Prospective Pharmacogenetic Testing in Practice: Vanderbilt PREDICT program and eMERGE-PGx

Josh Denny, MD, MS

1/29/12

The vision

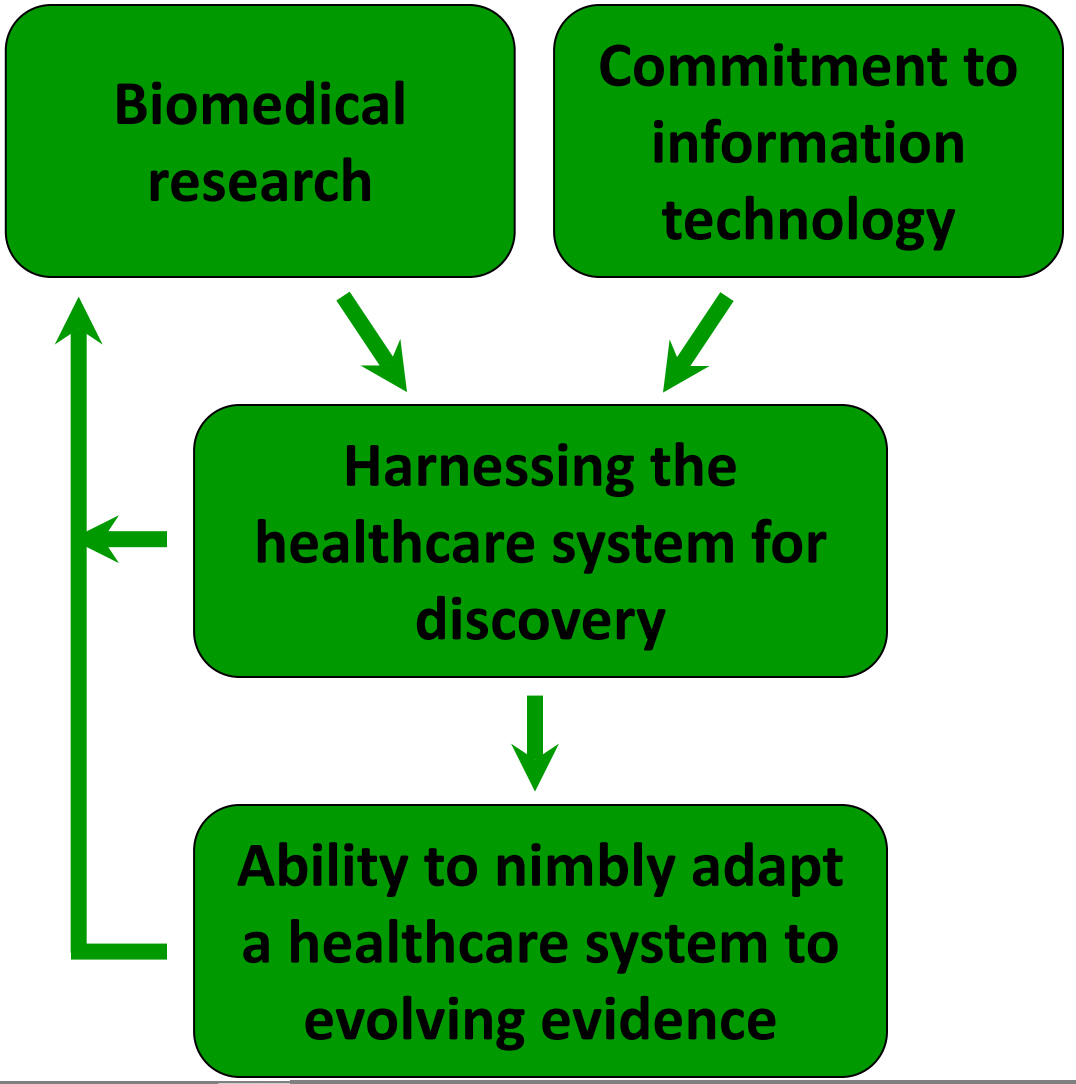
"Here's my sequence..."

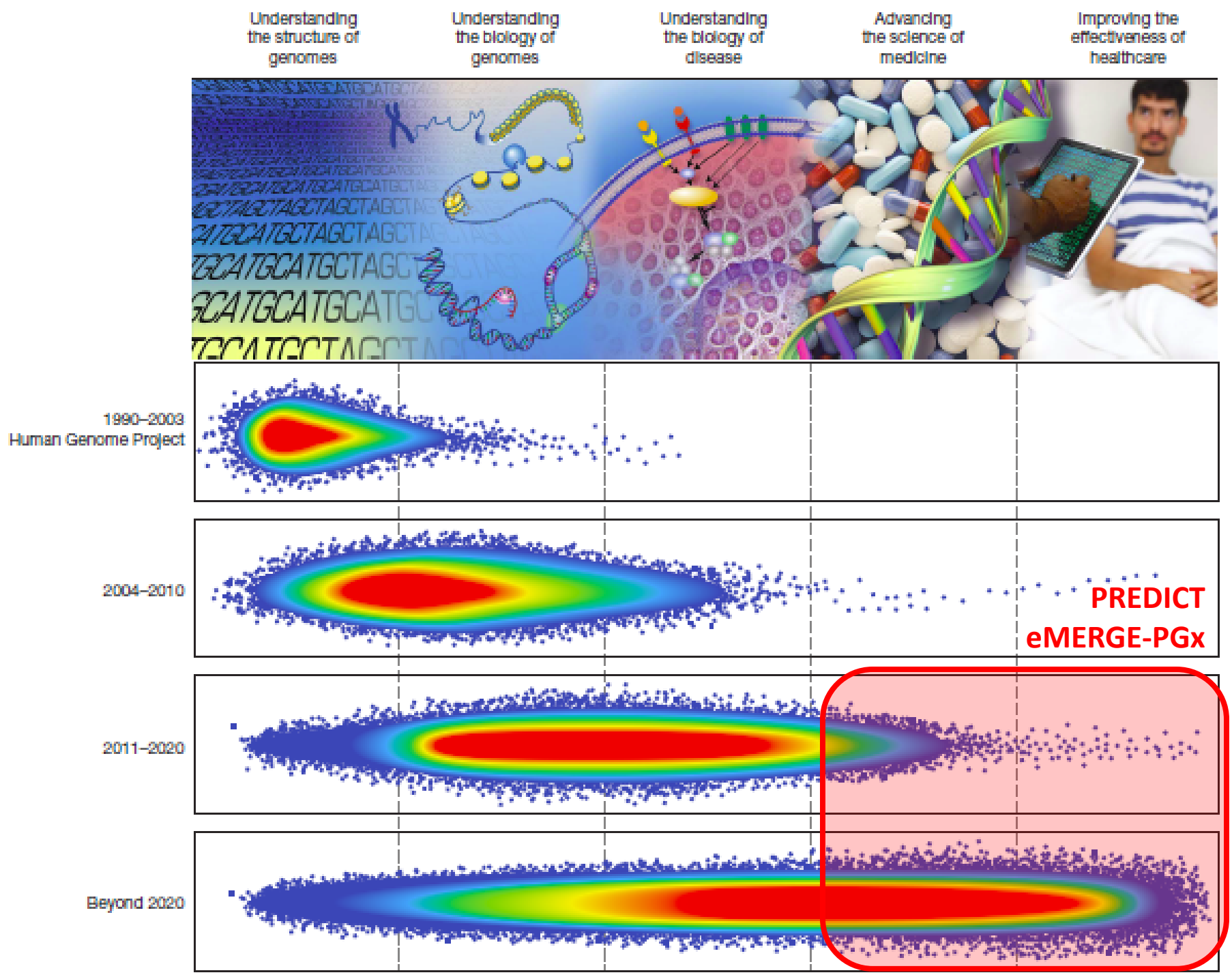
New Yorker, 2000

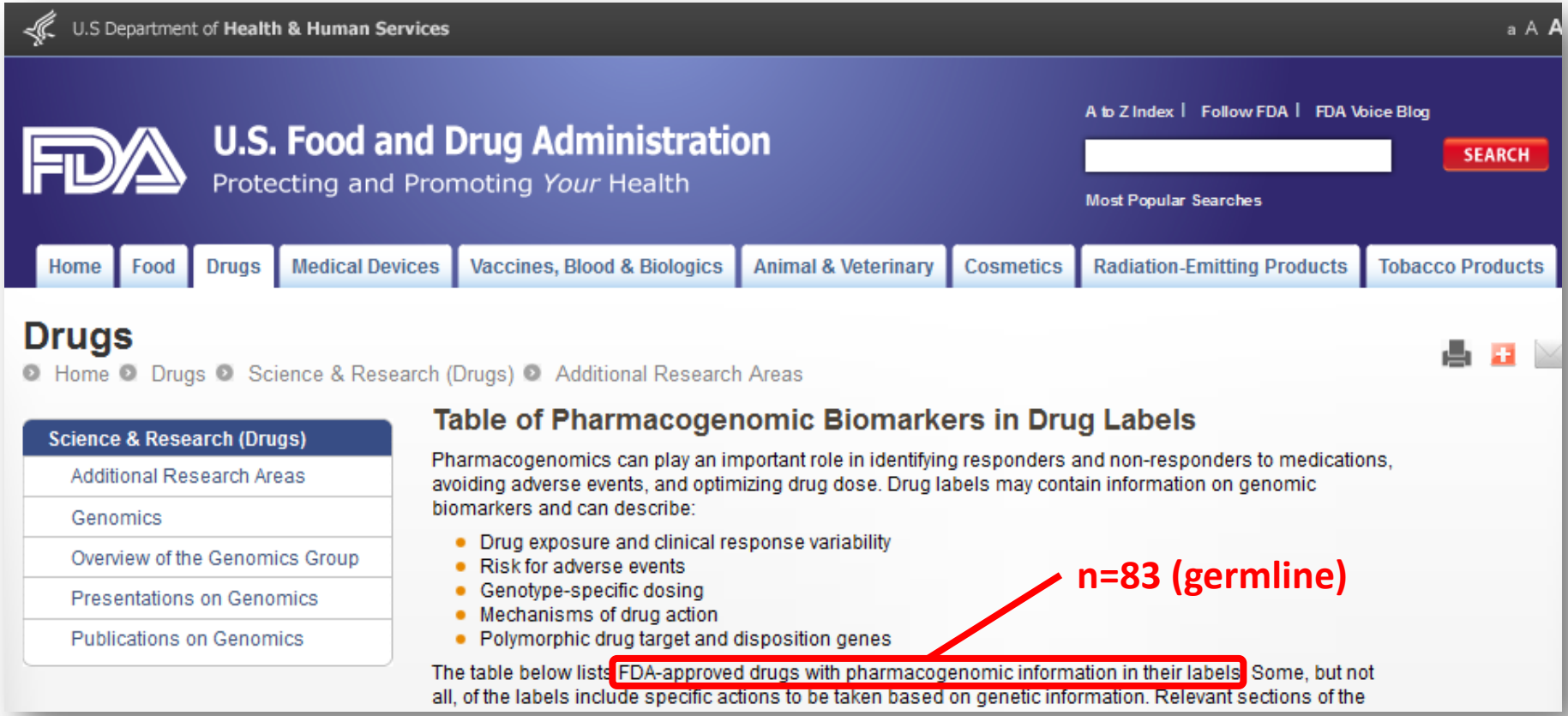
How will this vision actually start to be tested and become reality?

"Here's my sequence..."

