Implementation of Pharmacogenomics at VUMC

CPIC Webinar Series

June 2nd, 2016

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Department of Medicine
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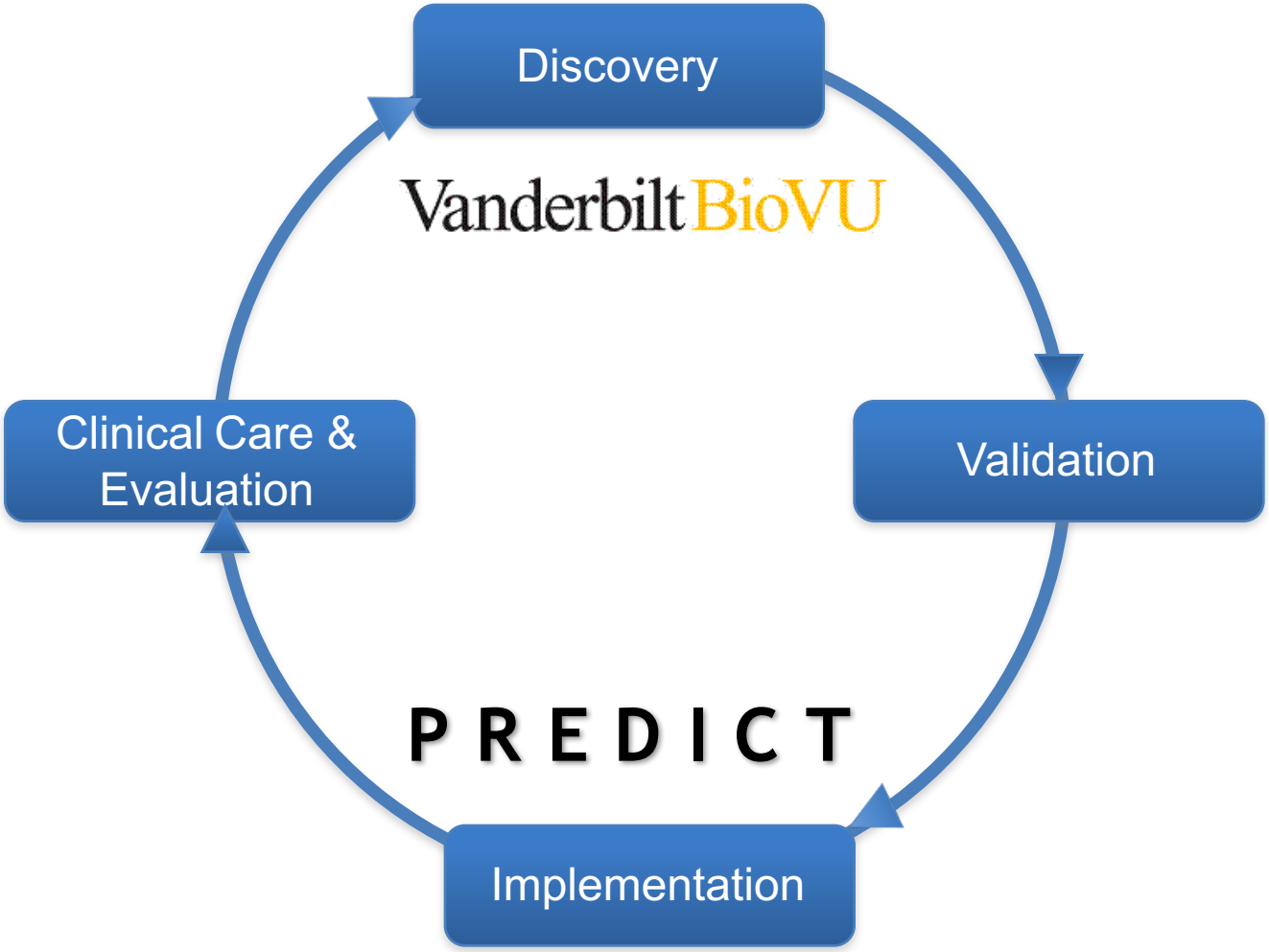
Genomic Learning Health Systems



