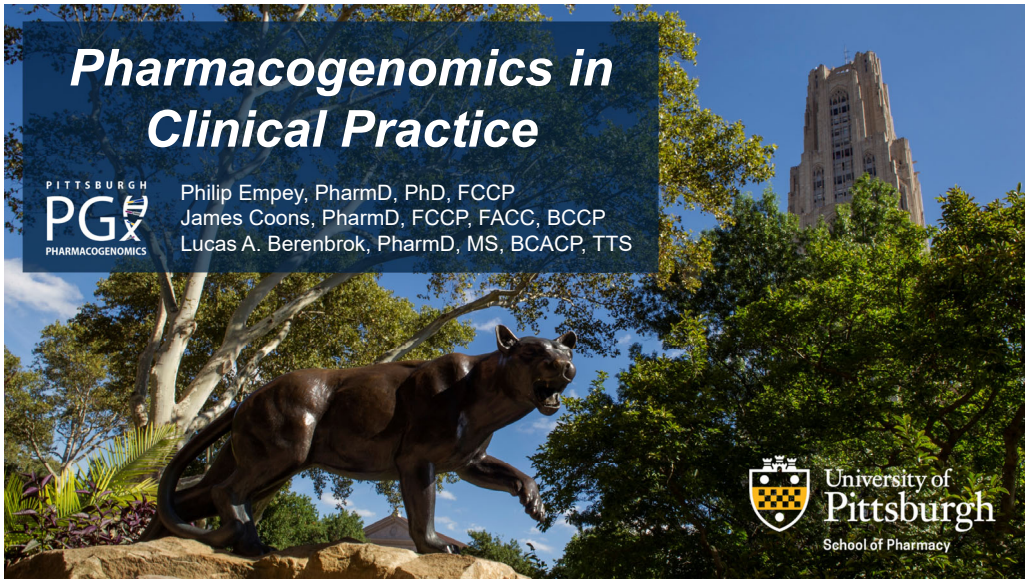


Pharmacogenomics in Clinical Practice

- **Pharmacogenomics (PGx): Science Driving Implementation**

Philip E. Empey, PharmD, PhD, FCCP
Director, Pharmacogenomics Center of Excellence
Associate Director of Pharmacogenomics, Institute for Precision Medicine
Associate Professor, School of Pharmacy

- **Clinical Application of PGx in the Hospital Setting**

James C. Coons, PharmD, FCCP, FACC, BCCP
Clinical Pharmacist, Cardiology, UPMC Presbyterian Hospital
PGY2 Cardiology Residency Director
Professor, School of Pharmacy

- **Clinical Application of PGx in Primary Care**

Lucas A. Berenbrok, PharmD, MS, BCACP, TTS
Associate Professor, School of Pharmacy

Pharmacogenomics (PGx): *Science Driving Implementation*

Philip Empey, PharmD, PhD
Director, Pharmacogenomics Center of Excellence
Associate Director, Institute for Precision Medicine
Associate Professor, Pharmacy & Therapeutics
pempey@pitt.edu, @philempey, @PittPGx

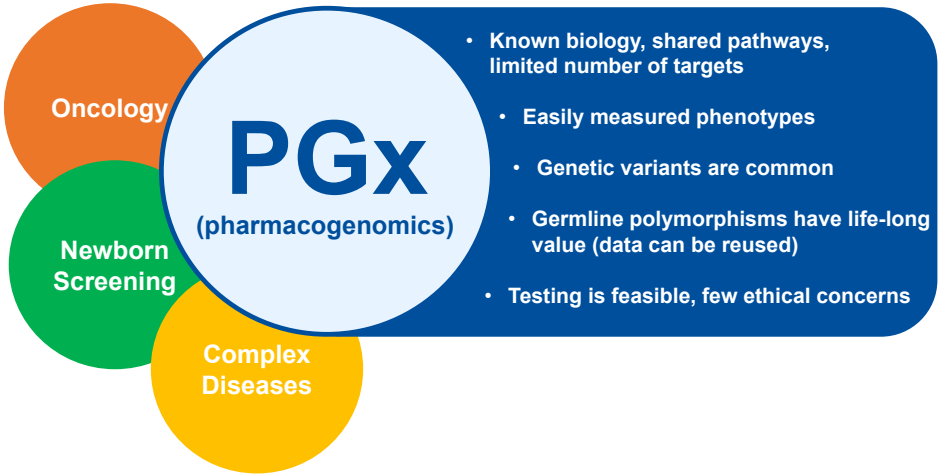
University of Pittsburgh | School of Pharmacy