New Yorker, 2000




Understanding the structure of genomes
Understanding the biology of genomes
Understanding the biology of disease
Advancing the science of medicine
Improving the effectiveness of healthcare
1990–2003 Human Genome Project
2004–2010
2011–2020
Beyond 2020
PREDICT
eMERGE-PGx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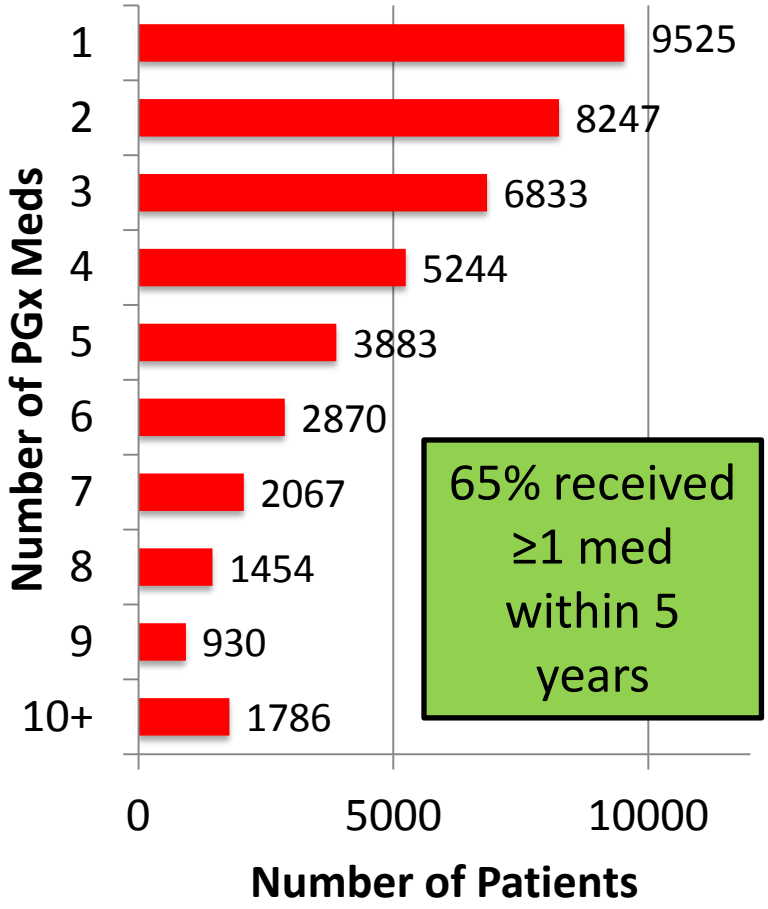
Tobacco Products
Drugs
Home Drugs Science & Research (Drugs) Additional Research Areas
Science & Research (Drugs)
Additional Research Areas
Genomics
Overview of the Genomics Group
Presentations on Genomics
Publications on Genomics
Table of Pharmacogenomic Biomarkers in Drug Labels
Pharmacogenomics can play an important role in identifying responders and non-responders to medications, avoiding adverse events, and optimizing drug dose. Drug labels may contain information on genomic biomarkers and can describe:
Drug exposure and clinical response variability
Risk for adverse events
Genotype-specific dosing
Mechanisms of drug action
Polymorphic drug target and disposition genes
n=83 (germline)
The table below lists FDA-approved drugs with pharmacogenomic information in their labels. Some, but not all, of the labels include specific actions to be taken based on genetic information. Relevant sections of the

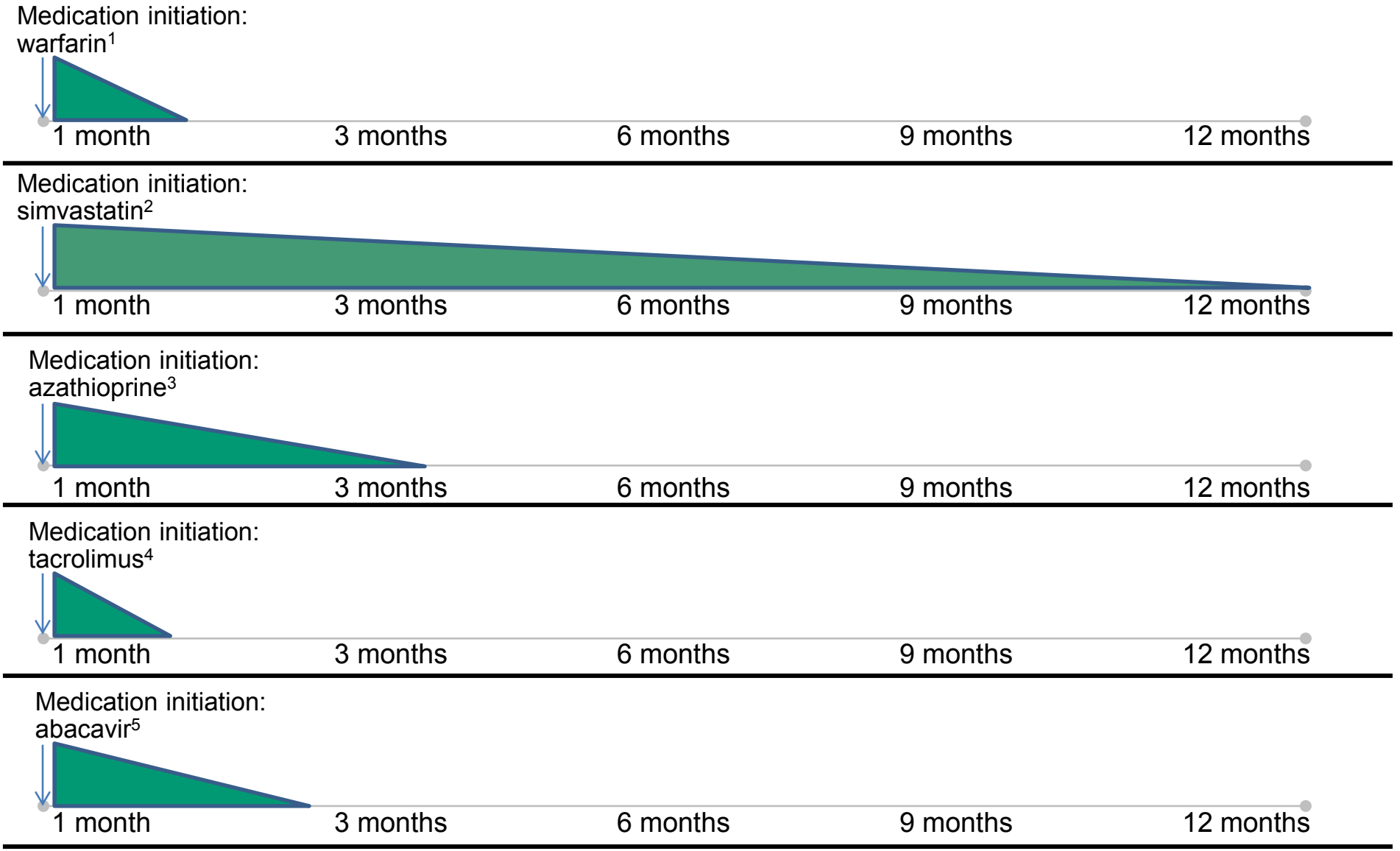
A case for preemptive genotyping & development of an "at risk" algorithm

In a cohort of 53,196 "Medical Home" patients followed for up to 5 years, how many received drug(s) that have a recognized pharmacogenetic "story"?



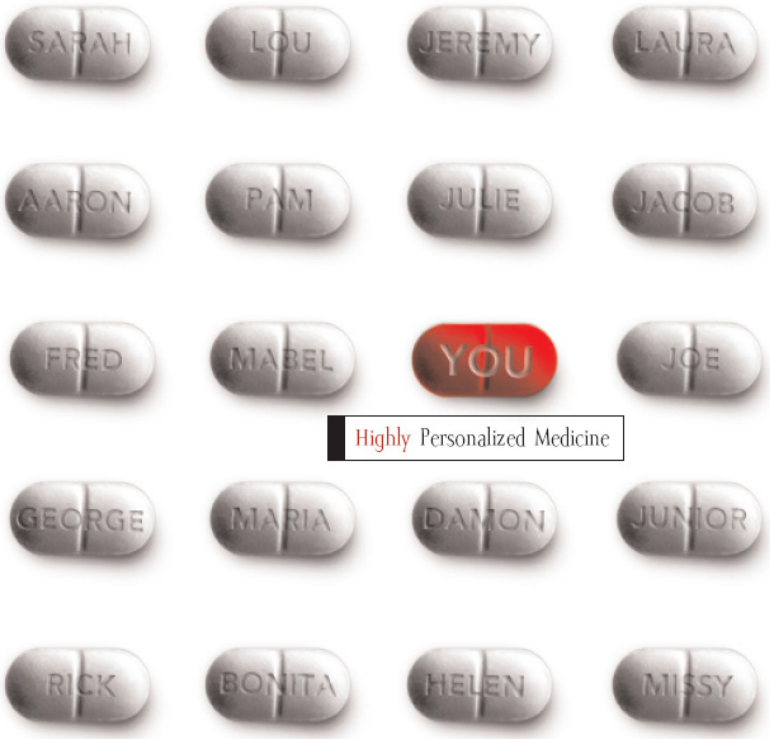
Schildcrout et al., CPT 2012

Why Prospective? Risk of Side Effects highest at drug start

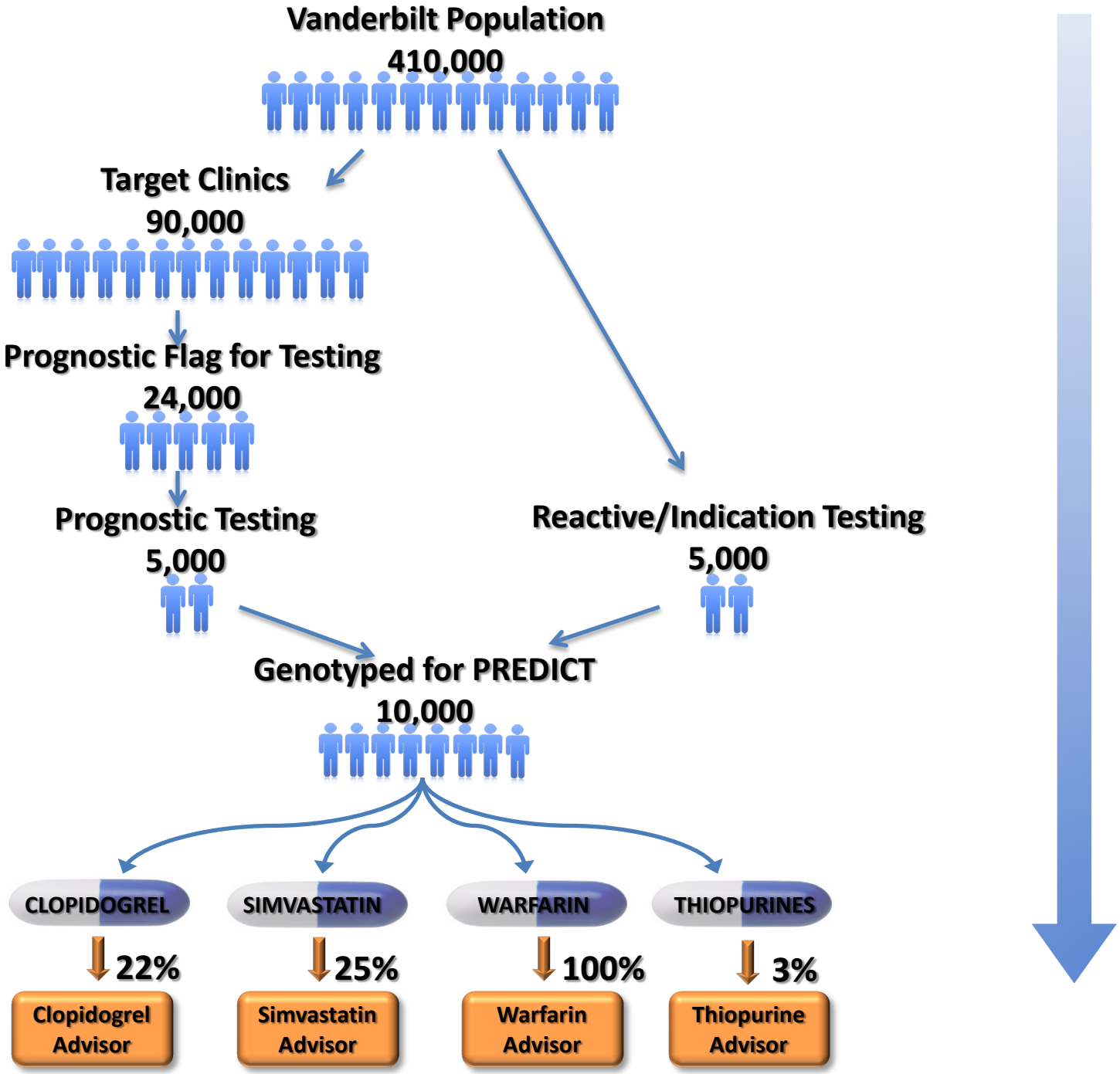


1. Ferder et al, Journal of Thrombosis and Haemostasis, 2010
2. The SEARCH Collaborative Group, NEJM 2008
3. Higgs et al, Pharmacogenomics 2010
4. Hesselink et al, 2008; Zhang et al, 2010
5. Mallal et al, NEGM 2008

