Pharmacogenomic Learning Health Systems

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December 8th, 2014
IOM Genomics Roundtable Workshop

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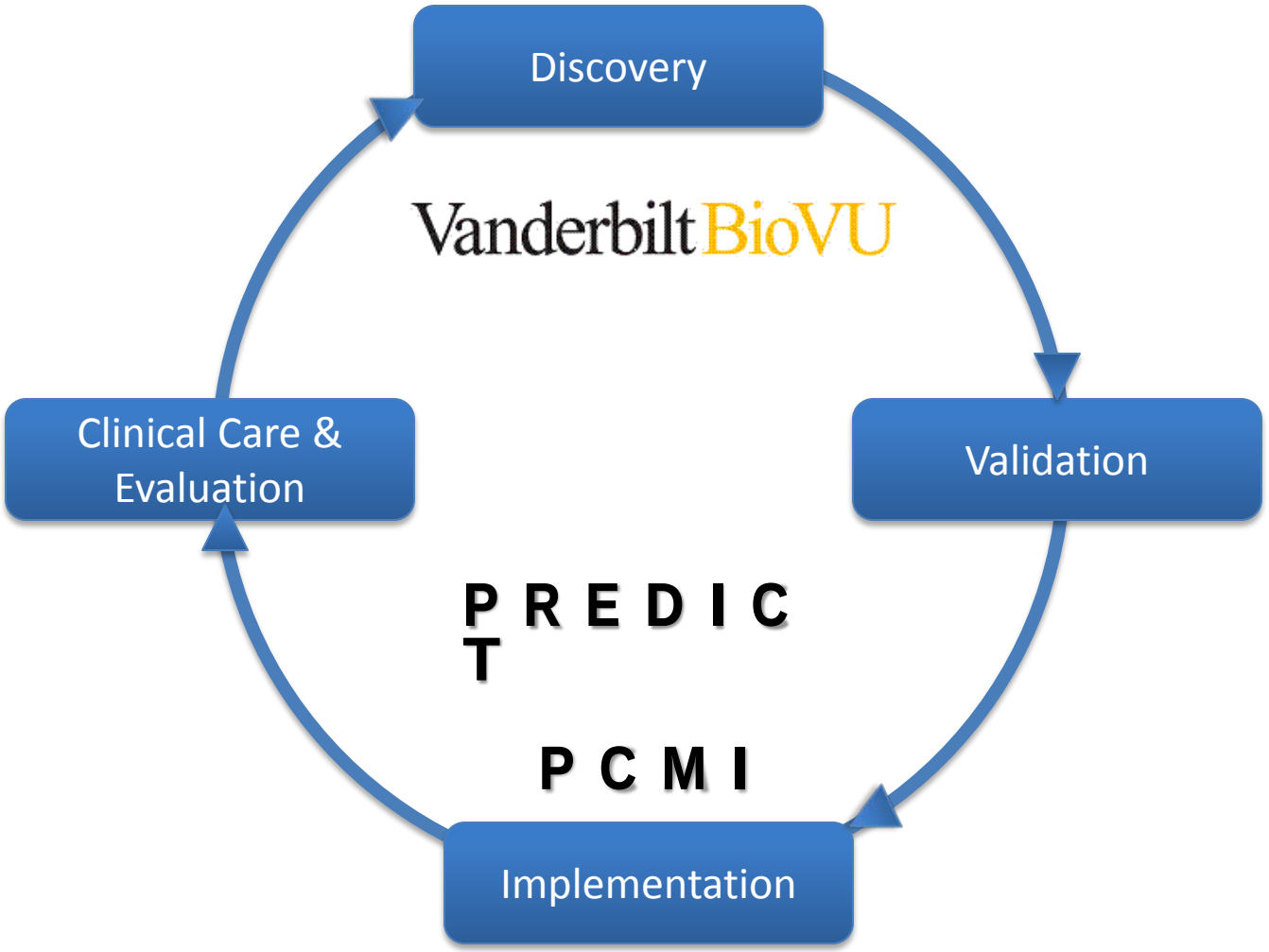

