VANDERBILT UNIVERSITY
MEDICAL CENTER

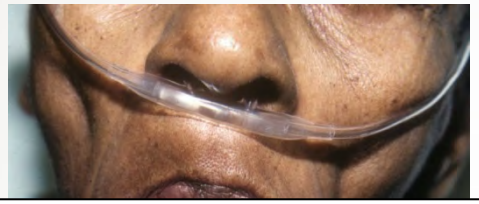
Pharmacogenomics Research Network (PGRN) programs related to genomic medicine implementation: CPIC, TPP, eMERGE-PGx

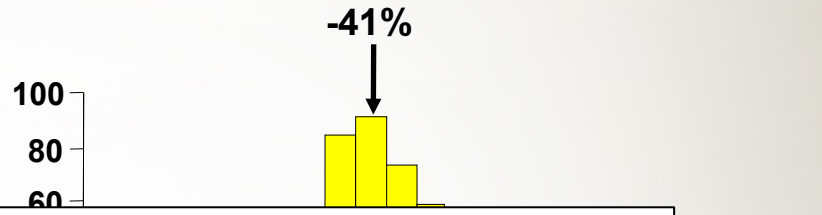
Dan M. Roden, MD
Assistant Vice Chancellor for Personalized Medicine
Vanderbilt University School of Medicine

Two faces of pharmacogenetics

Serious ADRs

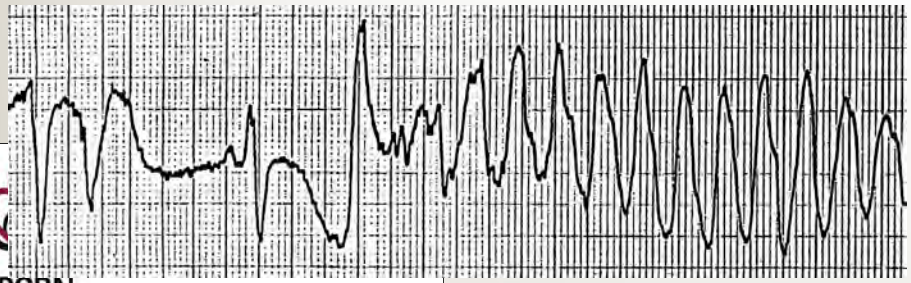
Variability in efficacy

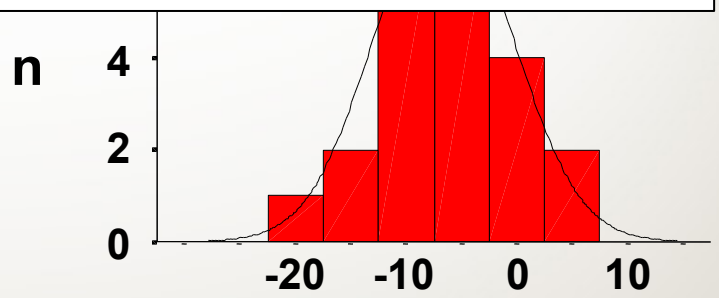




Pharmacogenomics Research Network

PGRN





NIGMS, NHLBI, NCI, NIDA, NICHD, NHGRI, NIMH, NIAMS, ORWH

- Research Groups
- Collaborating Sites
- Network Resources

PGRN Pharmacogenomics Research Network

Pharmacogenomics Research Network

PGRN

NEUROPSYCHIATRY

IMPLEMENTATION

Pharmacogenomics of Mood Stabilizers in Bipolar Disorder PGBD

Pharmacogenetics of Nicotine Addiction Treatment PNAT

Pharmacogenetics in Rural & Underserved Populations NWAP

External Scientific Panel ESP

Pharmacogenomics of Phase II Drug Metabolizing Enzymes PPII

Pharmacogenomics of Anti-Platelet Interventions PAPI

ONCOLOGY

CARDIOVASCULAR

Pharmacogenomics of Anticancer Agents PAAR

Global Alliance RIKEN CGM

Pharmacogenomics of Arrhythmia Therapy PAT

Steering Committee

Coordinating Committee

Investigators & NIH Staff

Pharmacogenomics of Anticancer Agents in Children PAAR4Kids

Pharmacogenomics of Antihypertensives PEAR

Pharmacogenomics of Membrane Transporters PMT

Pharmacogenomics and Risk of Cardiovascular Disease PARC

Publications

CNS

CV-Pul

Sys Biol

WORKING GROUPS

Expression Genetics in Drug Therapy XGEN

Pharmacogenomics of Rheumatoid Arthritis Therapy PhRAT

Pharmacogenomics of Asthma Treatment PHAT

IWPC

ISPC

CPIC

CONSORTIA at PharmGKB

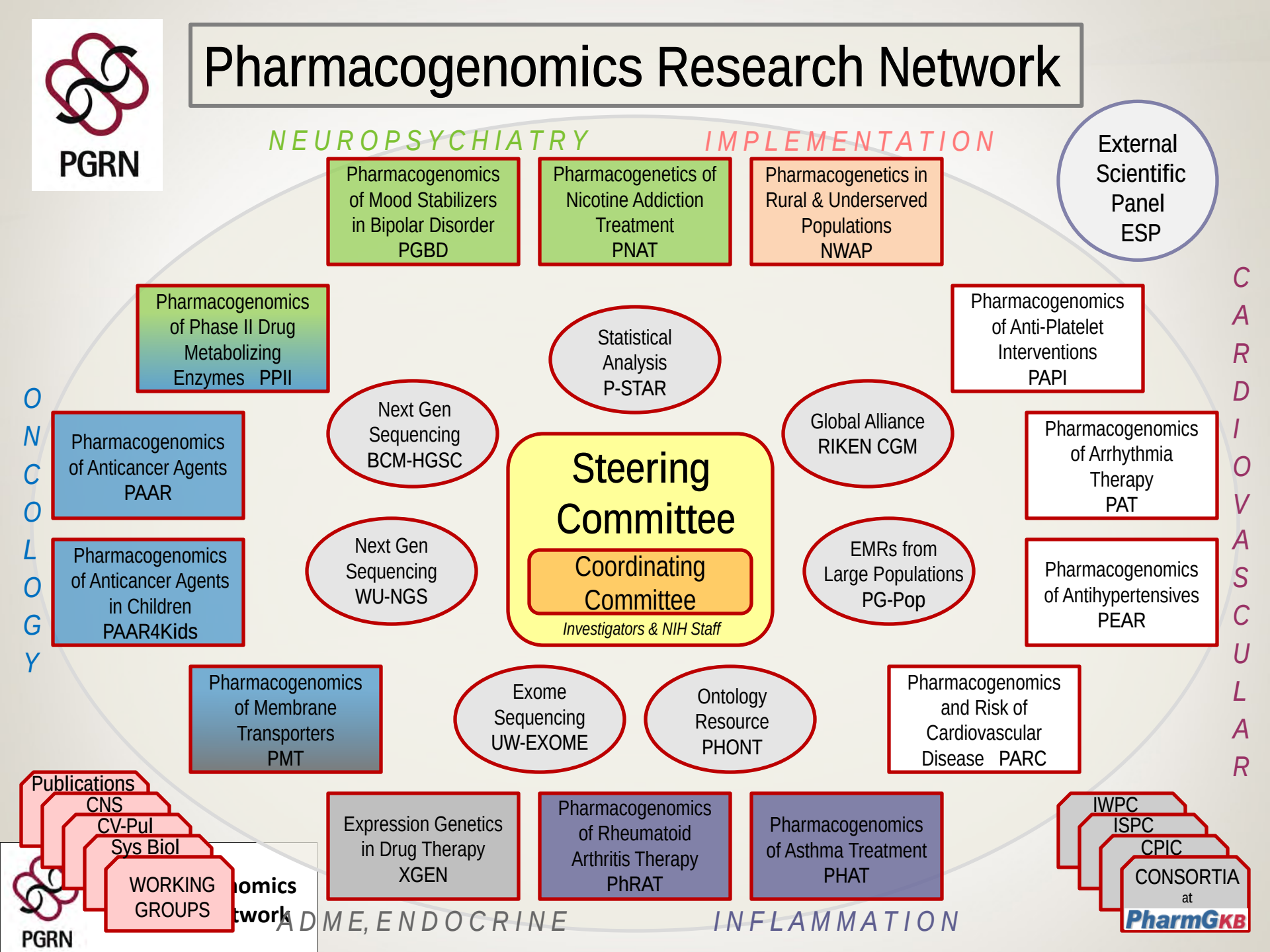
PGRN

omics

twork

ADME, ENDOCRINE

INFLAMMATION


PGRN
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Statistical Analysis P-STAR
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EMRs from Large Populations PG-Pop
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Exome Sequencing UW-EXOME
Ontology Resource PHONT
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PharmGKB

The Pharmacogenomics Knowledgebase

Pharmacogenomics. Knowledge. Implementation.

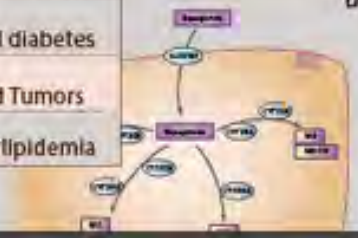
PharmGKB is a comprehensive resource that curates knowledge about the impact of genetic variation on drug response for clinicians and researchers.

About Us | News & Events | Projects | Search | Download | Help

Search PharmGKB: Search

CYP2C8 substrates

Drug Name	Indication
Repaglinide	Type II diabetes
Rosiglitazone	Type II diabetes
Paclitaxel	Solid Tumors
Cerivastatin	Hyperlipidemia



*How would **CYP2C8 variants** affect disposition and response to antidiabetic agents?*

Find out more

- CYP2C8 VIP Summary
- UGT1A1 VIP summary
- Venlafaxine PK Pathway
- CPIC TCAs/CYP2D6 and CYP2C19
- PharmGKB Knowledge Pyramid

Clinically-Relevant PGx

- Well-known PGx associations
- Clinically relevant PGx summaries
- PGx drug dosing guidelines
- Drug labels with PGx info
- Genetic tests for PGx
- Star (*) allele translations

PGx-Based Drug Dosing Guidelines

- CYP2C19 and CYP2D6/amitriptyline and nortriptyline:
  article and supplement
- HLA-B/allopurinol:
  article and supplement
- more guidelines...

CPIC Gene-Drug Pairs

TPP Gene Tables

PGx Research

- VIP: Very Important PGx gene summaries
- View PharmGKB pathways
  - Alphabetically
  - By therapeutic category
- Annotated SNPs by gene
- Drugs with genetic information

Research Network

PGRN

The implementation vision

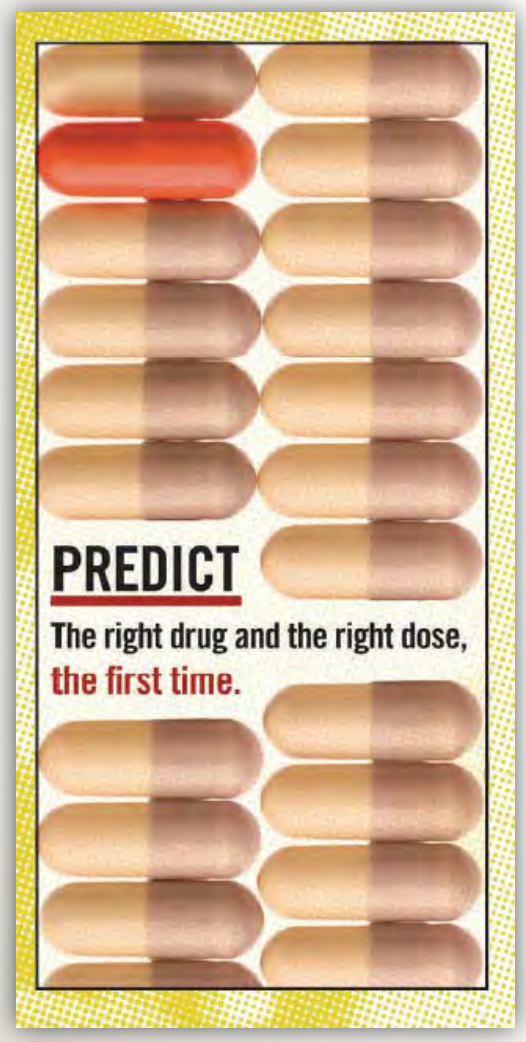
"Here's my sequence…"

New Yorker, 2000

- The Vanderbilt PREDICT program
- The Clinical Pharmacogenomics Implementation Consortium
- The Translational Pharmacogenomics Program in PGRN
- The eMERGE-PGx project

PREDICT

Pharmacogenomic Resource for Enhanced Decisions In Care and Treatment



1. Select populations of patients who are "**at high risk**" for receiving a drug with an actionable "pharmacogenetic" story.
2. Genotype all of them on a platform that assays genotypes important for variable actions of many drugs preemptively.
3. Store the genotypes, develop the informatics tools to provide point-of-care advice. Track outcomes. The "easy stuff".