PGx PITTSBURGH PHARMACOGENOMICS

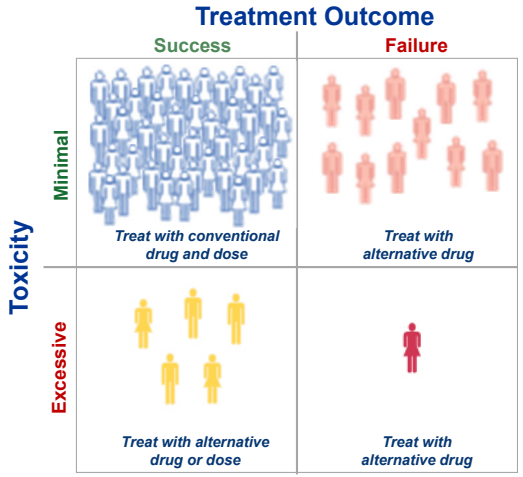
Learning Objectives

1. Describe why pharmacogenomics (PGx) is a leading use case for precision medicine and the role of pharmacists.
2. Identify pharmacogenomic resources that provide actionable information regarding how genetic variation in a large number of proteins, including drug transporters, drug metabolizing enzymes impacts drug response.
3. Discuss the current pharmacogenomic reimbursement landscape.

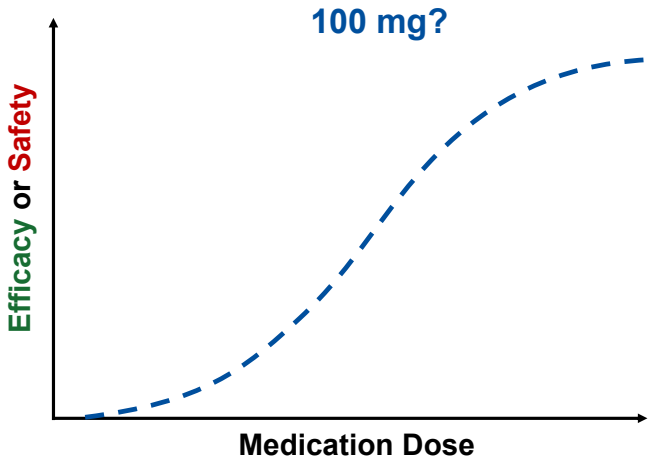
Why pharmacogenomics (PGx)?