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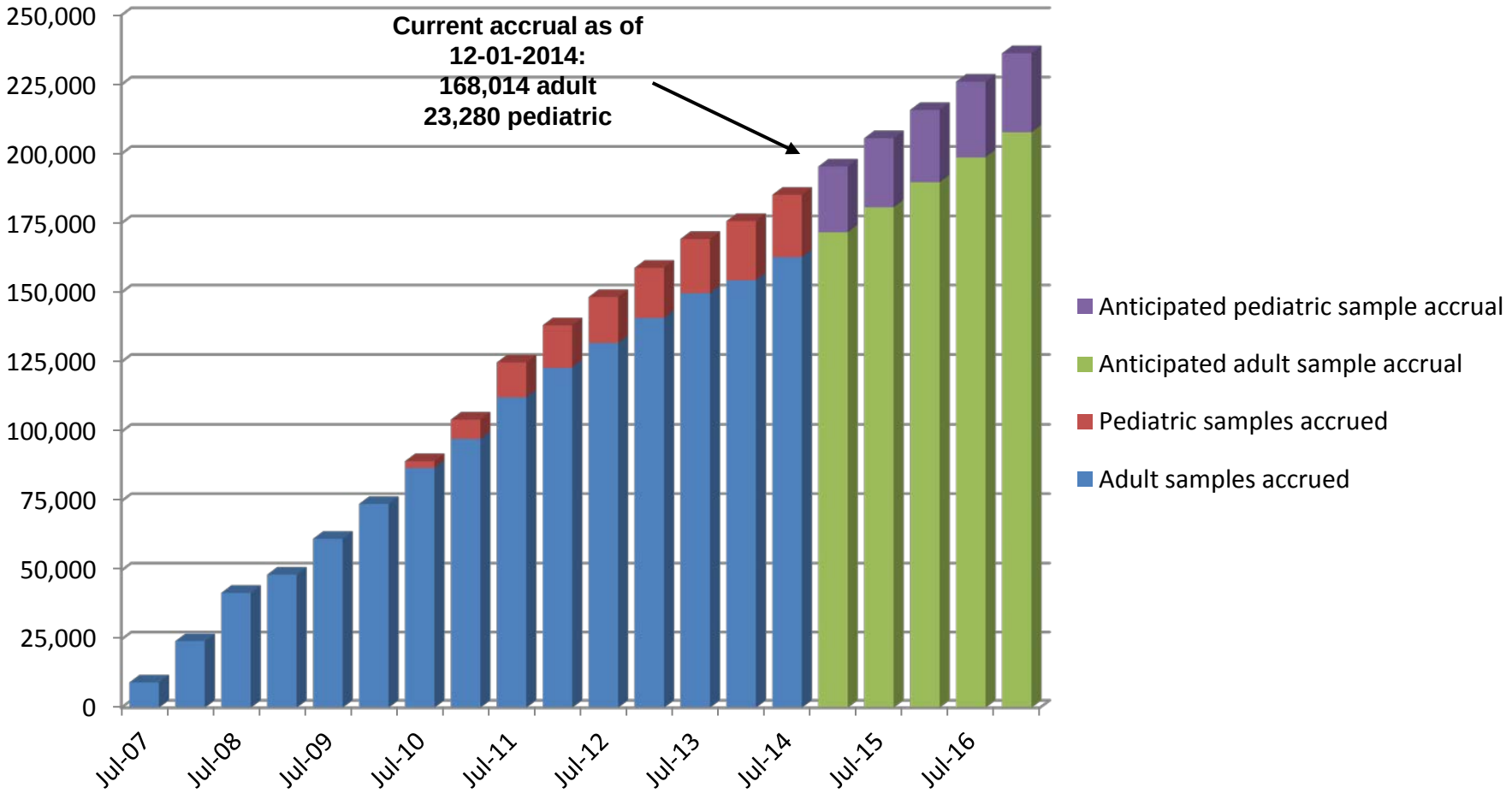
eMERGE Network
electronic medical records & genomics