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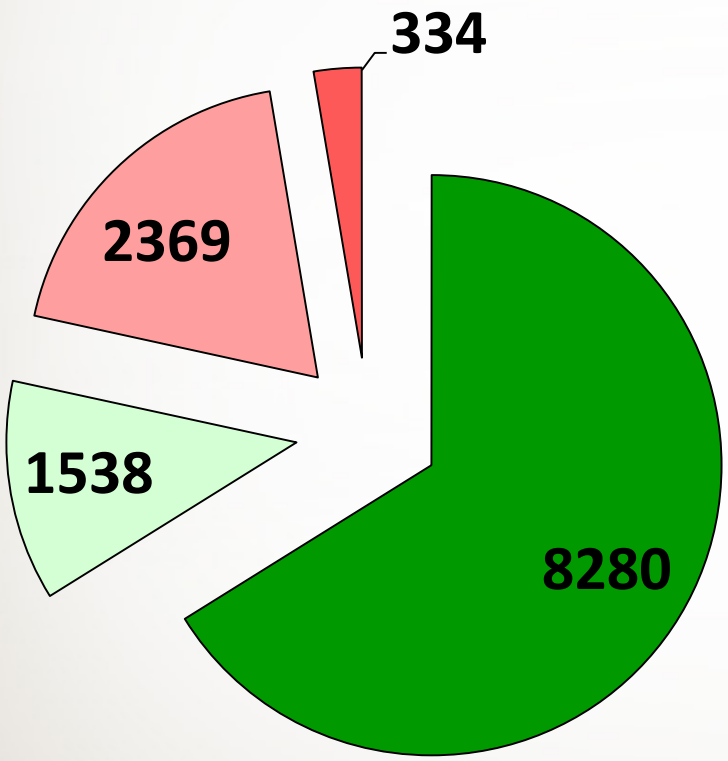
Clopidogrel label revision March 2010 identifies a high risk group

WARNING: DIMINISHED EFFECTIVENESS IN POOR METABOLIZERS

See full prescribing information for complete boxed warning.

- Effectiveness of Plavix depends on activation to an active metabolite by the cytochrome P450 (CYP) system, principally CYP2C19. (5.1)
- Poor metabolizers treated with Plavix at recommended doses exhibit higher cardiovascular event rates following acute coronary syndrome (ACS) or percutaneous coronary intervention (PCI) than patients with normal CYP2C19 function. (12.5)
- Tests are available to identify a patient's CYP2C19 genotype and can be used as an aid in determining therapeutic strategy. (12.5)
- Consider alternative treatment or treatment strategies in patients identified as CYP2C19 poor metabolizers. (2.3, 5.1)

CYP2C19 genotypes in 12,521 PREDICT patients (9/2010-4/2013)

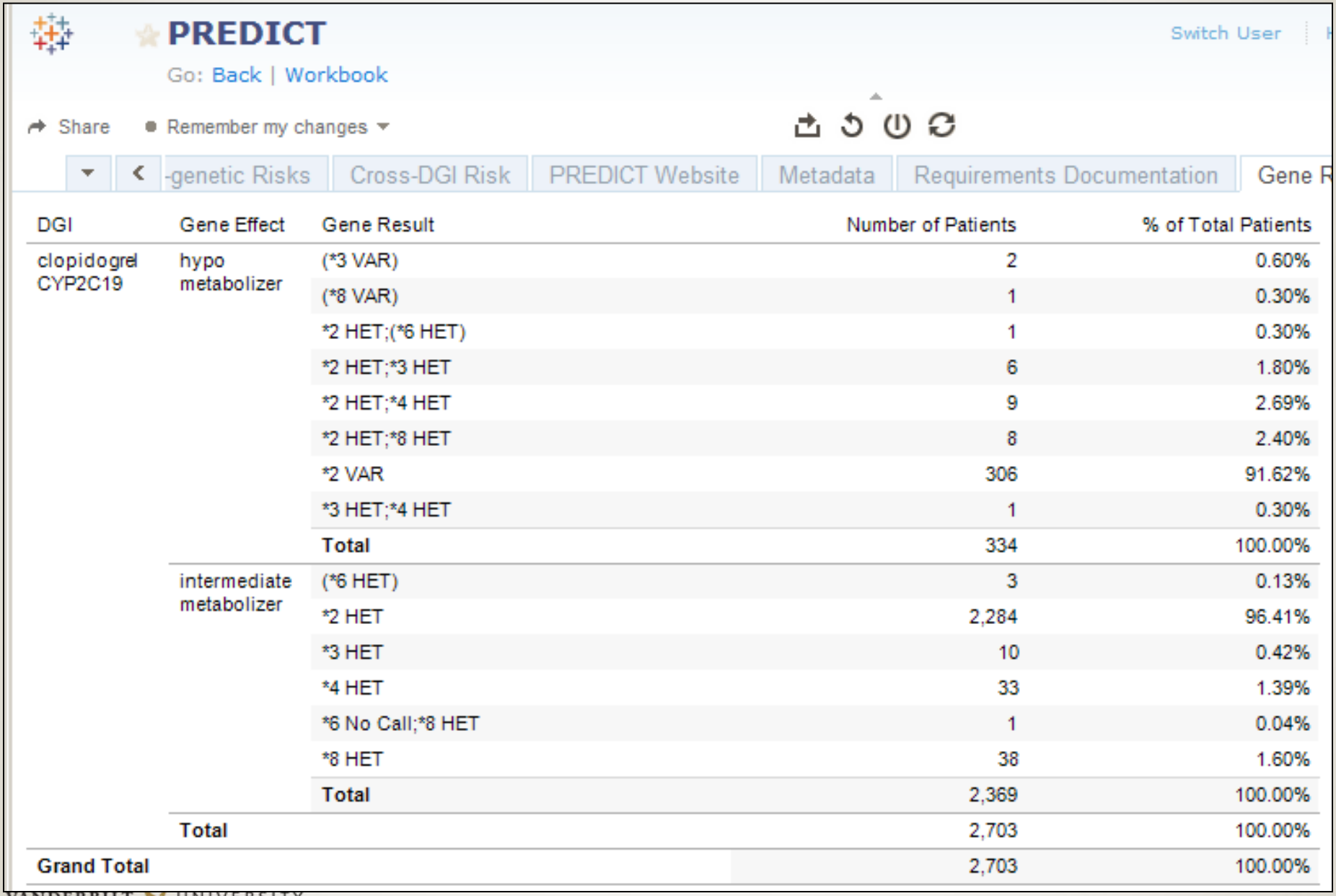


2.7% homozygous

18.9% heterozygous

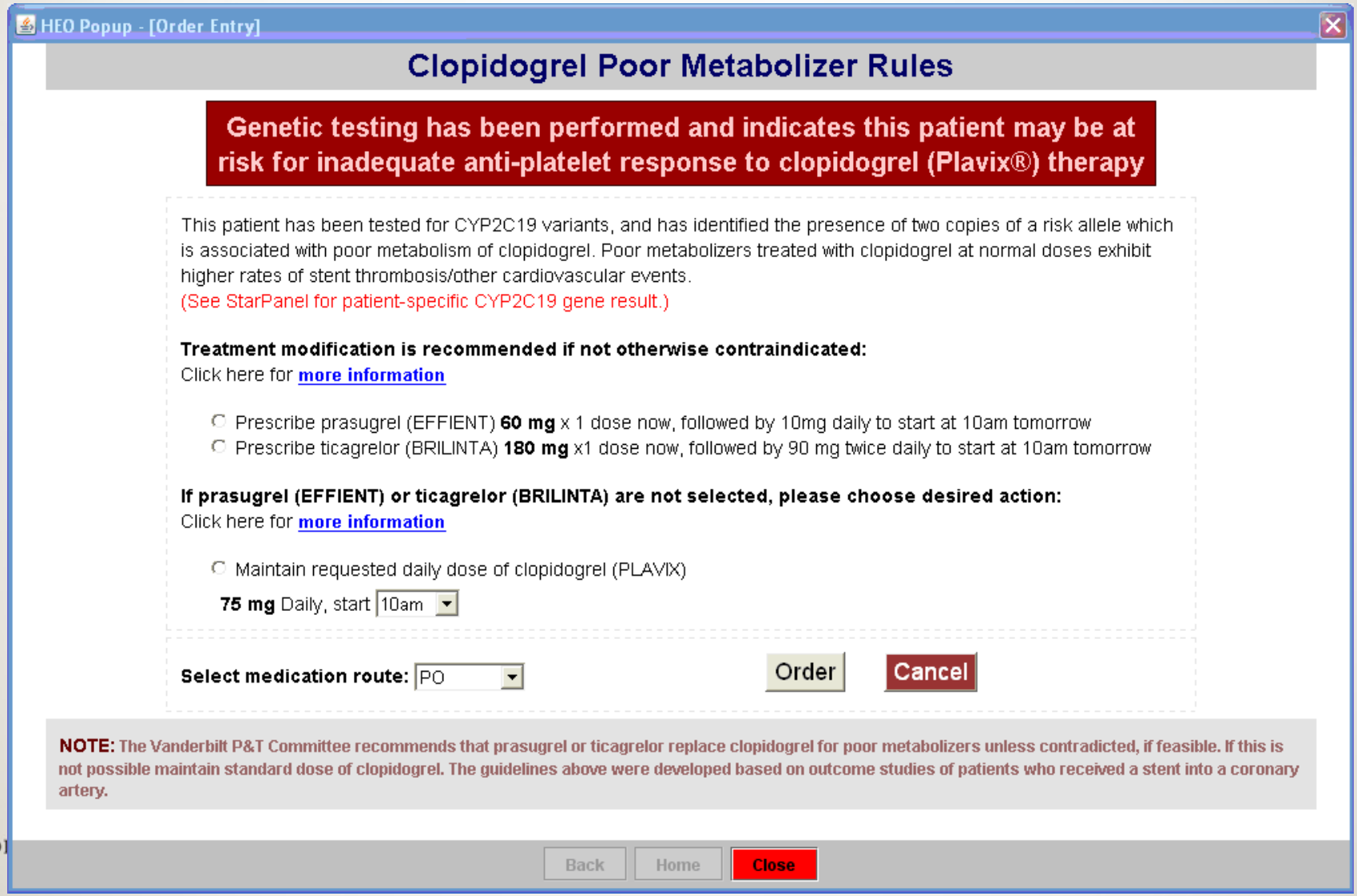
12.2% non-actionable variant

66.1% no common variant



DGI	Gene Effect	Gene Result	Number of Patients	% of Total Patients
clopidogrel CYP2C19	hypo metabolizer	(*3 VAR)	2	0.60%
		(*8 VAR)	1	0.30%
		*2 HET;(*6 HET)	1	0.30%
		*2 HET;*3 HET	6	1.80%
		*2 HET;*4 HET	9	2.69%
		*2 HET;*8 HET	8	2.40%
		*2 VAR	306	91.62%
		*3 HET;*4 HET	1	0.30%
		Total	334	100.00%
	intermediate metabolizer	(*6 HET)	3	0.13%
		*2 HET	2,284	96.41%
		*3 HET	10	0.42%
		*4 HET	33	1.39%
		*6 No Call;*8 HET	1	0.04%
		*8 HET	38	1.60%
		Total	2,369	100.00%
	Total		2,703	100.00%
Grand Total			2,703	100.00%

Point of care decision support Vanderbilt



Point of care decision support University of Maryland

Phenotype: POOR METABOLIZER

Treatment recommendation for this patient:

Problem: This patient's CYP2C19 genotype is associated with very impaired metabolic activation of the prodrug clopidogrel (Plavix) and impaired response to clopidogrel.