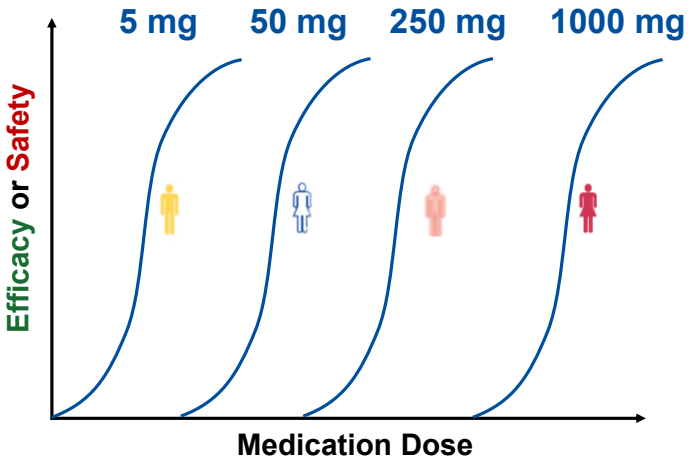
The Goal of Pharmacogenomics



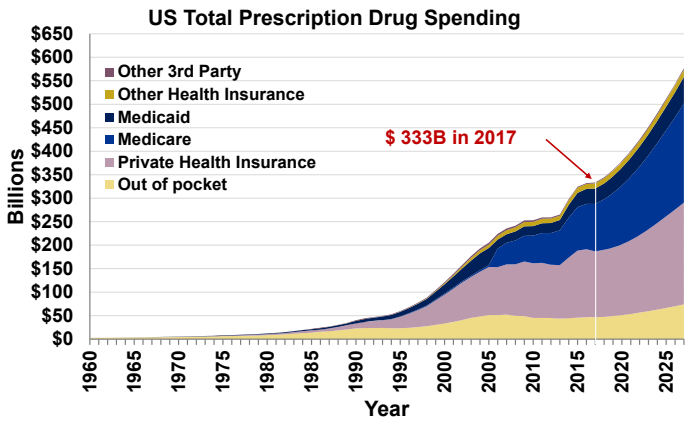
The problem with treating patients equally



The problem with treating patients equally



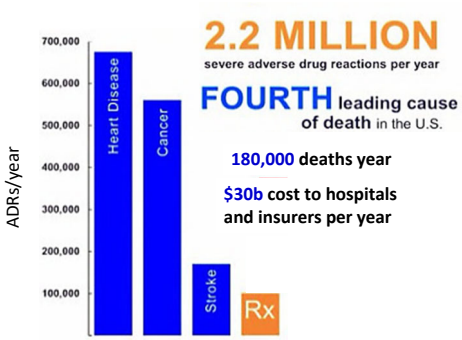
"Trial and Error" pharmacotherapy is not sustainable



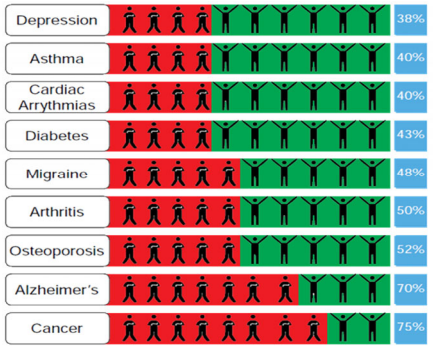
Drive to increase value in healthcare through precision prescribing

CMS, *National Healthcare Expenditures*, 2/22/2018.

"Trial and error" prescribing = ↑ outcome variability



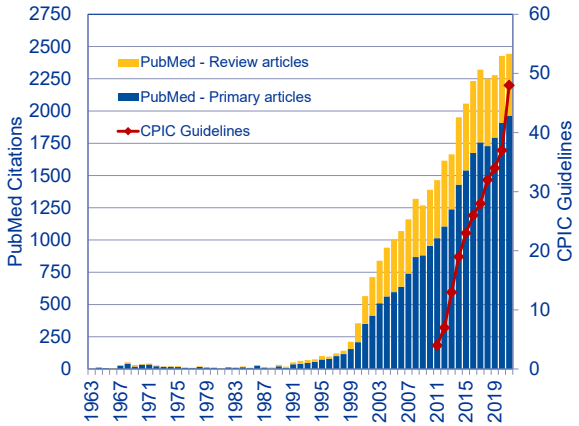
Adverse drug reactions are deadly/costly



Drug failure/poor efficacy is common

FDA. *Paving the way for personalized medicine*. 10/2013.

Why now?.... there is a wealth of PGx data!