IGNITE Implementing GeNomics In practicE

BioVU Sample Accrual – 191,162



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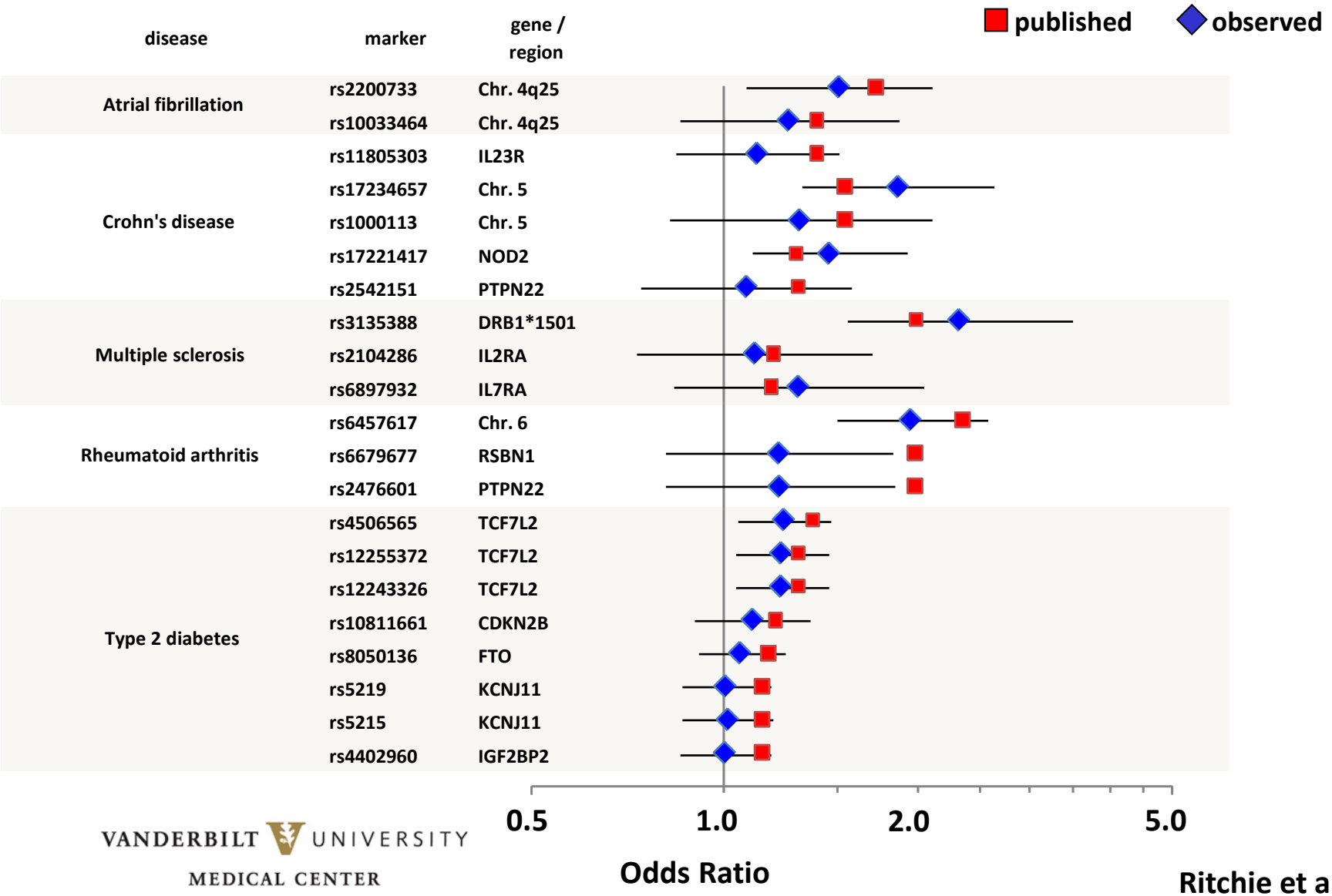
GWAS Replication of Known Associations