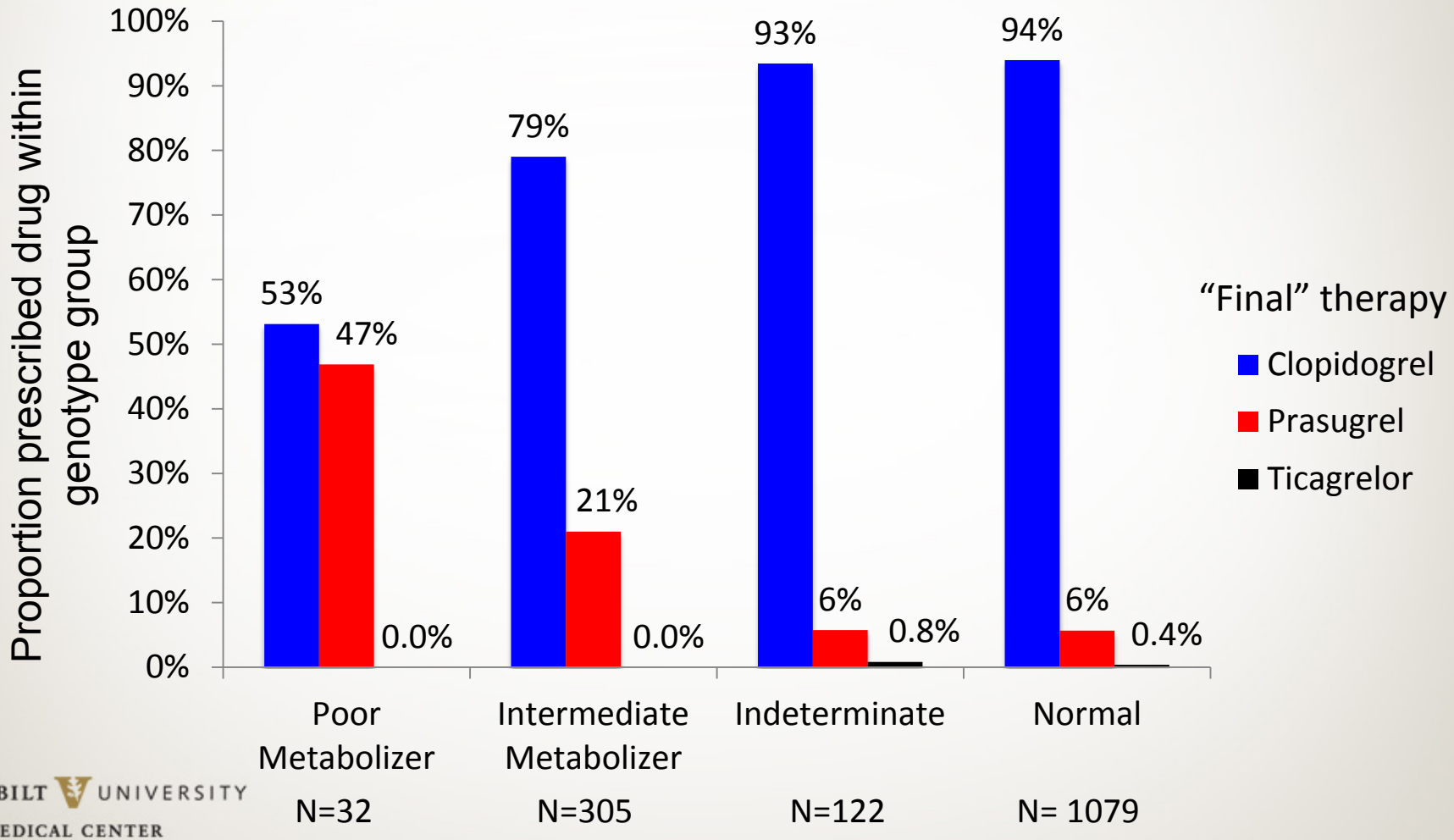
Reasons: In patients with ACS or who undergo PCI, reduced clopidogrel activation in this genotype results in significantly reduced active metabolite levels, reduced platelet inhibition, increased residual platelet aggregation, and decreased clinical efficacy (elevated risk for recurrent major cardiovascular events, including stent thrombosis).

Recommendations:
MODIFY TREATMENT BY CHOOSING ONE OF THE FOLLOWING:
Prescribe:
Prasugrel (EFFIENT) 60 mg loading dose followed by 10 mg daily
or
Ticagrelor (BRILINTA) 180 mg loading dose followed by 90 mg twice daily

PGRN

First data peek…

- 7405 PREDICT genotyped patients from 10/1/2010 to 6/30/2012:
  - 1620 with stent placed
  - "final" antiplatelet therapy identified at 90 days



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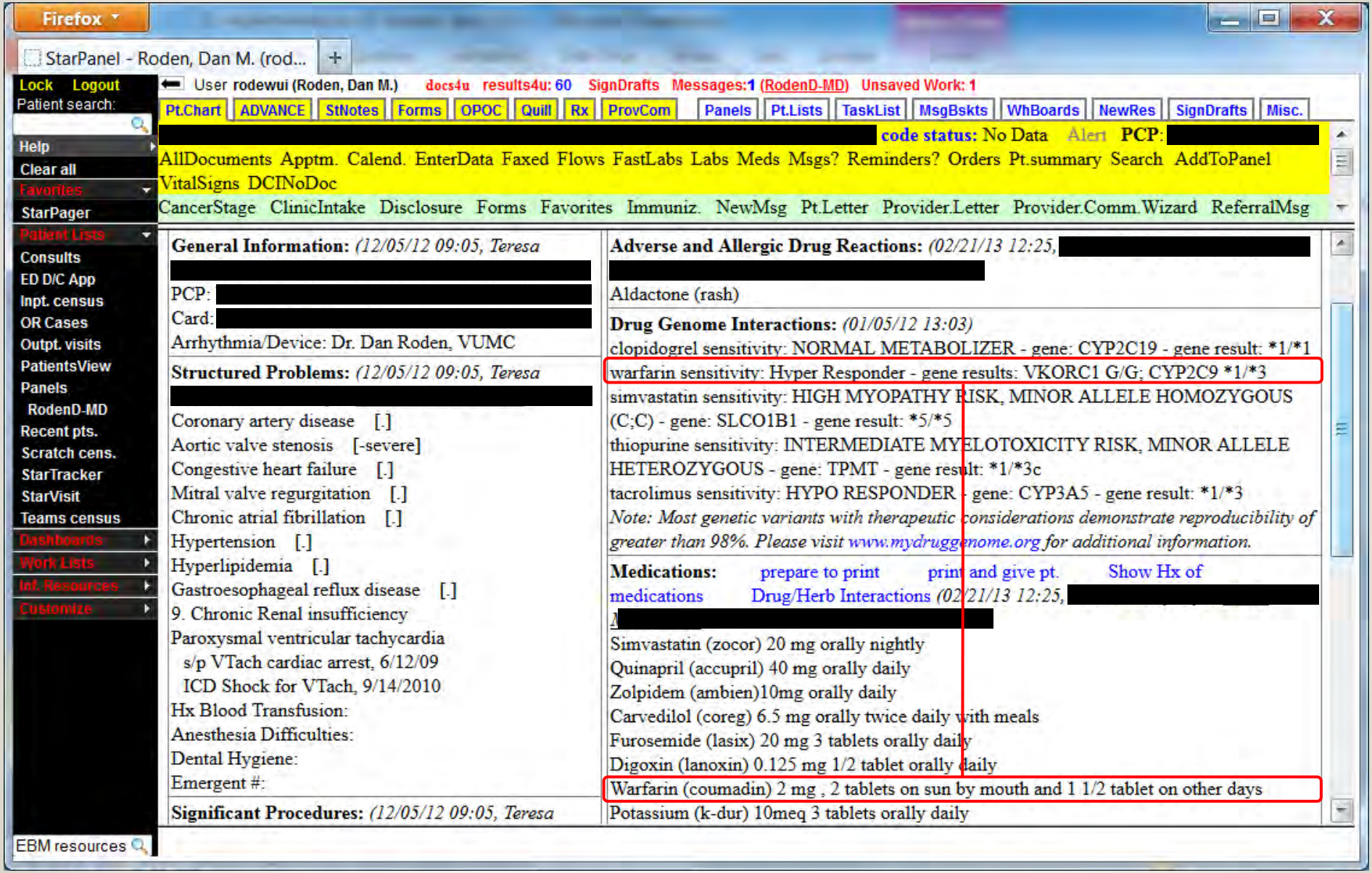
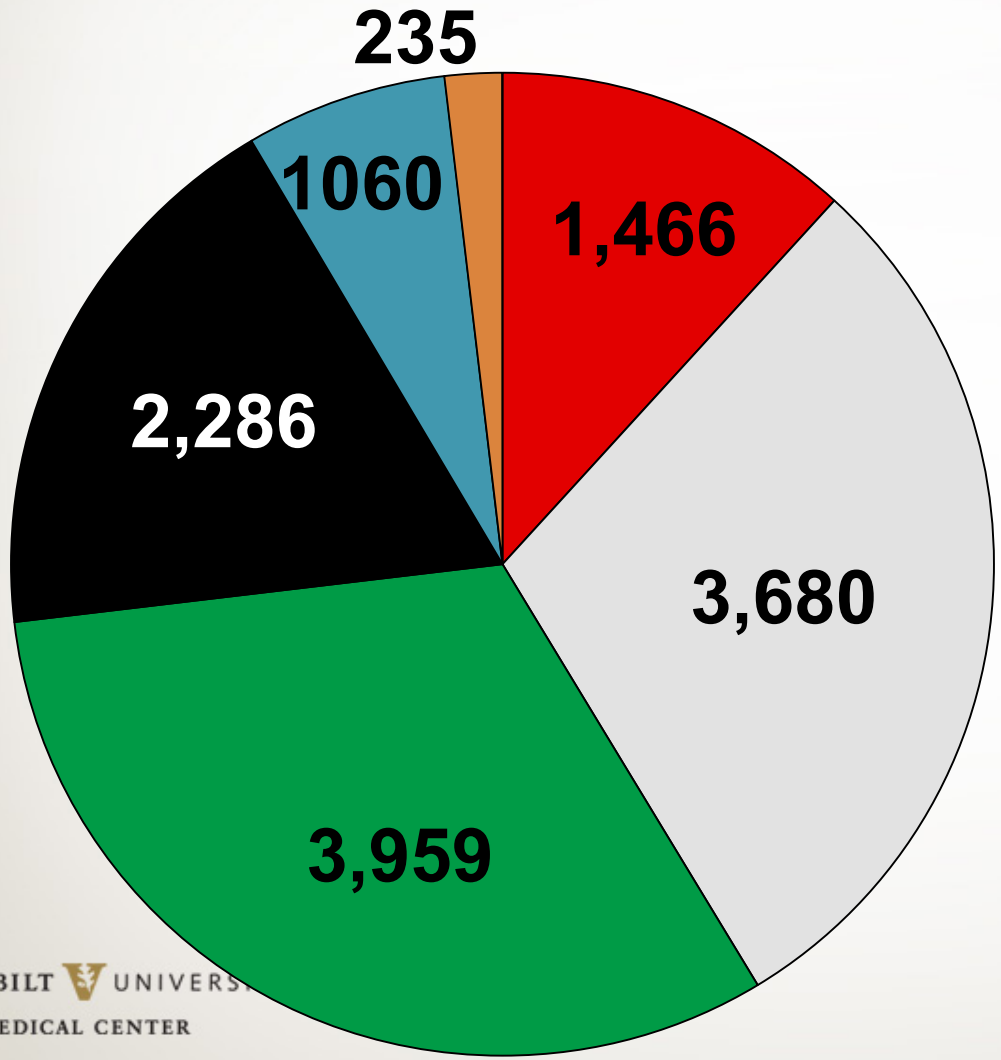

Firefox
StarPanel - Roden, Dan M. (rod...
Lock Logout
Patient search:
Help
Clear all
Favorites
StarPager
Patient Lists
Consults
ED D/C App
Inpt. census
OR Cases
Outpt. visits
PatientsView
Panels
RodenD-MD
Recent pts.
Scratch cens.
StarTracker
StarVisit
Teams census
Dashboards
Work Lists
Inf. Resources
Customize
EBM resources
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 MsgBskts WhBoards NewRes SignDrafts Misc.
[redacted] code status: No Data Alert PCP: [redacted]
AllDocuments Apptm. Calend. EnterData Faxed Flows FastLabs Labs Meds Msgs? Reminders? Orders Pt.summary Search AddToPanel
VitalSigns DCINoDoc
CancerStage ClinicIntake Disclosure Forms Favorites Immuniz. NewMsg Pt.Letter Provider.Letter Provider.Comm.Wizard ReferralMsg
General Information: (12/05/12 09:05, Teresa
[redacted]
PCP: [redacted]
Card: [redacted]
Arrhythmia/Device: Dr. Dan Roden, VUMC
Structured Problems: (12/05/12 09:05, Teresa
[redacted]
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]
[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 MYELOTOXICITY 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

Multiplexed testing for pharmacogenetic variants

(after 5 drug-gene pairs…)



Total n=12,451
(9/10-4/13)

