



VANDERBILT UNIVERSITY
MEDICAL CENTER

PGx Implementation Research Programs at Vanderbilt

Josh Denny, MD MS

Professor of Biomedical Informatics and Medicine

Director, Center for Precision Phenomics

Vanderbilt University Medical Center

5/2/17

The vision



"Here's my sequence..."

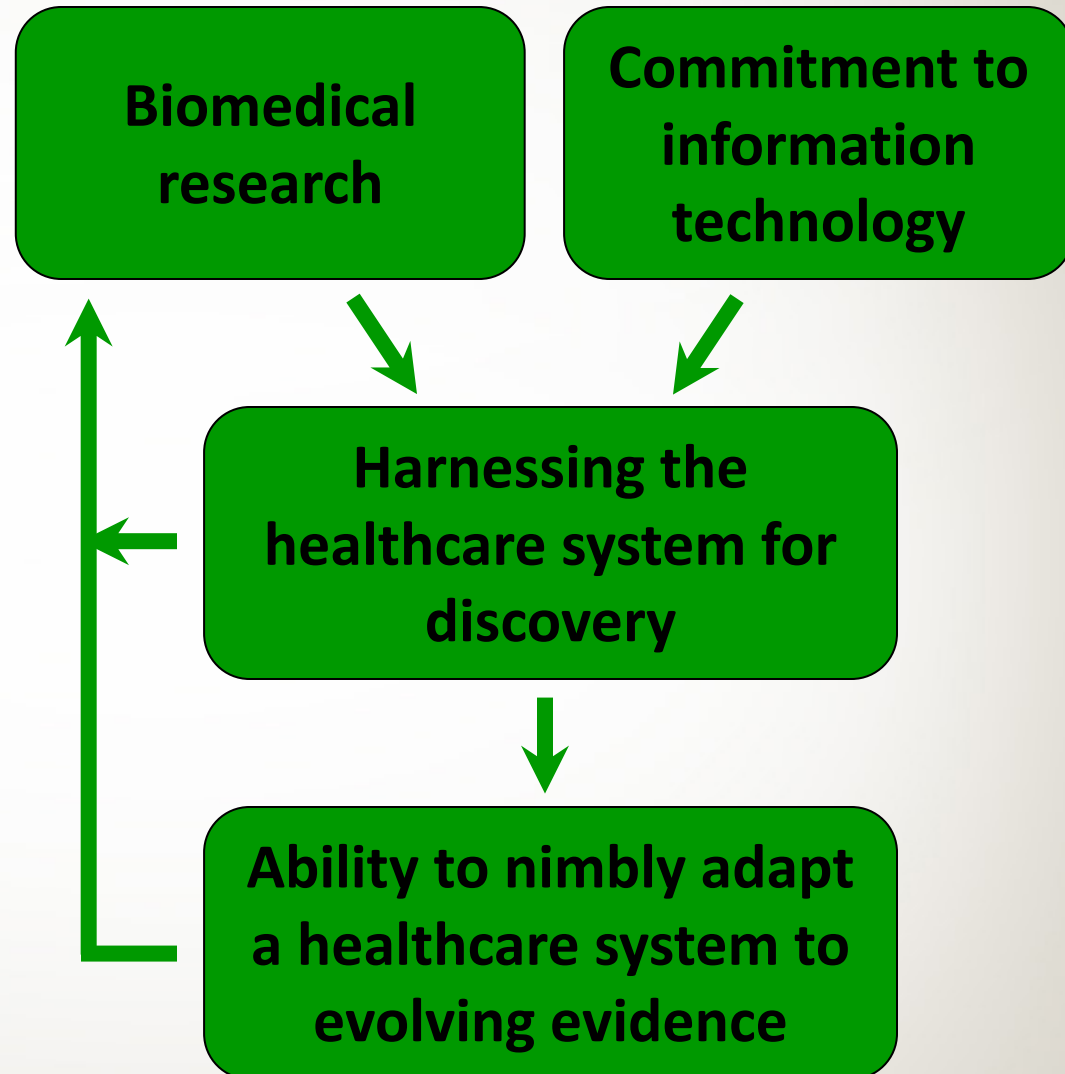
New Yorker, 2000

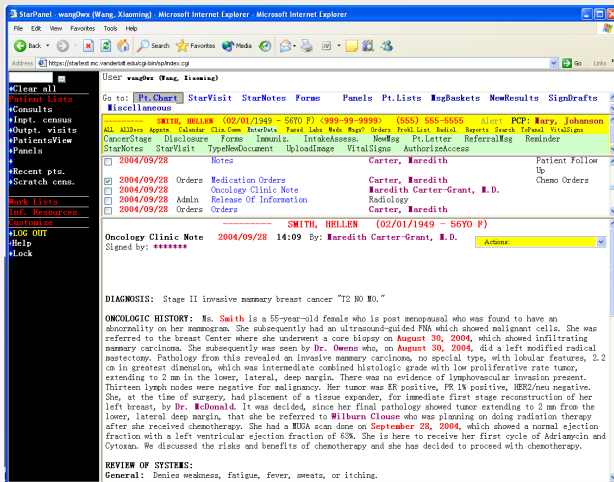
How will this vision actually start to be tested and become reality?



"Here's my sequence..."

New Yorker, 2000





EHR feeds both discovery and implementation

Discovery



VanderbiltBioVU
De-identified DNA repository
>235k samples

Implementation

PREDICT, IGNITE, (eMERGE)

- CLIA genomics lab
- Integrated decision support for genomics
- Genomic databases
- Track outcomes

Discovery: Resources for EMR-based research at Vanderbilt

The Synthetic Derivative

A de-identified and continuously-updated image of the EMR: ~2.5 million subjects

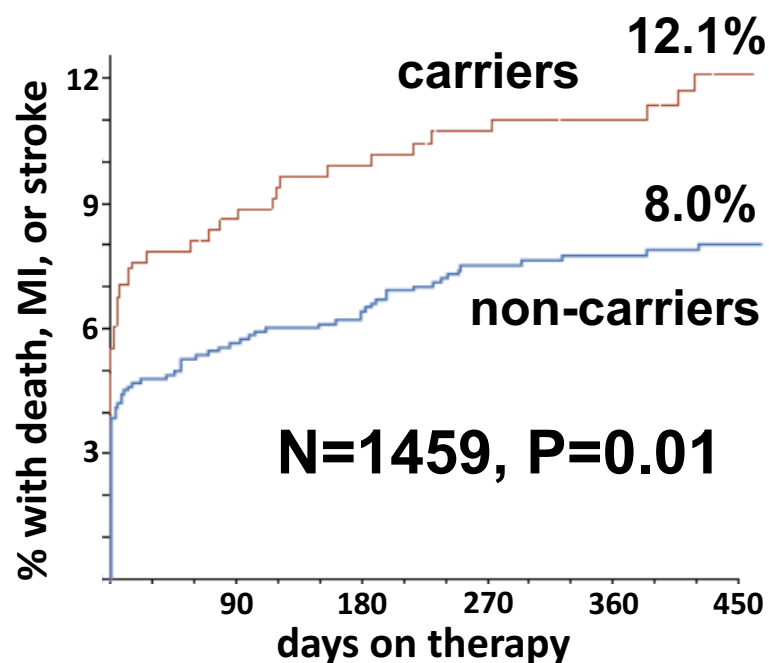
BioVU

Subjects with DNA: ~235k

EHRs for drug response:

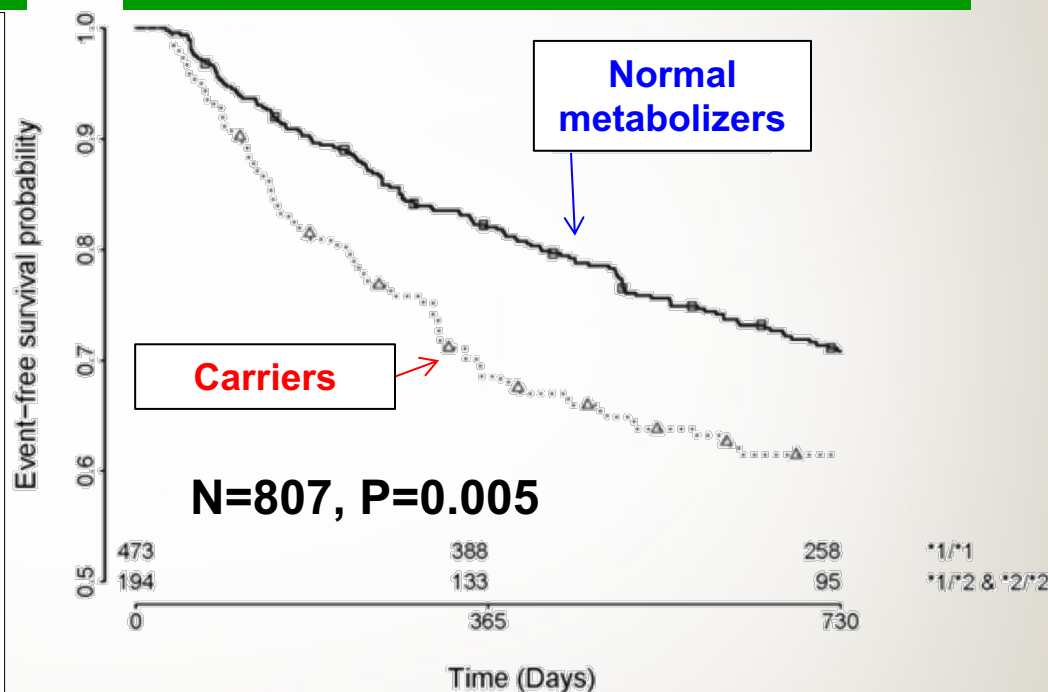
Clopidogrel adverse events associated with *CYP2C19* status

From clinical trials



Mega et al., 2009

From the EHR



Delaney et al. *Clin Pharm Ther.* 2012

How do we routinize PGx implementation?

PREDICT: Pharmacogenomic Resource for Enhanced Decisions
In Care and Treatment



"Here's my sequence..."



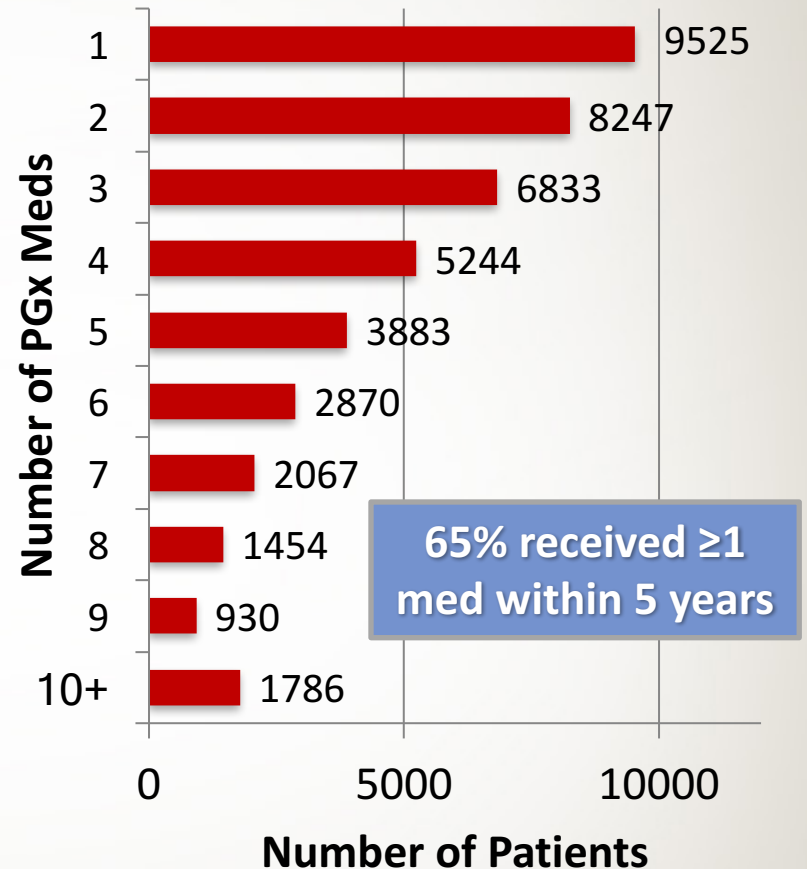
...the right drug, the
first time.

A Case for Prospective Genotyping:

identifying a **high risk** group

52,942 Vanderbilt “Medical Home” patients followed for up to 5 years....