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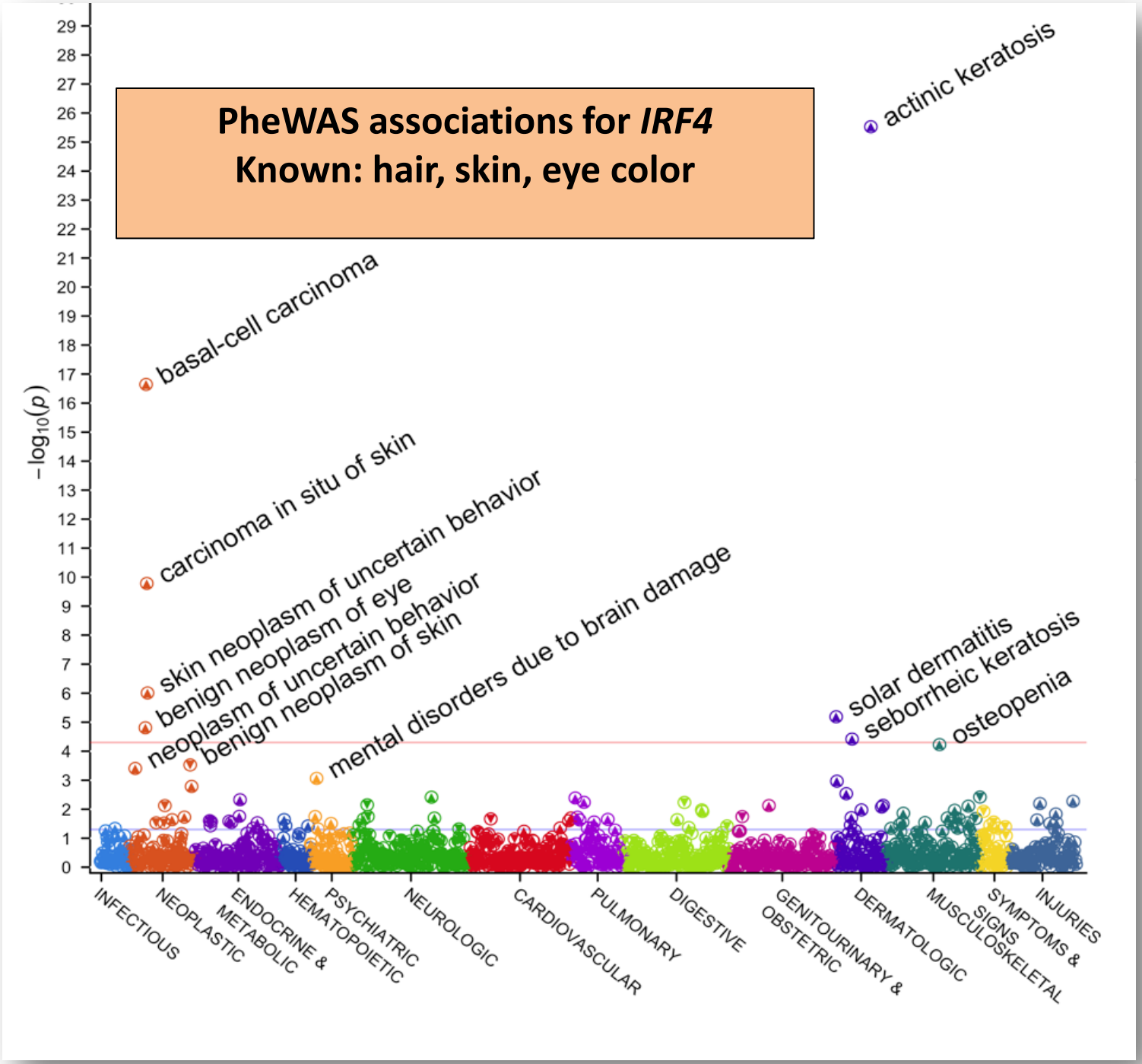
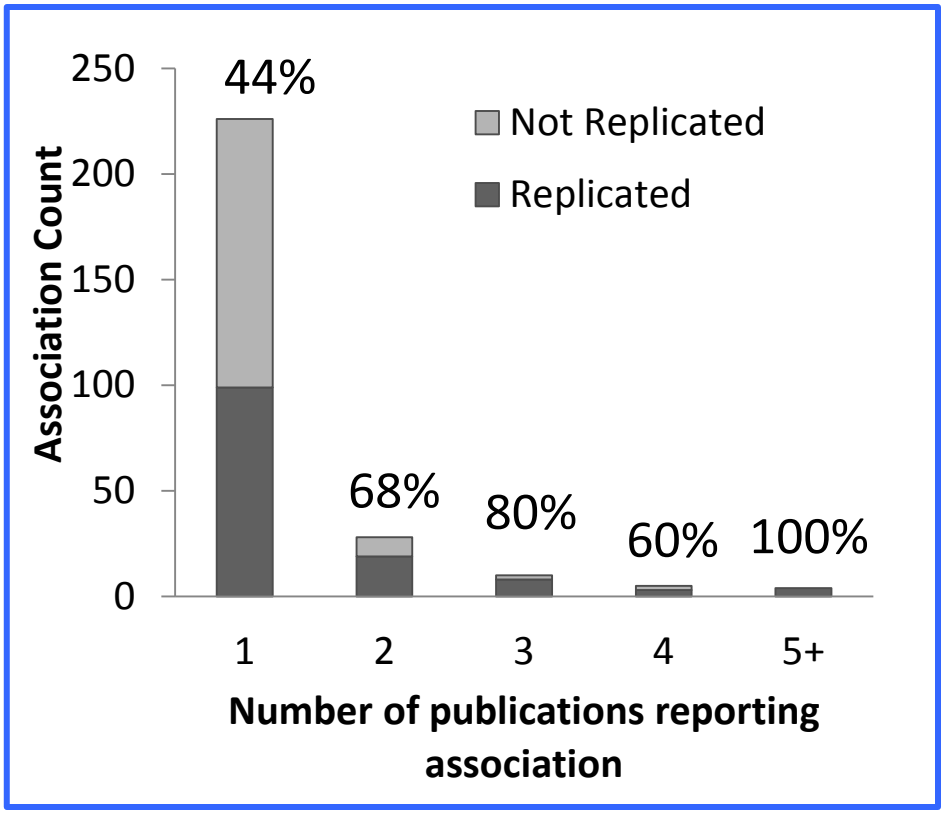
Ritchie et al, 2010