CPIC® Clinical Pharmacogenetics Implementation Consortium

119 genes; 79 drugs at CPIC A

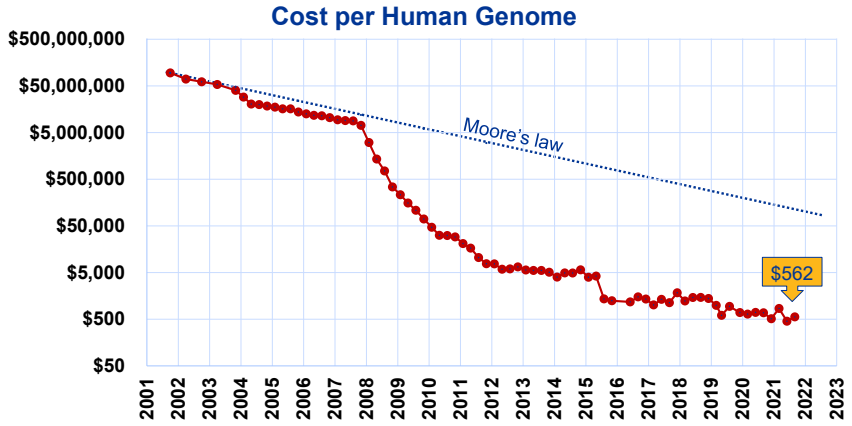
PharmGKB

25,329 annotations in 736 drugs

FDA U.S. FOOD & DRUG ADMINISTRATION

Unpublished data from Pubmed.gov, CPICPGx.org, PharmGKB,org, accessed 1/2022

Rapid decrease in testing costs



NHGRI, *DNA Sequencing Costs: Data*, Accessed 1/19/22

Which of the following organizations have make specific statements, whitepapers, policies advancing the role of pharmacists in providing PGx-based care?

a) ACCP
b) ASHP
c) APhA
d) All of the above

Pharmacists have taken PGx professional responsibility

ASHP REPORT

ASHP Statement on the Pharmacist's Role in Clinical Pharmacogenomics

Haidar et al, AJHP, 2022.

Endorsed 17 CPIC guidelines

ACCP WHITE PAPER

Precision pharmacotherapy: Integrating pharmacogenomics into clinical pharmacy practice

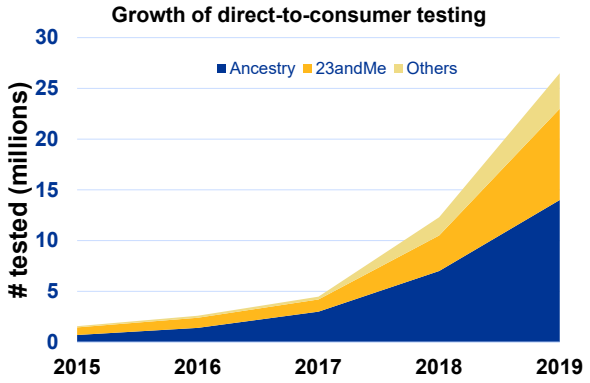
J. Kevin Hicks Pharm.D., Ph.D.[1] | Christina L. Aquilante Pharm.D., FCCP[2] | Henry M. Dunnenberger Pharm.D.[3] | Roseann S. Gammal Pharm.D.[4] | Ryan S. Funk Pharm.D., Ph.D.[5] | Samuel L. Aitken Pharm.D.[6] | David R. Bright Pharm.D.[7] | James C. Coons Pharm.D., FCCP[8] | Kierra M. Dotson Pharm.D.[9] | Christopher T. Elder Pharm.D.[10] | Lindsey T. Groff B.S.[11] | James C. Lee Pharm.D.[12]

Hicks et al, JACCP, 2019.

"APhA recognizes pharmacists as the health professional best suited to provide medication-related consultation and services based on a patient's genomic information.
-- House of Delegates 2018