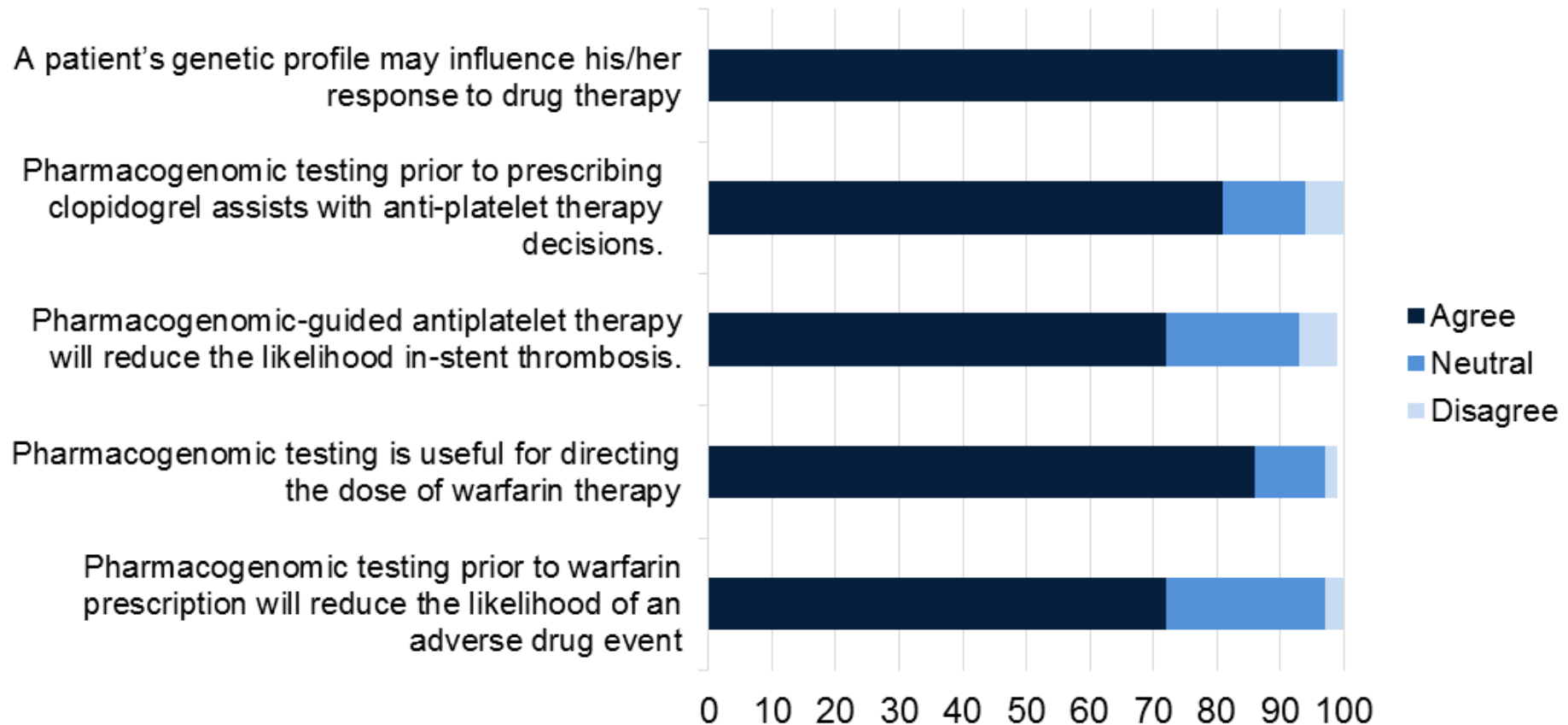
How many patients received drug(s) that have a recognized pharmacogenetic story?



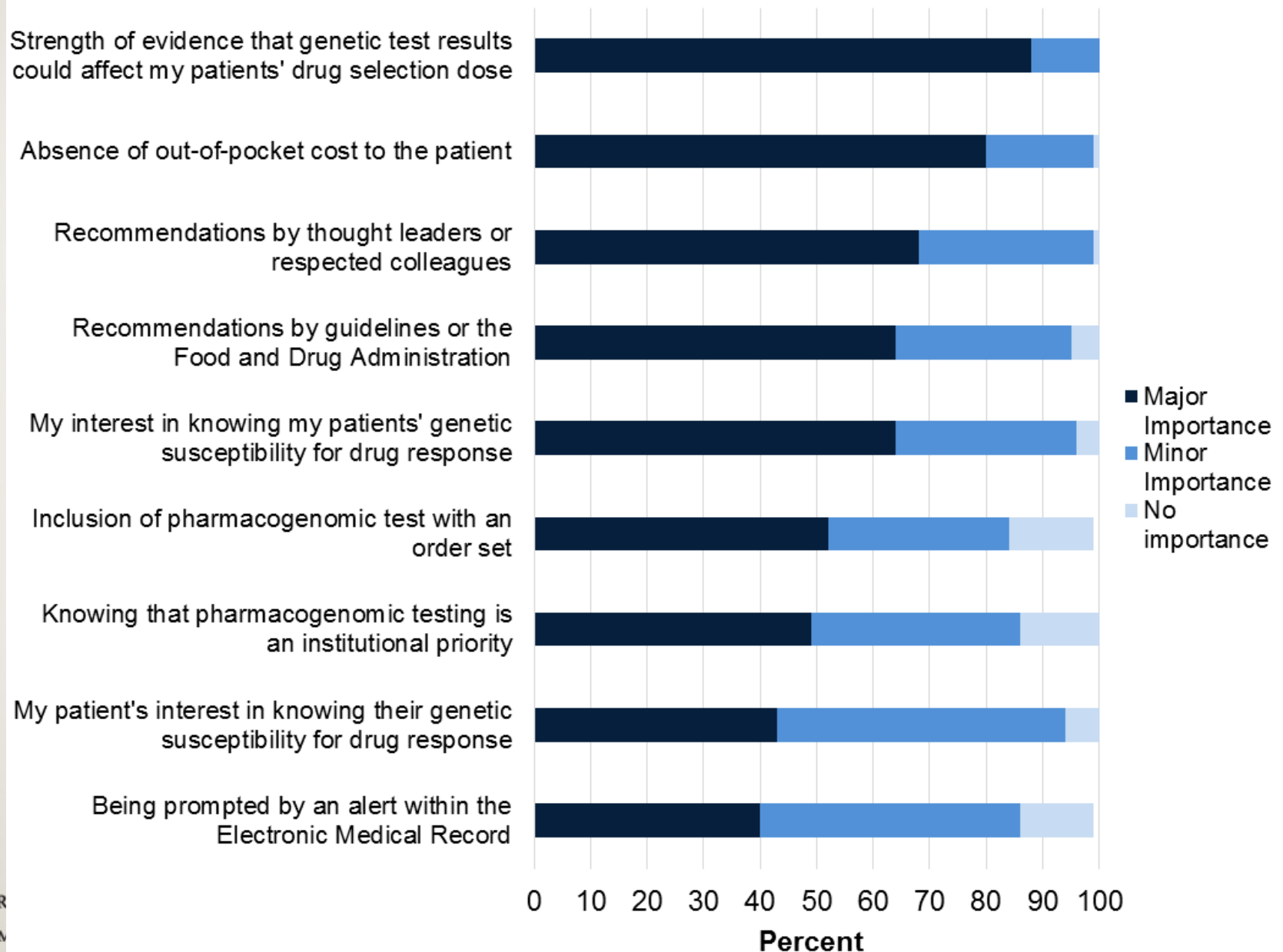
Estimated number of severe adverse events mitigated : 383
(~12-18 events for the average PCP over 5 years)