- 0 variants (11.8%)
- 1 variant (29.6%)
- 2 variants (31.8%)
- 3 variants (18.4%)
- 4 variants (6.6%)
- ≥5 variants (1.9%)

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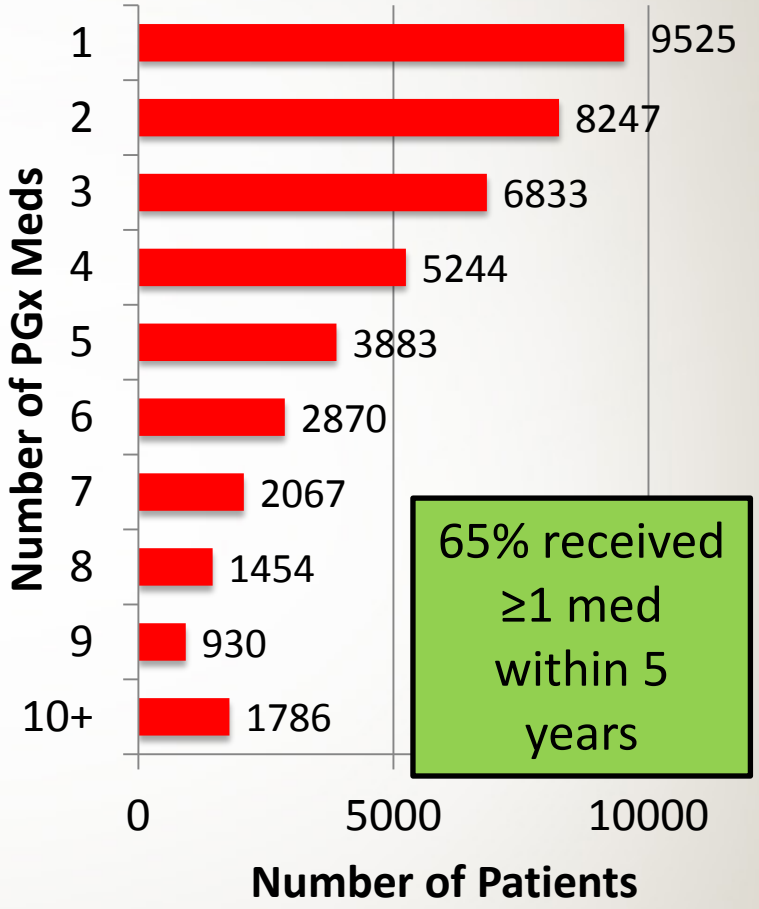
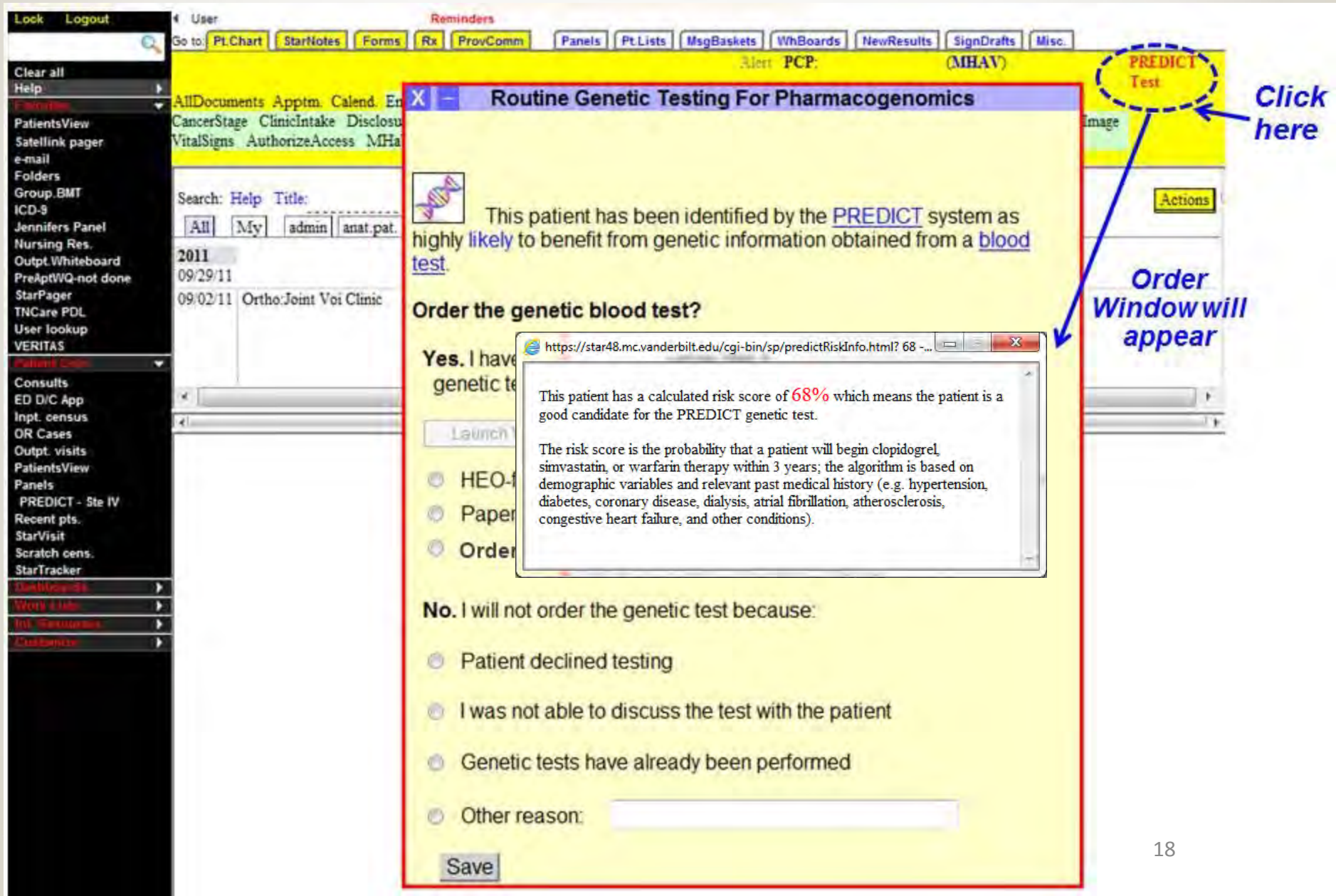
Another group at "high risk"

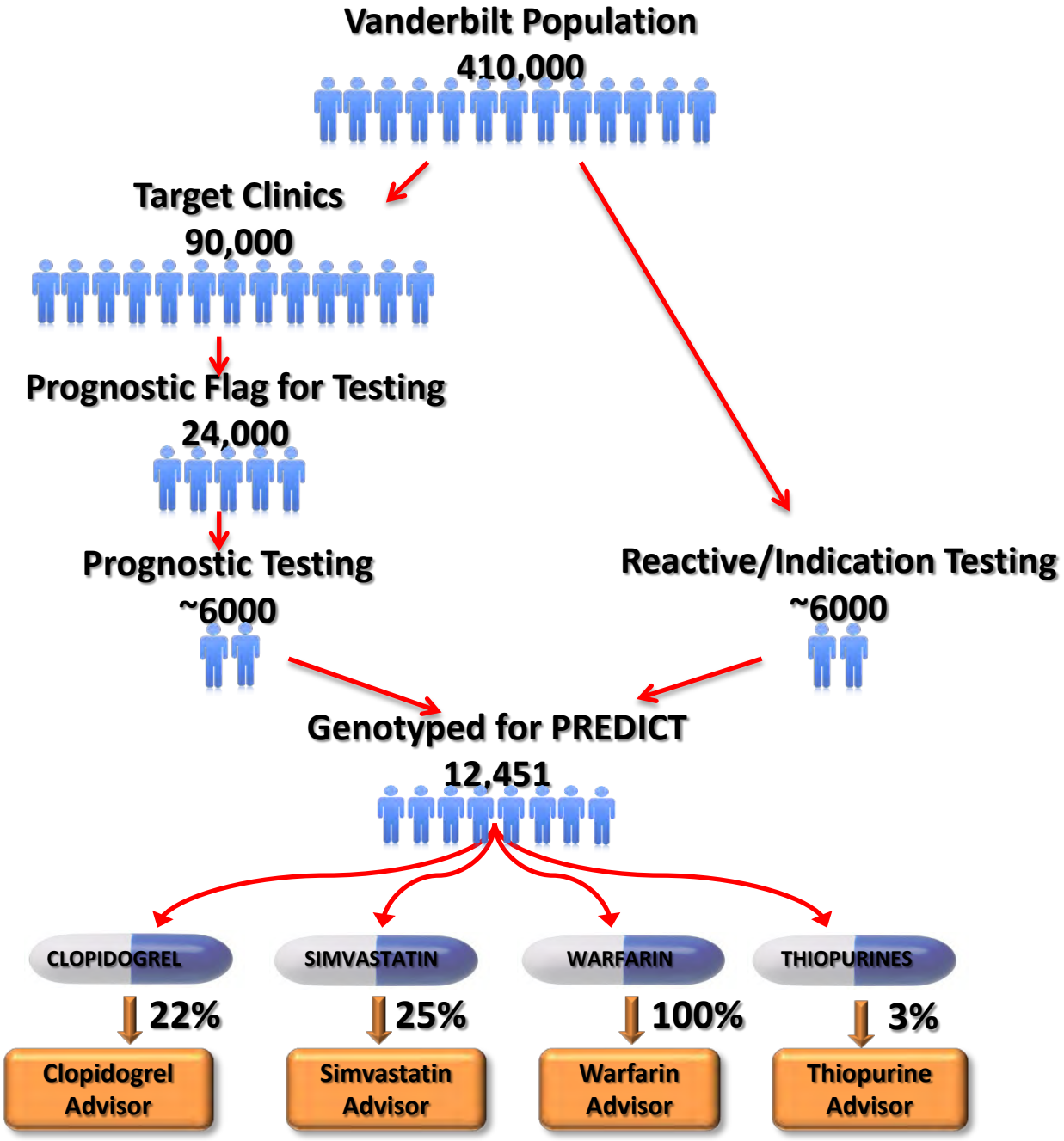
A case for preemptive genotyping

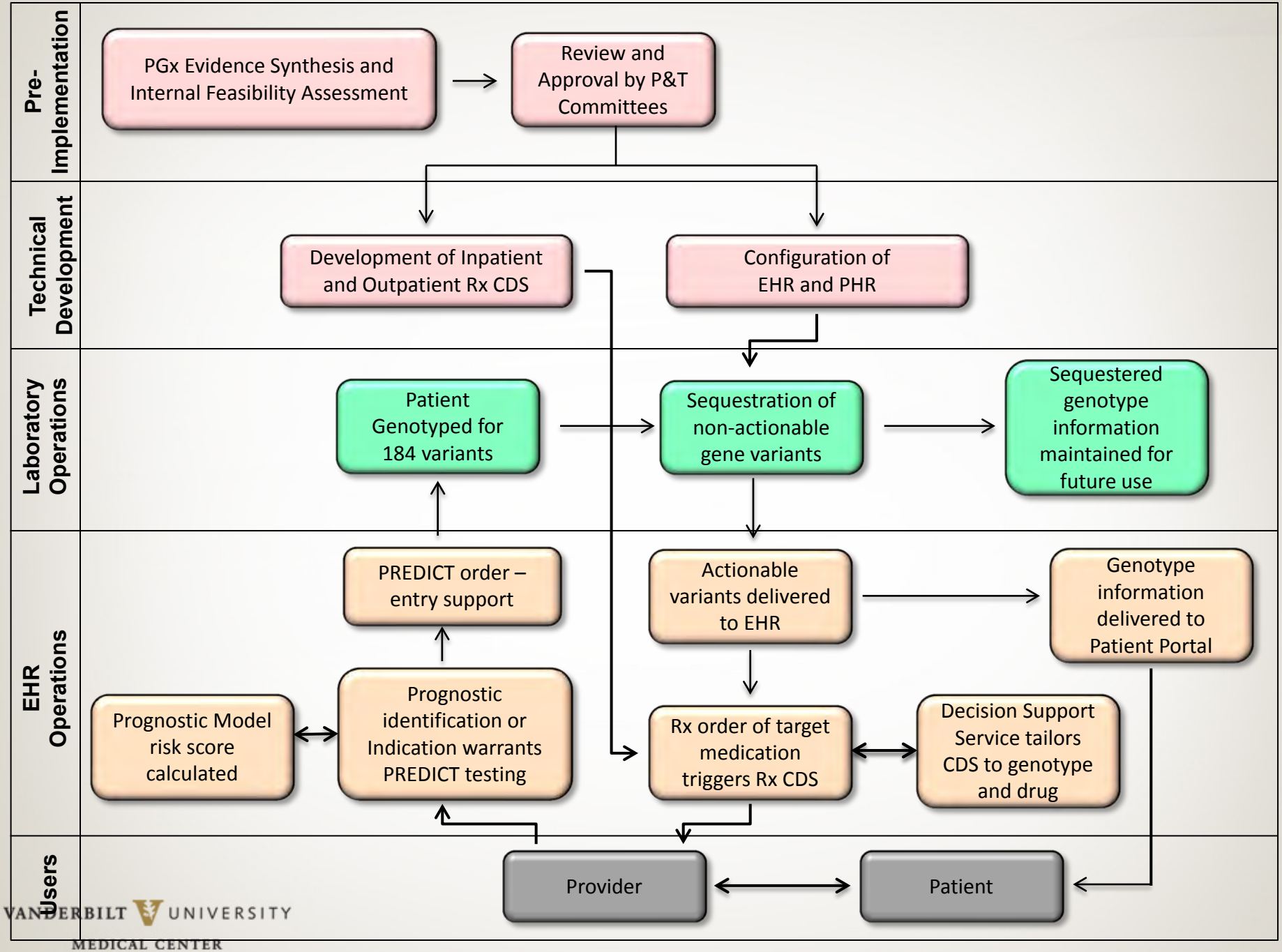
In a cohort of 53,196 "Medical Home" patients followed for up to 5 years, how many received one of 58 drug(s) that include PGx information in their FDA label?