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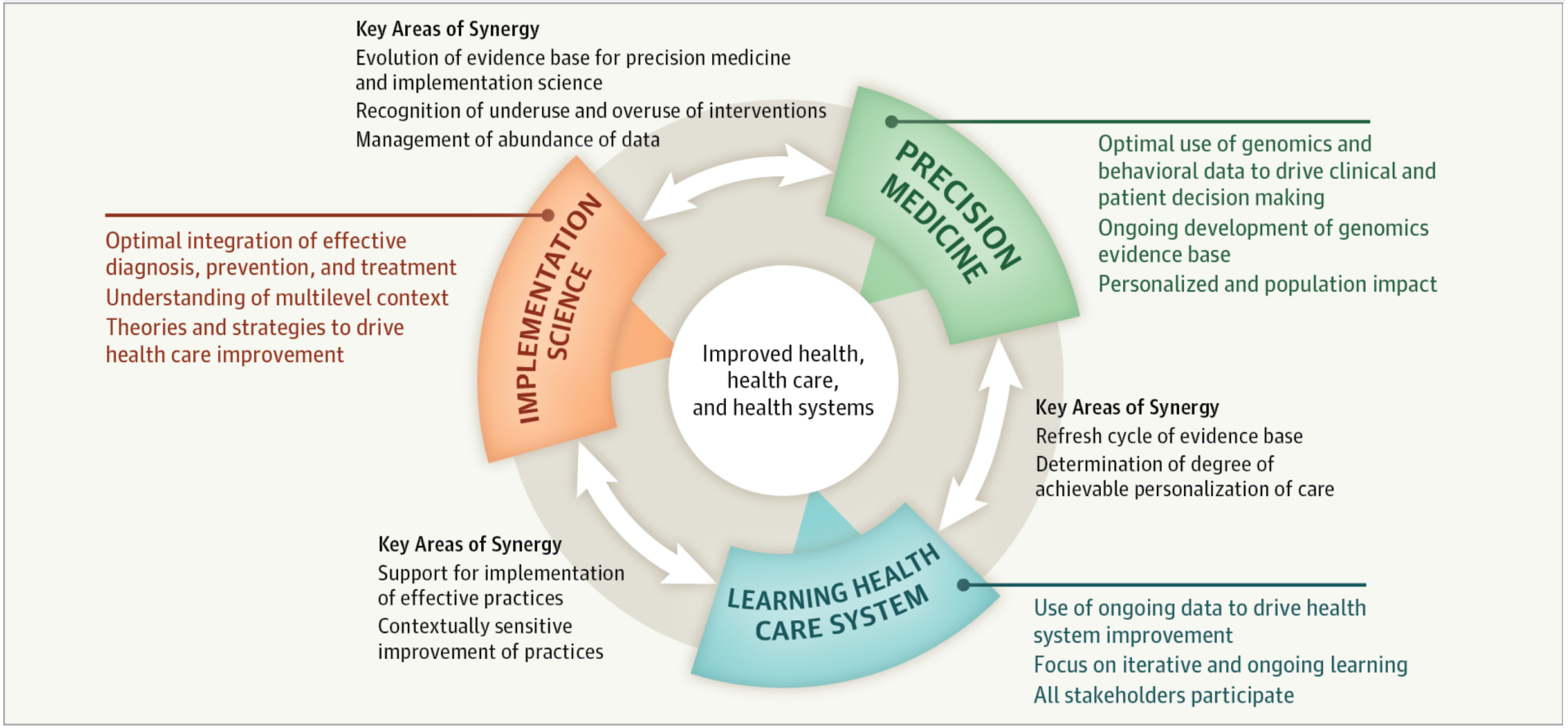
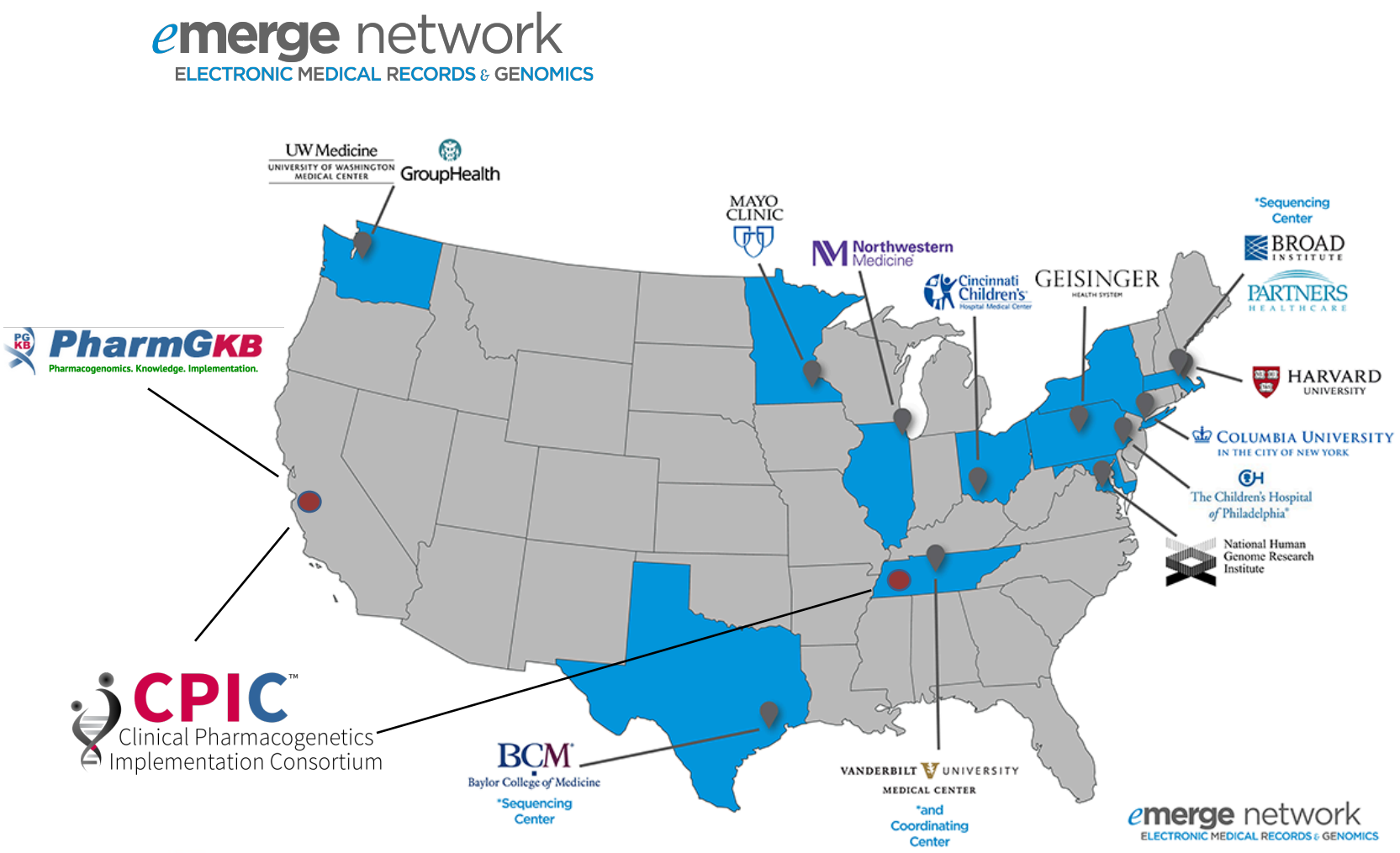
Convergence of Implementation Science, Precision Medicine, and the Learning Health Care System: A New Model for Biomedical Research