Provider Opinions

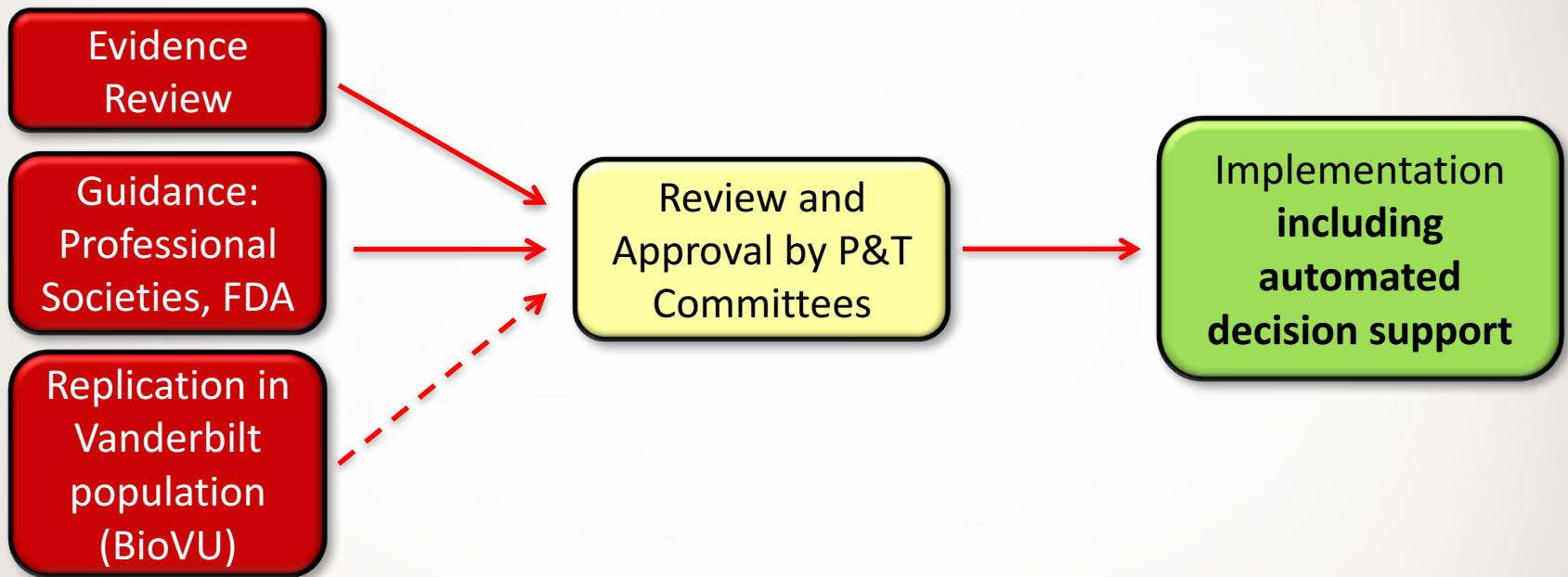
Surveyed 121 VU providers encountering PGx prescribing; 80 responded (66% response rate)



Factors influencing ordering of PGx tests



Selection of PREDICT Drug-Gene Interactions



Genetic results visible passively in EHR

Firefox

StarPanel - Roden, Dan M. (rod...)

User rodewui (Roden, Dan M.) docs4u results4u: 60 SignDrafts Messages:1 (RodenD-MD) Unsaved Work: 1

Pt.Chart ADVANCE StNotes Forms OPOC Quill Rx ProvCom Panels Pt.Lists TaskList Ms Misc.

code st

AllDocuments Apptm. Calend. EnterData Faxed Flows FastLabs Labs Meds Msgs? Reminders?

VitalSigns DCINoDoc

CancerStage ClinicIntake Disclosure Forms Favorites Immuniz. NewMsg Pt.Letter Provider.Letter Provider.Letter Wizard ReferralMsg

Drug Genome Interactions in the Patient Summary

General Information: (12/05/12 09:05, Teresa)

PCP: [REDACTED]

Card: [REDACTED]

Arrhythmia/Device: Dr. Dan Roden, VUMC

Structured Problems: (12/05/12 09:05, Teresa)

Coronary artery disease [.]

Aortic valve stenosis [-severe]

Congestive heart failure [.]

Mitral valve regurgitation [.]

Chronic atrial fibrillation [.]

Hypertension [.]

Hyperlipidemia [.]

Gastroesophageal reflux disease [.]

9. Chronic Renal insufficiency

Paroxysmal ventricular tachycardia

s/p VTach cardiac arrest, 6/12/09

ICD Shock for VTach, 9/14/2010

Hx Blood Transfusion:

Anesthesia Difficulties:

Dental Hygiene:

Emergent #:

Significant Procedures: (12/05/12 09:05, Teresa)

Adverse and Allergic Drug Reactions: (02/21/13 12:25, [REDACTED])

Aldactone (rash)

Drug Genome Interactions: (01/05/12 13:03)

clopidogrel sensitivity: NORMAL METABOLIZER - gene: CYP2C19 - gene result: *1/*1

warfarin sensitivity: Hyper Responder - gene results: VKORC1 G/G; CYP2C9 *1/*3

simvastatin sensitivity: HIGH MYOPATHY RISK, MINOR ALLELE HOMOZYGOUS (C;C) - gene: SLCO1B1 - gene result: *5/*5

thiopurine sensitivity: INTERMEDIATE MYELOTXICITY RISK, MINOR ALLELE HETEROZYGOUS - gene: TPMT - gene result: *1/*3c

tacrolimus sensitivity: HYPO RESPONDER - gene: CYP3A5 - gene result: *1/*3

Note: Most genetic variants with therapeutic considerations demonstrate reproducibility of greater than 98%. Please visit www.mydruggenome.org for additional information.

