitivity** to Warfarin

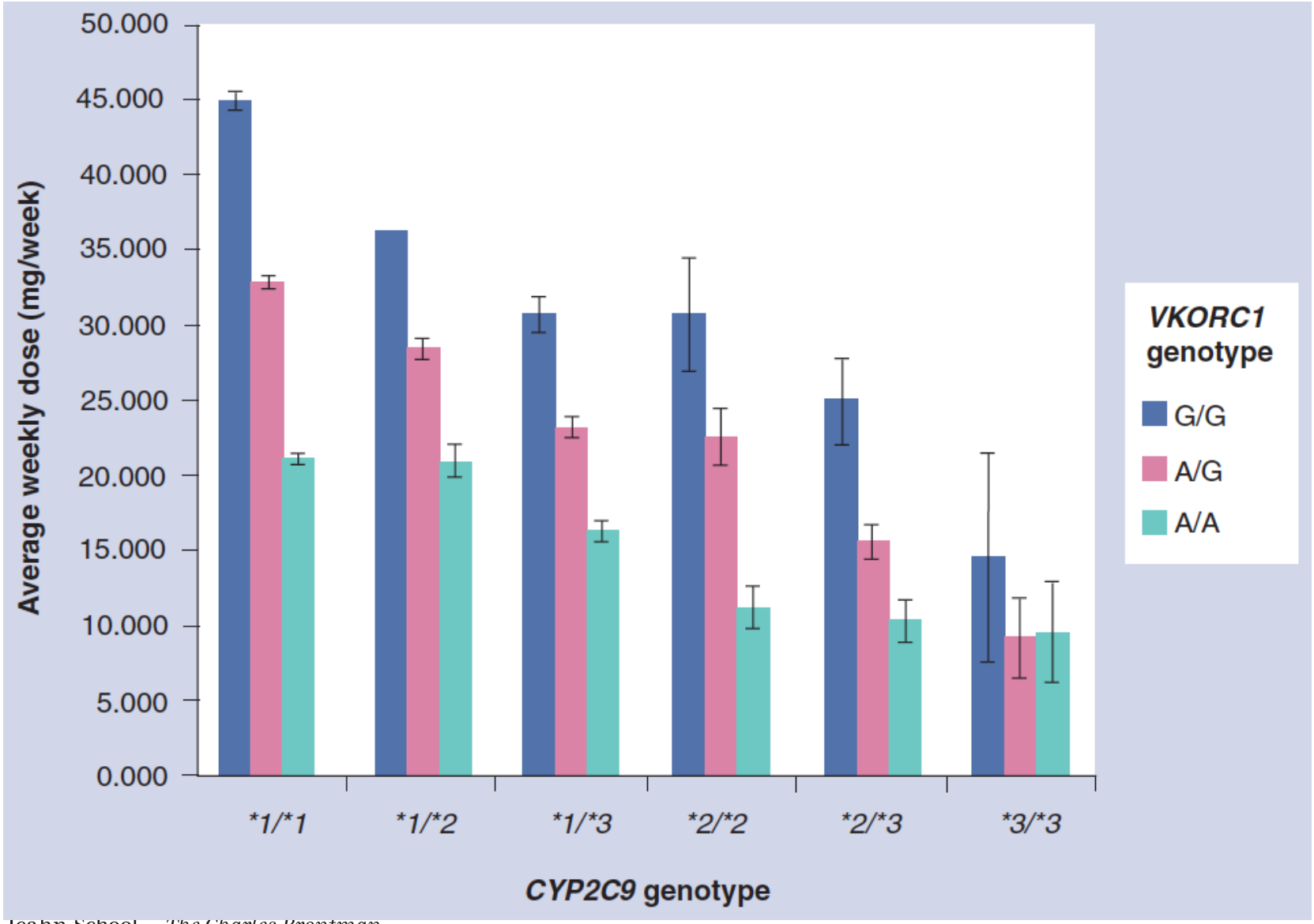
- CYP2C9 *1 – normal metabolization
- CYP2C9 *2/*3 –reduced metabolization

VKORC1

Variant allele of *VKORC1* gene (-1639G>A) associated with **lower dose requirement**