PREDICT: Pharmacogenomic Resource for Enhanced Decisions In Care and Treatment



- Multiplexed genotyping with Illumina ADME chip
- Prospective identification of those at risk to receive candidate medications
- Coupled with EMR-based Decision Support
- Work with Pharmacy & Therapeutics committee

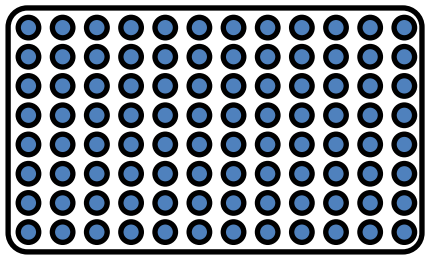

Vanderbilt Population
410,000
Target Clinics
90,000
Prognostic Flag for Testing
24,000
Prognostic Testing
5,000
Reactive/Indication Testing
5,000
Genotyped for PREDICT
10,000
CLOPIDOGREL
SIMVASTATIN
WARFARIN
THIOPURINES
22%
25%
100%
3%
Clopidogrel Advisor
Simvastatin Advisor
Warfarin Advisor
Thiopurine Advisor

Prospective Genotyping
Using the Prognostic Model

- Model identifies patients who are highest risk for starting warfarin, clopidogrel, or simvastatin therapy within the next three years as candidates for preemptive genotyping
- Used medical home population not on a target med previously (N~18000)
- Factors include:
  - Age, gender, race, and BMI when height is available (or weight when BMI is not available)
  - History of…Diabetes, coronary disease, atrial fibrillation, hypertension, atherosclerosis, congestive heart failure, previous DVT/PE, and end stage renal disease

Patient comes in, selected for genotyping (cardiac cath, predictive algorithm, etc)

184 variants



Drop variants that don't work well

Genotype DB

~130 other variants validated of unknown significance

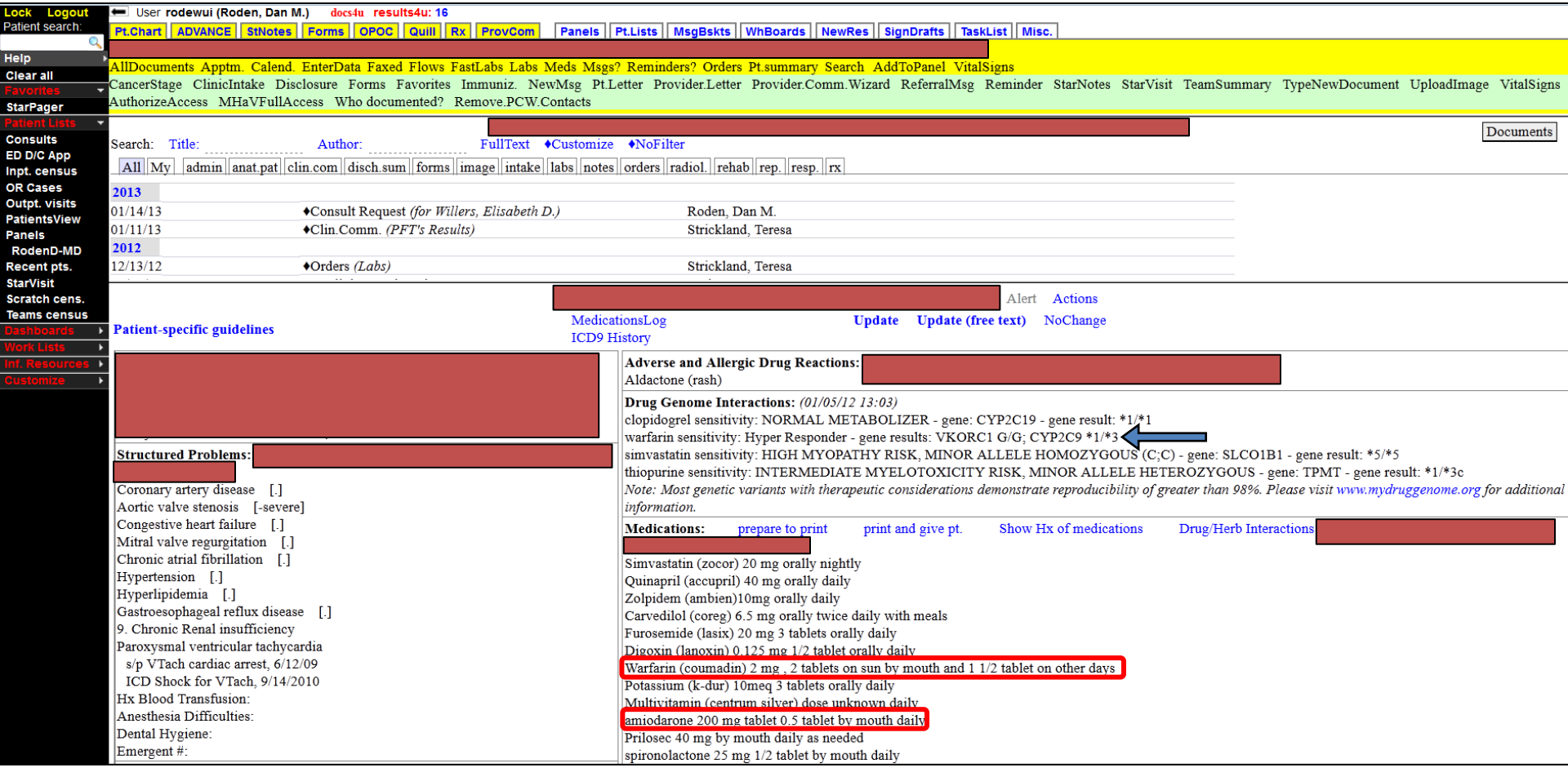
Select variants put into EMR

- Validated
- CDS
- P&T review

New research for drug-genome interaction discovery

P&T Committee

PREDICT research team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StarVisit
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2013
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warfarin sensitivity: Hyper Responder - gene results: VKORC1 G/G; CYP2C9 *1/*3
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thiopurine sensitivity: INTERMEDIATE MYELOTOXICITY RISK, MINOR ALLELE HETEROZYGOUS - gene: TPMT - gene result: *1/*3c
Note: Most genetic variants with therapeutic considerations demonstrate reproducibility of greater than 98%. Please visit www.mydruggenome.org for additional information.
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Congestive heart failure [.]
Mitral valve regurgitation [.]
Chronic atrial fibrillation [.]
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s/p VTach cardiac arrest, 6/12/09
ICD Shock for VTach, 9/14/2010
Hx Blood Transfusion:
Anesthesia Difficulties:
Dental Hygiene:
Emergent #:
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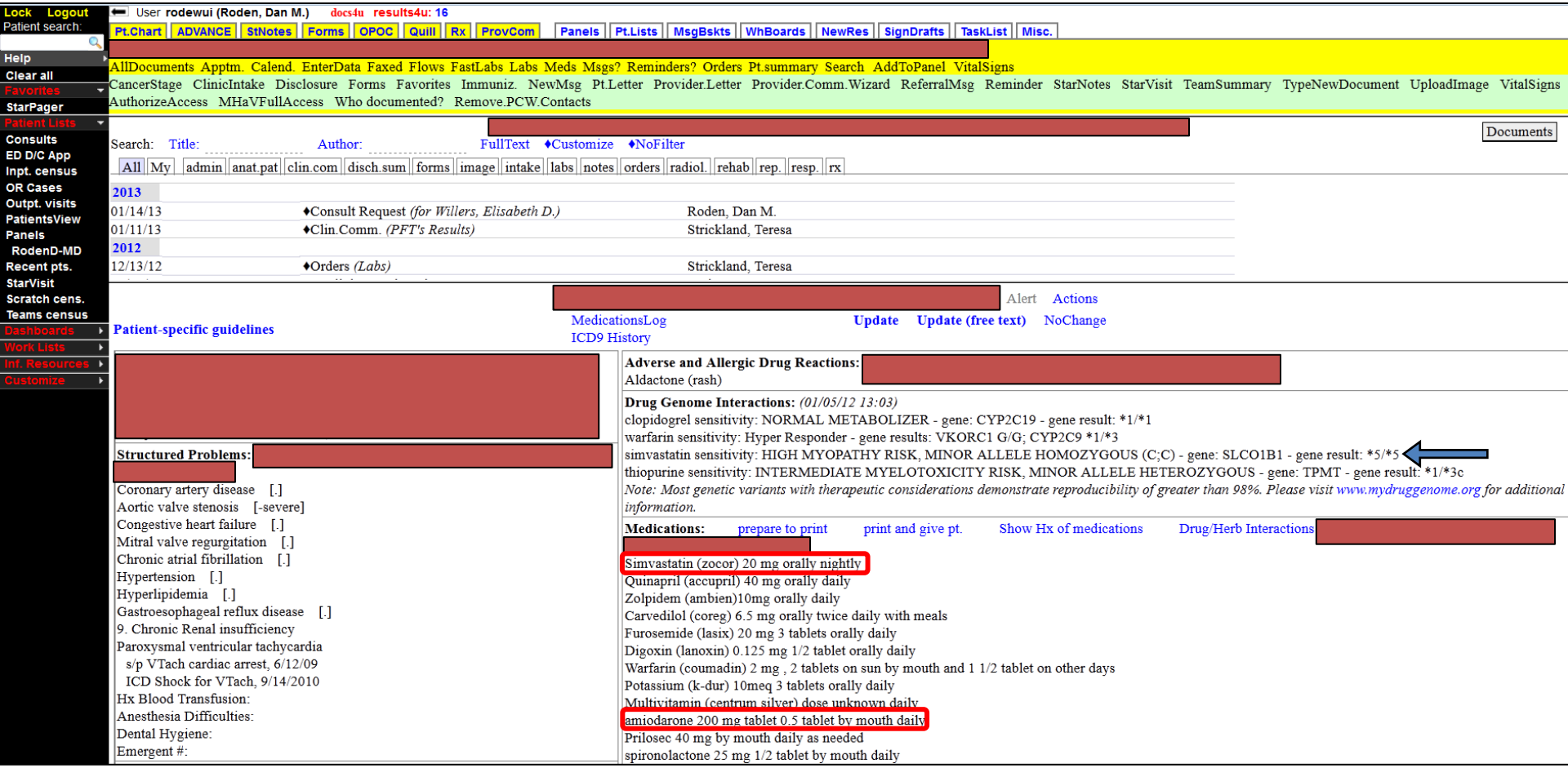
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AuthorizeAccess MHaVFullAccess Who documented? Remove.PCW.Contacts
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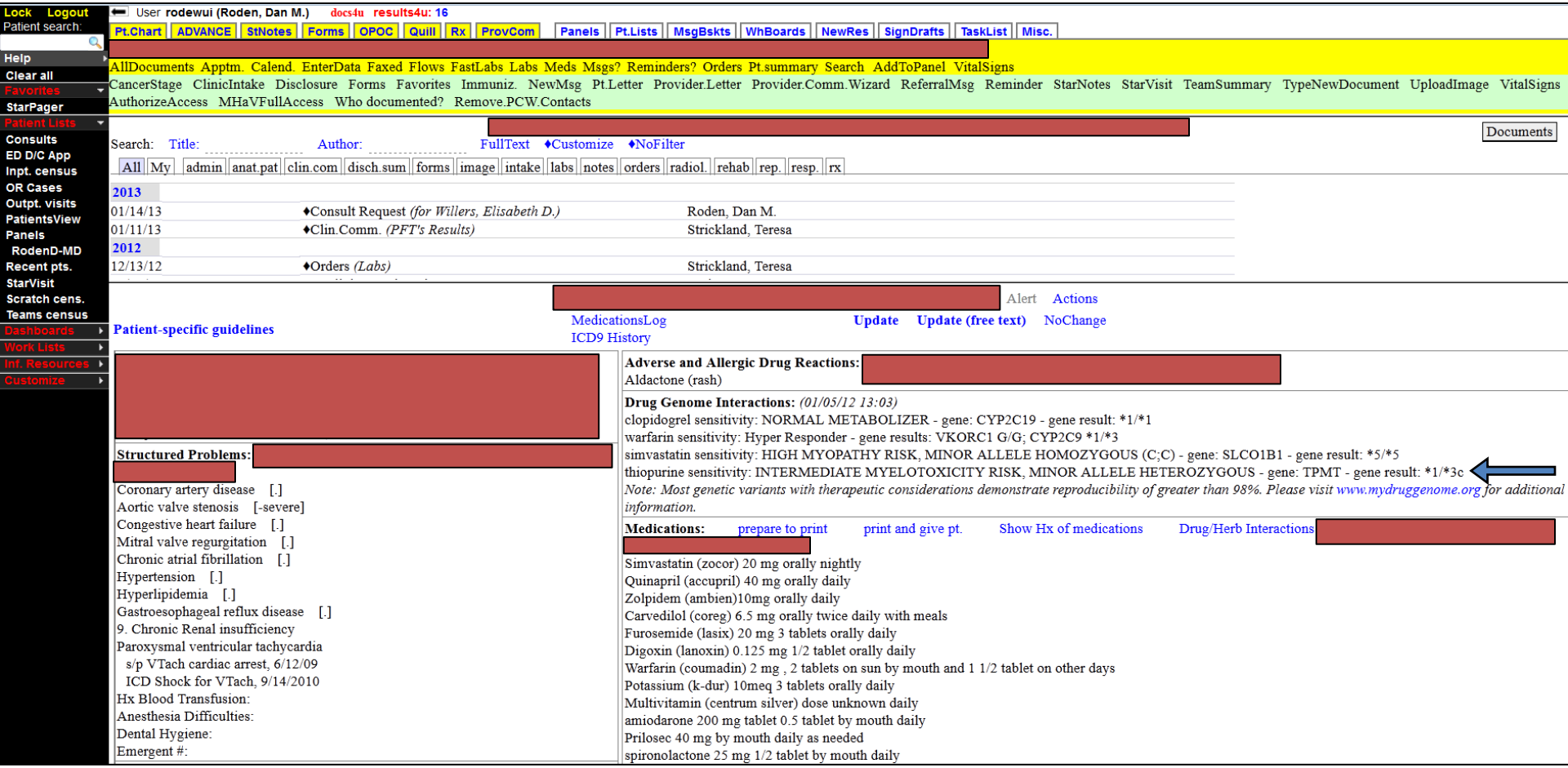
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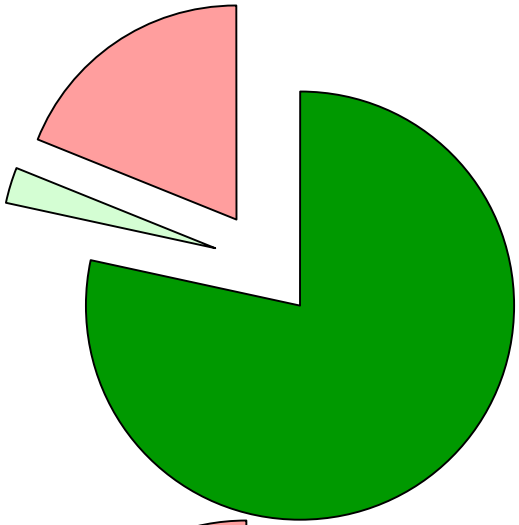
10,489 PREDICT patients
(9/2010-1/2013)