Medications: [prepare to print](#) [print and give pt.](#) [Show Hx of medications](#) [Drug/Herb Interactions](#) (02/21/13 12:25, [REDACTED])

Simvastatin (zocor) 20 mg orally nightly

Quinapril (accupril) 40 mg orally daily

Zolpidem (ambien) 10mg orally daily

Carvedilol (coreg) 6.5 mg orally twice daily with meals

Furosemide (lasix) 20 mg 3 tablets orally daily

Digoxin (lanoxin) 0.125 mg 1/2 tablet orally daily

Warfarin (coumadin) 2 mg, 2 tablets on sun by mouth and 1 1/2 tablet on other days

Potassium (k-dur) 10meq 3 tablets orally daily

EBM resources

Clinical Decision Support within E-Prescribing

Drug-Genome Advisor

Intermediate Metabolizer - clopidogrel (Plavix) - Rare Risk Allele
Substitution recommended due to increased cardiovascular risks

If not otherwise contraindicated:

- ☐ Prescribe prasugrel (Effient) 10 mg daily

Prasugrel should not be given to patients:

- history of stroke or transient ischemic attack
- ≥ 75 years of age [Current patient age: 51]
- with body weight < 60 kg [Current patient weight: 59.0 kg as of 10/12/2012]

- ☐ Prescribe ticagrelor (Brilinta) 90 mg twice daily

Ticagrelor should not be given to patients:

- history of severe hepatic impairment
- intracranial bleed

- ☒ Continue with clopidogrel (Plavix) prescription

Primary override reason:

- ☐ Contraindicated for prasugrel or ticagrelor
- ☐ Potential side effects
- ☐ Provider/Patient opts for clopidogrel
- ☐ Cost

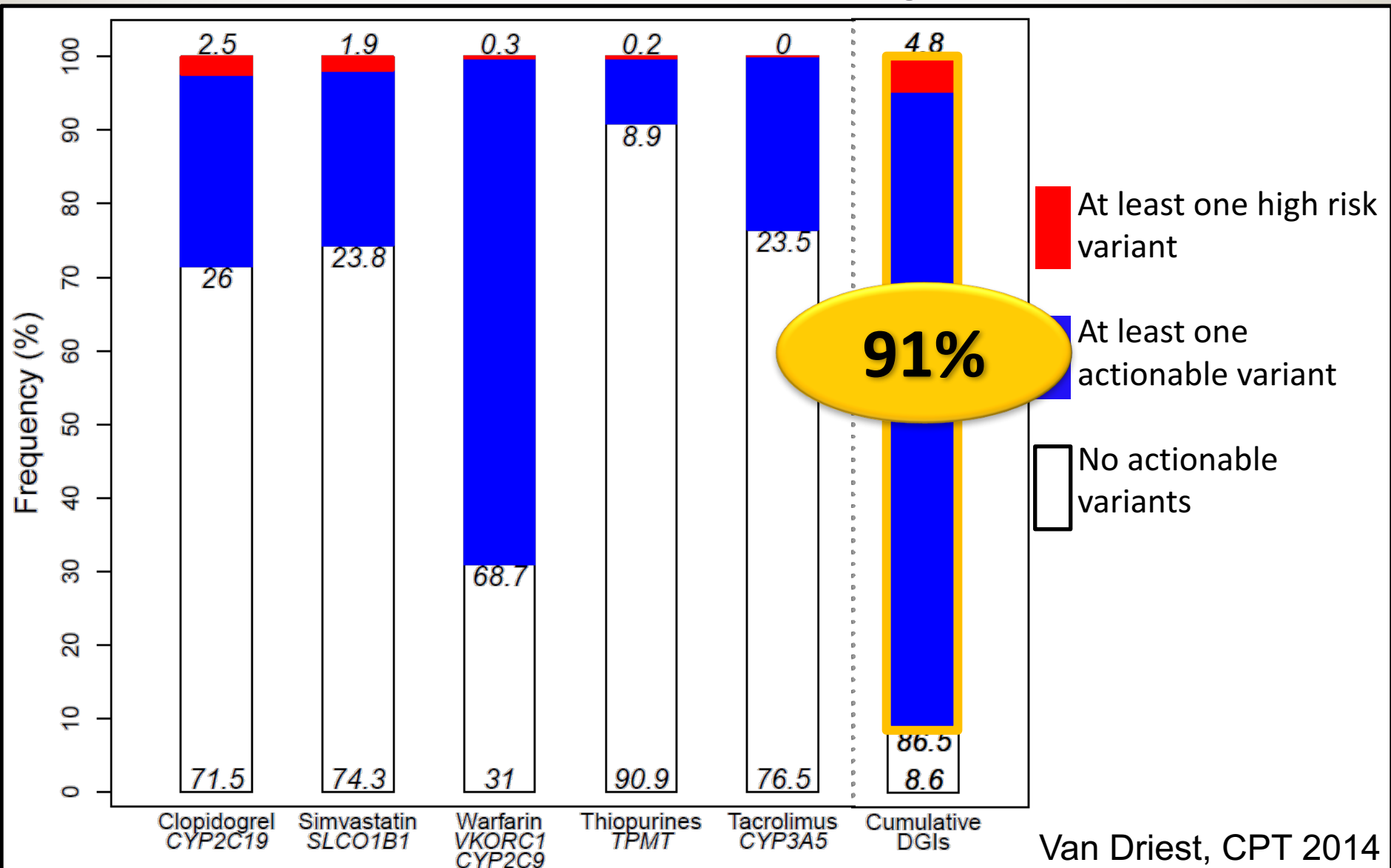
[Evidence Link](#)

This patient has been tested for CYP2C19 variants which has identified the presence of one copy of a rare risk allele which is associated with intermediate metabolism of clopidogrel. Intermediate metabolizers treated with clopidogrel at normal doses are associated with higher rates of stent thrombosis and other cardiovascular events. The Vanderbilt P&T Committee recommends that prasugrel or ticagrelor replace clopidogrel for poor metabolizers unless contraindicated. If not feasible, maintain standard dose of clopidogrel. The guidelines above were developed based on the outcome studies of patients who received a drug-eluting stent into a coronary artery. However, there is not a national consensus on drug/dose guidance particularly associated with the population possessing extremely rare genetic variants.