- G/G – normal dose
- G/A – intermediate dose
- A/A – low dose

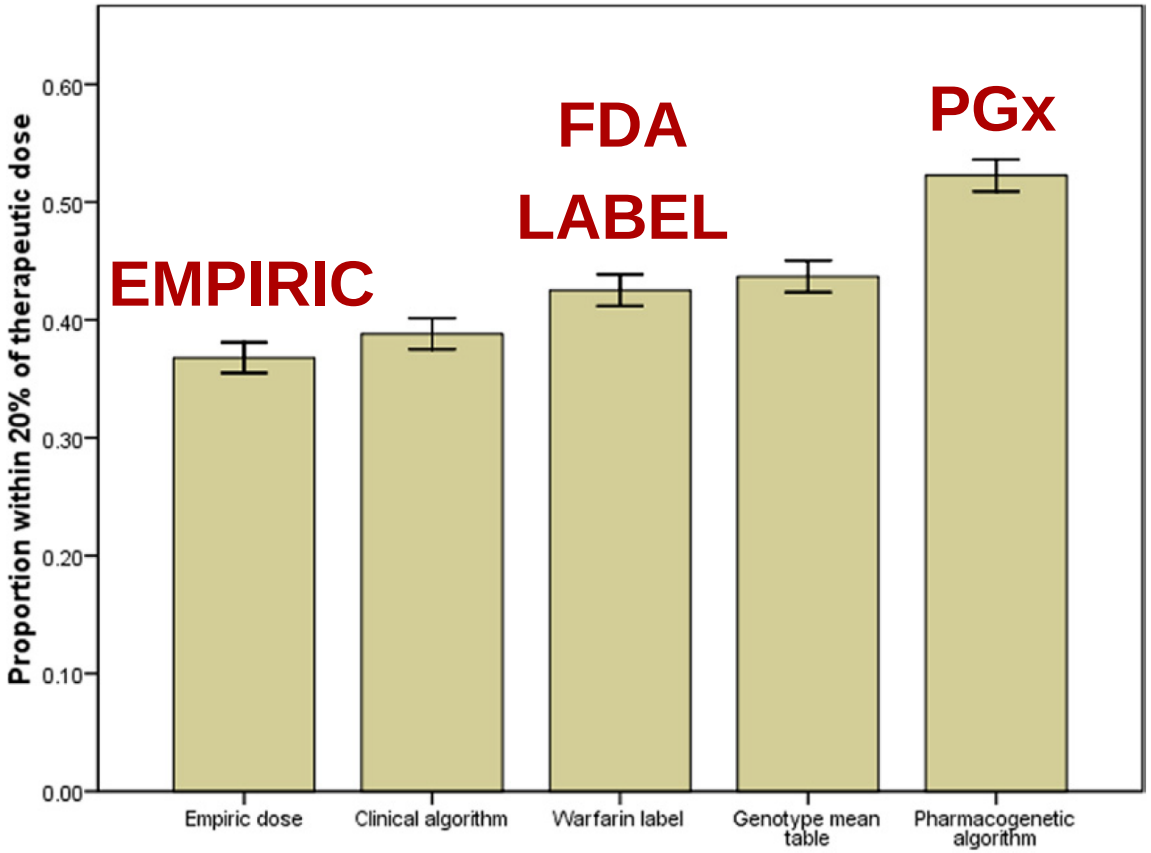
Warfarin Pharmacogenetics: Background



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.

Warfarin Pharmacogenetics: Trials

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

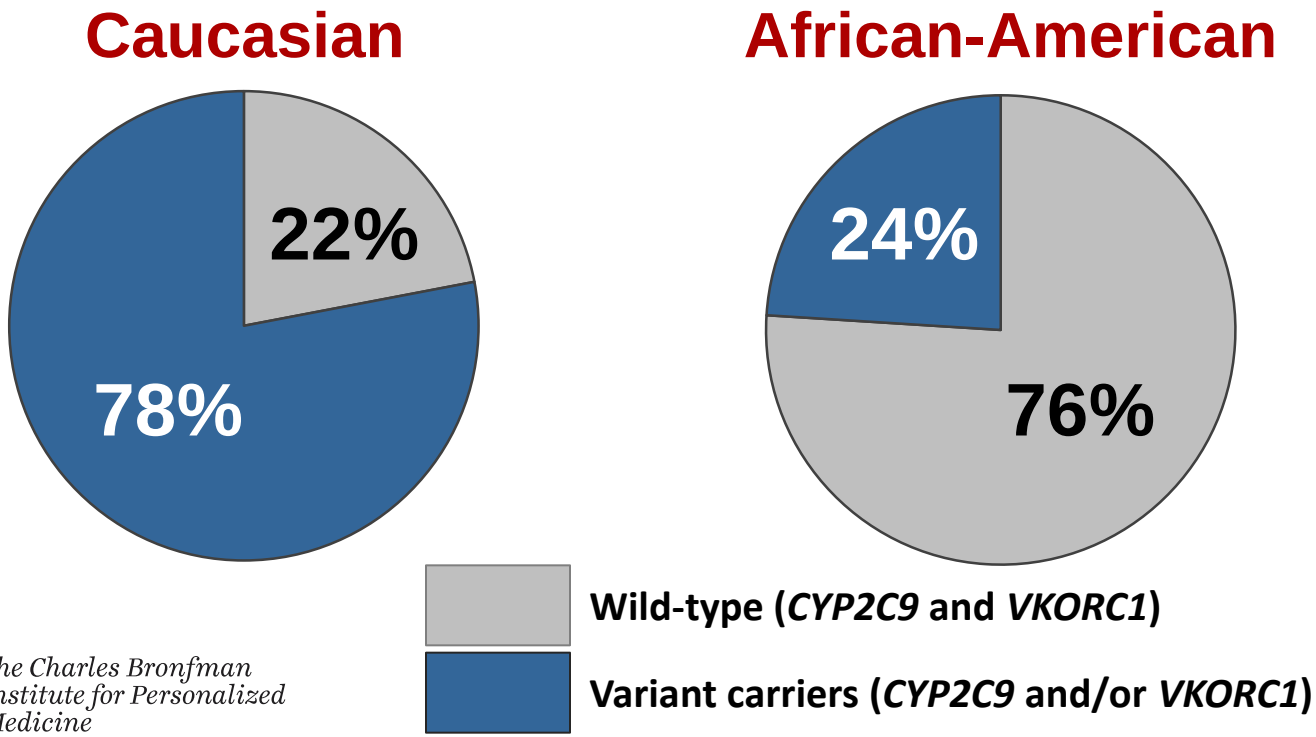
WPGx Trial	Year	Design	n	Comparison Arm	Primary End point	Result
CoumaGen	**2007**	**RCT**	206	**Standard dosing**	Out of range (OOR) INRs	**1. PGx more accurate** **2. No difference in OOR INR**
Medco-Mayo	**2010**	**CE**	896/ 2688	**Standard dosing** (concurrent+historical)	Incident event rate	**Hospitalizations: 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:**



Icahn School of Medicine at Mount Sinai
The Charles Bronfman Institute for Personalized Medicine

Scott SA, et al. Pharmacogenomics, 2010.