Denny JD, Nature Biotech 2013

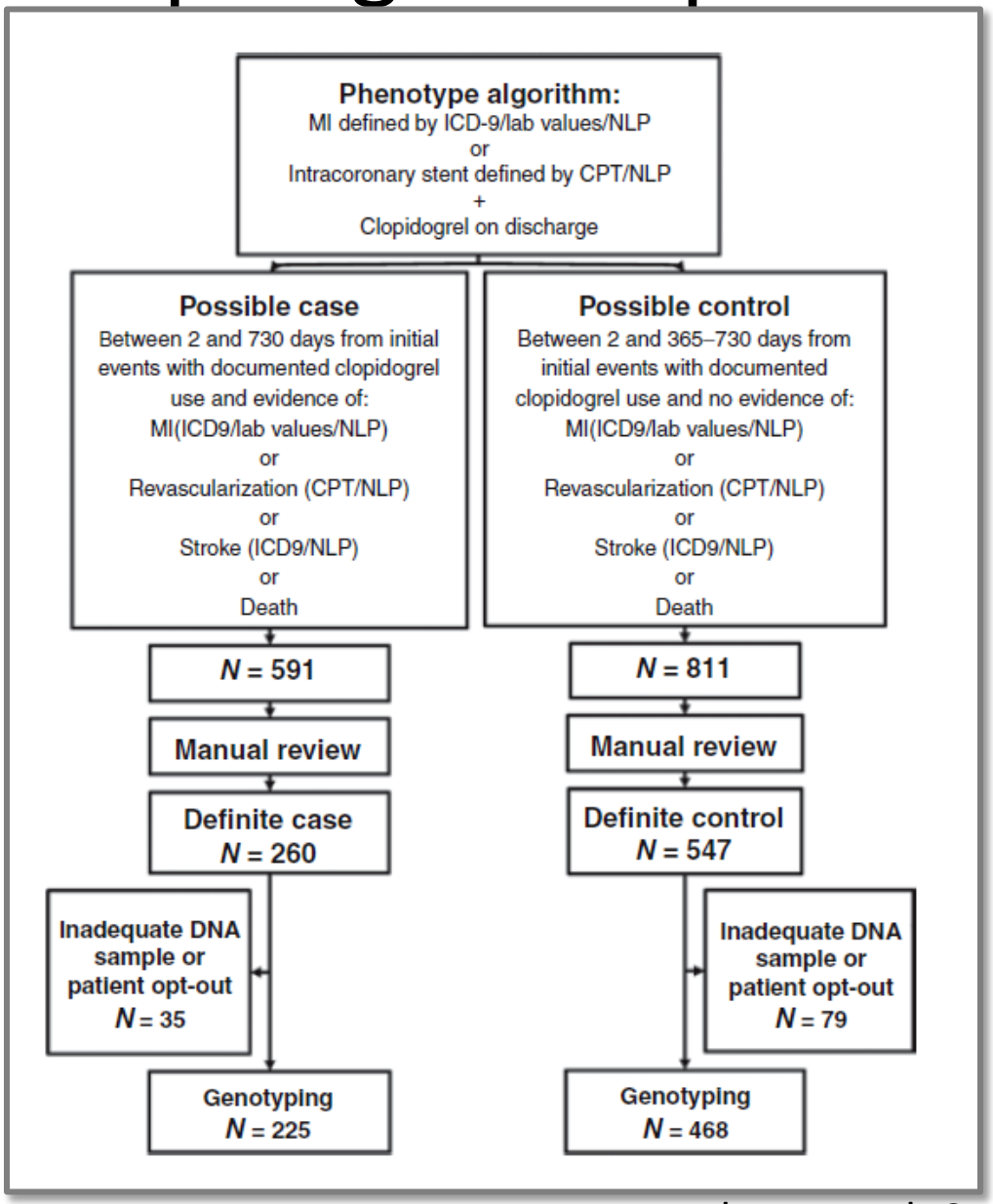
Factors associated with replication

- Number of prior publications
- Exactness of phenotype match



Predicting Clopidogrel Response

BioVU Validation of CYP2C19 LOF Variants and Clopidogrel Effiacy



Delaney et al, CPT 2012

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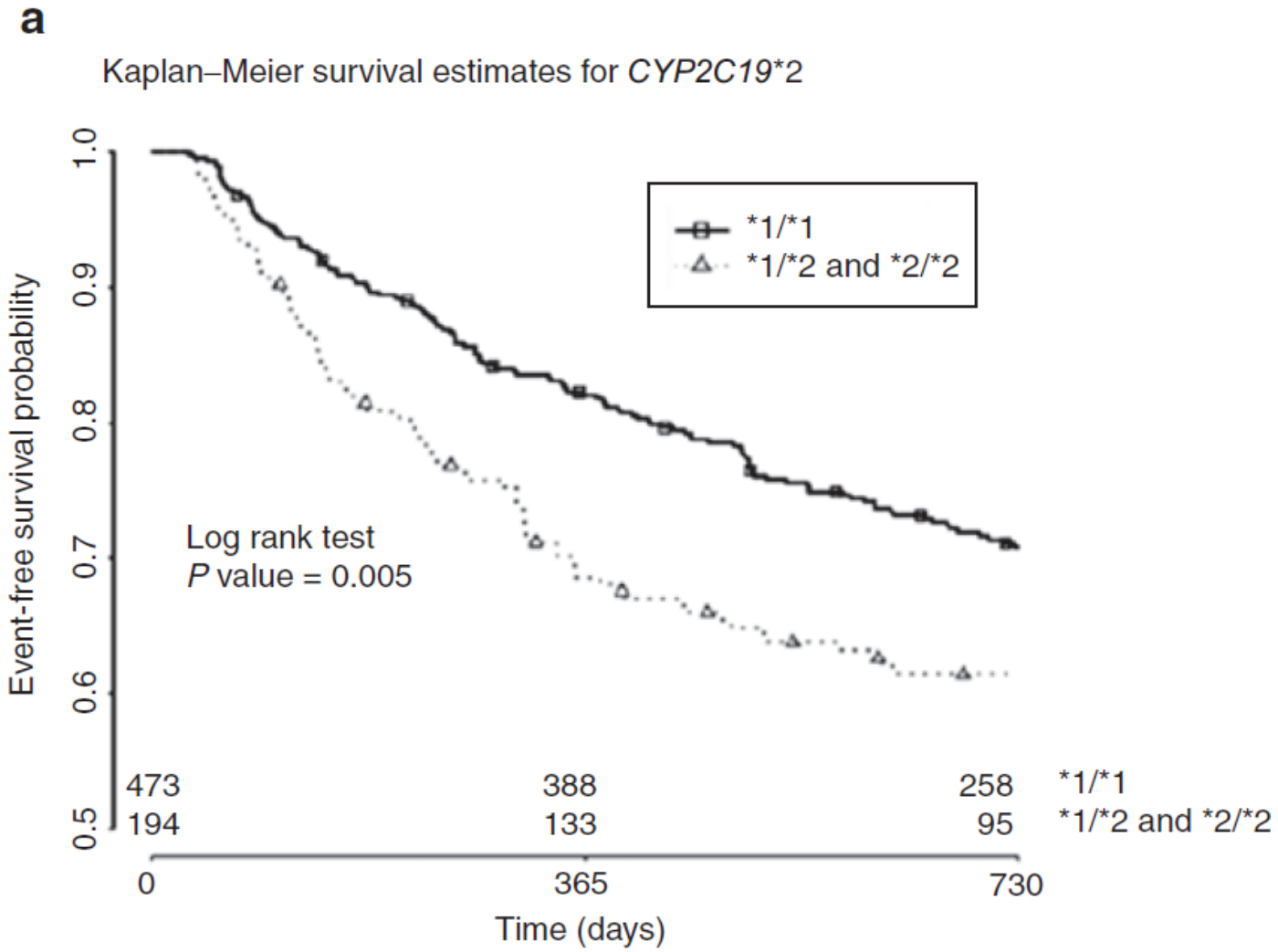
Predicting Clopidogrel Response

Increased MACE with Impaired Clopidogrel Metabolism



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Delaney, CPT 2012

Warfarin Dosing Algorithm

	Formula to Calculate WEEKLY DOSE	
	Starting value	4.999
	Age	-0.281 x age in decades
	Height	+0.015 x height in cm
	Weight	+0.011 x weight in kg
Gene Results	**VKORC1 status (absent = 0, present =1)**	-0.816 x VKORC1 A/G status -1.808 x VKORC1 A/A status
Gene Results	**CYP2C9 status (absent = 0, present =1)**	-0.441 x CYP2C9 *1/*2 status -0.964 x CYP2C9 *1/*3 status -1.160 x CYP2C9 *2/*2 status -1.527 x CYP2C9 *2/*3 status -3.003 x CYP2C9 *3/*3 status
Other Meds	**Is patient taking amiodarone?**	-0.827 x amiodarone status
Other Meds	**Is patient taking an enzyme inducer?** (e.g., Rifampin, Diltiazem, Tegretol)	+0.188 x enzyme inducer status