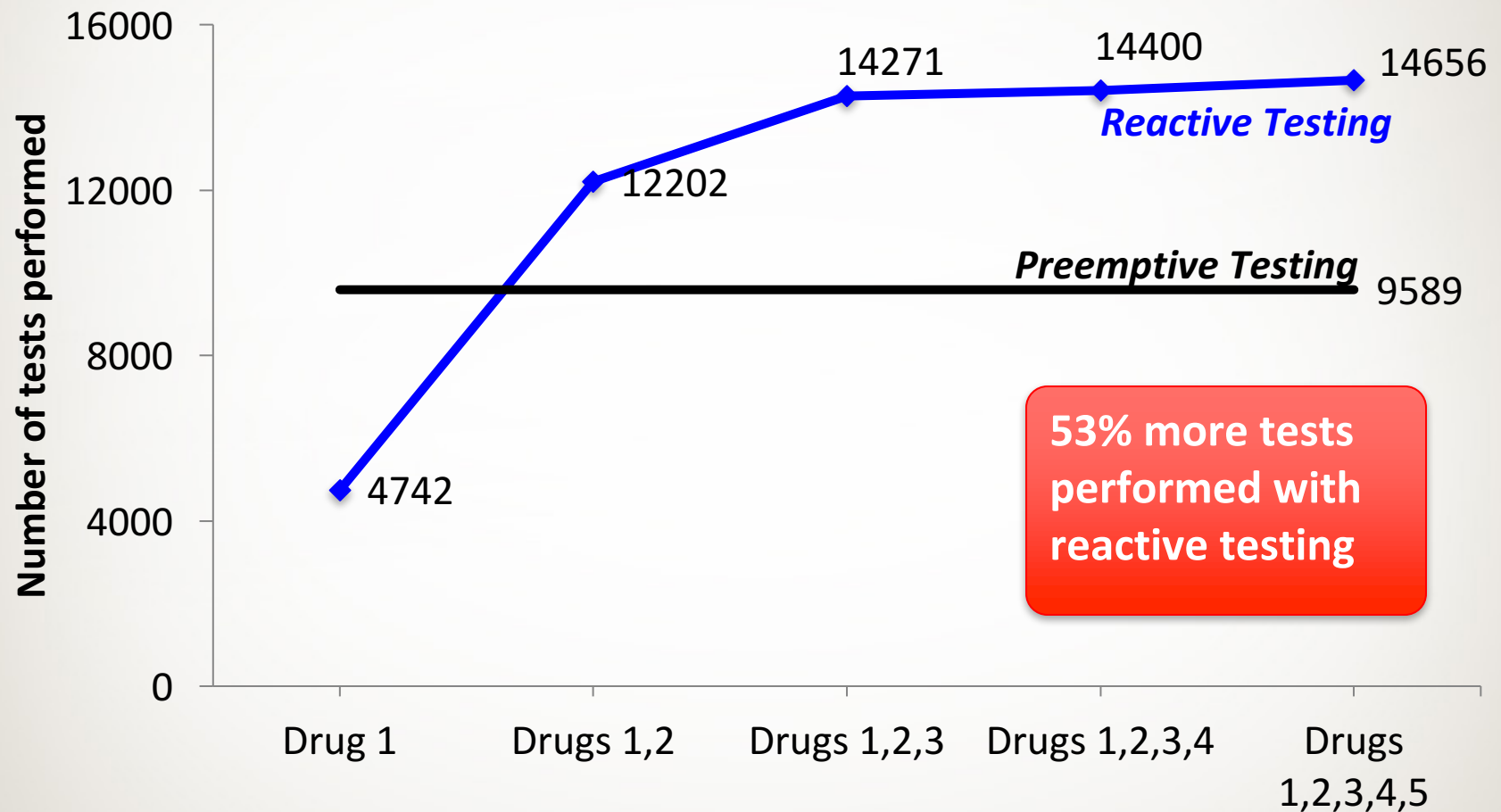
Continue

Cancel

Frequency of actionable genotypes in the first 10,000 PREDICT patients

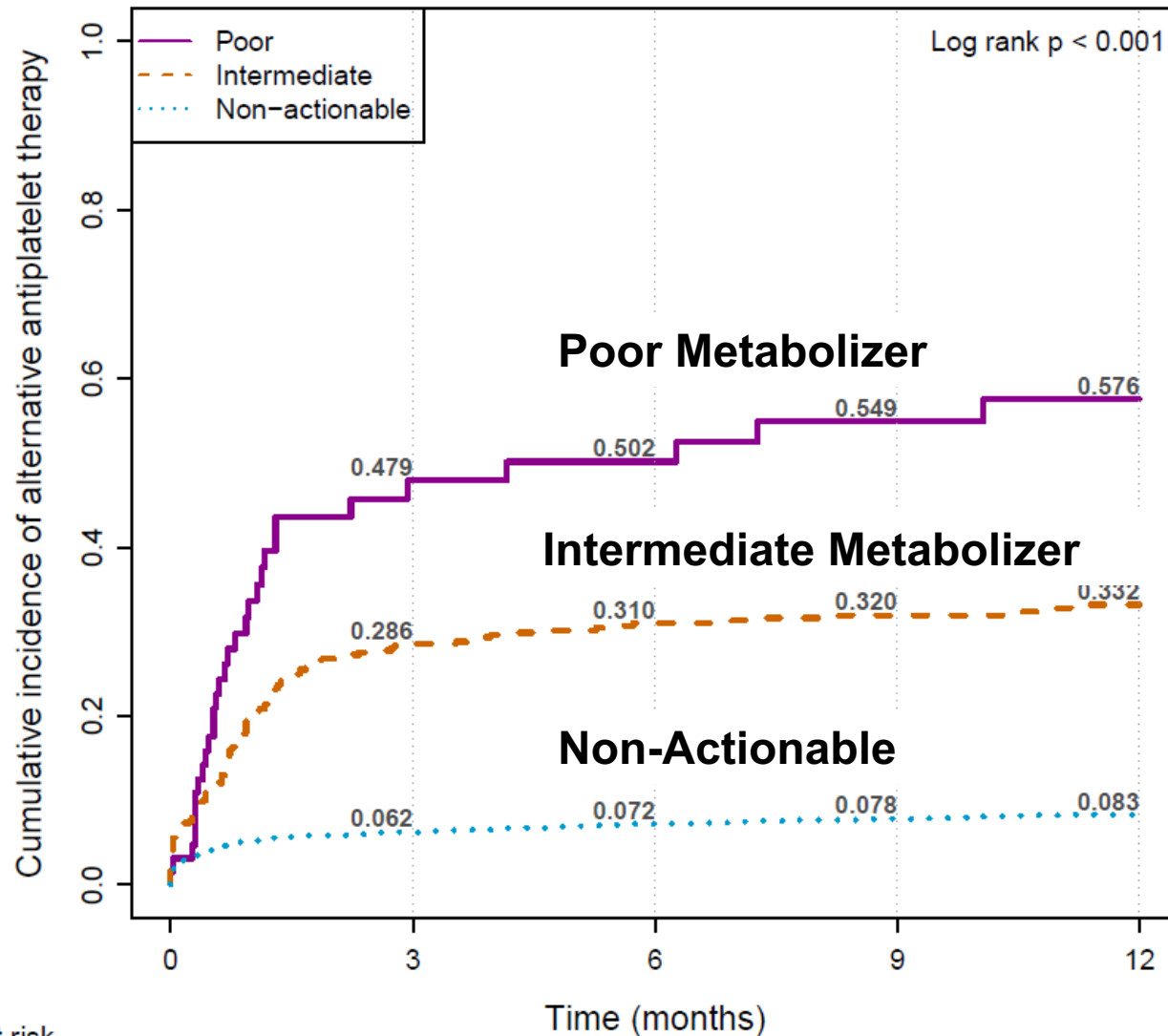


Multiplexed Genetics Testing can save money too



Do providers follow recommendations?