Clopidogrel

(CYP2C19*2)

↑risk of drug failure



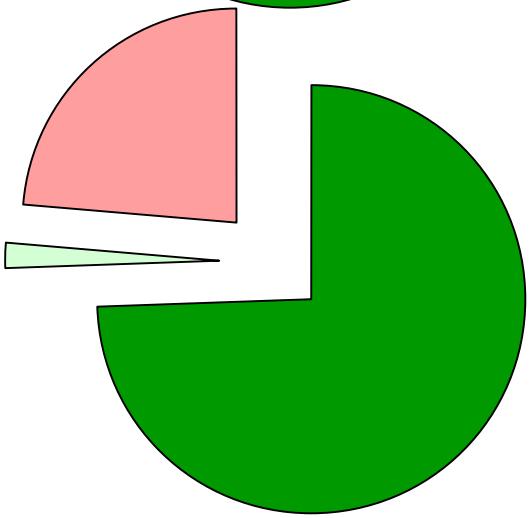
high risk: 2.7%

any risk: 21.7%

Simvastatin

(SLCO1B1*5)

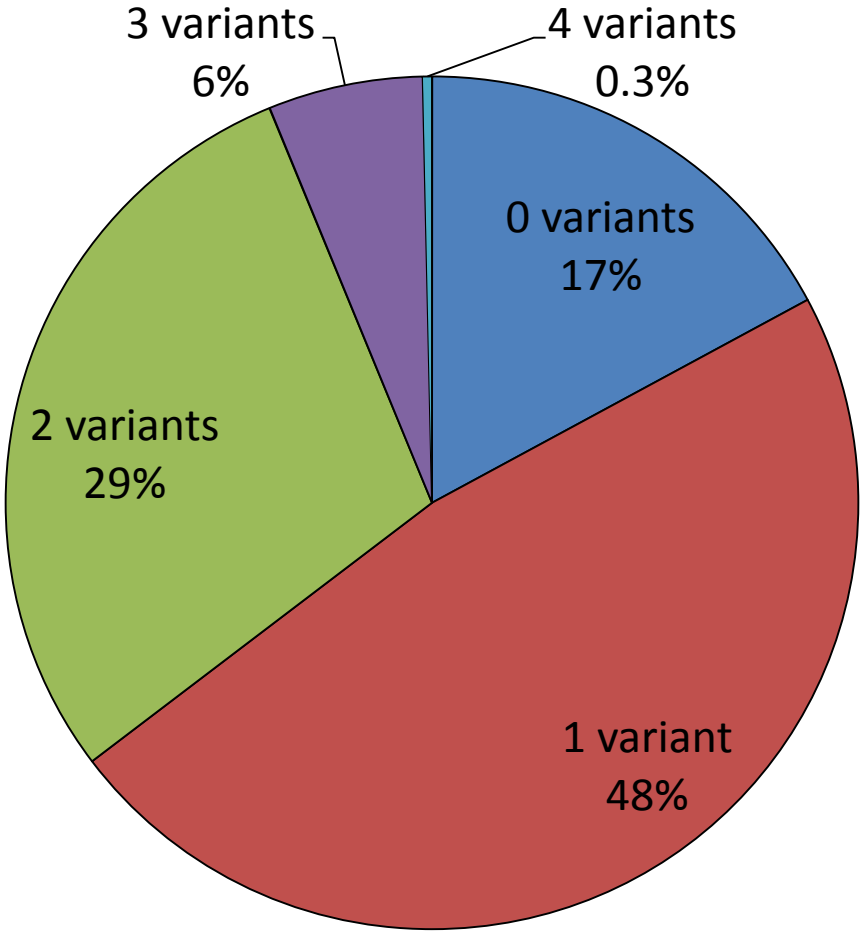
↑risk of muscle pain



high risk: 1.9%

any risk: 25.7%

Multiplex testing for pharmacogenetic variants



Risk Variants

CYP2C19 *2-*8

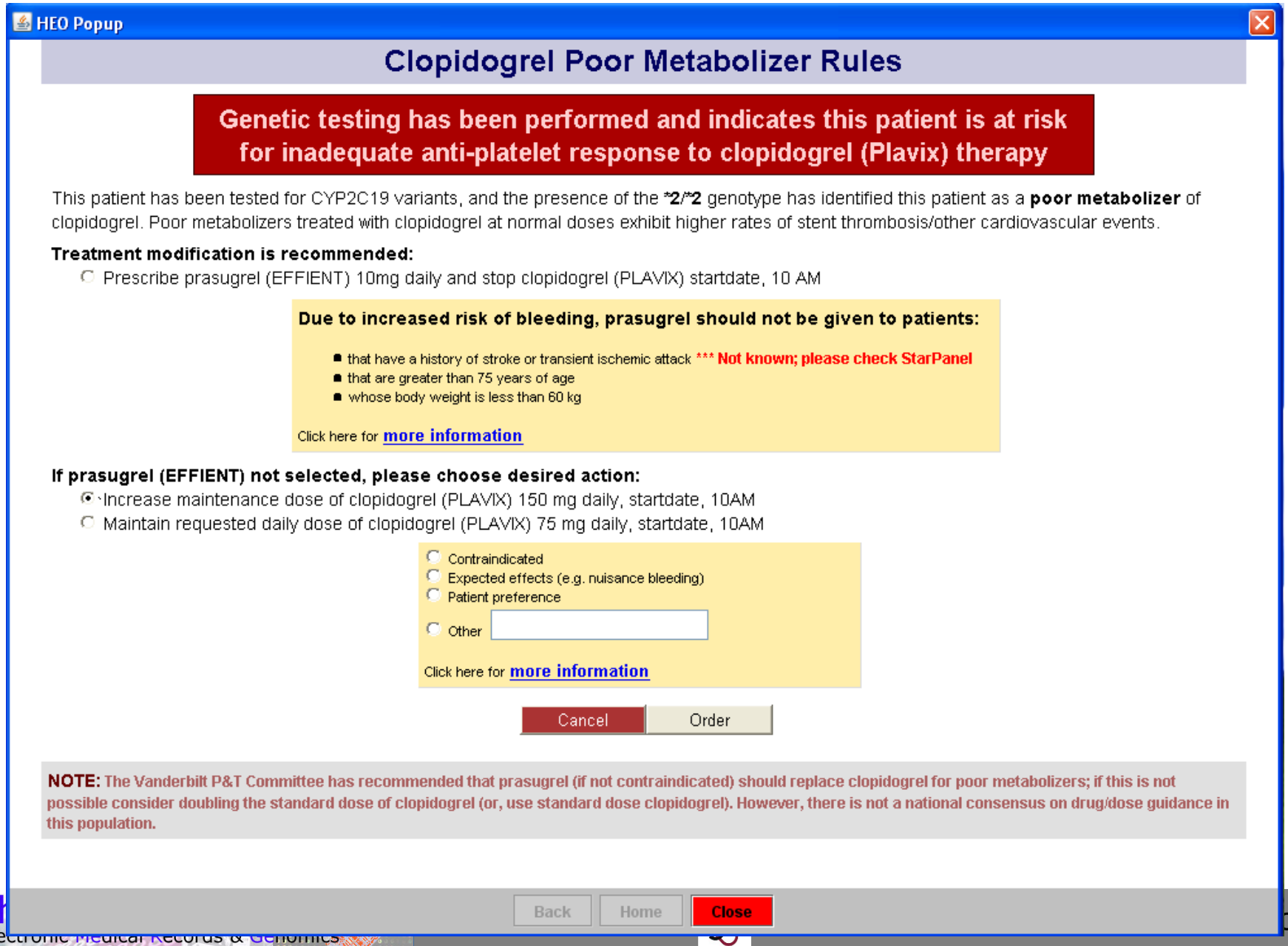
SLOC1B1 *5

CYP2C9 / VKORC1

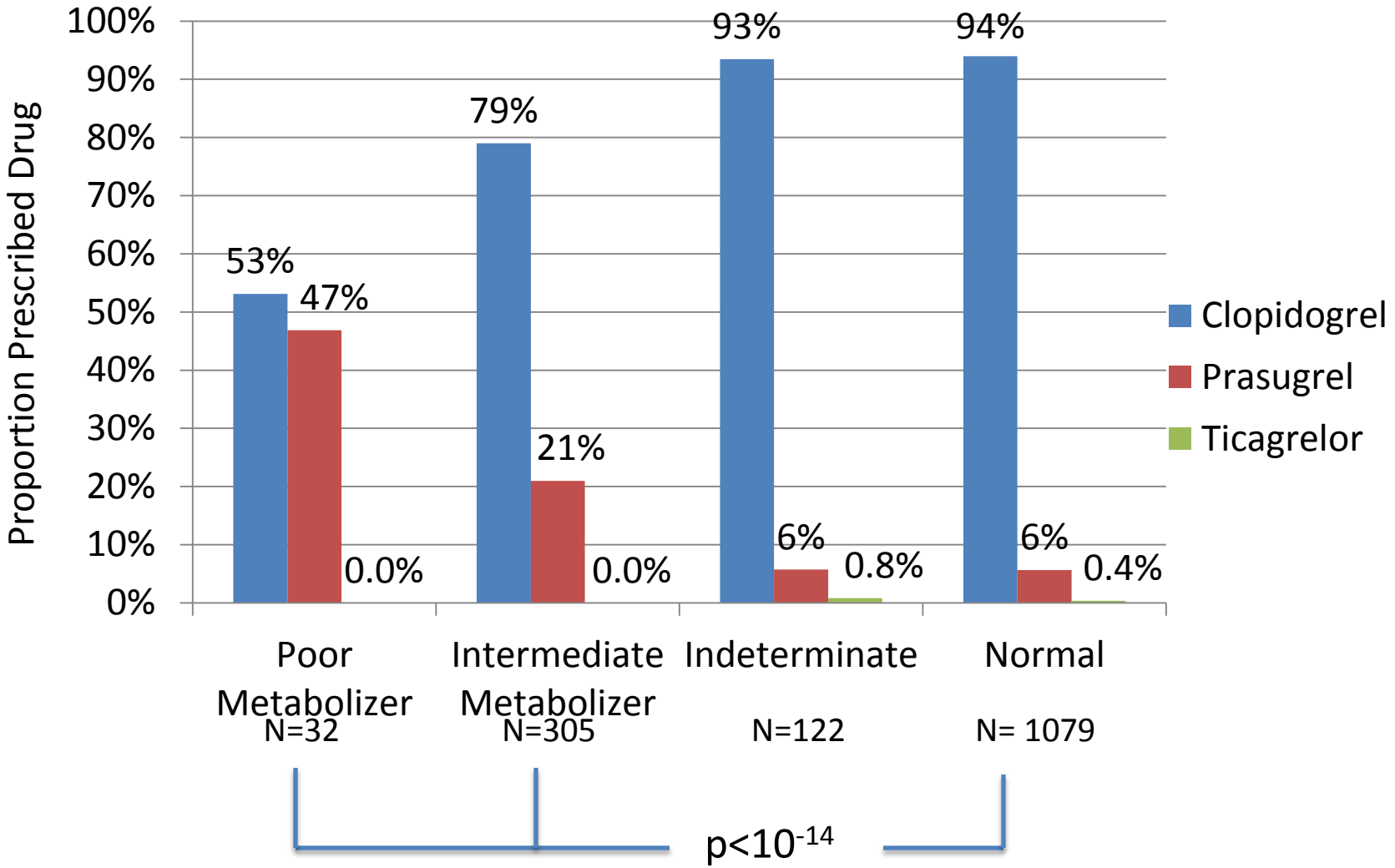
TPMT *2-*3

Total n=10,489

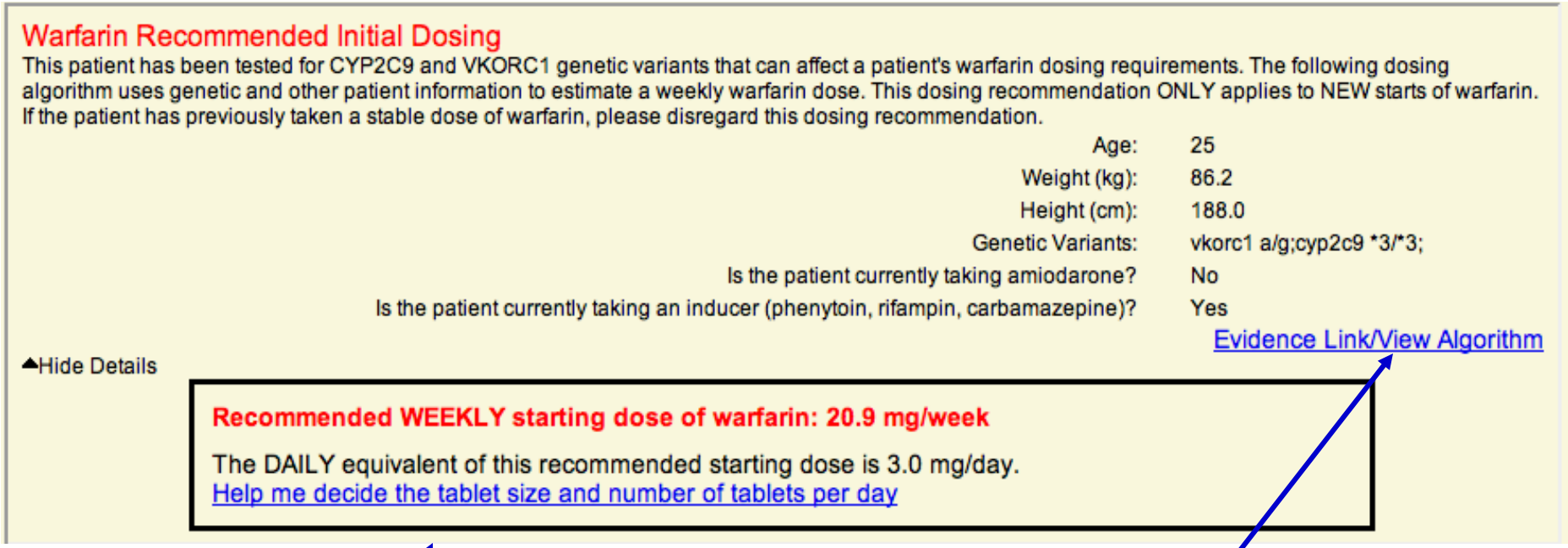
Point-of-care Decision Support



Antiplatelet Drug Selection by CYP2C19 Phenotype



Decision Support for Warfarin Initial Dose



The advisor appears in the black box and shows the Recommended initial WEEKLY & DAILY dose

Links to clinical evidence and dosing table.