Prognostic Model Ordering CDS



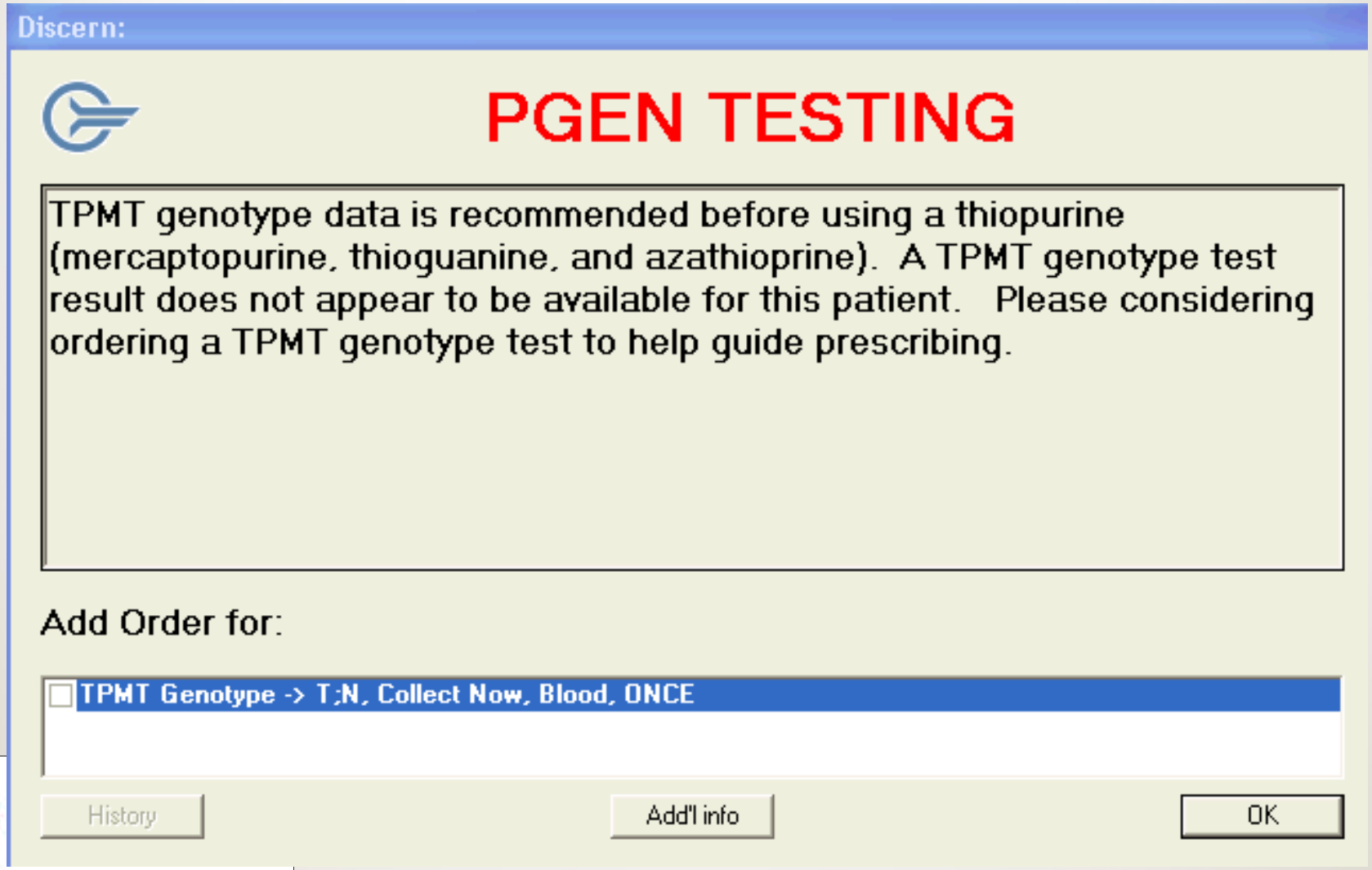

Vanderbilt Population
410,000
Target Clinics
90,000
Prognostic Flag for Testing
24,000
Prognostic Testing
~6000
Reactive/Indication Testing
~6000
Genotyped for PREDICT
12,451
CLOPIDOGREL
SIMVASTATIN
WARFARIN
THIOPURINES
22%
25%
100%
3%
Clopidogrel Advisor
Simvastatin Advisor
Warfarin Advisor
Thiopurine Advisor


Pre-Implementation
PGx Evidence Synthesis and Internal Feasibility Assessment
Review and Approval by P&T Committees
Technical Development
Development of Inpatient and Outpatient Rx CDS
Configuration of EHR and PHR
Laboratory Operations
Patient Genotyped for 184 variants
Sequestration of non-actionable gene variants
Sequestered genotype information maintained for future use
EHR Operations
PREDICT order – entry support
Actionable variants delivered to EHR
Genotype information delivered to Patient Portal
Prognostic Model risk score calculated
Prognostic identification or Indication warrants PREDICT testing
Rx order of target medication triggers Rx CDS
Decision Support Service tailors CDS to genotype and drug
Users
Provider
Patient

St. Jude patients frequently receive 33 high risk drugs

- In 2011, 2023 of 4245 patients (48%) who received medications at St. Jude received orders for at least one of 33 “high-risk” drugs.
- Over 18% of patients received codeine or tramadol
  - 12% of these patients can be expected to have high-risk diplotypes and therefore require alternative agents

TPMT Pre-pharmacogenetic test warning: at point of care to prescriber



PGRN

WARNING

This patient has an active entry on the problem list CYP2D6 ULTRA-RAPID METABOLIZER. Ultra-rapid metabolizers of codeine are expected to experience a higher incidence of side effects from codeine than normal. Other pain medicines or cough suppressants should be considered. Please consult a clinical pharmacist or review the clinical pharmacy consult note related to this problem.

Alert Action

- Cancel entry
- Continue w/order
- modify entry

OK

Pharmacogenomics Research Network

PGRN

CPIC: Implementing PGx

a PharmGKB & PGRN collaboration

- CPIC's framework: if you had the genotype result, how should you act on it?
  - > 60 Clinicians, scientists
  - 33 institutions
  - 12 countries
  - Observers: NIH and FDA

PGRN Translational Pharmacogenetics Project (TPP)

- Goal: Implement CPIC guidelines into diverse real-world clinical settings
  - Harness the multidisciplinary expertise of the PGRN to implement routine 'actionable' pharmacogenetic based dosing and drug selection within diverse health care systems.

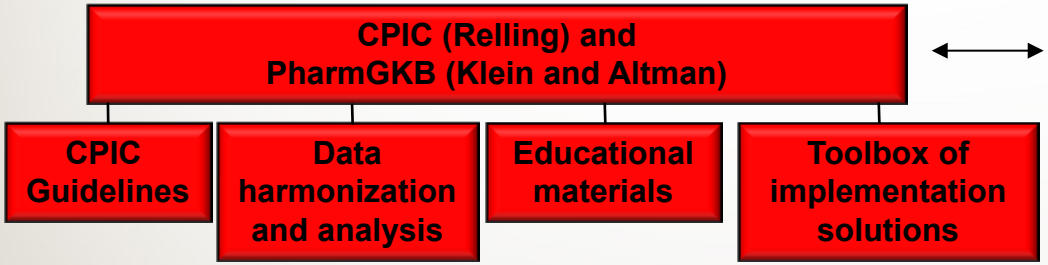
……the "Science of Translation"

Pharmacogenomics Research Network

PGRN

PGRN Translational Pharmacogenomics Project (TPP): Translating CPIC Guidelines into Clinical Practice

- Aim 1: Accelerate writing/publication of CPIC guidelines
- Aim 2: Implementation of CLIA-approved evidence-based pgx tests for patient care.
  - Egs., *TPMT*/thiopurines; *CYP2C19*/clopidogrel; *CYP2C9, CYP4F2* and *VKORC1*/warfarin; DMET/preemptive testing; custom panels
  - Report results in EHR/develop clinical decision support tools
  - Track implementation metrics (test adoption rates, test turnaround times, test results, genotype failure rates, and the number of prescription modifications)
- Aim 3: Develop and implement methodologies and standardized formats to report results to prescribers
  - Identify common logistical barriers and develop a "tool-box" of solutions
- Aim 4: Facilitate adoption of pgx; disseminate information

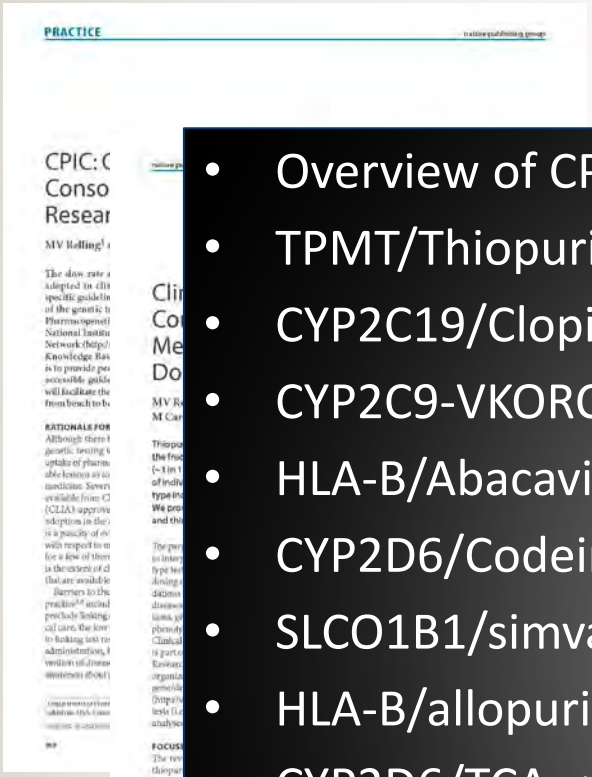


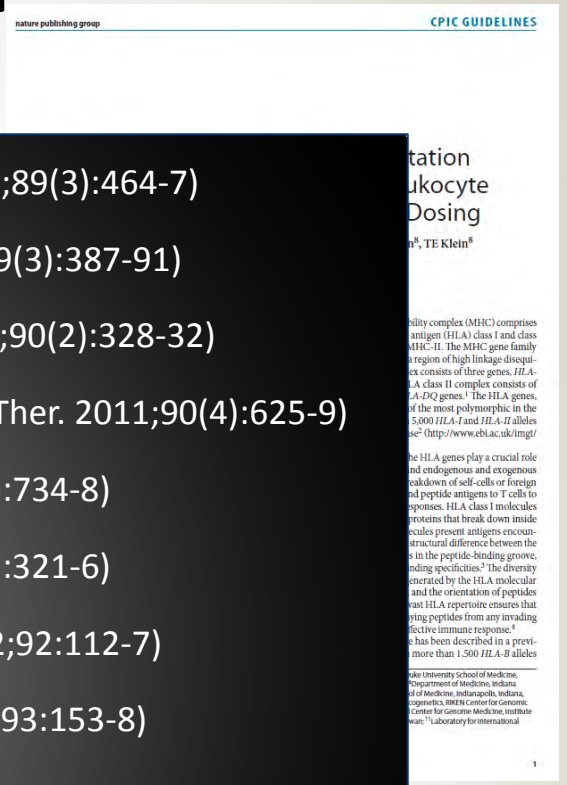
Implementation Sites

- **University of Maryland (Shuldiner – PI)**
- **University of Florida (Johnson)**
- **Vanderbilt University (Roden and Peterson)**
- **St Judes Children's Research Hospital (Relling)**
- **Ohio State University (Sadee and Embi)**
- **Mayo Clinic (Weinshilboum and Pereira)**
- **University of Chicago (Ratain and O'Donnell)**
- **Partners/Harvard (Weiss and Tantisira)**