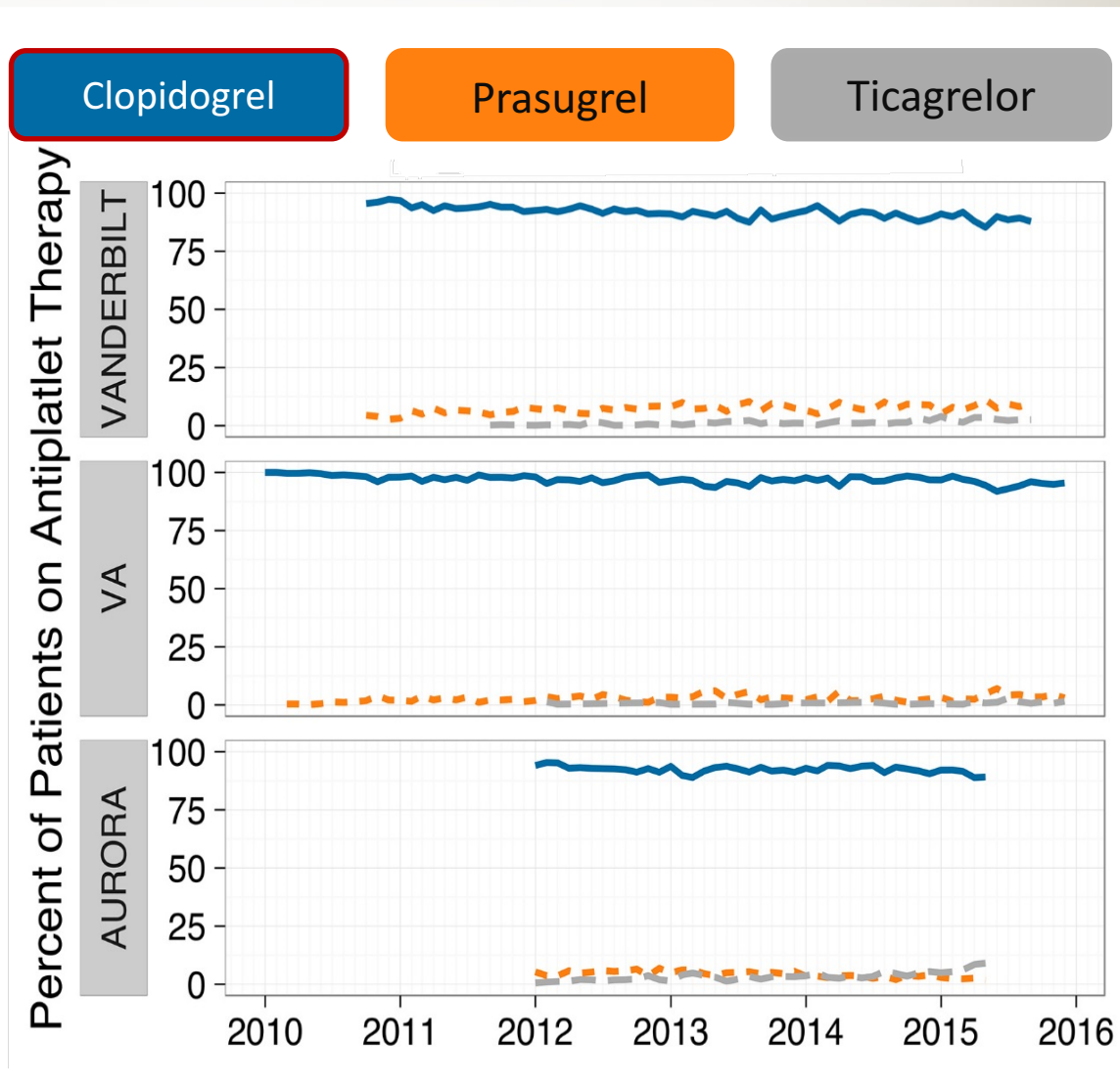
Genotype tailored therapy



Rate	Adjusted HR
58%	8.1 (5.4,12.1)
33%	5.0 (4.0,6.3)
8%	Ref

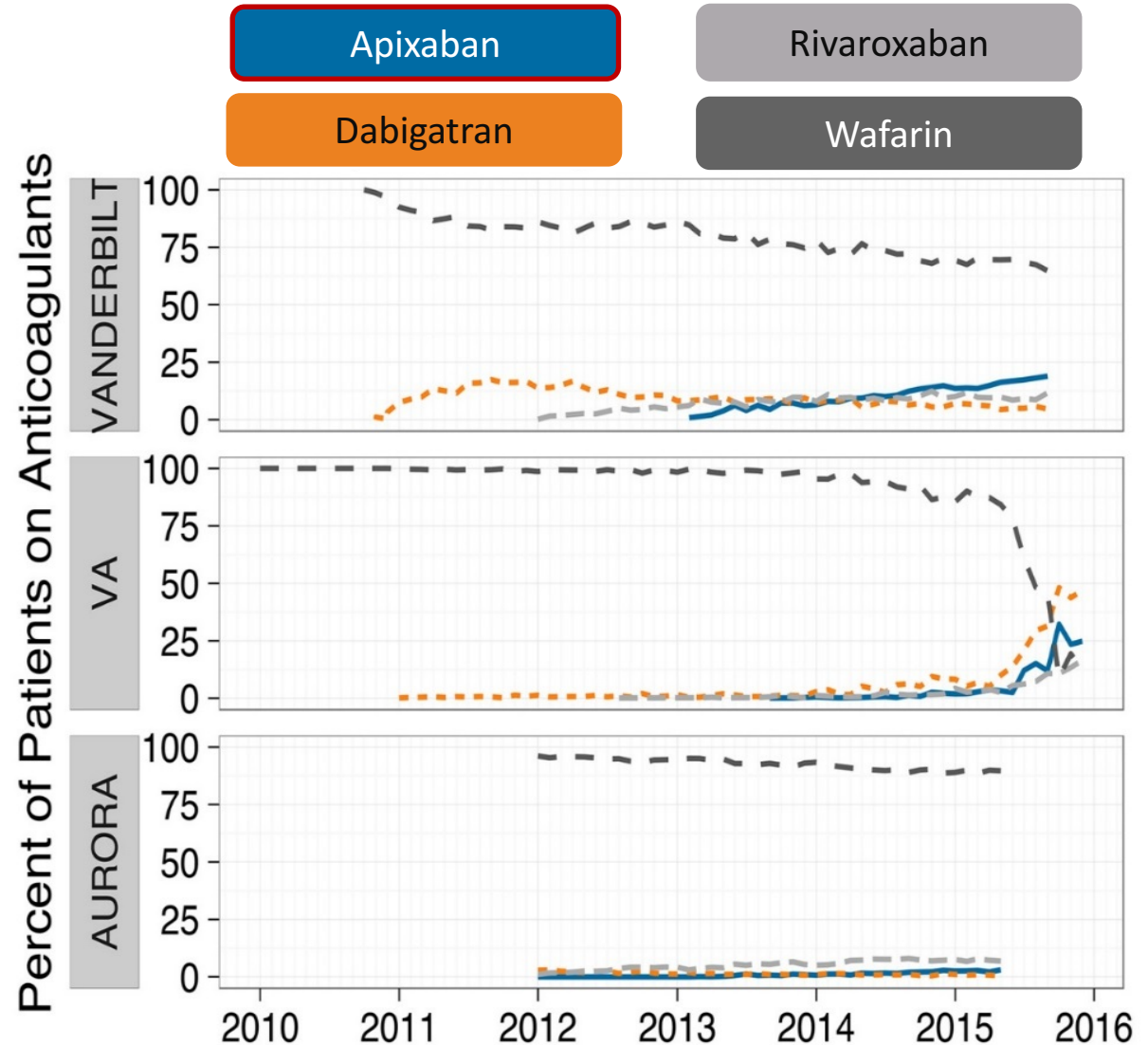
IGNITE CPIC Prescribing Study: Antiplatelet drugs