DA Chambers JAMA. 2016

Network Effect of Genomic Medicine Programs



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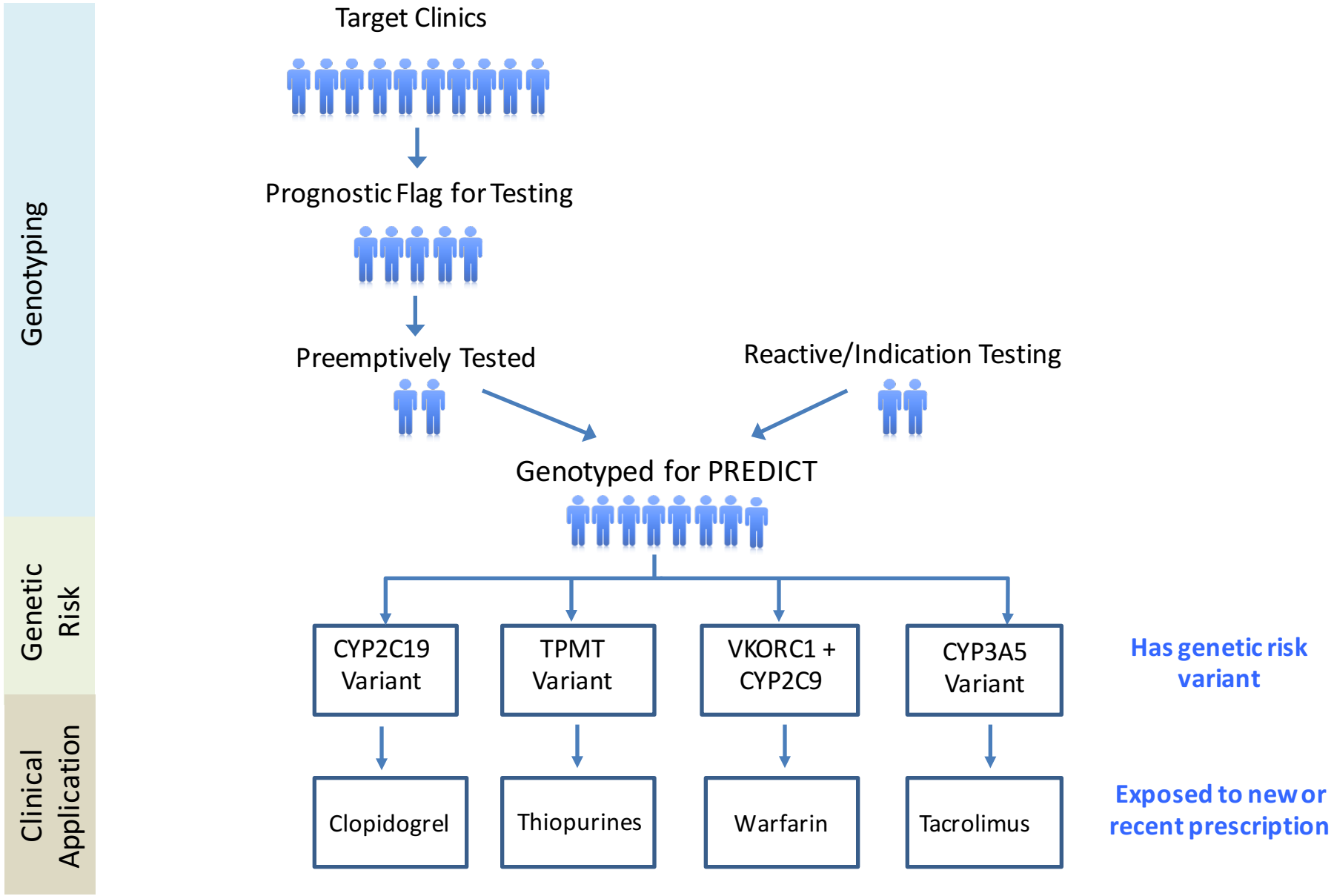
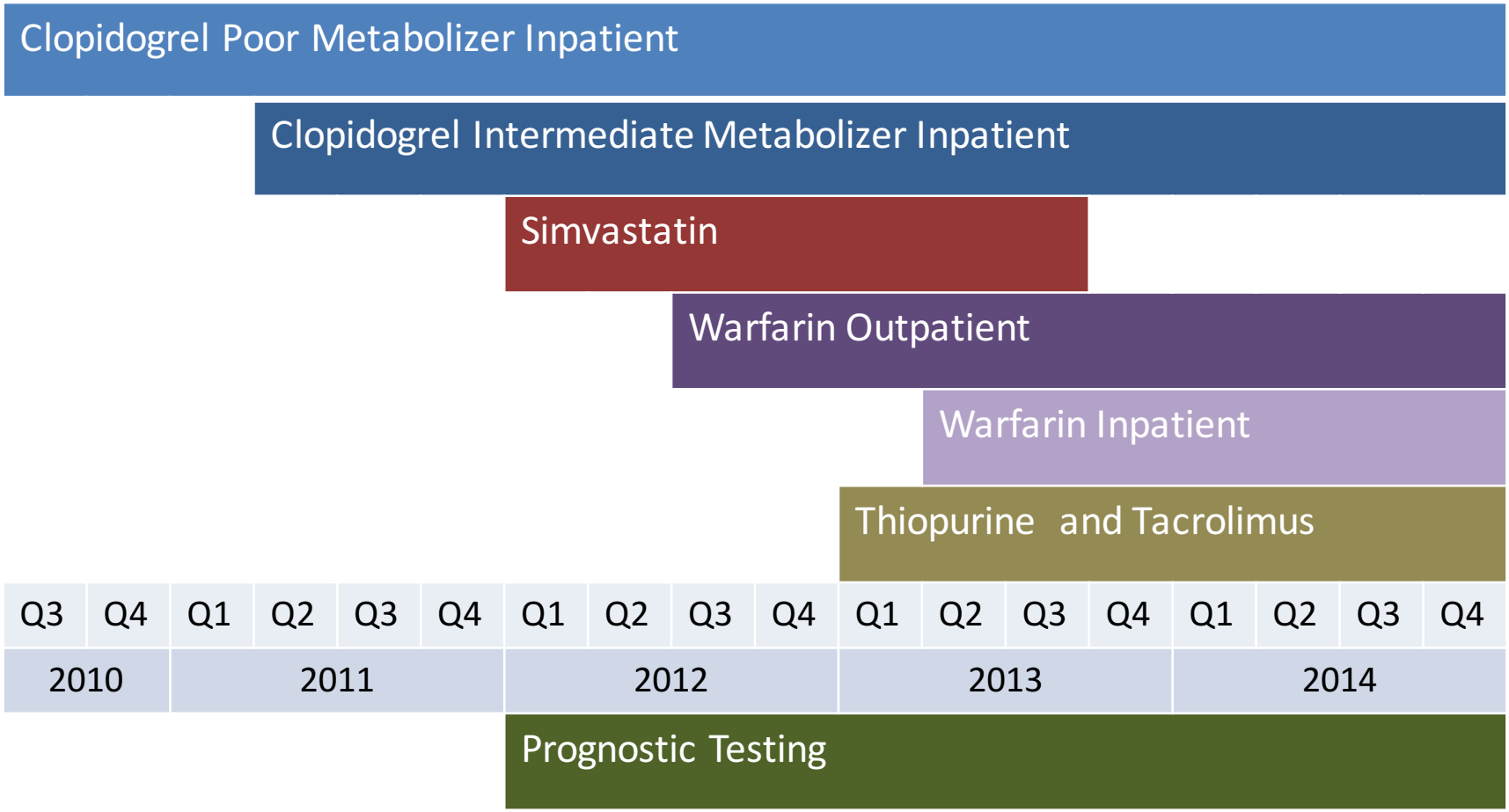
https://emerge.mc.vanderbilt.edu

PREDICT Model



5-Year Implementation Timeline



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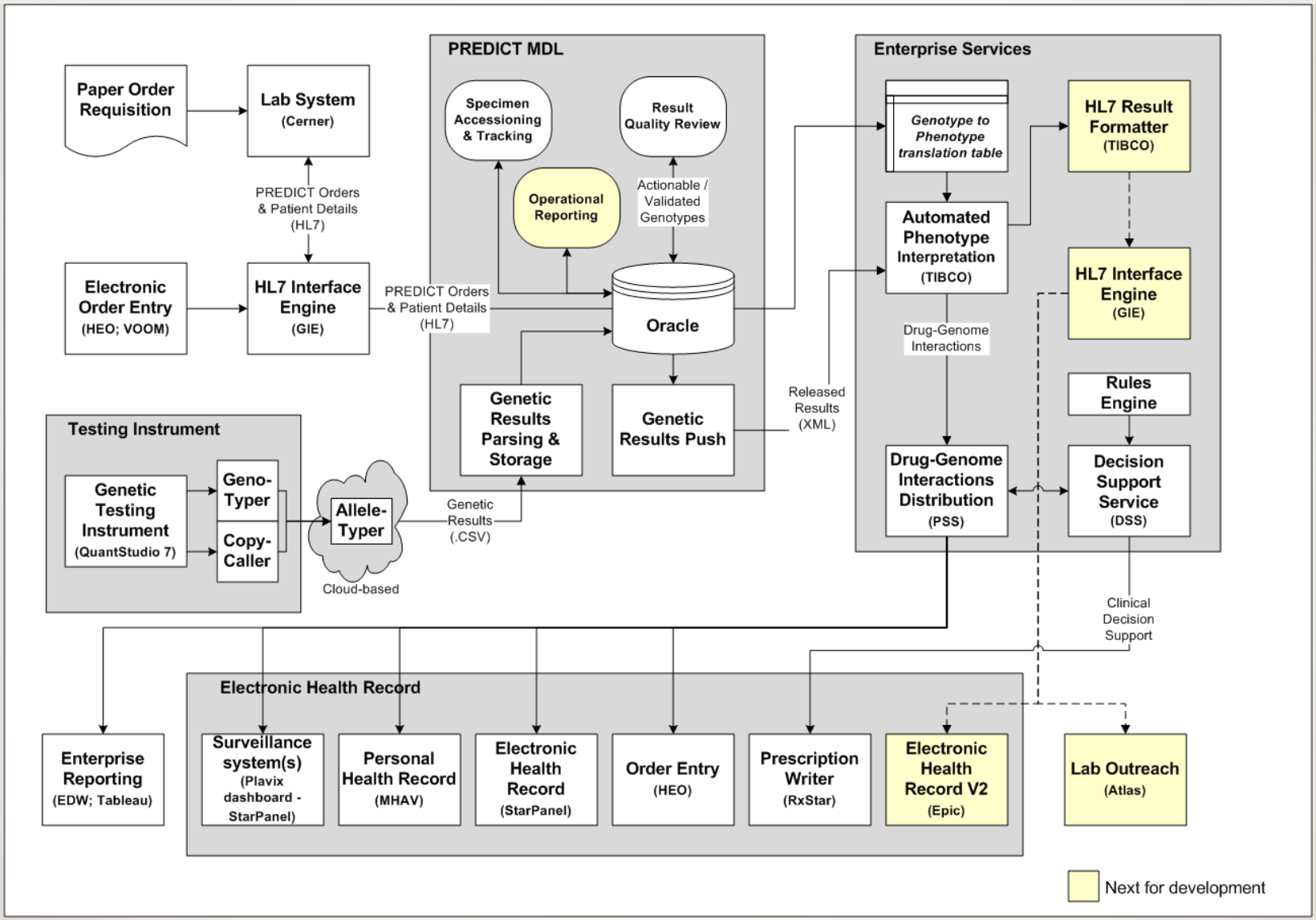
High level component architecture – Solution