Warfarin advisor – Week 1

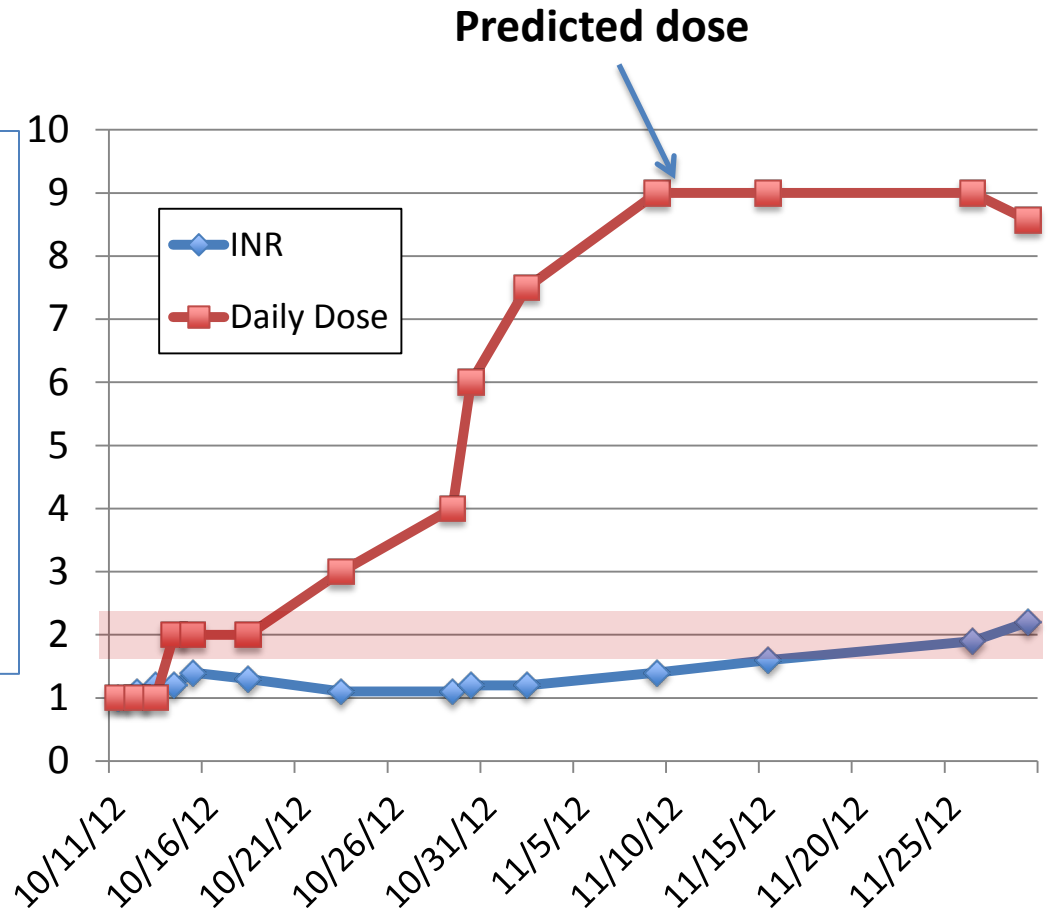
- 31 new inpatient starts of warfarin recorded in EMR
- 7/31 had received PREDICT testing
- 2/7 had genetic differences

Take home: Only 6/32 patients were started on the "traditional" dose of 5mg daily

Warfarin CDS Surveillance Example

Recommended Daily Dose = 9 mg/d
Initial Dose Prescribed = 1mg/d

Gene Results = warfarin normal responder
Recommended Weekly Dose = 63.0
Amiodarone = 0
Inducer = 0
Age = 39
Height = 180
Weight = 78.5

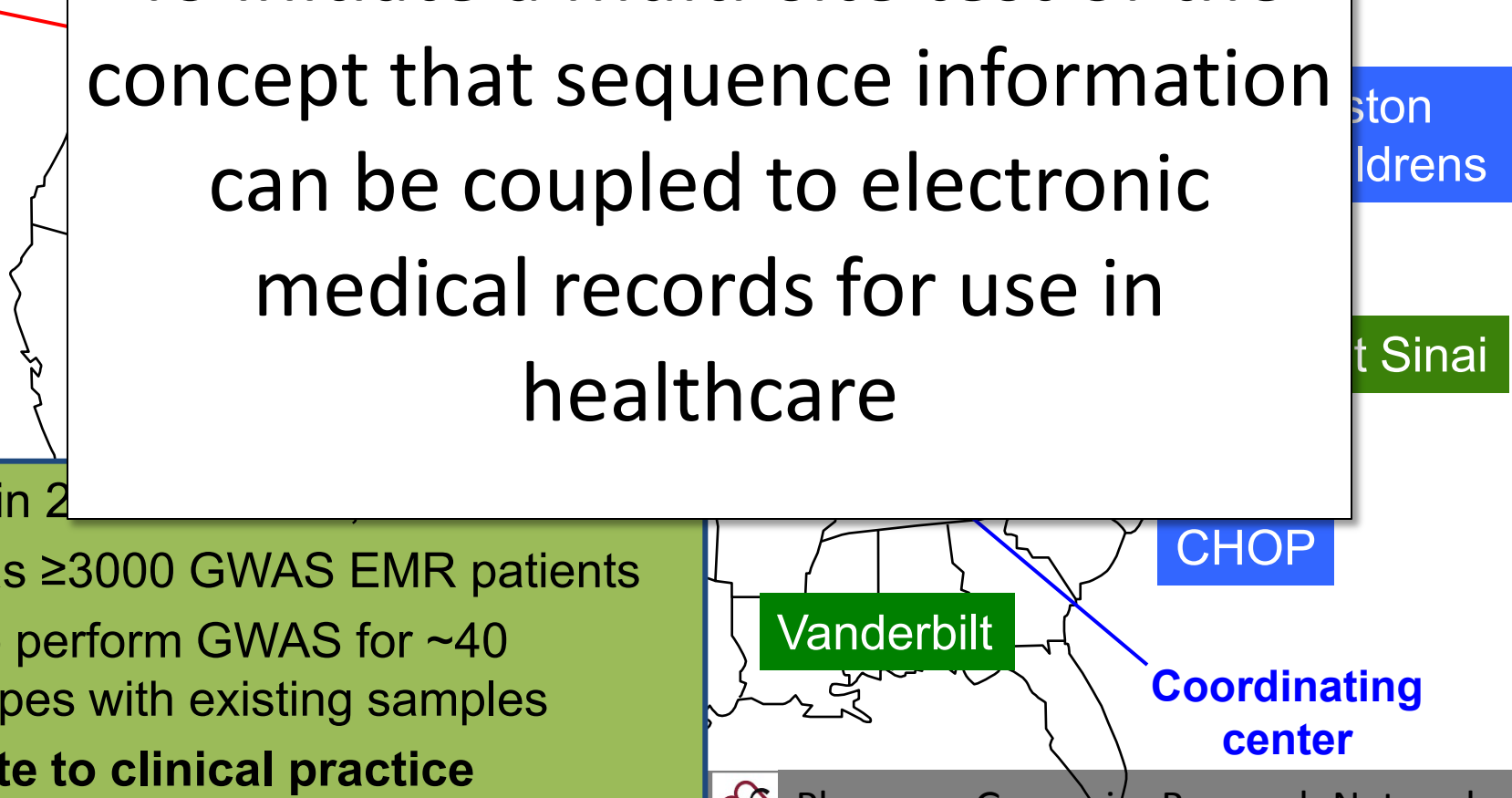


The eMERGE Network

electronic Medical Records & Genomics

eMERGE-PGx – Overall Goal

To initiate a multi-site test of the concept that sequence information can be coupled to electronic medical records for use in healthcare