Clopidogrel remains
the most commonly
prescribed
antiplatelet drug

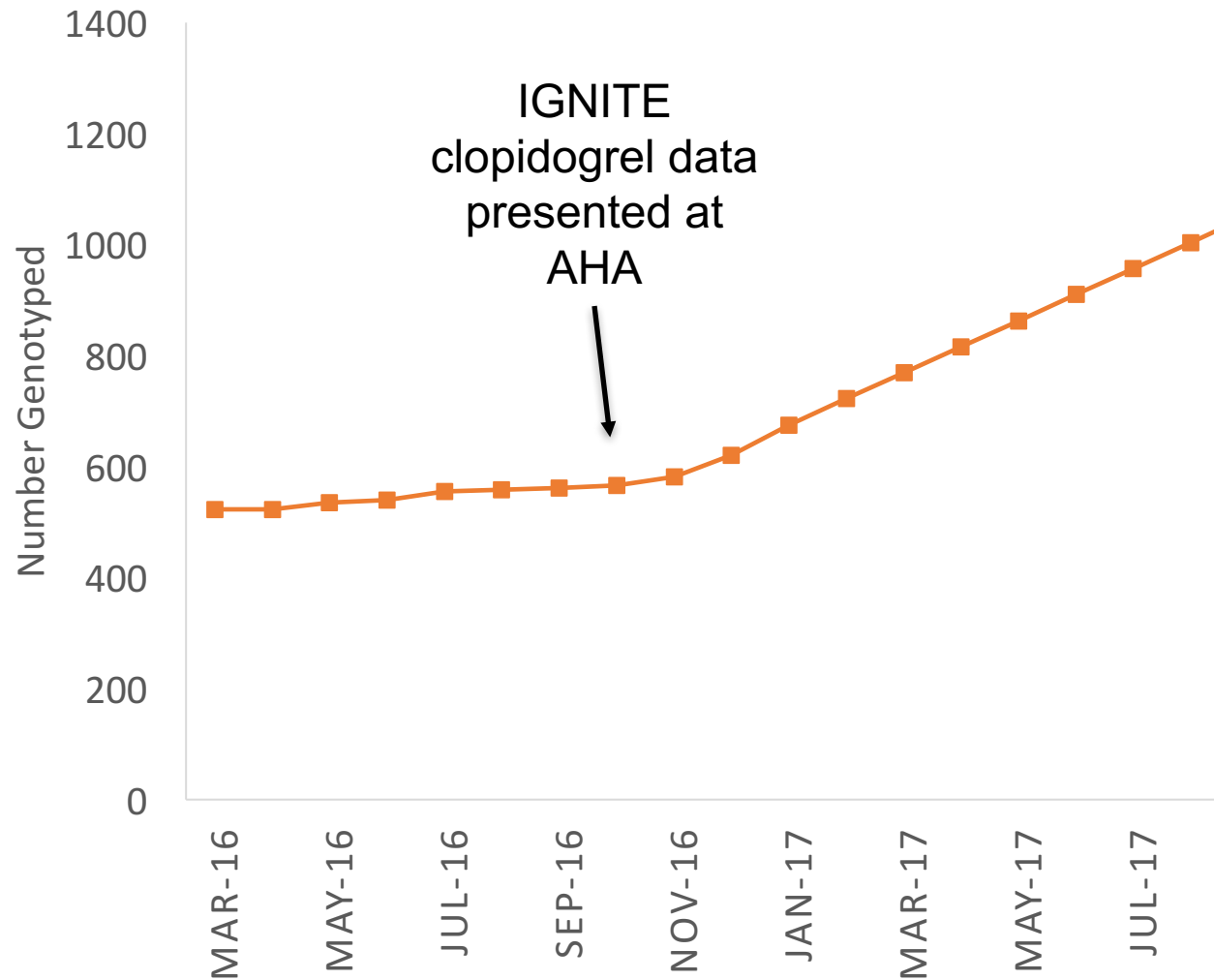


IGNITE CPIC Prescribing Study: Anticoagulants

Warfarin still
most frequent
anticoagulant
except at VA



Increasing Adoption at Sanford Health (part of our IGNITE site)



Preliminary results - Evaluating cost effectiveness

PGx Scenario	Incremental cost effectiveness ratio of genotyping
Clopidogrel – CYP2C19	\$36,618
Simvastatin – SLC01B1	\$1,405,163
Warfarin – CYP2C9/VKORC1	\$371,649



RATIONAL INTEGRATION OF
GENOMIC HEALTHCARE TESTING

beta site:
<https://rightsim.org/RIGHT/>

A few of the lessons learned

- Implementation is about the lab, process, EHR, and people
 - PGx is a “bleeding edge” of lab tests
 - MU-mediated EHR upheaval
 - Each EHR implementation has been different
- Local provider buy-in driven by 1) belief in clinical efficacy, 2) ease of use (e.g., CDS), 3) familiarity
- Advice changes frequently and opportunities to (re)use data accrue over time
 - Need for surveillance

What personalizing medicine really means

57yo with DM2,
FHx heart disease,
↑chol admitted for
chest pain,
receives stent

In-stent
thrombosis,
restent

Recath, stent
“Plavix x 1 year minimum.
ASA life long.”

In-stent
thrombosis,
restent

Cath, more stents

9th admission, 5th intervention,
9th stent
CYP2C19*2/*2
clopidogrel poor metabolizer

January

April

December

clopidogrel started

Switched to prasugrel



A sampling of the team