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Nomenclature and Interpretations

Tacrolimus and CYP3A5 interaction

Result

Gene	Nucleotide variation[a]:	Effect on CYP3A5 protein
CYP3A5	6986A>G 31611C>T	Splicing defect

Genotype & Phenotype

CYP3A5 *3/*3 → Tacrolimus Poor metabolizer

Interpretation

This result signifies that the patient has two copies of a non-functional allele (*3). Patients with this genotype are expected to require **standard tacrolimus dosing**. Please consult a clinical pharmacist for more specific dosing information.

A Electronic Health Record – Patient Summary

Drug Genome Interactions: *(02/27/12 13:23, Byrd, Jeff)*
clopidogrel sensitivity: POOR METABOLIZER, REDUCED ANTI-PLATELET EFFECT - gene: CYP2C19 - gene result: *2/*2
warfarin sensitivity: Hyper Responder - gene results: VKORC1 Invalid Result; CYP2C9 *3/*3
simvastatin sensitivity: INTERMEDIATE MYOPATHY RISK, MINOR ALLELE HETEROZYGOUS (C;T) - gene: SLCO1B1 - gene result: *5 HET
thiopurine sensitivity: HIGH MYELOTOXICITY RISK, MINOR ALLELE HOMOZYGOUS - gene: TPMT - gene result: *3c/*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.

B Electronic Health Record – Lab Results

```
MolecDiag
Last modified: 04/09/2013 15:14    acc.# ps-19201747-DGI      Reminder  Pt.Letter
  TACROLIMUS CYP3A5                    tacrolimus sensitivity: HYPO RESPONDER -
gene: CYP3A5 - gene result: *1/*3

Last modified: 04/09/2013 15:14    acc.# ps-19201743-DGI      Reminder  Pt.Letter
  WARFARIN VKORC1/CYP2C9               warfarin sensitivity: Hyper Responder -
gene results: VKORC1 Invalid Result; CYP2C9 *3/*3

Last modified: 04/09/2013 15:14    acc.# ps-19201721-DGI      Reminder  Pt.Letter
  THIOPURINES TPMT                     thiopurine sensitivity: HIGH MYELOTOXICITY
RISK, MINOR ALLELE HOMOZYGOUS - gene: TPMT - gene result: *3c/*3c

Last modified: 02/27/2012 13:23    acc.# ps-15622404-DGI      Reminder  Pt.Letter
  SIMVASTATIN SLCO1B1                  simvastatin sensitivity: INTERMEDIATE
MYOPATHY RISK, MINOR ALLELE HETEROZYGOUS (C;T) - gene: SLCO1B1 - gene result: *5
HET

Last modified: 07/01/2011 16:36    acc.# ps-8895618-DGI       Reminder  Pt.Letter
  CLOPIDOGREL CYP2C19                  clopidogrel sensitivity: POOR METABOLIZER,
REDUCED ANTI-PLATELET EFFECT - gene: CYP2C19 - gene result: *2/*2
```

C Outpatient Substitution Advisor

Drug-Genome Advisor
Poor Metabolizer - clopidogrel (Plavix)
Substitution recommended due to increased cardiovascular risks

If not otherwise contraindicated:

☐ Prescribe prasugrel (Effient) 10 mg daily
Contraindications include:
- history of stroke or transient ischemic attack
- >= 75 years of age [Current patient age: 38]
- body weight < 60 kg [Current patient weight: 90.7 kg as of 11/14/2012]

☐ Prescribe ticagrelor (Brilinta) 90 mg twice daily
Contraindications include:
- history of severe hepatic impairment
- history of intracranial bleed

☐ Continue with clopidogrel (Plavix) prescription

Evidence Link

D Inpatient Substitution Advisor

Clopidogrel Intermediate Metabolizer Rules for Rare Risk Allele

Genetic testing has been performed and indicates this patient may be at risk for inadequate anti-platelet response to clopidogrel (Plavix®) therapy

This patient has been tested for CYP2C19 variants, and 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 exhibit higher rates of stent thrombosis/other cardiovascular events.
(See StarPanel for patient-specific CYP2C19 gene result.)

Treatment modification is recommended if not otherwise contraindicated:

○ Prescribe prasugrel (EFFIENT) **10 mg** daily and stop clopidogrel (PLAVIX), startdate 10 AM
○ Prescribe ticagrelor (BRILINTA) **180 mg** x1 dose, startdate 10 AM, followed by 90 mg twice daily

Prasugrel should not be given to patients:
- that have a history of stroke or transient ischemic attack*** Please check StarPanel if unsure
- that are greater than 75 years of age
- whose body weight is less than 60 kg (Caution patient's weight: 0 kgs)

Ticagrelor should not be given to patients:
- that have a history of severe hepatic impairment or intracranial bleed *** Please check StarPanel if unsure

Click here for more information

If prasugrel (EFFIENT) or ticagrelor (BRILINTA) are not selected, please choose desired action:

○ Maintain requested daily dose of clopidogrel (PLAVIX) **75 mg** daily, startdate 10AM