Warfarin PGx: African Ancestry Variants

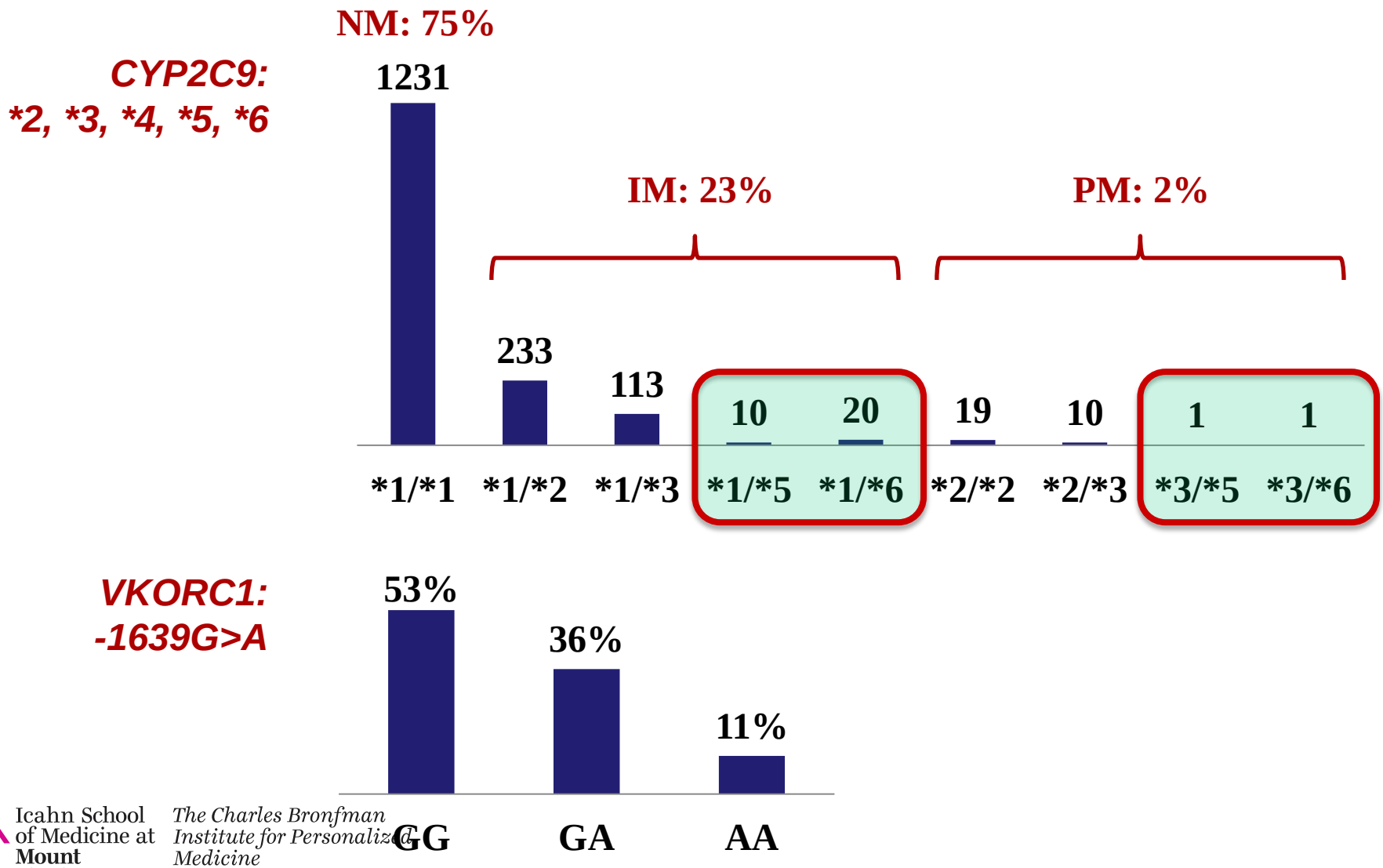
- ***DISCOVERY:*** **Novel variants in the African-American population (IWPC-GWAS).**
  - ***CYP2C*** **region: rs12777823 ($p=0.5x10^{-12}$); AA MAF: 25%**
  - **Explains ~5% of dosing variability in AA population.**
  - ***Perera MA, et al. Lancet, 2013.***