PGRN **Pharmacogenomics Research Network**

Aim 1: CPIC Guidelines/Updates





- Overview of CPIC (Relling and Klein, Clin Pharmacol Ther. 2011;89(3):464-7)
- TPMT/Thiopurines (Relling et al., Clin Pharmacol Ther. 2011;89(3):387-91)
- CYP2C19/Clopidogrel (Scott et al., Clin Pharmacol Ther. 2011;90(2):328-32)
- CYP2C9-VKORC1/Warfarin (Johnson et al., Clin Pharmacol Ther. 2011;90(4):625-9)
- HLA-B/Abacavir (Martin et al., Clin Pharmacol Ther. 2012; 91(4):734-8)
- CYP2D6/Codeine (Crews et al. Clin Pharmacol Ther. 2012;91(2):321-6)
- SLCO1B1/simvastatin (Wilke et al., Clin Pharmacol Ther. 2012;92:112-7)
- HLA-B/allopurinol (Hershfield et al. Clin Pharmacol Ther. 2013;93:153-8)
- CYP2D6/TCAs (Hicks et al. Clin Pharmacol Ther. 2013;93:402-8)
- HLA-B/carbamazepine (Leckband et al., submitted)
- Updates (TPMT/Thipurines, in press; CYP2C19/clopidogrel, in press)
- Others in progress:
  - DPYD-5FU/capecitabine, HLA-B/phenytoin, G6PD/rasburicase, Septra, UGT1A1/irinotecan, IL28B/pegintron, CTFR/Ivacaftor, CYP2D6/SSRIs

CPIC Guidelines
Immediate future plans

- New CPIC Guidelines in Progress or Planned
  - DPYD-5FU/capecitabine
  - HLA-B/phenytoin
  - G6PD/rasburicase, Septra
  - UGT1A1/irrenotecan
  - IL28B/pegintron
  - CTFR/Ivacaftor
  - CYP2D6/SSRIs
- Updates (6)
- Improved linkage between CPIC guidelines and PGRN tools

Aim 2: Implementation

- CYP2C19/clopidogrel – all sites
- Others (1 or more sites)
  - TPMT-azathioprine, thioguanine, mercaptopurin
  - HLA-B*5701-Abacavir
  - HLA-B*1502-Carbamazepine
  - IL28B-Ribavirin-Pegylated Interferon
  - CYP2D6-codeine, amitriptyline, tramadol, fluoxetine, paroxetine, ondansetron
  - SLCO1B1-simvastatin
  - CYP2C9/VKORC1-CYP2C9
- Models
  - Targeted rapid turn-around
    - Single gene (UMD, Mayo)
  - Pre-emptive
    - Multiplex
      - DMET/ADME platform (VU, St. Jude, OSU)
      - Custom panels (UFl)

Aim 2:
Implement PGx

University of Florida	
CYP2C19	Count
*1/*2	115
*1/*8	1
*2/*17	32
*2/*2	7
*2/*3	2
*8/*17	1
Total Actionable	158
Total Results	598
Percent Actionable	26%

St. Jude (PAAR4Kids)	
TPMT	Count
*1/*3A,*3B/*3C	33
*1/*3C	19
*1/*8	7
*1/*1,*1/*2,*2/*2	1
Total Actionable	60
Total results	610
Percent Actionable	10%

Vanderbilt	
SLC01B1	Count
*1/*1	7264
*1/*5	2379
*5/*5	190
Invalid Result	5
Uncharacterized genotype	213
Grand Total	10051

Pharmacogenomics Research Network

PGRN

Tracking Implementation Metrics

Pharmacogenetic (Pgx) Testing Adoption
Platform (e.g., Illumina ADME Chip, Affy DMET Array, Taqman, etc.)
Genes
Target populations
Testing volume (cumulative total; by month)
Test ordered and mode of order entry (e.g., Computerized Physician Order Entry, EMR, Paper, Automated rule)
Role of provider ordering the test
Practice setting where the order originated (e.g., inpatient, outpatient)
Cost of testing
Number of tests ordered but not completed
Other lab QA measures: genotype failure rates, call rates, concordance, test turnaround time
Pharmacogenetic test adoption rates for a prospective or anticipatory model
Pharmacogenetic test adoption rates for a prescription and indication specific model
Pharmacogenetic Test Results
Timing of result: Median time between Pgx order and Pgx report to prescribers
Median time between Pgx result and new or revised target drug order
Genotype distribution by haplotype
Proportion of tested patients with actionable genotypes (meet criteria for consult or CDS)
Pgx Consultation and Clinical Decision Support (CDS)
Number of Pre-emptive tests (Automated trigger vs. Provider requested / On-demand)
Automated clinical decision support delivery vehicle (e-prescribing / CPOE / EMR), method [active (interruptive)/passive)], recommendation, and user response
Manual clinical decision support delivery – role, communication mode, successful contact w/ primary decision maker, response
Provider Genotype-Guided Prescription Metrics
Proportion of patients with Pgx Consultation/CDS leading to a new or revised prescription for target drug
Time between Pgx result and new or revised target drug order
Adherence to CPIC Pharmacogenomic Guidelines
Adherence to recommendation based on genotype
Reasons for non-adherence
Communication of Pharmacogenomic Information to Patients
Role of provider communicating results
Mode of communication (documented verbal discussion, messaging)

Lessons Being Learned

- More complicated than one might think
  - Engagement of many parties within the healthcare system especially “clinician champions”
- Strong institutional support
- Need for active clinical decision support that interactively interprets genetic data and guides providers through prescription options
- Recurrent education/in-service programs
- Iterative process:
  - Monitoring uptake of pharmacogenomic testing and genotype-tailored prescriptions as an early signal for implementation barriers that need to be addressed.

Aim 3: Develop standardized formats to report results to prescribers

- Results summary/TPP metrics tables
- Diplotype-phenotype and CDS "Look-up Tables"
  - CYP2C19
  - CYP2D6
  - TPMT

http://www.pharmgkb.org/page/tppTables

Aim 4: Dissemination

The Pharmacogenomics Research Network Translational Pharmacogenetics Program: Overcoming Challenges of Real-World Implementation

AR Shuldiner[1,2], MV Relling[3], JF Peterson[4,5], K Hicks[3], RR Freimuth[6], W Sadee[7], NL Pereira[8], DM Roden[4,9], JA Johnson[10] and TE Klein[11]; for the Pharmacogenomics Research Network Translational Pharmacogenetics Program Group

The pace of discovery of potentially actionable pharmacogenetic variants has increased dramatically in recent years. However, the implementation of this new knowledge for individualized patient care has been slow. The Pharmacogenomics Research Network (PGRN) Translational Pharmacogenetics Program seeks to identify barriers and develop real-world solutions to implementation of evidence-based pharmacogenetic tests in diverse health-care settings. Dissemination of the resulting toolbox of "implementation best practices" will prove useful to a broad audience.

Despite a number of important pharmacogenetic discoveries, substantial evidence supporting clinical utility, and US Food and Drug Administration labels recommending use of pharmacogenetic testing, few pharmacogenetic tests have made their way into routine clinical practice. Barriers to adoption of pharmacogenetic tests into practice are substantial and include (i) logistics of performing accurate and rapid turnaround genotyping in a Clinical Laboratory Improvement Amendments–approved laboratory setting; (ii) lack of a standardized format for the return of test results into the electronic health record; (iii) lack of prospective genotype-directed pharmacogenetic randomized clinical trials validating treatment algorithms; (iv) inexperience of many clinicians in interpreting and acting on pharmacogenetic information; (v) paucity of clear recommendations for pharmacogenetic testing by professional associations; (vi) lack of information infrastructure to provide decision support for genomic medicine; and (vii) cost considerations and reimbursement.

One barrier to clinical implementation addressed by the PGRN is the lack of clear, curated, peer-reviewed pharmacogenetic guidelines that translate laboratory test results into actionable prescribing decisions for specific drug–gene pairs. The PGRN Clinical Pharmacogenetics Implementation Consortium (CPIC) is a shared initiative between the Pharmacogenomics Knowledgebase (PharmGKB) and the PGRN. The CPIC produces clinical guidelines that are gene–drug pair specific, peer-reviewed, published, and posted to PharmGKB; the guidelines specifically do not consider how or why the genotype data were obtained but instead how to act on genotype data that have been obtained. CPIC guidelines contain information needed for clinical implementation, including tables that summarize the relevant functional gene variants and probable phenotypes, and recommendations regarding drug dosing or drug choice based on phenotype[1] (http://www.pharmgkb.org/page/cpic). All CPIC recommendations are extensively annotated and supported by graded evidence; in addition the strength of the recommendations is indicated. The guidelines are freely available at PharmGKB (http://www.pharmgkb.org/page/cpicGeneDrugPairs), are updated on a regular basis, and are not linked to any commercial services, genotyping platforms, or financial interests. CPIC guidelines published to date include

[1]Program in Personalized and Genomic Medicine and Department of Medicine, University of Maryland School of Medicine, Baltimore, Maryland, USA; [2]Geriatric Research and Education Clinical Center, Veterans Administration Medical Center, Baltimore, Maryland, USA; [3]Department of Pharmaceutical Sciences, St. Jude Children's Research Hospital, Memphis, Tennessee, USA; [4]Department of Medicine, Vanderbilt University School of Medicine, Nashville, Tennessee, USA; [5]Department of Biomedical Informatics, Vanderbilt University School of Medicine, Nashville, Tennessee, USA; [6]Department of Health Sciences Research, Mayo Clinic, Rochester, Minnesota, USA; [7]Ohio State University Program in Pharmacogenomics, XGEN Group, College of Medicine, The Ohio State University, Columbus, Ohio, USA; [8]Division of Cardiovascular Diseases, Department of Medicine, Mayo Clinic, Rochester, Minnesota, USA; [9]Department of Clinical Pharmacology, Vanderbilt University School of Medicine, Nashville, Tennessee, USA; [10]Department of Pharmacotherapy and Translational Research, and Center for Pharmacogenomics, University of Florida, Gainesville, Florida, USA; [11]Stanford University School of Medicine, Palo Alto, California, USA. Correspondence: AR Shuldiner (ashuldin@medicine.umaryland.edu)

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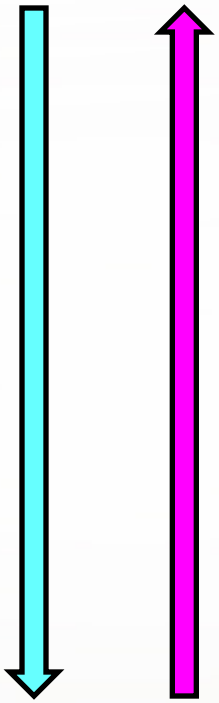
PGRN Pharmacogenomics Research Network

eMERGE-PGRN Partnership

PGRN Pharmacogenomics Research Network

PGx capabilities:

- Array-based assay for pharmacogenes
- Drug-gene guidelines
- CLIA & QC standards



EMR-informatics capabilities

- Privacy
- Electronic phenotyping
- Large populations

The *eMERGE* Network
electronic Medical Records & Genomics

PGRN Pharmacog Research Network

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

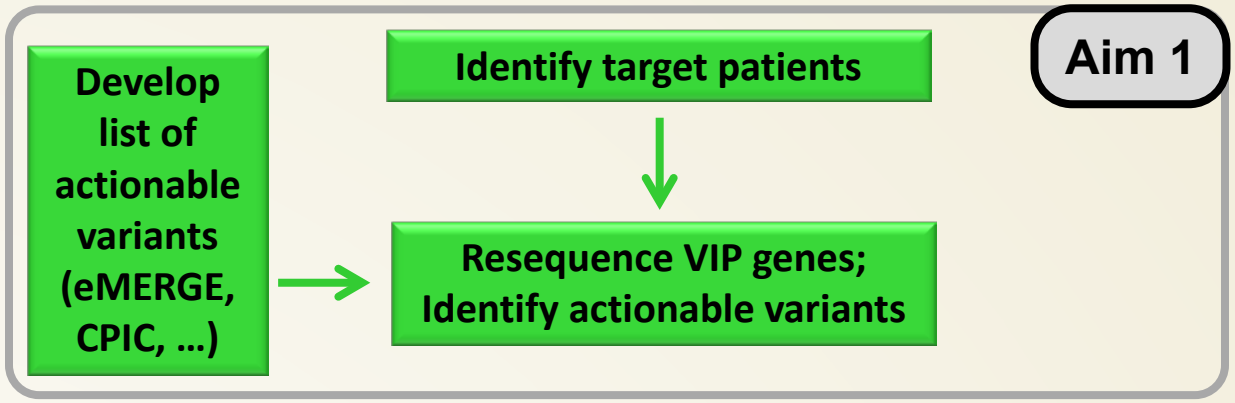
Average SNVs per Individual

Panel	Total SNVs	Novel SNVs	Unique SNVs
Panel 1- HapMap (n=64)	1325	45	33
Panel 2 - Golden (n=92) Thummel	1259	35	13