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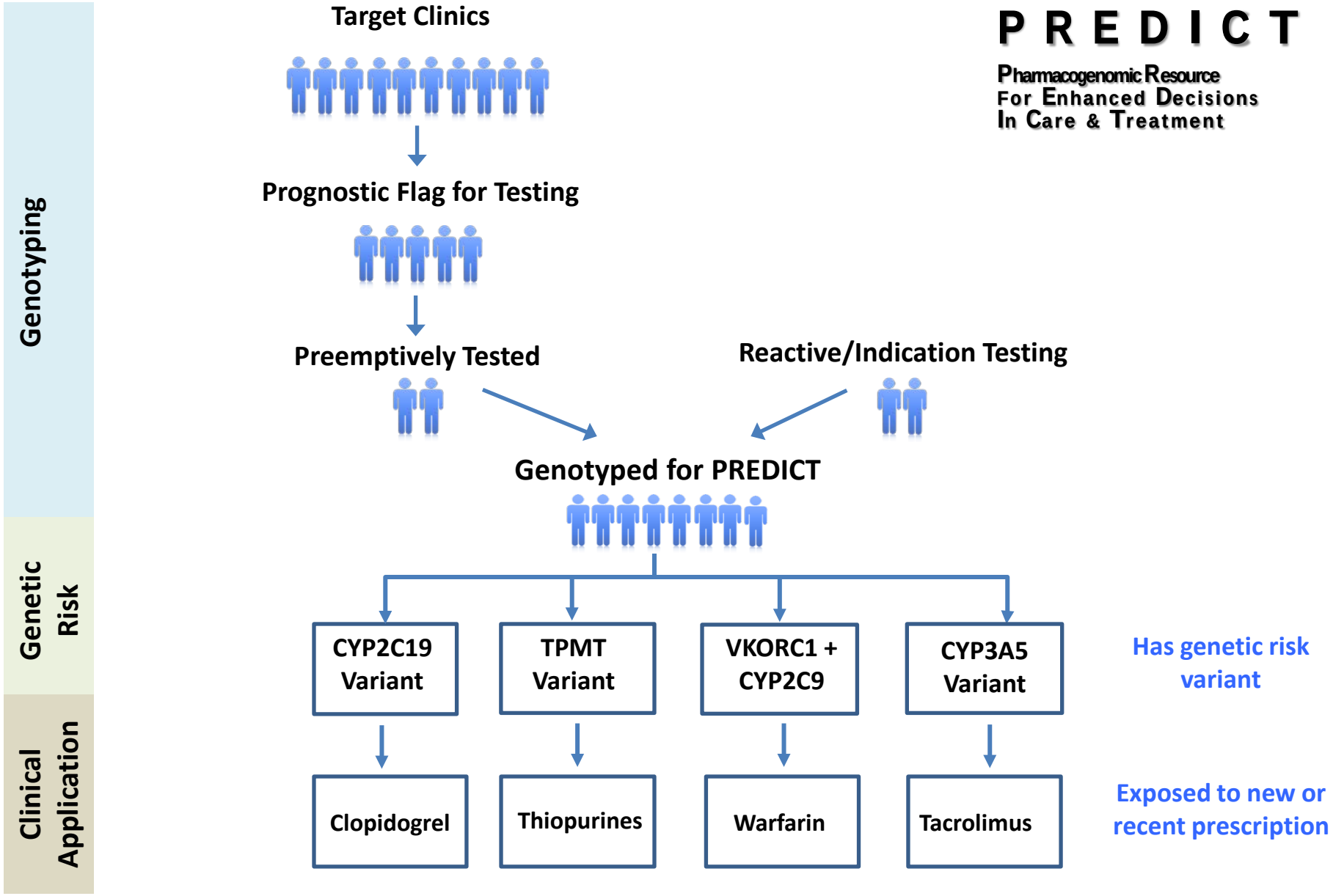
Warfarin Dosing Model Fidelity

BioVU Data Validation

Algorithm	Mean Absolute Error (mg/wk)
Fixed 5 mg Dose	13.9
International Warfarin Pgx Consortium (IWPC)	12.2
Warfarindosing.org	11.9
Vanderbilt-specific Model	9.7



PREDICT

Pharmacogenomic Resource For Enhanced Decisions In Care & Treatment

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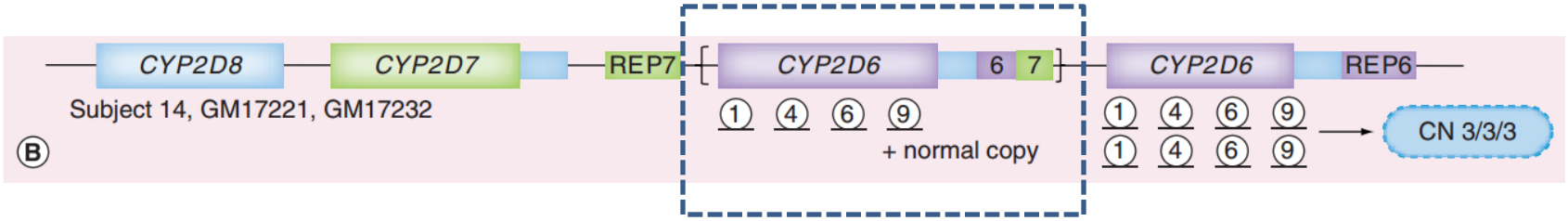
PREDICT Genotyping Accuracy

Gene Variants	Call Rate for Actionable Variants	Concordance on Repeat Samples	CAP Certification
CYP2C19 *2-*8	99.9%	100%	Concordant
SLC01B1 *5	99.7%	100%	*
VKORC1	99.8%	100%	Concordant
CYP2C9 *2,*3	99.4%	100%	Concordant
TPMT *2, *3	99.7%	100%	*

Quality of Genotyping

- Genotyping platforms for pharmacogenomics are high quality with known trouble spots

1) CYP2D6 copy number variation:



Policy and Infrastructure Barriers

Standards for exchanging genomic results

Labcorp Report

LabCorp
Laboratory Corporation of America

February 8, 2013

Labcorp Of America
Oncology Department RTP
1912 Alexander Drive
RESEARCH TRIANGL, NC 27709

Test Results of: CYTOCHROME, DUMMY
DOB: 01/01/1980 Age: 33.1 Y Sex: NI
Collected on: 02/07/2013
Received on: 02/07/2013
Reported on: 02/08/2013

Patient ID#:

Branch Number: NCB13
Account Number: 90001325
Specimen Number: 038-225-9005-0
Specimen Type: Blood

Physician:

Test: CYTOCHROME P450 2C19

Result:

CYP2C19 *1 / *1, Extensive Metabolizer

Interpretation:
The phenotype assigned is based on an FDA-cleared algorithm introduced in 2005 using the highest functioning allele to predict the metabolizer phenotype for that individual. Emerging data suggests that, at least for some drugs such as clopidogrel, gene dosage drug response differences can be clinically significant.