- ***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*

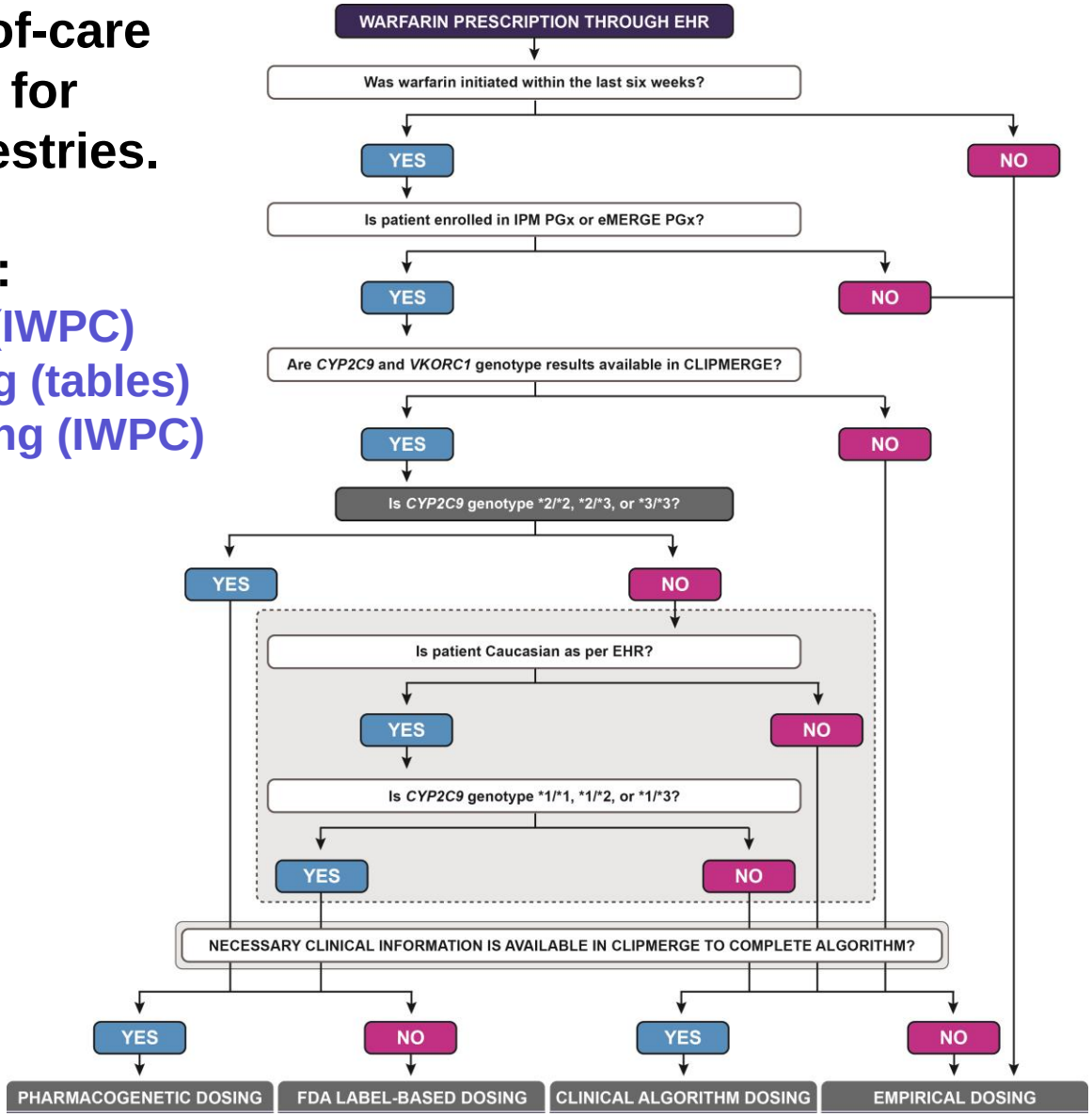
- Mount Sinai IPM PGx / eMERGE PGx Cohort (n=1641):