Testing is increasingly sought by patients

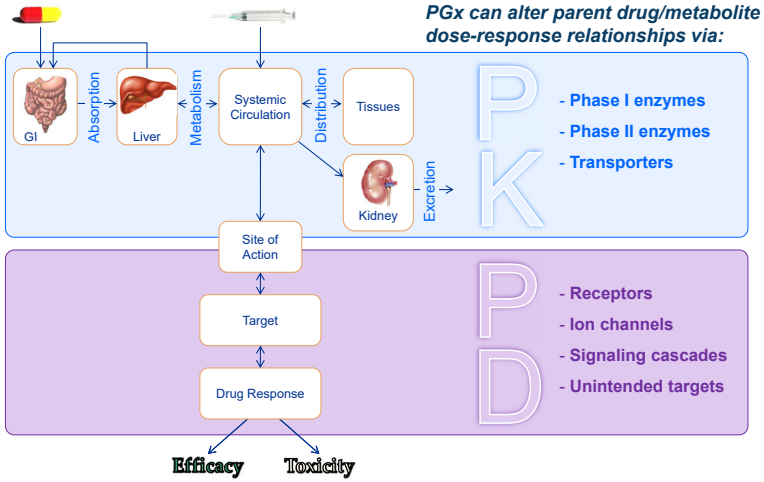
1 in 12 people in the US



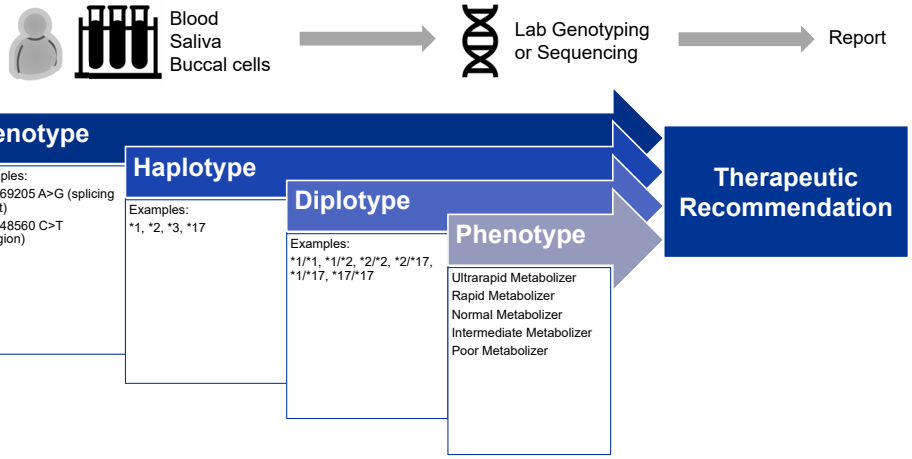
Regalado et al. *MIT Technology Review.* 2019

Pharmacogenomics and PK/PD

PGx can alter parent drug/metabolite dose-response relationships via:



The PGx Testing Process



Types of tests and technology

GENE 1

AGCCTAGCAACACGGCATGCCGA

Single gene /targeted genotyping

Types of tests and technology

GENE 1

AGCCTAGCAACACGGCATGCCGA

Single gene /targeted genotyping

Types of tests and technology

GENE 1 AGCCTAGCAACACGGCATGCCGA

GENE 2 CTCTTTCGAGCCCTTCCTAAGCC

Multiple gene (panel) genotyping

- \+ More data
- − More data
- − Increased cost?

Types of tests and technology

GENE 1 AGCCTAGCAACACGGCATGCCGA

GENE 2 CTCTTTCGAGCCCTTCCTAAGCC

Sequencing

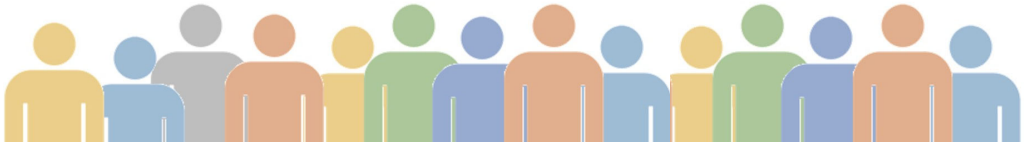
- More data
- More robust
- Discovery possible

- More data
- Increased cost
- More complex analysis
- Accuracy?