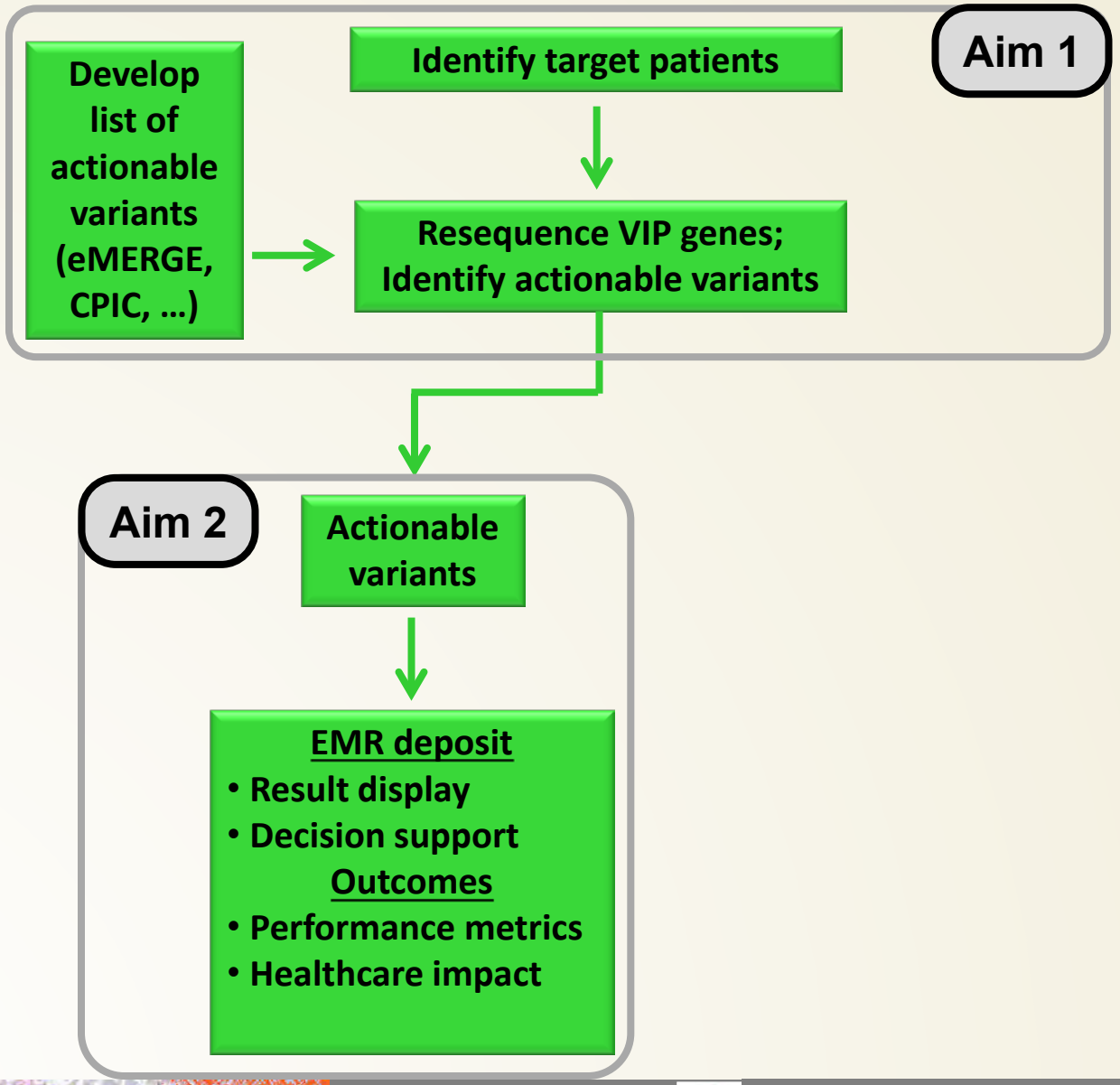
PGRN-Seq: Status/issues

- 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
- Comparison to Illumina ADME: 88/95 HapMap samples concordant at ~150 sites; one site accounts for discordance in 7 samples

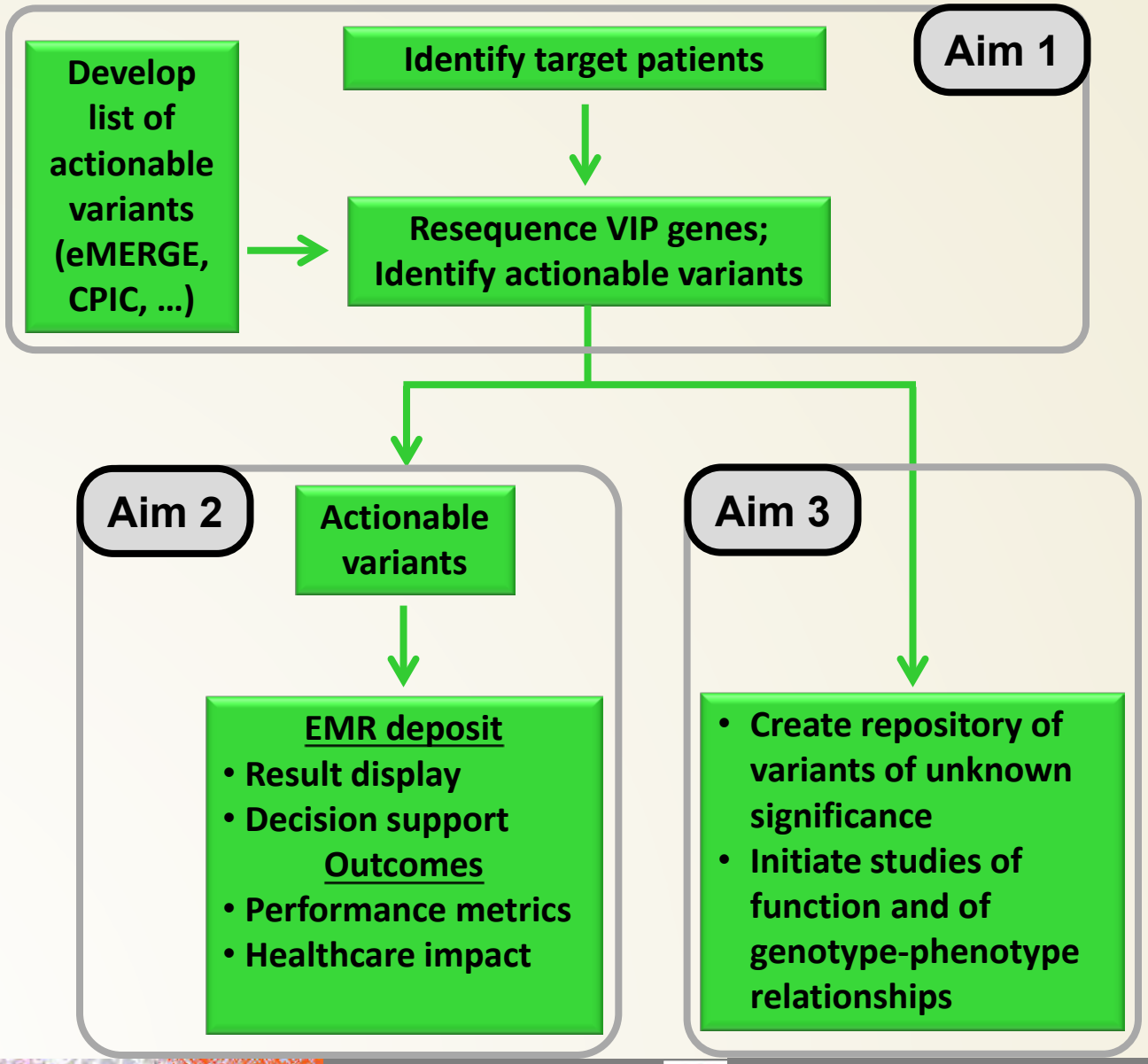
eMERGE-PGx project



eMERGE-PGx project



eMERGE-PGx project



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)**

Initial target drugs

NU	clopidogrel and warfarin have been approved Revisit simvastatin
Geisinger	Have not made a final decision, but likely simvastatin. Others are in planning stages.
GHC/UW	carbamazepine (other pairs implemented at the UW)
Mayo	abacavir, interferon, thiopurines, carbamazepine In planning: warfarin, clopidogrel, simvastatin
Vanderbilt	clopidogrel, warfarin, simvastatin in place. In planning: thiopurines
Marshfield	clopidogrel, warfarin, simvastatin
Mt. Sinai	clopidogrel, warfarin, simvastatin
CHOP	carbamazepine, thiopurines
BCH/CCMH	codeine

Subject selection

NU	Recruitment goal = 750 participants from internal medicine Selected using a predictive algorithm (modified from Vanderbilt)
Geisinger	Have already applied the Vanderbilt algorithm (modified) to MyCode® population and identified candidates.
GHC/UW	900 subjects selected using a predictive algorithm (Vanderbilt). A subset of 450 will be selected for confirmatory testing and return of results, to include all those with an actionable finding per the PGx chip and the balance to be be made up of randomly selected subjects who did not have an actionable finding
Mayo	Modified VU algorithm as applied to our biobank. Invitations sent to 2000 individuals by 10/15/12. We expect to complete consent of 1000 subjects by 12/31/12
Vanderbilt	Identified as likely to be prescribed the target medications (clopidogrel, warfarin, simvastatin) within next 3 years, trained on ~18,000 patients
Marshfield	Best algorithm for preemptive testing: Over 50 with no prior Rx
Mt. Sinai	Based on Vanderbilt's algorithm for eMERGE-PGx
CHOP	Adverse events database, asthma, ….
BCH/Cinn	Codeine/CYP2D6

eMERGE PGx – Progress by Aim

Aim 1: Deploy the PGRN-Seq platform across eMERGE.

- > 3000 samples collected to date of 9500 total samples expected
- 1st 300 samples in process on PGRN-Seq at CIDR
- Expect ≥ 100 samples / site sequenced with variants called and displayed along with basic phenotypic information in a searchable database by end of 2013

Aim 2: Integrate validated genotypes into the EMR and assess uptake, acceptance, and clinical impact.

- Process outcomes measures to be collected across the network developed and being vetted at upcoming Steering Committee meeting

Aim 3: Analyze variants of unknown significance.