Warfarin PGx: Implementation Strategy

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

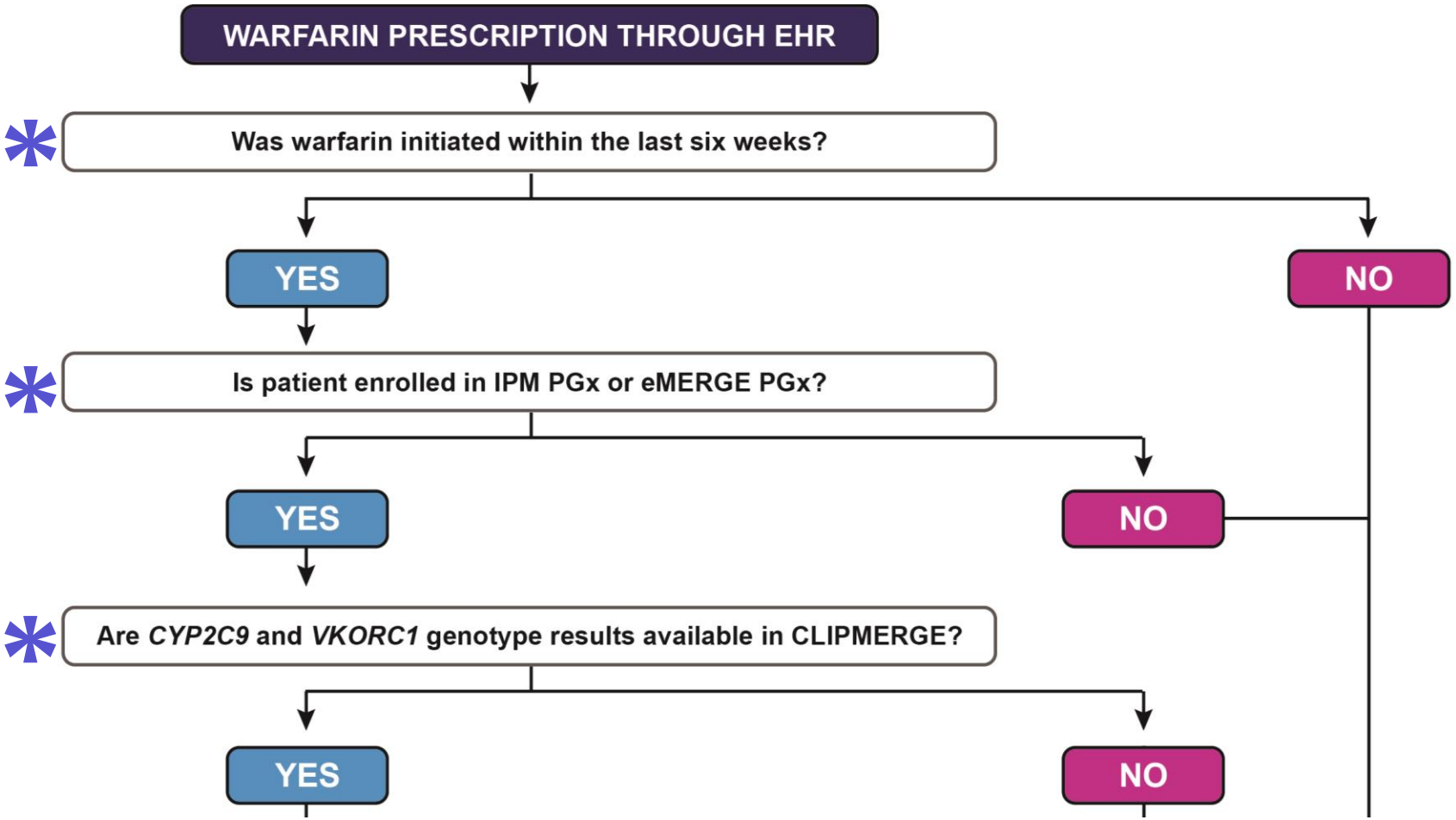
- **Four possible outcomes:**
  1. **PGx algorithm dosing (IWPC)**
  2. **FDA label-based dosing (tables)**
  3. **Clinical algorithm dosing (IWPC)**
  4. **Empiric dosing**