- Started in 2
- Each has ≥3000 GWAS EMR patients
- **Goal:** to perform GWAS for ~40 phenotypes with existing samples
- **Translate to clinical practice**

PharmacoGenomics Research Network

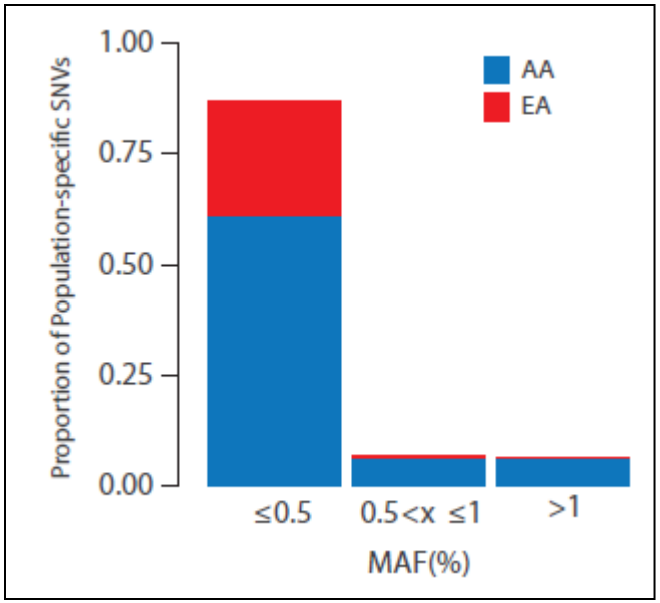
eMERGE-PGx: a PGRN-eMERGE alliance

Pharmacogenomics Research Network (PGRN)

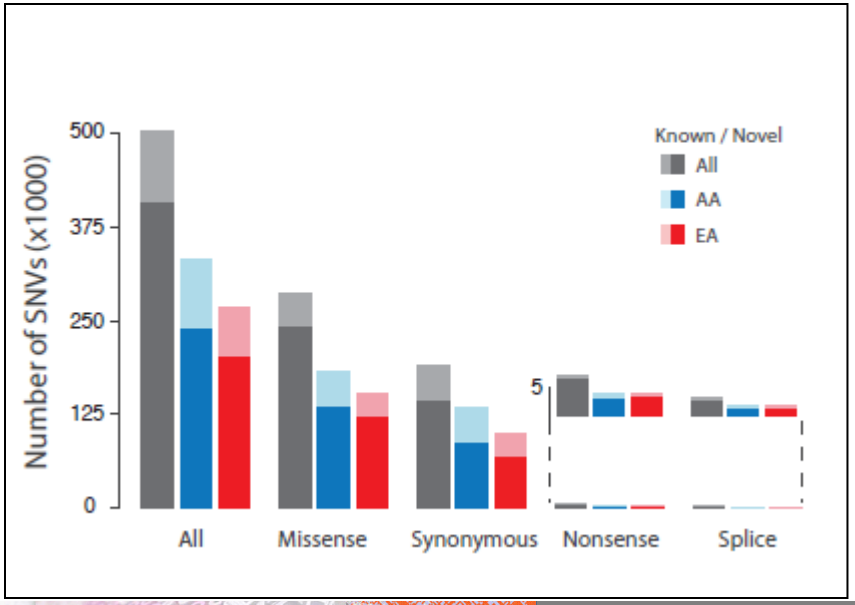
- Clinical Pharmacogenomics Implementation Consortium (CPIC)
- Translational Pharmacogenomics Project (TPP)
- PGRN-Seq and other platforms

eMERGE

- developing and validating electronic phenotyping algorithms (including for drug responses)
- integration with EHR
- developing and deploying clinical decision support



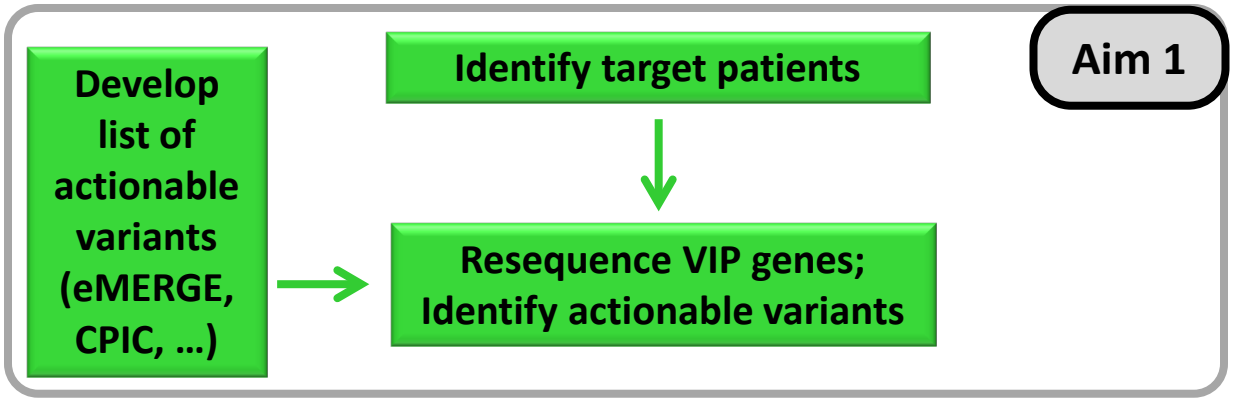
The vast majority of sequence variation across exomes is rare…



…and most variants seen are missense

Tennessen et al., 2012

eMERGE-PGx Aims



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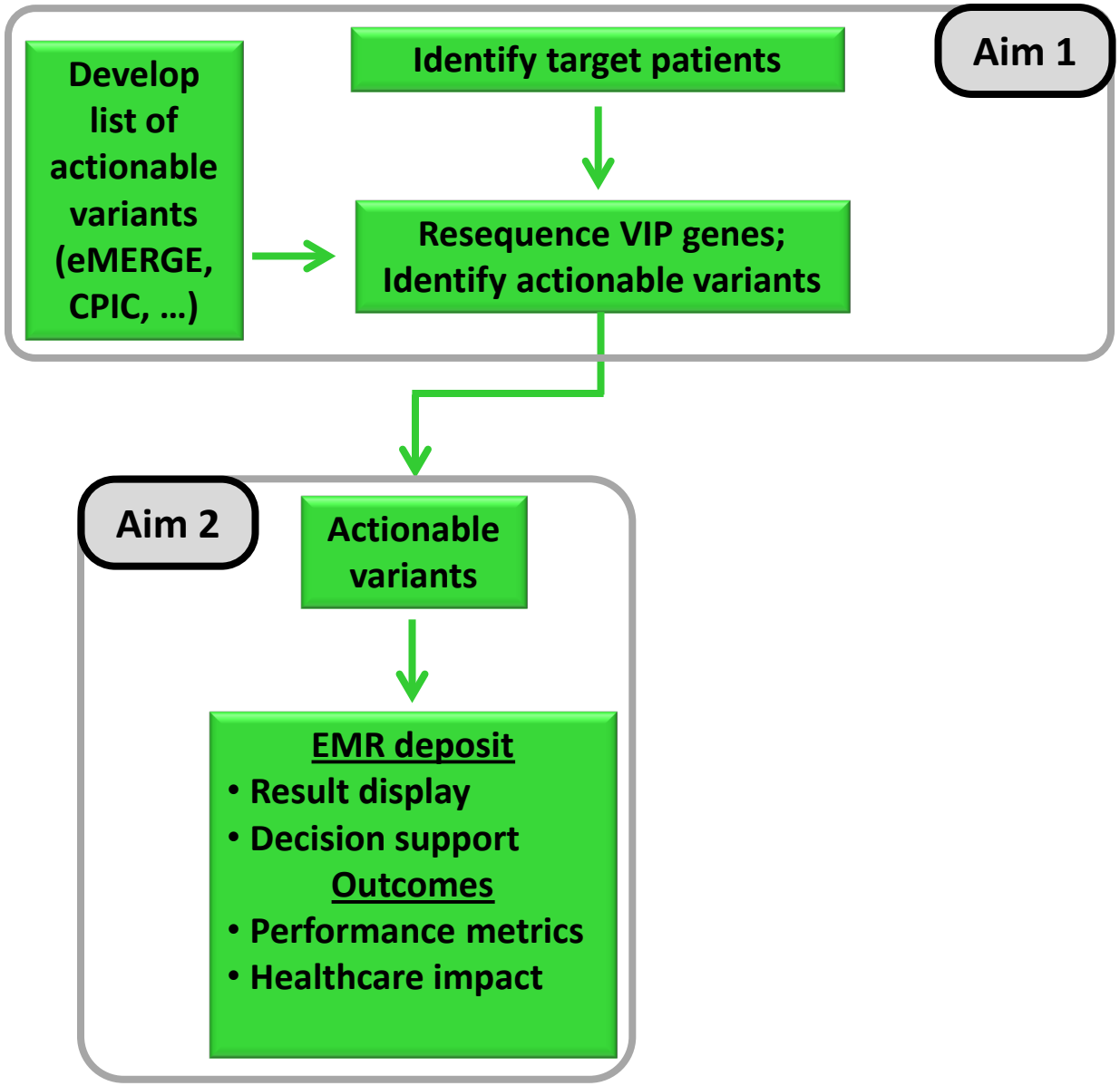