Cancel | Order

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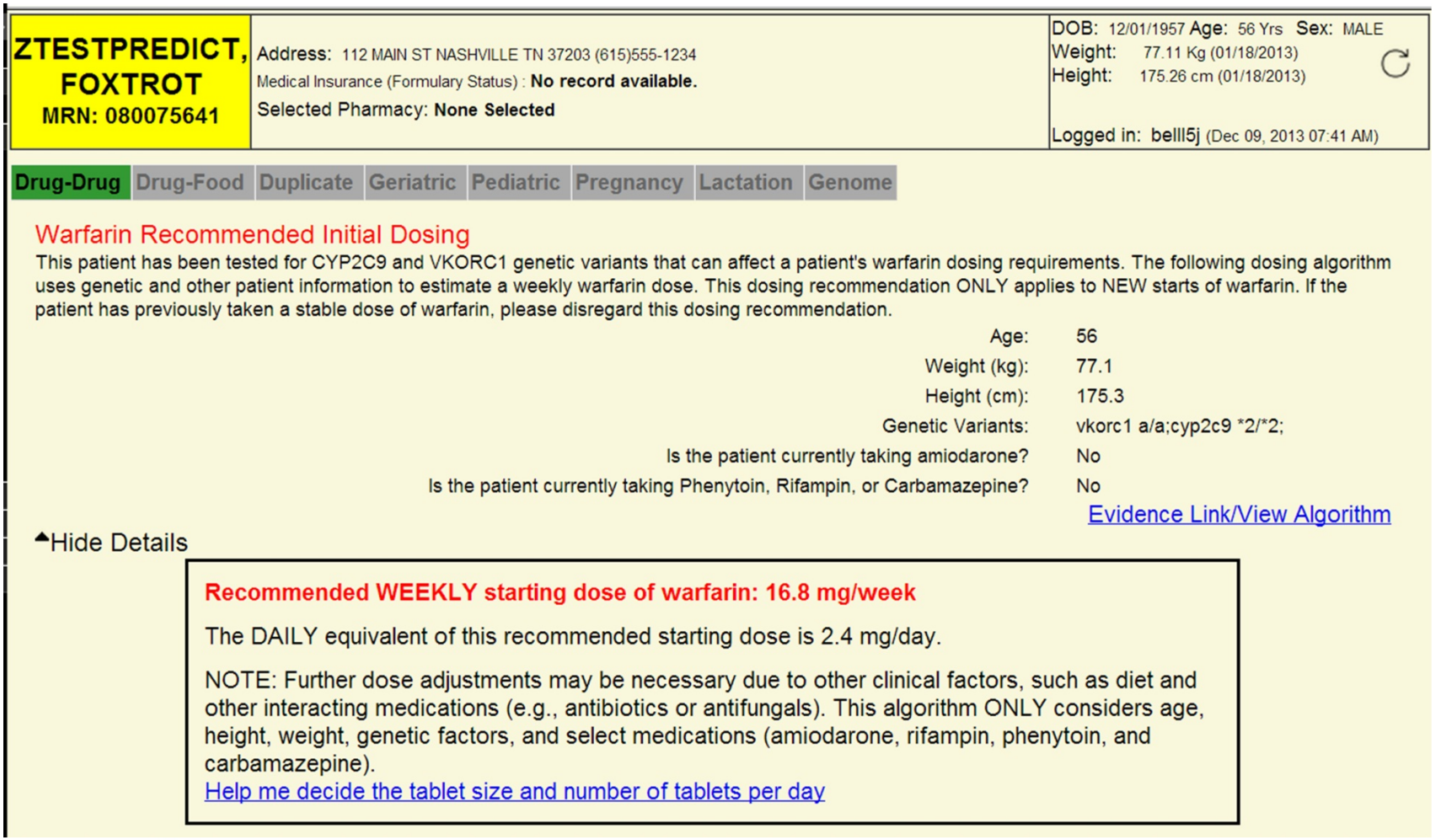
JF Peterson. Genetics in Medicine 2013

Warfarin CDS



ZTESTPREDICT, FOXTROT
MRN: 080075641

Address: 112 MAIN ST NASHVILLE TN 37203 (615)555-1234
Medical Insurance (Formulary Status) : **No record available.**
Selected Pharmacy: **None Selected**

DOB: 12/01/1957 Age: 56 Yrs Sex: MALE
Weight: 77.11 Kg (01/18/2013)
Height: 175.26 cm (01/18/2013)

Logged in: belll5j (Dec 09, 2013 07:41 AM)

Drug-Drug | Drug-Food | Duplicate | Geriatric | Pediatric | Pregnancy | Lactation | Genome

Warfarin Recommended Initial Dosing

This patient has been tested for CYP2C9 and VKORC1 genetic variants that can affect a patient's warfarin dosing requirements. The following dosing algorithm uses genetic and other patient information to estimate a weekly warfarin dose. This dosing recommendation ONLY applies to NEW starts of warfarin. If the patient has previously taken a stable dose of warfarin, please disregard this dosing recommendation.

Age:	56
Weight (kg):	77.1
Height (cm):	175.3
Genetic Variants:	vkorc1 a/a;cyp2c9 *2/*2;
Is the patient currently taking amiodarone?	No
Is the patient currently taking Phenytoin, Rifampin, or Carbamazepine?	No

Evidence Link/View Algorithm

▲Hide Details

Recommended WEEKLY starting dose of warfarin: 16.8 mg/week

The DAILY equivalent of this recommended starting dose is 2.4 mg/day.

NOTE: Further dose adjustments may be necessary due to other clinical factors, such as diet and other interacting medications (e.g., antibiotics or antifungals). This algorithm ONLY considers age, height, weight, genetic factors, and select medications (amiodarone, rifampin, phenytoin, and carbamazepine).

Help me decide the tablet size and number of tablets per day

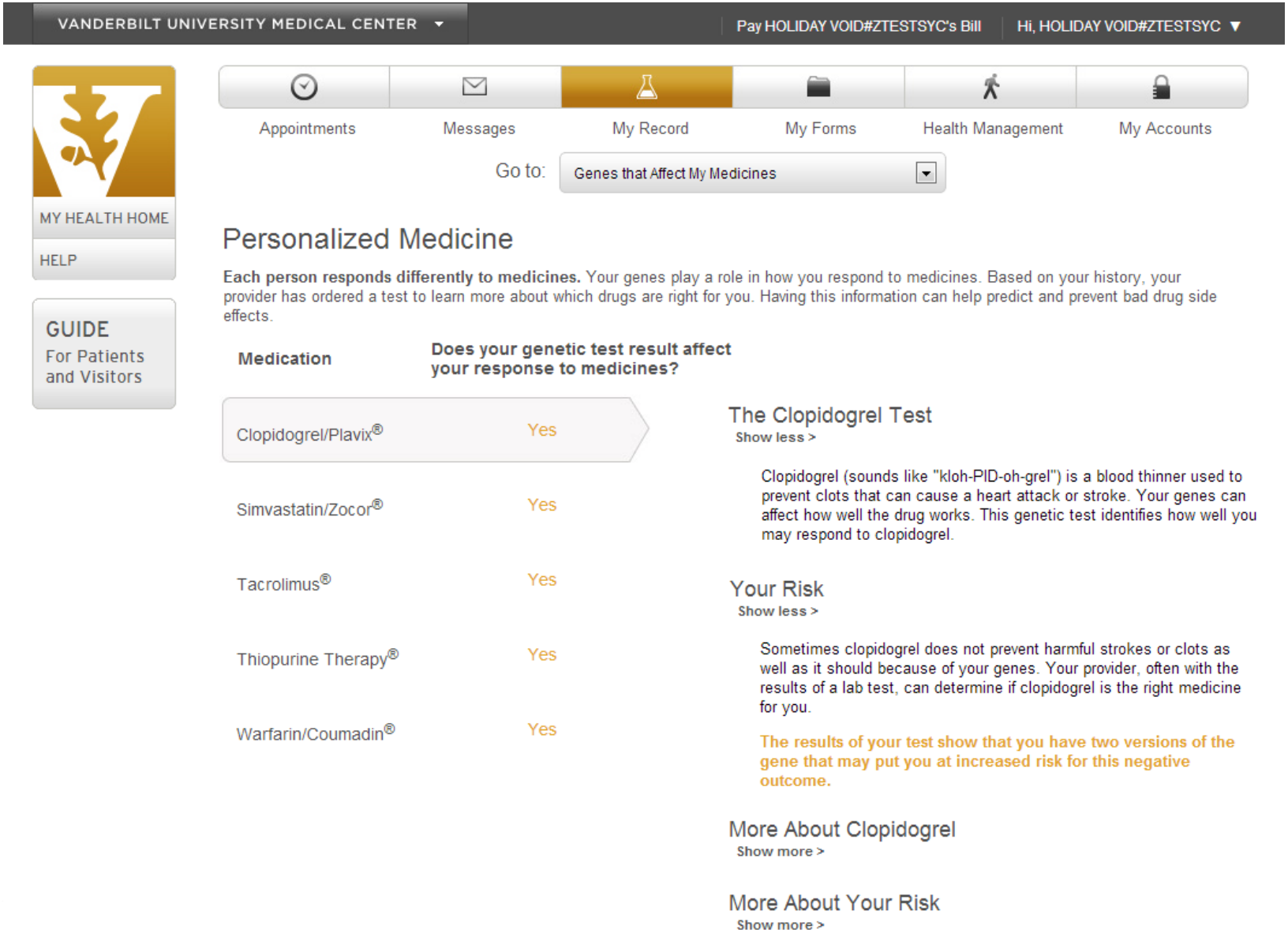
Pharmacy Surveillance of High Risk Genotype