- Extensive metabolizers (EM) are anticipated to have an expected response to a standard drug dose.
- Poor metabolizers (PM) have significantly reduced or absent enzyme activity. Drugs are metabolized slowly or not at all causing increased concentrations of active drug with the potential for serious side effects.
- Intermediate metabolizers (IM) have reduced enzyme activity, and may experience some, or none, of the consequences similar to poor metabolizers.
- Ultra-rapid metabolizers (UM) have elevated enzyme activity. UM individuals may not reach therapeutic levels of active drug due to rapid clearance, and may be at increased risk for adverse reactions due to reaching higher concentrations of active metabolite than expected.

The metabolism of drugs is also influenced by race, ethnicity, diet and other medications and all factors should be considered prior to initiating therapy. All results must be interpreted in the context of other test results and clinical findings. This does not rule out the possibility of variant alleles in other drug metabolism pathways.

Common† prescription medications that may be impacted by CYP2C19 gene variants are listed below.

Drug	Important Interactions
Platelet aggregation inhibitor: Clopidogrel	Poor metabolizers (PM) and intermediate metabolizers (IM) are at risk for recurrence of cardiovascular atherosclerotic disease. Ultra-metabolizers (UM) will have an enhanced response to clopidogrel, and may be at increased risk of bleeding. Co-administration of clopidogrel alongside CYP2C19 inhibitors such as omeprazole, esomeprazole, cimetidine, fluconazole, ketoconazole, voriconazole, etravirine, felbamate, fluoxetine, fluvoxamine and ticlopidine can reduce clopidogrel's platelet inhibition.
Tri-cyclic antidepressants (TCA): amitriptyline, nortriptyline	Studies suggest that PMs may benefit from a lower starting dose.
Selective Serotonin Reuptake Inhibitor (SSRI): paroxetene, fluoxetine, sertraline	Mean clearance rates may be decreased in PMs as compared with EMs. Studies suggest that PMs may be at risk for SSRI related cardiotoxicity.
Proton pump inhibitors: omeprazole	Data suggests improved cure rates for EM and PM with double or triple therapy.
Anti-epileptics: diazepam, phenytoin	Diazepam half-life is significantly prolonged in 2C19 PM and may cause prolonged sedation, particularly if administered with inhibitors of 2C19.

†Common drugs are those included in the Top 300 Drugs prescribed in 2004. This table is intended as a guide and may not be inclusive of all clinically relevant 2C19

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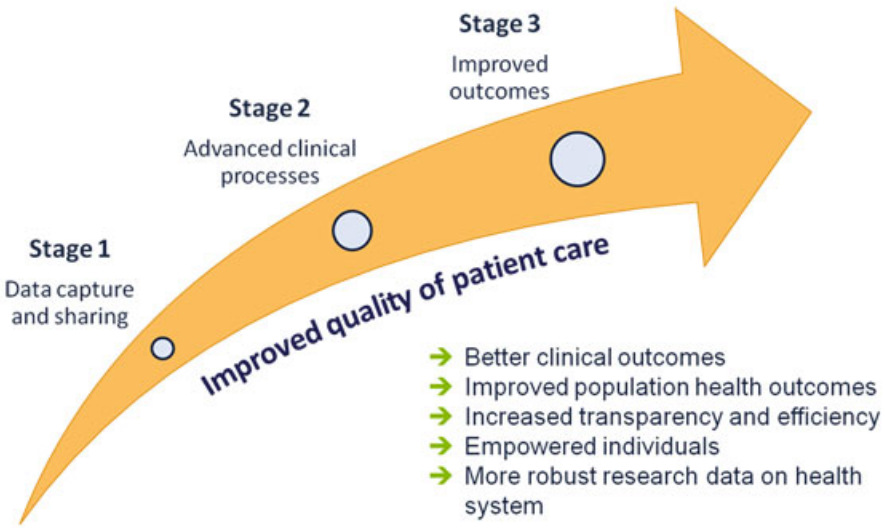
Regulatory clarity around patient access to results

Patient Access to Health Records

- HIPAA & HITECH



An individual has a right of access to inspect and obtain a copy of protected health information about the individual in a designated record set, for as long as the protected health information is maintained in the designated record set.
-- HITECH Act

Shared knowledge resources

- Phenotyping algorithm libraries
- Variant calling
- Clinical interpretation
- CDS rule repository

PheKB

ClinVar

ClinGen

HGNC
HUGO Gene Nomenclature Committee

MY CANCER GENOME™
GENETICALLY INFORMED CANCER MEDICINE

PharmGKB

CDS consortium

myDRUGGENOME
The right drug, the right dose, the first time.

CPIC: Implementing PGx
a PharmGKB & PGRN collaboration

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