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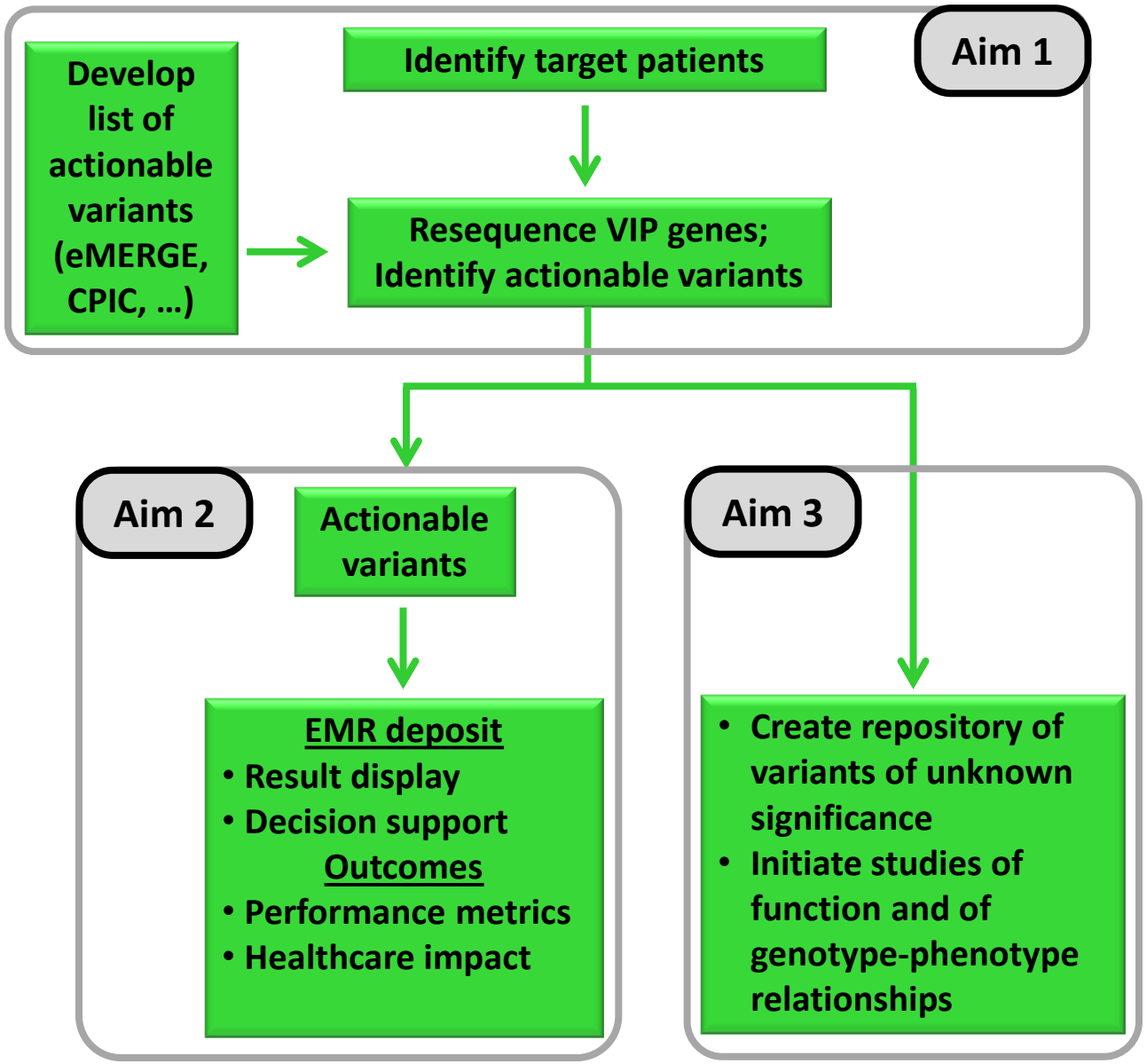
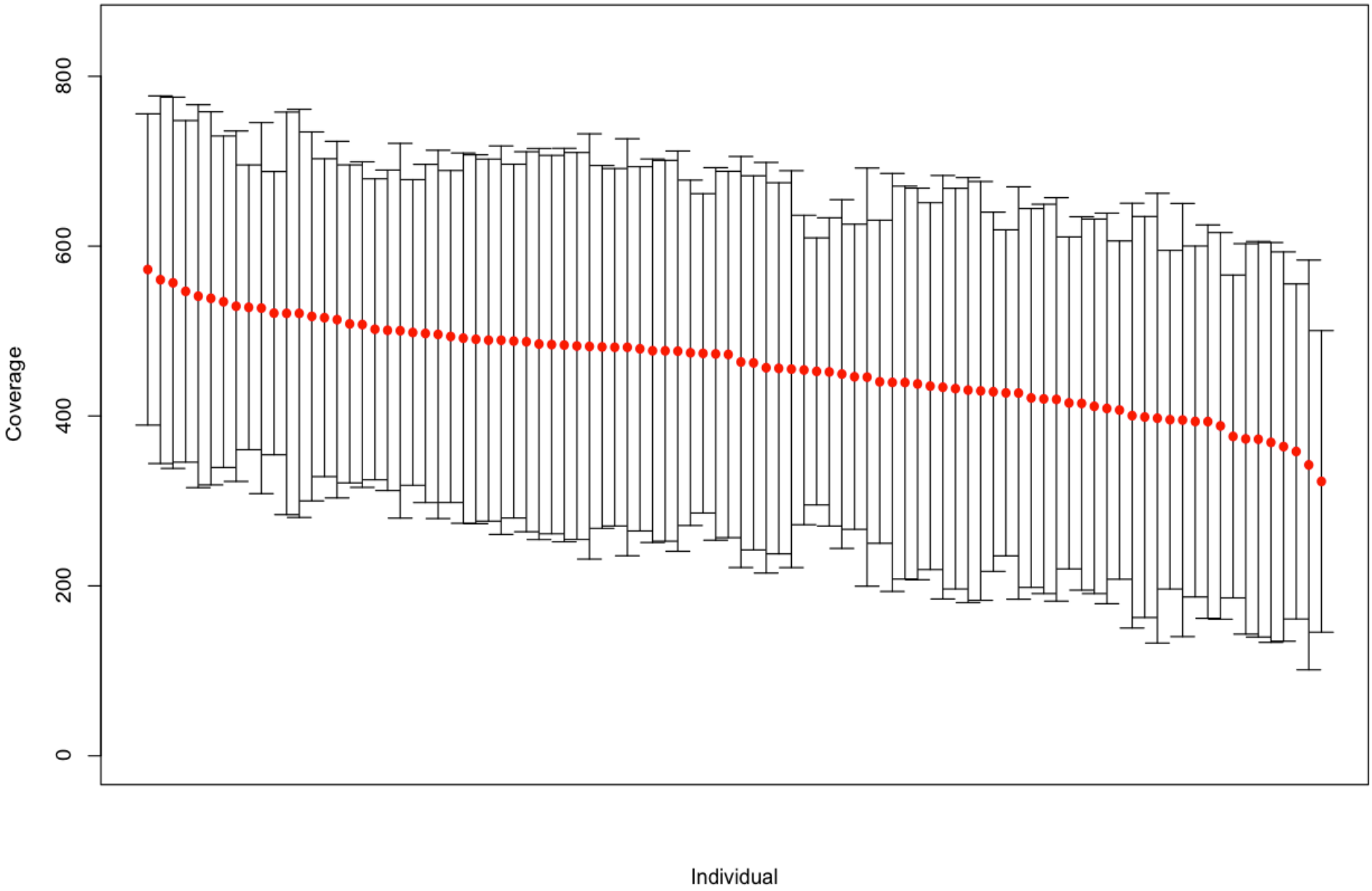


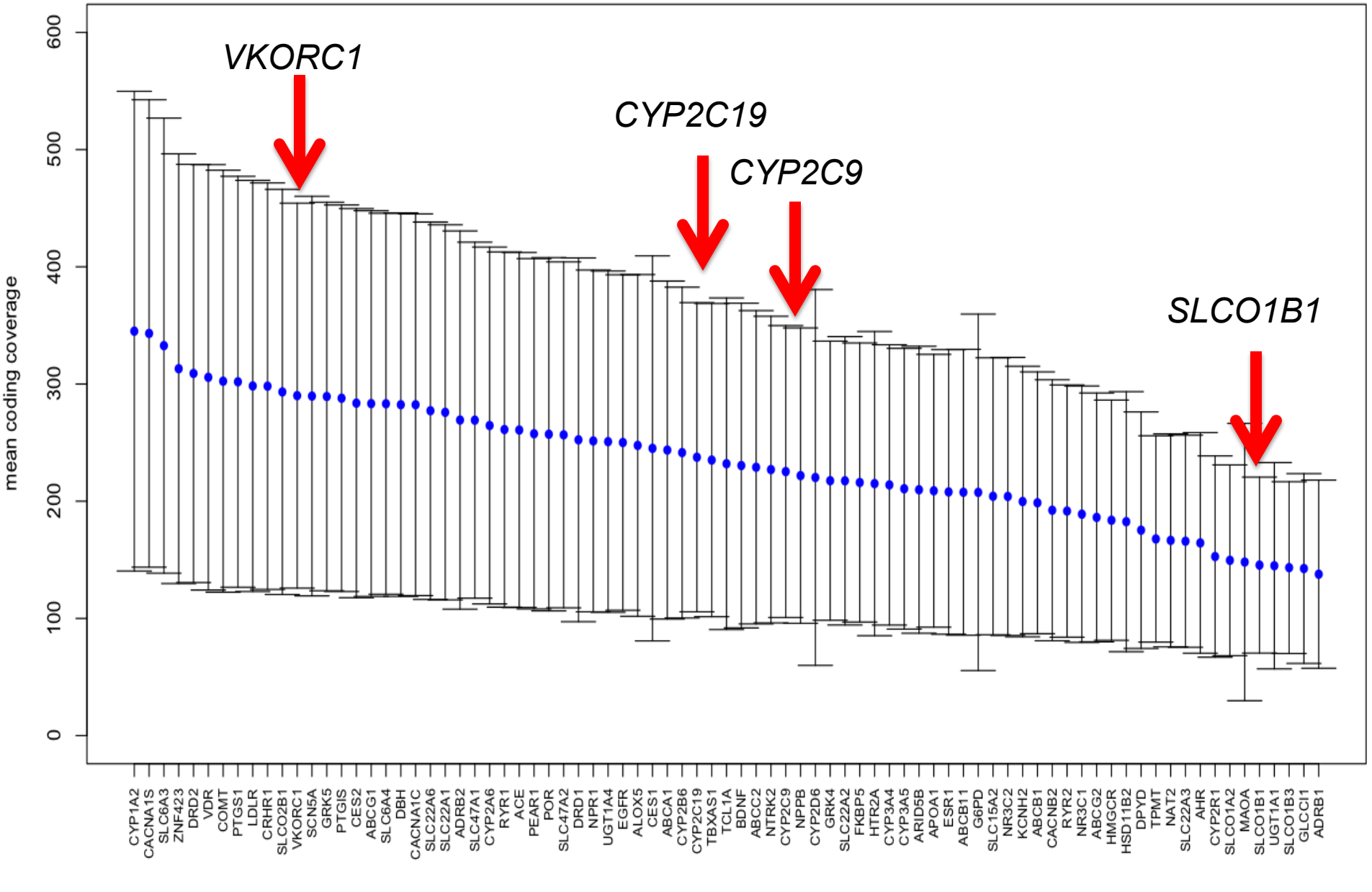
The platform: PGRN-Seq

- 84 Very Important Pharmacogenes
- Nominated by the 14 PGRN sites
- Multiple rounds of balloting
- Each site was able to include ≥2 genes of its choosing
- Drug metabolism, transporters, targets
- Nimblegen custom capture array; coding UTRs + probes for each variant on Illumina and Affy ADME/DMET platforms
- **PGRN-Seq is available for use by others**