None | Search patients by mrn

Status	Patient Name	Mrn	Last Checked	Service	Age	Weight(kg)	Result	Resulted Date
survey completed	xxxx, xx	xxxx	Never	CAR	70	85.28	DGI1:Plavix Sensitivity intermediate metabolizer	xxxx-xx-xx xx:xx:xx
survey completed	xxxx, xx	xxxx	Never	CAR	77	63.503	DGI1:Plavix Sensitivity intermediate metabolizer	xxxx-xx-xx xx:xx:xx
survey completed	xxxx, xx	xxxx	Never	OUT	56	78.02	DGI1:Plavix Sensitivity hypo metabolizer	xxxx-xx-xx xx:xx:xx
thirty day survey finished	xxxx, xx	xxxx	Never	CAR	50	71.4	DGI1:Plavix Sensitivity intermediate metabolizer	xxxx-xx-xx xx:xx:xx
thirty day survey finished	xxxx, xx	xxxx	Never	CAR	54	99.1	DGI1:Plavix Sensitivity intermediate metabolizer	xxxx-xx-xx xx:xx:xx
thirty day survey due	xxxx, xx	xxxx	Never	CAR	61	98.63	DGI1:Plavix Sensitivity intermediate metabolizer	xxxx-xx-xx xx:xx:xx
survey completed	xxxx, xx	xxxx	Never	OUT	90	52.62	DGI1:Plavix Sensitivity hypo metabolizer	xxxx-xx-xx xx:xx:xx

Khan, et al. AMIA 2011

PREDICT Results in the Patient Portal



Responsibility for Genomic Results

"I think it's going to be important to come up with good processes to educate referring physicians as well as ordering physicians and specialists on how to handle this information. Who do you need to notify? Who's responsible for acting on the information?"

"It's important to me to know the [consequences] of a cardiologist ordering a test that has implications when the patient is prescribed Azathioprine, or an SSRI, or a non-cardiac drug."

Unertl, Personalized Medicine. 2015

Responsibility for Prescription Change

Prior PREDICT Testing

Who, within Vanderbilt, should take responsibility for following up with the patient or outside providers? (check all that apply)

15%	Vanderbilt provider who has seen the patient most recently
54%	Vanderbilt provider who ordered the pharmacogenomic test
67%	PREDICT staff should contact the providers
27%	PREDICT staff should contact the patient directly

Peterson. The Pharmacogenomics Journal. 2015

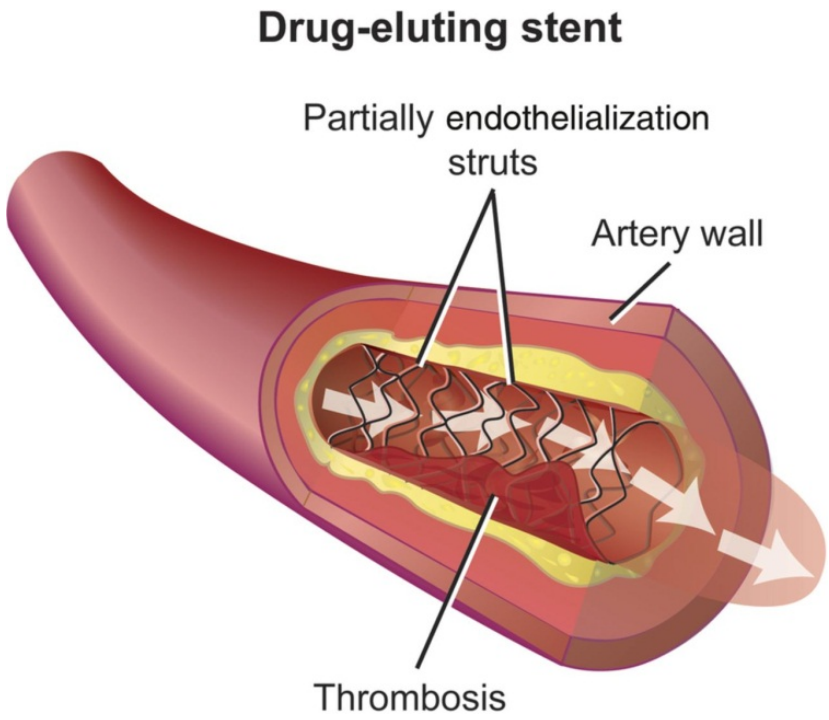
Clopidogrel & CYP2C19 Variants

Post-PCI Population

Expected benefit of tailored therapy vs standard therapy

Absolute risk difference: **4.1%** for the composite outcome, major adverse coronary events (MACE).

Number needed to genotype to potentially avert one adverse cardiac outcome: **25**