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

WARFARIN PGx: IMPLEMENTATION STRATEGY

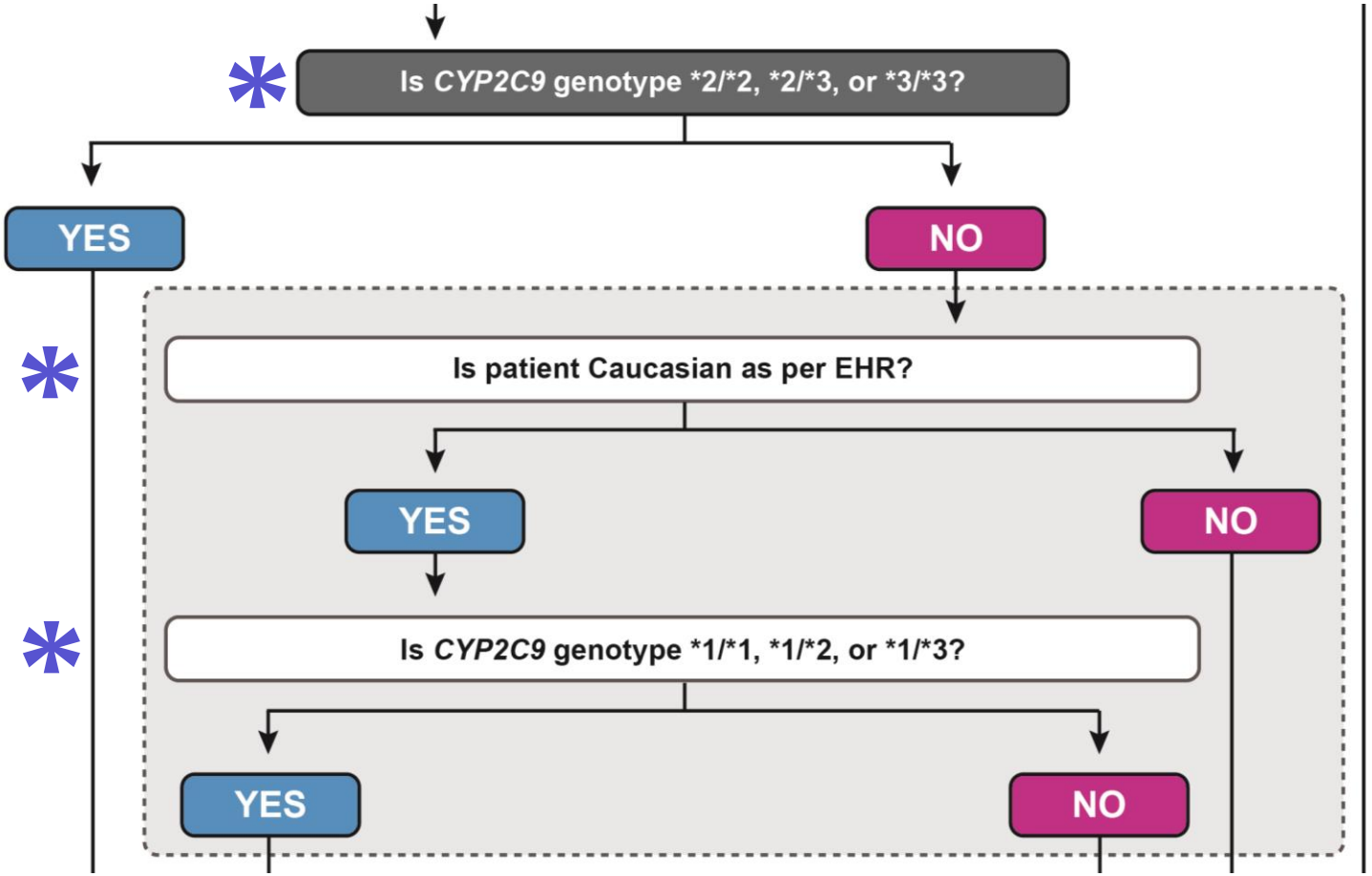
- ***Stage 1:***



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

Warfarin PGx: Implementation Strategy

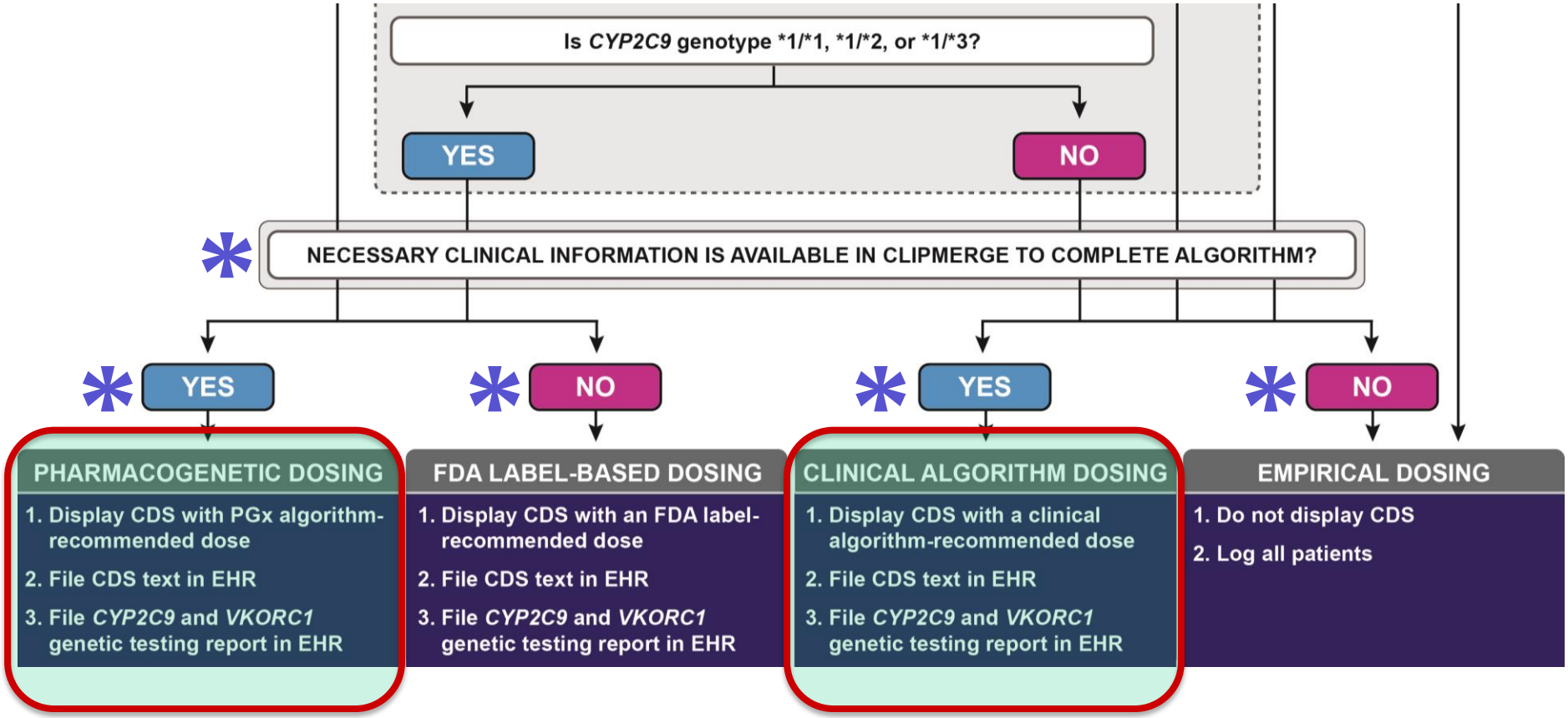
- ***Stage 2:***



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

Warfarin PGx: Implementation Strategy

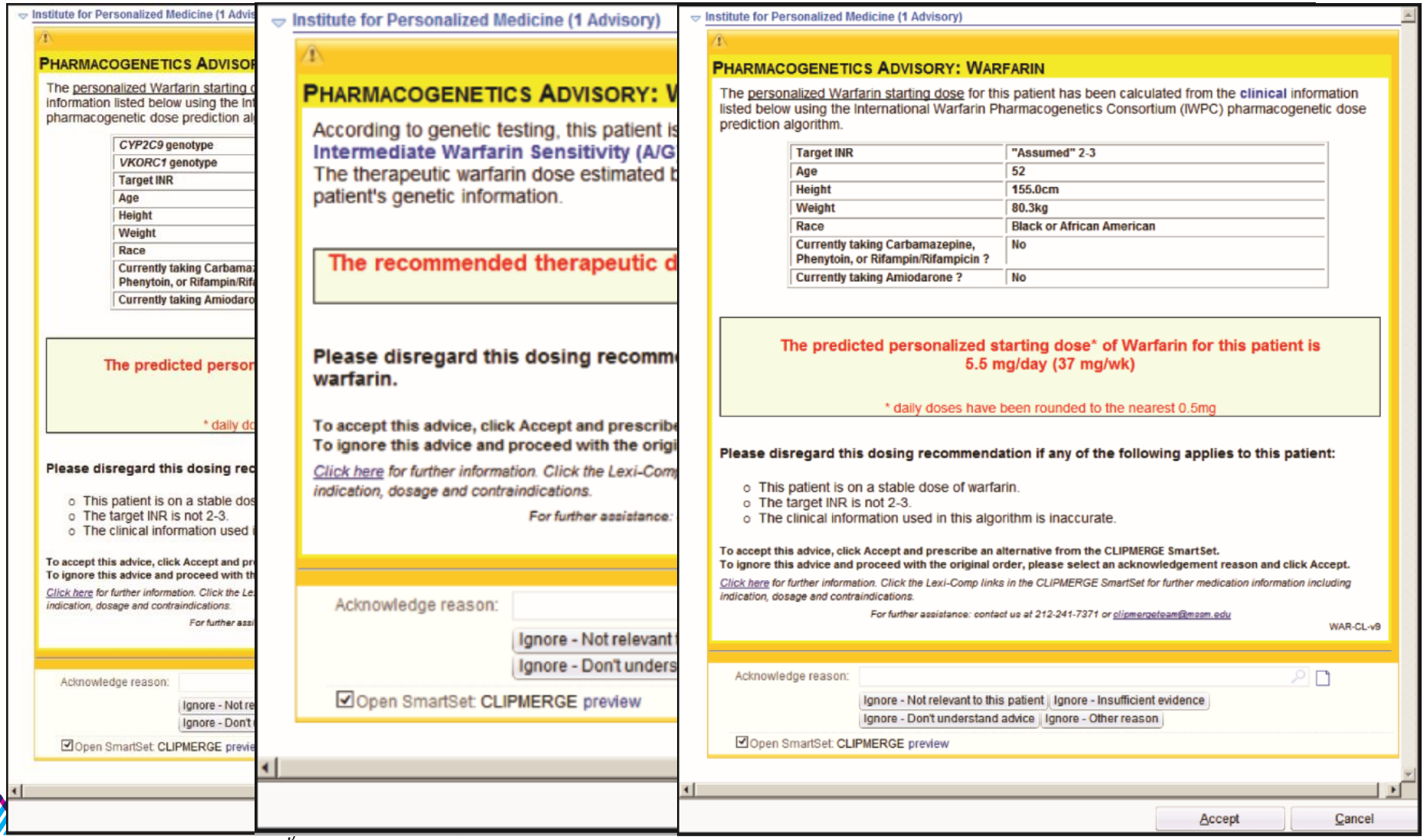
- ***Stage 3:***



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

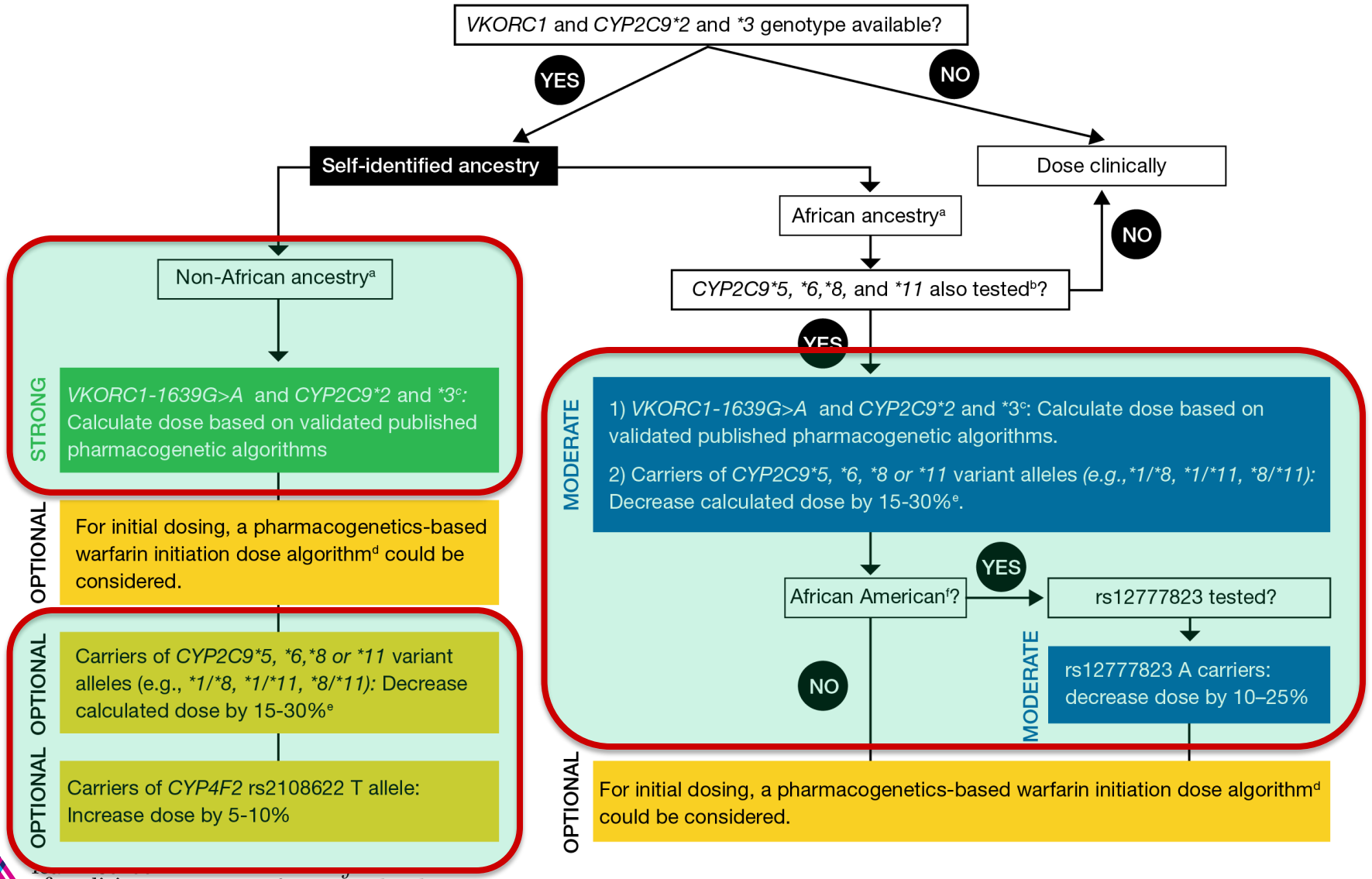
Warfarin PGx: Point-Of-Care CDS

- **Clinical Decision Support:**



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

Warfarin PGx: ISMMS and CPIC 2017



of Medicine at Mount Sinai

Institute for Personalized Medicine

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

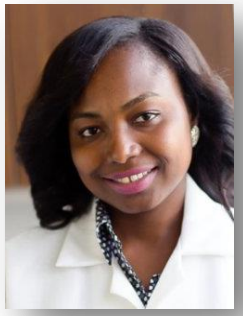