Mean Read Depth per Individual



Mean Read Depth per Gene



PGRN-Seq: Status/issues

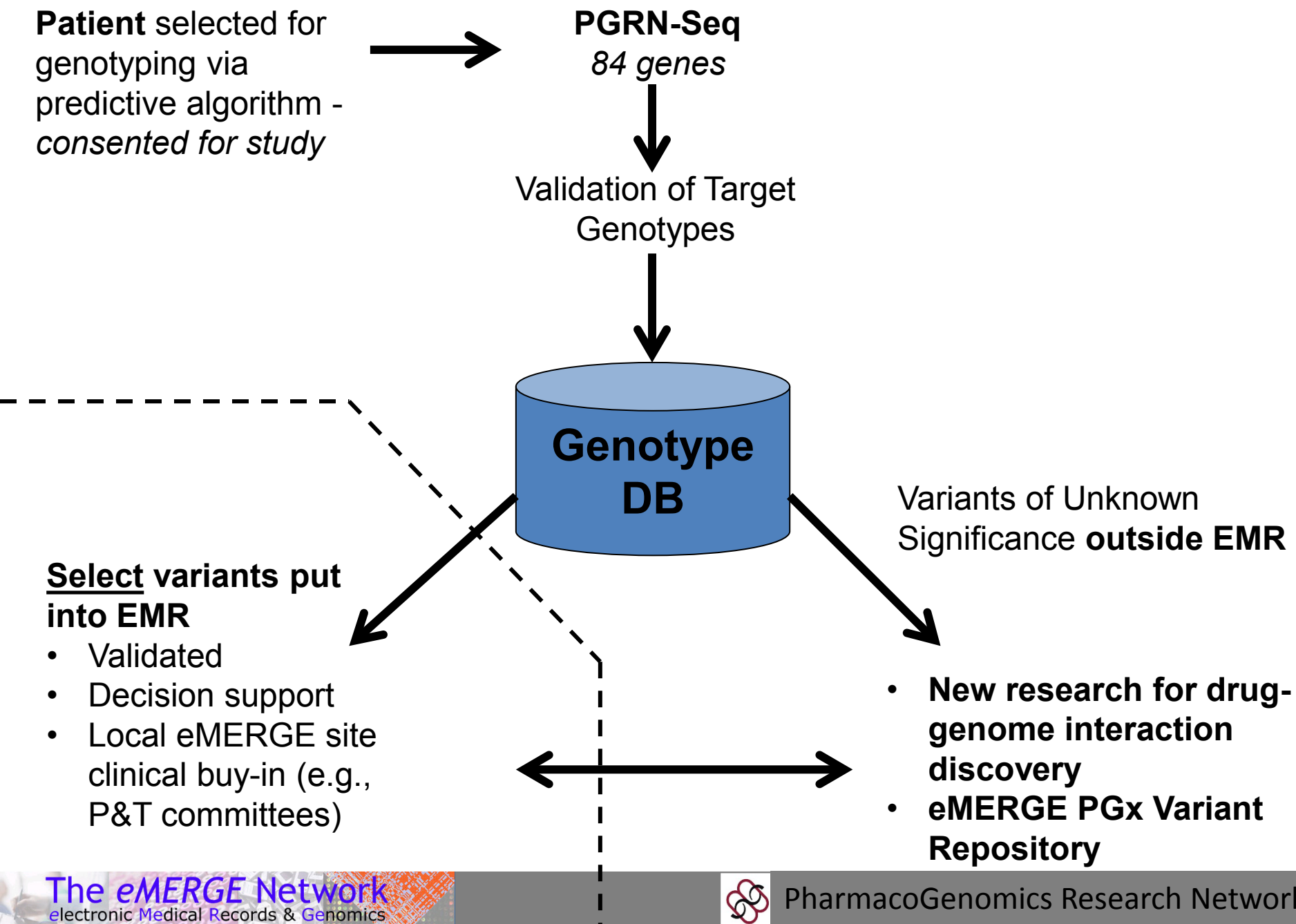
- Comparison to Illumina ADME: 88/95 HapMap samples concordant at ~150 sites
- CYP2D6 problematic: many variants, pseudogene, phenotype of interest is the compound heterozygote; may also be an issue for other platforms
- HLA: May be able to interrogate specific variants of interest but unlikely to be able to resequence with current technology approach

PGx candidate drug-gene pairs

Gene	Drug	Comment
CYP2C19	clopidogrel	Best evidence in patients with coronary stents
CYP2C9 *VKORC1* *CYP4F2*	Warfarin	Algorithms to predict starting dose available. Vary by ancestry
SLCO1B1	Simvastatin	Especially at higher dosages or with interacting drugs
TPMT	Thiopurines (6-MP, azathioprine)	

Targeted enrollment

Study site	American Indian/Alaska Native	Asian	Native Hawaiian or Other Pacific Islander	Black or African American	White	Total (% of Females)
CCHMC/CHB	0	8	0	54	438	500 (41)
CHOP	0	64	0	516	709	1289 (50)
Geisinger	0	8	0	24	768	800 (66)
GHC	16	23	1	35	825	900 (37)
Marshfield	0	0	0	0	750	750 (56)
Mayo Clinic	0	20	0	20	960	1000 (50)
Mt. Sinai	0	0	0	486	414	900 (60)
Northwestern	3	44	0	191	512	750 (62)
Vanderbilt	2	5	0	100	893	1000 (52)
Total	**21**	**172**	**1**	**1426**	**6269**	**7889 (53)**


Patient selected for genotyping via predictive algorithm - *consented for study*
PGRN-Seq
84 genes
Validation of Target Genotypes
Genotype DB
Variants of Unknown Significance **outside EMR**
Select variants put into EMR
• Validated
• Decision support
• Local eMERGE site clinical buy-in (e.g., P&T committees)
• **New research for drug-genome interaction discovery**
• **eMERGE PGx Variant Repository**

Genotyping sites and validation

	Sequencing*	Validating*
NU	CIDR	Mt. Sinai: ADME
Geisinger	Geisinger	Geisinger: Taqman
GHC/UW	UW (Nickerson)	CIDR Sequenom
Mayo	Mayo	Mayo: Sanger
Vanderbilt	CIDR	Vanderbilt: Illumina ADME
Marshfield	UW (Nickerson)	Marshfield: Sequenom
Mt. Sinai	Mt. Sinai	Mt. Sinai: ADME
CHOP	CHOP	CHOP: Illumina ADME/sanger
BCH/CCMH	UW (Nickerson)	BCH/CCMH: PCR (CYP2D6)

*All sites will have extra genotyping and Sequenom validation at CIDR

Initial target drugs

NU	clopidogrel, warfarin, simvastatin
Geisinger	clopidogrel, warfarin, simvastatin
GHC/UW	carbamazepine (other pairs implemented at UW)
Mayo	clopidogrel, warfarin, simvastatin Also: abacavir, interferon, thiopurines, carbamazepine
Vanderbilt	clopidogrel, warfarin, simvastatin, thiopurines
Marshfield	clopidogrel, warfarin, simvastatin
Mt. Sinai	clopidogrel, warfarin, simvastatin
CHOP	carbamazepine, thiopurines
BCH/CCMH	codeine (using local PCR)

Subject selection

NU	Predictive algorithm from internal medicine clinics
Geisinger	Predictive algorithm to MyCode® population and identified candidates.
GHC/UW	Predictive algorithm to identify 900 subjects. A subset of 450 will be selected for confirmatory testing and return of results.
Mayo	Predictive algorithm.
Vanderbilt	Predictive algorithm among general outpatient population
Marshfield	Predictive algorithm
Mt. Sinai	Predictive algorithm
CHOP	Cross-reference the CAG biobank with CHOP's adverse events database.
BCH/Cinn	6-18 year olds evaluated for idiopathic scoliosis or pectus excavatum

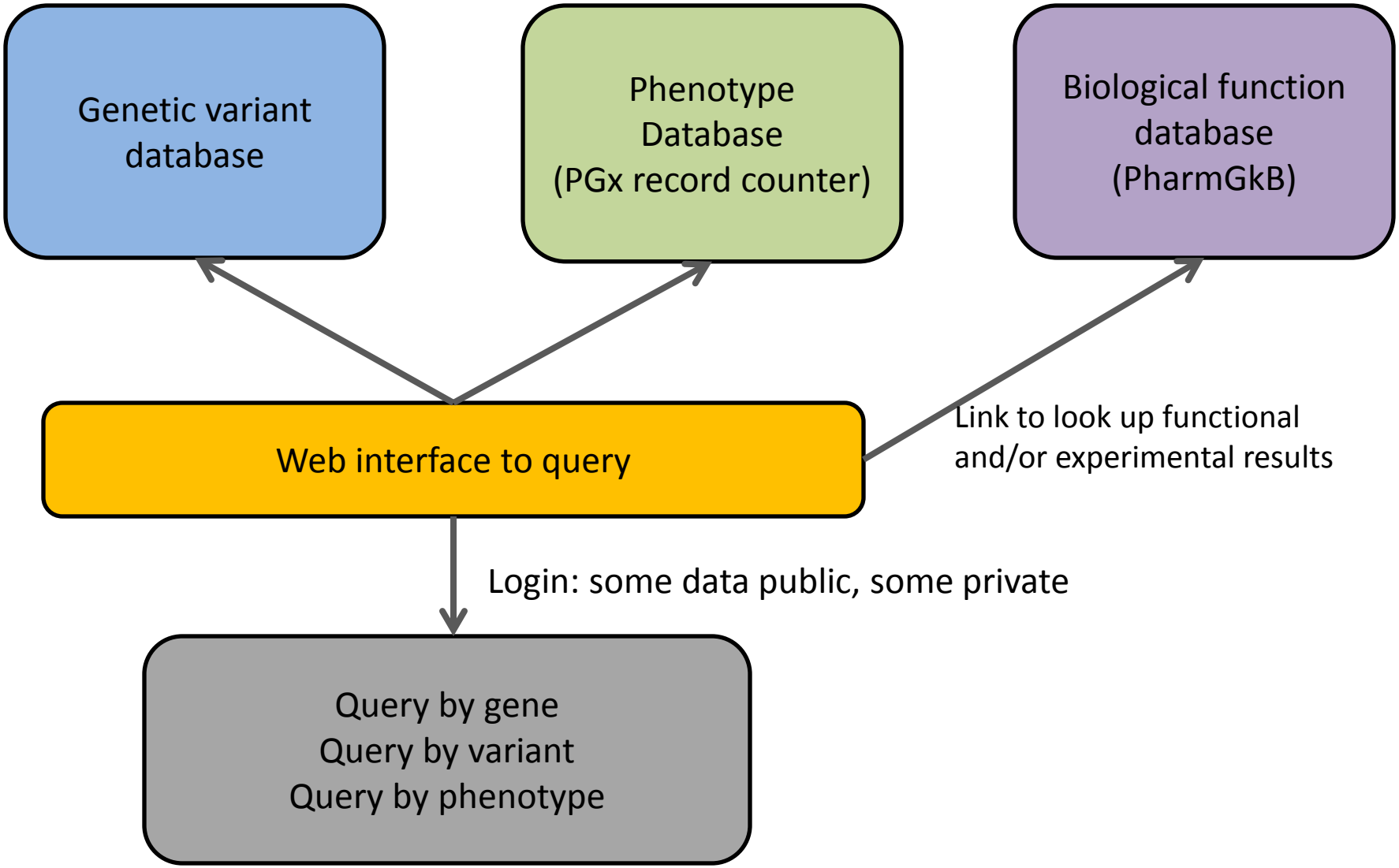
CLIA Validation of PGRN-Seq (CIDR)

(Initial) Drug target	Primary Variant(s)
clopidogrel	CYP2C19 *2
	CYP2C19 *3
	CYP2C19 *4
	CYP2C19 *5
	CYP2C19 *6
	CYP2C19 *7
	CYP2C19 *8
warfarin	CYP2C9 *2
	CYP2C9 *3
	VKORC1 rs9923231
simvastatin	SLCO1B1 *5

Integration with the EHR

- eMERGE EHR Integration working group
- EHRs: Epic, GE, Cerner, homegrown
- Store variants of known significance in structured ways
- Need to develop electronic decision support advisors
- Working with HL7 standards groups

Future eMERGE-PGx Variant Server



Phenotype Database

- **Very much in development**
- Likely will be limited to broadly-available, non-curated EMR phenotype data
- Demographics (Age, Gender, Race/Ethnicity)
- Diagnosis and procedure codes (ICD9, CPT)
- Medication exposures (based on prescriptions)
- Potential for a few “detailed PGx phenotypes” related to specific drug exposures

Process Measures

- **Very much in development**
- Surveys of providers and patients
- Accrual measures
- Performance of PGRN-Seq compared to validation methods
- Genotype distributions
- Patient views of genetic data in Patient Portals
- Number of patients who get prescribed target medications over time
- Adherence to genome-guided recommendations
- Outcomes on rare variants with target medications

Prospective for collaborations

- Use of PGRN-Seq platform
- Sharing of data in central repository from eMERGE
- Placing data into repository

eMERGE-PGx leadership:

- Laura Torvik-Rasmussen
- Dan Roden
- Josh Denny

eMERGE Sites:

- Boston Children's
- Children's Hospital of Philadelphia
- Cincinnati Children's
- Geisinger Health System
- Group Health/Univ of Washington
- Marshfield
- Mayo
- Mount Sinai
- Northwestern
- Vanderbilt

PREDICT leadership:

- Dan Roden
- Jill Pulley
- Erica Bowton
- Josh Peterson
- Josh Denny

PGRN-Seq:

- Debbie Nickerson
- Steve Scherer

EHR Integration WG leaders:

- Erwin Bottinger
- Justin Starren