- Variant repository structure developed in conjunction with PGRN
- Important genotype / phenotype use cases may include:
  - CACNA1S malignant hyperthermia
  - KCNH2 channelopathy/arrhythmia
  - LDLR familial hypercholesterolemia
  - RYR1 malignant hyperthermia
  - RYR2 channelopathy/arrhythmia
  - SCN5A channelopathy/arrhythmia

Extra slides…

2010-2013 Implementation Timeline

Drugs Proposed for Implementation in eMERGE-PGx, by Site

Site	abacavir	carbamazepine	clopidogrel	codeine	interferon	montelukast	morphine	omeprazole	ranitidine	simvastatin	thiopurines	warfarin
CHOP		X				X	X	X	X		X	
CCHMC				X								
Geisinger			X							X		X
GHC/UW		X										
Marshfield			X							X		X
Mayo	X	X	(X)		X					(X)	X	(X)
Mount Sinai			X							X		X
NU			X							(X)		X
Vanderbilt			X							X	X	X

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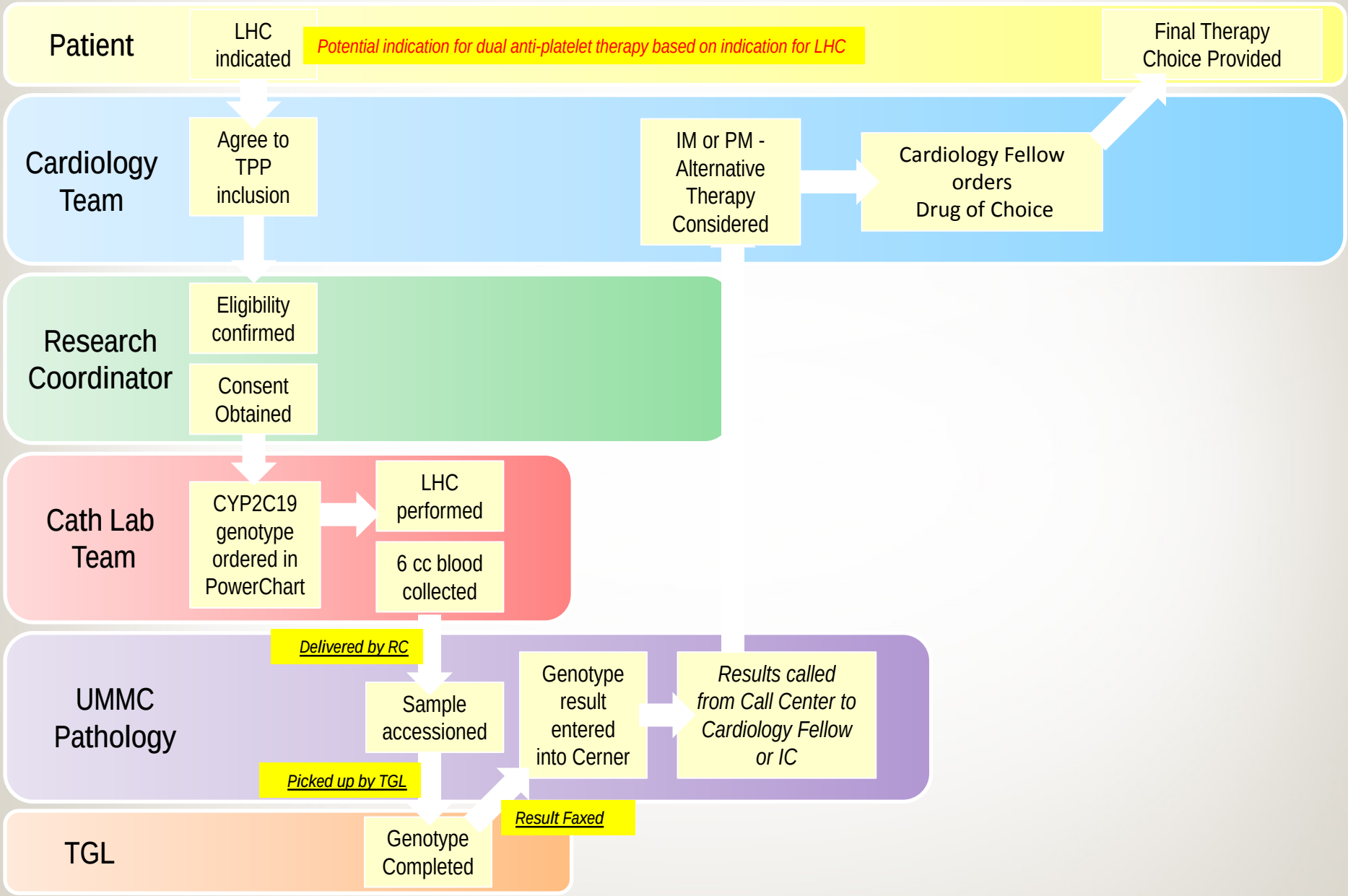
(X) = planned

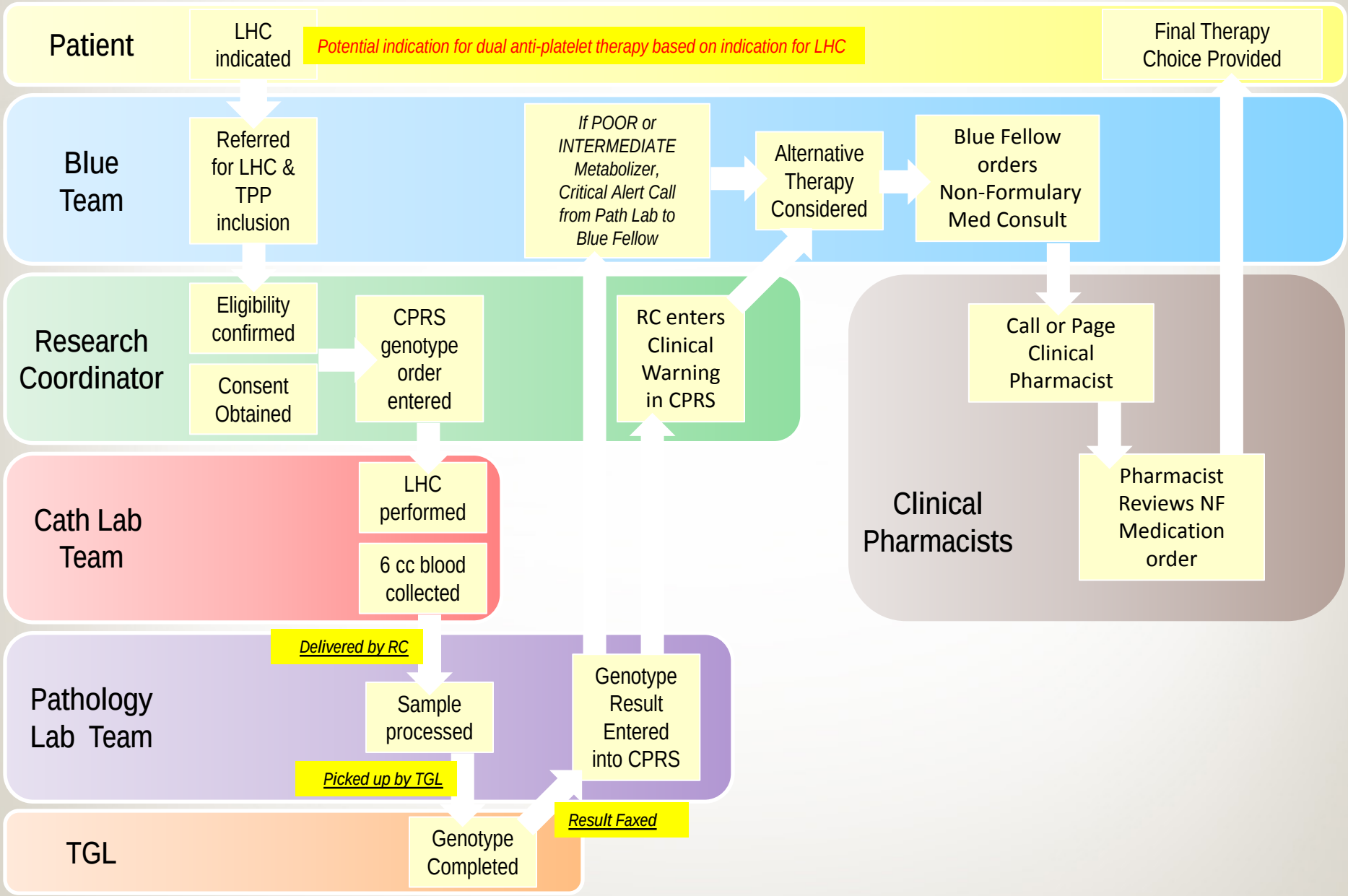
Personalized DAPT - CYP2C19 - UMMC Workflow

(5-hour turnaround)



Personalized DAPT - CYP2C19 Baltimore VAMC Workflow

(5-hour turnaround)



Proposal: Year 03-04 Continuation:

Aims 3 and 4: Develop standardized formats to report results; facilitate adoption of pgx through dissemination

- Diplotype-phenotype and CDS “Look-up Tables” and templates suitable for uploading in EHRs (EPIC, Cerner)
  - Companions to all CPIC guidelines
- Implement “Look up” templates at TPP implementation sites
- Dissemination
  - Make “Look-up” and TPP implementation table templates available for downloading on PharmGKB ((http://www.pharmgkb.org/page/tppTables))
  - TPP and individual group publications
  - Education tools

Examples of pharmacogenetically high-risk drugs used in 2011 at St Jude

Affected drugs	Number of pts receiving drug	Number of orders	Relevant gene	% of pts with high-risk diplotypes
Codeine/tramadol	779	3011	CYP2D6	12%
Thiopurines	317	6223	TPMT	9%
Fluoropyrimidines	12	154	DPYD	2%
Sulfamethoxazole	793	5571	G6PD	5%
Amitriptyline	51	294	CYP2D6	12%

St. Jude patients frequently receive these 33 high risk drugs

- In 2011, 2023 of 4245 patients (48%) who received medications at St. Jude received orders for at least one of 33 “high-risk” drugs.
- Over 18% of our patients received codeine or tramadol
  - 12% of these patients can be expected to have high-risk diplotypes and therefore require alternative agents

Pharmacogenetics Implementation Status

Drug	Thiopurines		Codeine		Tramadol	Amitriptyline	Fluoxetine	Paroxetine	Abacavir	Simvastatin	Fluorouracil	Irinotecan
Gene	TPMT		CYP2D6		CYP2D6	CYP2D6	CYP2D6	CYP2D6	HLA-B*5701	SLCO1B1	DPYD	UGT1A1
Adverse Outcomes	Myelosuppression		Increased toxicity or therapeutic failure		Increased toxicity or therapeutic failure	Increased toxicity or therapeutic failure	Increased toxicity or therapeutic failure	Increased toxicity or therapeutic failure	Hypersensitivity	Myopathy	Myelosuppression	Neutropenia
Implementation Status	Live		Live		Live	Live	Live	Live	Live	Dec-12		Live
	Clinical	PG4KDS	Clinical	PG4KDS	PG4KDS	PG4KDS	PG4KDS	PG4KDS	Clinical	PG4KDS		
Clinical impact of negative outcomes significant		✓		✓	✓	✓	✓	✓	✓	✓	✓	✓
Scientific evidence for drug gene effect		✓		✓	✓	✓	✓	✓	✓	✓	✓	✓
Patient target identifiable before they receive drug		✓		✓	✓	✓	✓	✓	✓	✓	✓	✓
Alternative therapy available				✓	✓	✓	✓	✓	✓	✓		
Gene added to DMET tracker	--	✓	--	✓	✓	✓	✓	✓	--	✓		--
Gene specific look up tables created	--	✓	--	✓	✓	✓	✓	✓	--	✓		--
Consult template written	✓	✓	✓	✓	✓	✓	✓	✓	✓			
Consult database updated	--	✓	--	✓	✓	✓	✓	✓	--			--
CDS language developed	✓	✓	✓	✓	✓	✓	✓	✓	✓			
Patient letters	--	✓	--	✓	✓	✓	✓	✓	--			--
Gene specific "Do you Know…" sheet	✓	✓	✓	✓	✓	✓	✓	✓				
Patient medication card	✓	✓	✓	✓	✓	✓	✓	✓				
PGEN formulary table updated	✓	✓	✓	✓	✓	✓	✓	✓	✓			
Drug monograph updated in formulary	✓	✓	✓	✓	✓	✓	✓	✓	✓			
St Jude PG4KDS webpage updated	--	✓	--	✓	✓	✓	✓	✓	--			--
Staff education	✓	✓	✓	✓	✓	✓	✓	✓				
Competencies	✓	✓	✓	✓	✓	✓	✓	✓				
P & T Communication	✓	✓	✓	✓	✓	✓	✓	✓				
POC Communication	--	✓	--	✓	✓	✓	✓	✓				--
MEDICAL CENTER Go-Live Date	1/7/2010	5/18/2011	11/7/2007	5/18/2011	2/10/2012	5/30/2012	5/30/2012	5/30/2012	10/11/2012			

My Health *at* Vanderbilt

Personalized Medication Treatment

Each person responds differently to medicines. Your genes play a role in how you respond to medicines. Based on your history, your provider has ordered a test to learn more about which drugs are right for you. Having this information can help predict and prevent bad drug side effects.

Medication	Does your genetic test result affect your response to medications?
Clopidogrel/Plavix®	Yes
Simvastatin/Zocor®	Yes

The Clopidogrel Test

Show less >

Clopidogrel (sounds like "kloh-PID-oh-grel") is a blood thinner used to prevent clots that can cause a heart attack or stroke. Your genes can affect how well the drug works. This genetic test identifies how well you may respond to clopidogrel.

Your Risk

Show less >

Sometimes clopidogrel does not prevent harmful strokes or clots as well as it should because of your genes. Your provider, often with the results of a lab test, can determine if clopidogrel is the right medicine for you.

patient results →

The results of your test show that you have two versions of the gene that may put you at increased risk for this negative outcome.

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