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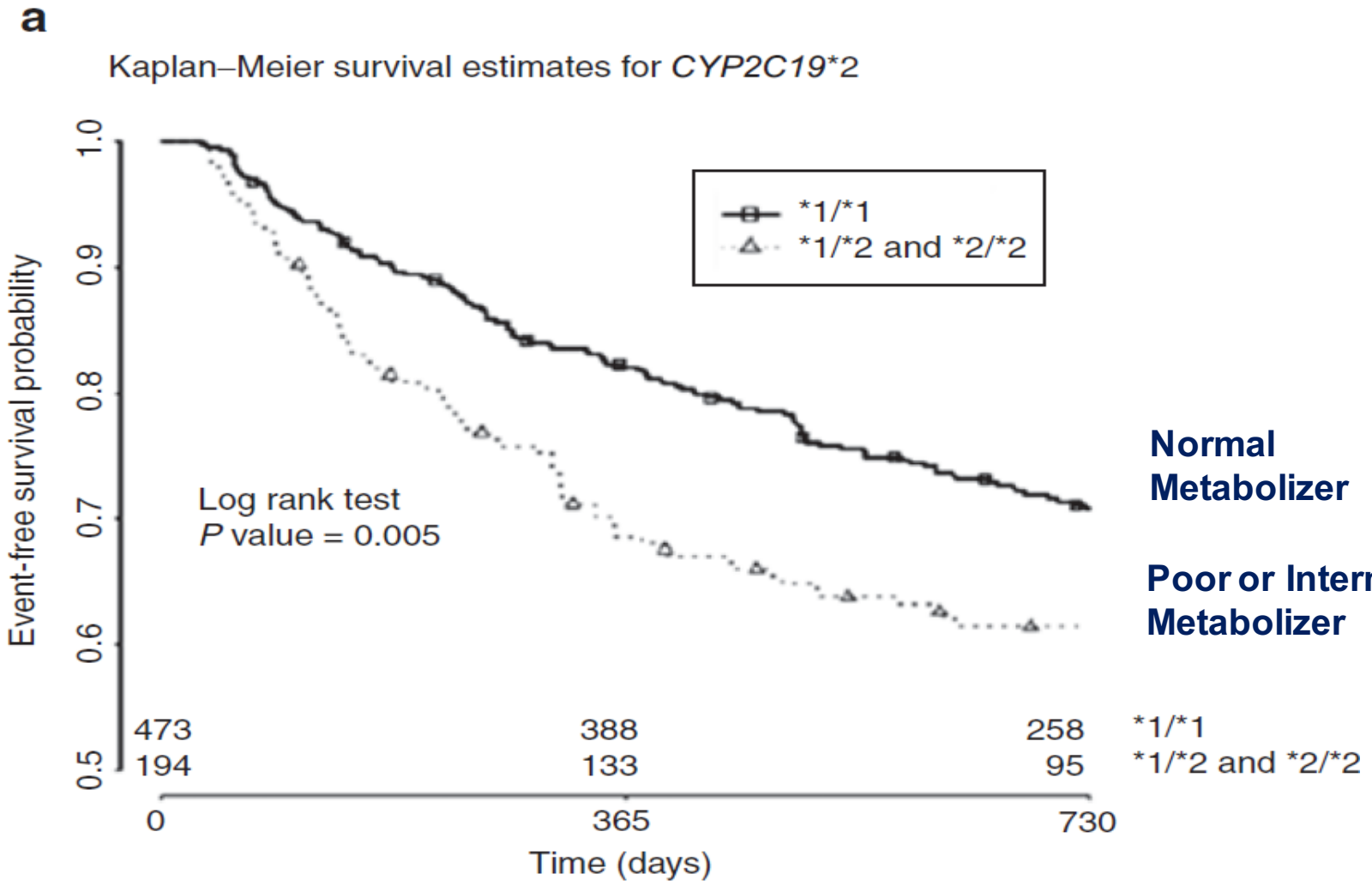
Pre-Implementation Retrospective Study

Clopidogrel and CYP2C19 : 96% of cases are stented



Normal Metabolizer

Poor or Intermediate Metabolizer

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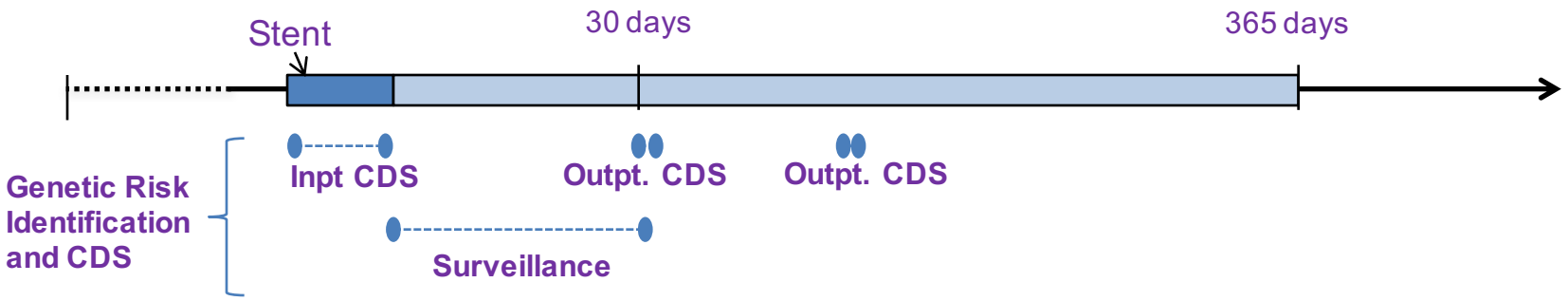
Delaney, CPT 2012

Clinician Response

CYP2C19 Genotyping



CYP2C19 Metabolizer Status	Genotype Tailored Therapy
Poor Metabolizer	58%
Intermediate Metabolizer	33%
Non-Actionable	8%

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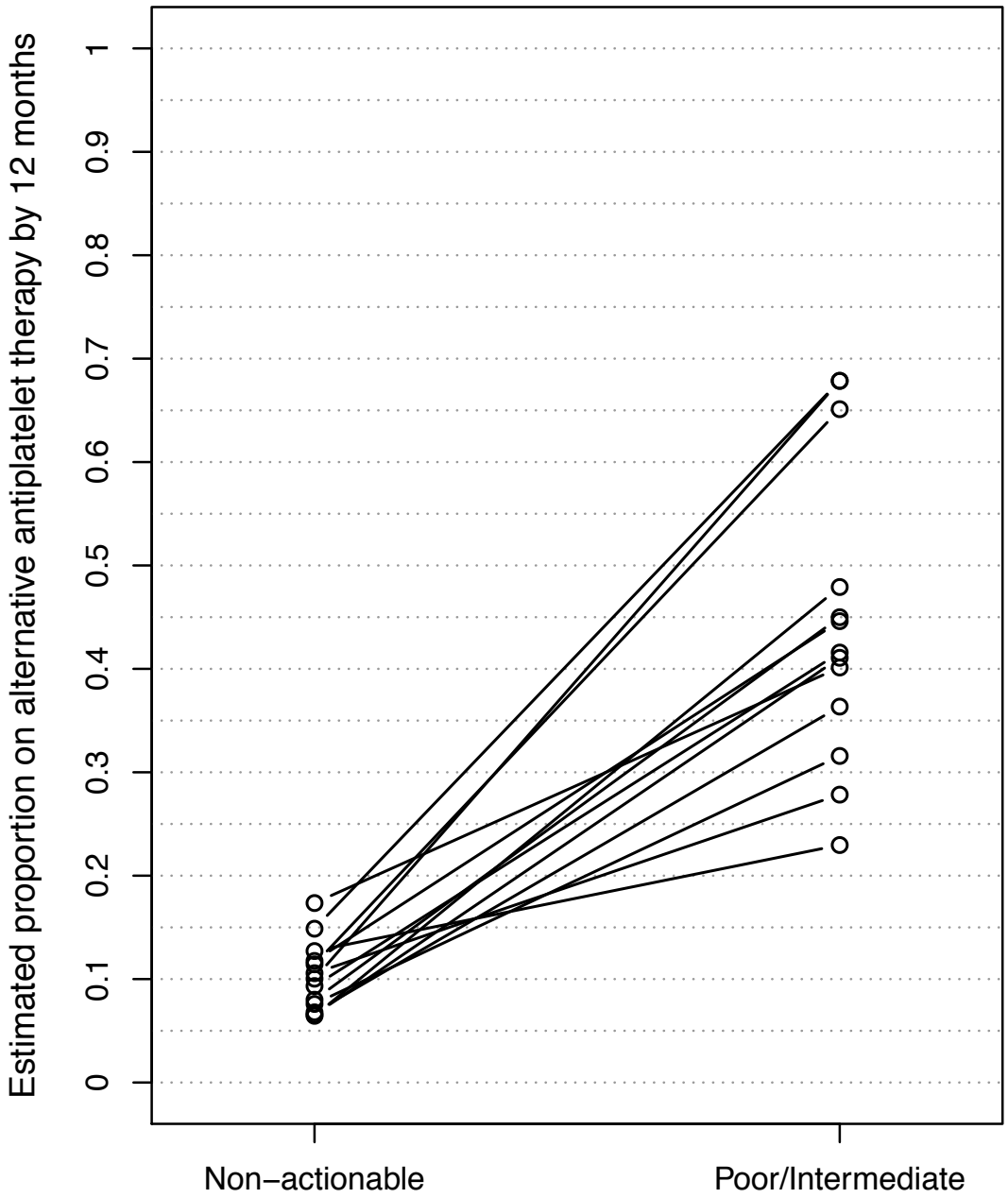
Peterson, CPT 2016