Lessons Learned and Future Directions

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

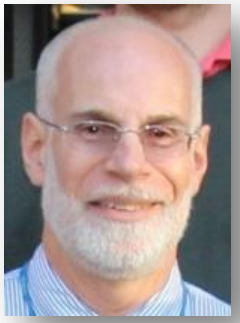
2. **Ancestry informed algorithm-based point-of-care warfarin dosing is accepted by majority of exposed providers.**
   - **Enabled more accurate prescribing than empirical dosing.**

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.**

Our Team – IPM PGx Program



Aniwaa Owusu Obeng
Clinical Pharmacogenomics Coordinator



Steve Ellis
IT - CLIPMERGE

Stuart Scott
Clinical and Laboratory Genetics

Tom Kaszemacher
IT - CLIPMERGE

Acknowledgements

IPM:
Erwin Bottinger, MD
Judy Cho, MD
Stuart Scott, PhD
Steve Ellis
Tom Kaszemacher
Noura Abul-Husn, MD, PhD
Omri Gottesman, MD
Rajiv Nadukuru
Vaneet Lotay
Amanda Merkelson
Ana Mejia
Bernadette Liggayu
Patrick Shanley

GGS and Genome Institute:
Robert J. Desnick, PhD, MD
Eric E. Schadt, PhD
Inga Peter, PhD
Yao Yang, PhD
Mariana Botton, PhD

FPA and IMA:
Aida Vega, MD
Eva Waite, MD

MGTL:
Lisa Edelmann, PhD
Ruth Kornreich, PhD
Rajasekar R-Chakravarthi

Epic Team
Kristin Myers
Joseph Kannry, MD
Kevin Delaney
Aditi Vakil
Riya Deepak
Elizabeth Kerch
Noel Howard
Paul Francaviglia
Karen Trommer
Jason Martin
Daniel Edonyabo
Daniel Katselnik

NIH / NIGMS (PGRN)

Questions?

Translational Initiatives in Pharmacogenomics

Icahn School of Medicine at Mount Sinai

Email: aniwaa.owusu-obeng@mssm.edu

Translational Pharmacogenomics at Mount Sinai and Beyond

Aniwaa Owusu Obeng, PharmD

Assistant Professor
The Charles Bronfman Institute for Personalized Medicine
Department of Medicine
Department of Genetics and Genomic Sciences
Icahn School of Medicine at Mount Sinai

Clinical Pharmacogenomics Coordinator
The Mount Sinai Hospital
Pharmacy Department