Differences in Adoption Among High Volume Interventionalists



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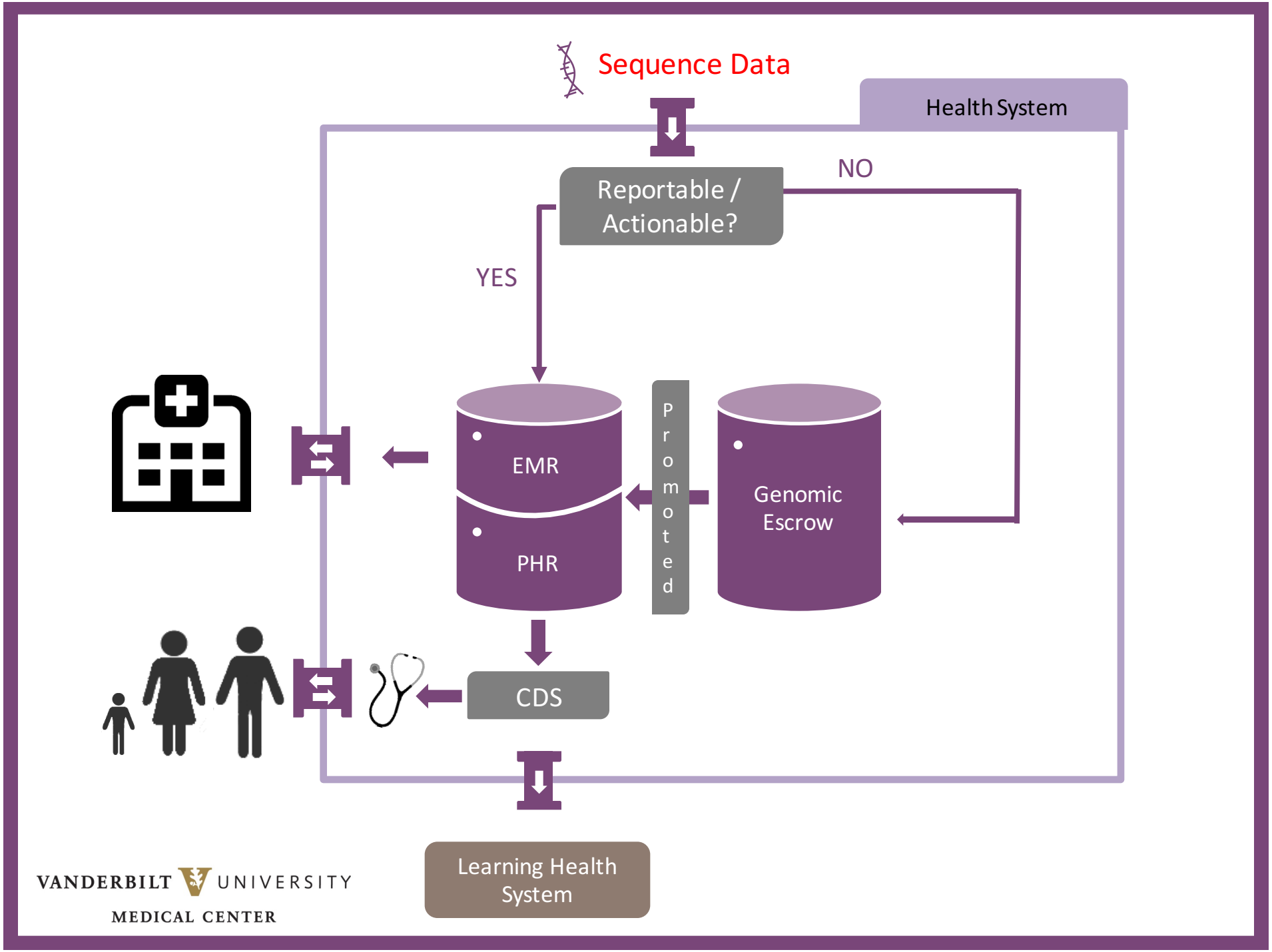
Peterson, CPT 2016

Implementation of Whole Genome Sequencing

"Our initial concerns were cost and data accuracy, but the major challenges turned out to be the logistics of delivering genome sequence information to clinicians, how clinicians use the data, and how patients and their families deal with the secondary (incidental) findings."

Jacob, et al.
Science Translational Medicine 2013


Sequence Data
Health System
Reportable / Actionable?
NO
YES
EMR
PHR
Promoted
Genomic Escrow
CDS
Learning Health System
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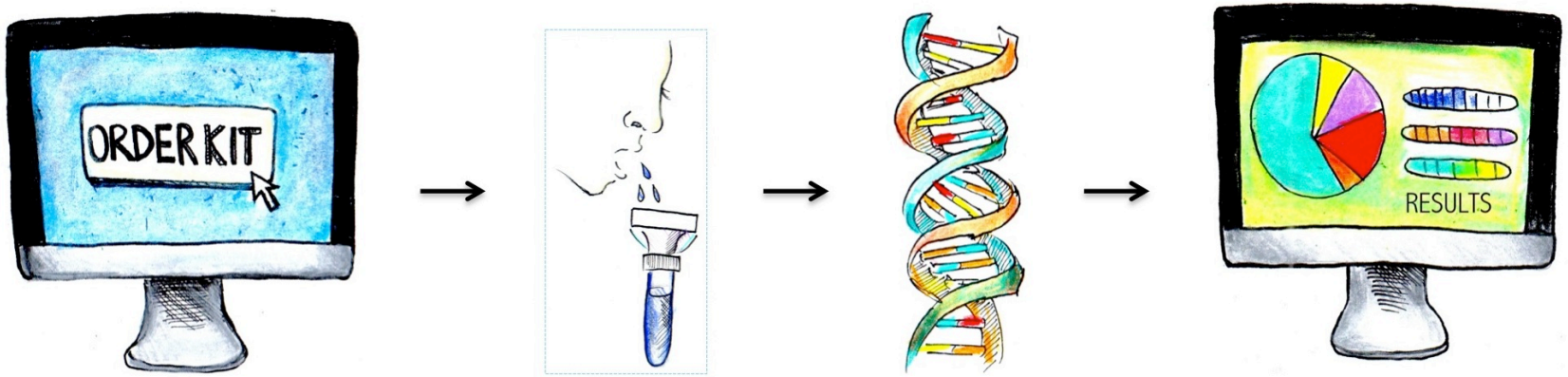
Who will be the stewards of our genetic data?

Clinical Laboratories ⟷ Health Systems



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