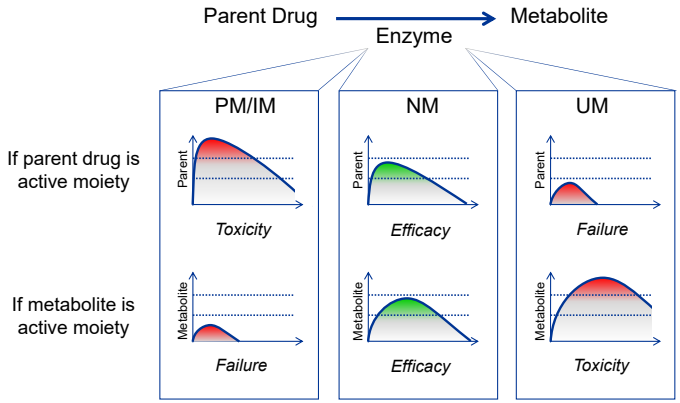
Pharmacists PGx Clinical Decision Making

Important factors to consider:

1. Functional consequence of variation
2. Variant frequency in population
3. Drug dependence on pathway
4. Active moiety and therapeutic index
5. Concomitant drug therapy (dis) or polygenic factors
6. Is there testing/clinical outcome data? What do established guidelines recommend?



How to assess clinical importance



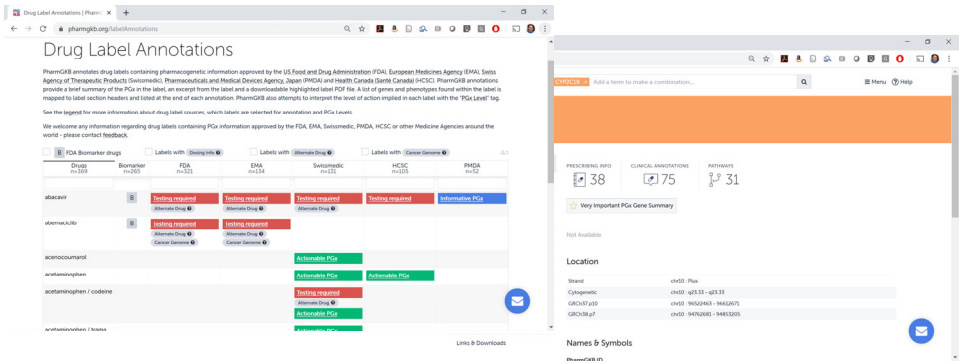
Empey PE. *Crit Care Med.* 2010 (6 Suppl):S106-16.

Which of the following resources develops peer-reviewed, evidence guidelines for the use of pharmacogenomics results in clinical care?

a) Clinical Pharmacogenetics Implementation Consortium (CPIC)
b) Pharmacogenomics Knowledgebase (PharmGKB)
c) Food and Drug Administration (FDA)
d) Genetics / Genomics Competency Center (G2C2)

Trustworthy PGx resources

PharmGKB collects, curates and disseminates knowledge about the impact of human genetic variation on drug response.



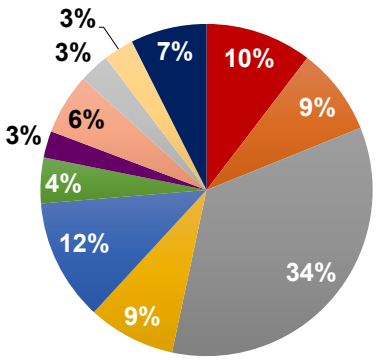
PharmGKB.org

PGx regulatory guidance (FDA)

FDA Table of Pharmacogenomic Biomarkers in Drug Labeling
FDA Table of Pharmacogenomic Associations

PGx regulatory guidance (FDA)

>300 medications currently have PGx in product labeling



Therapeutic areas:

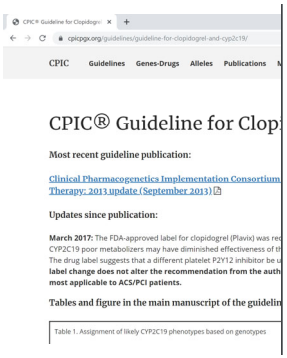
- psychiatry
- neurology
- oncology
- cardiovascular/hematology
- infectious disease
- gastrointestinal
- endocrinology
- anesthesiology/pain
- pulmonary
- rheumatology
- other

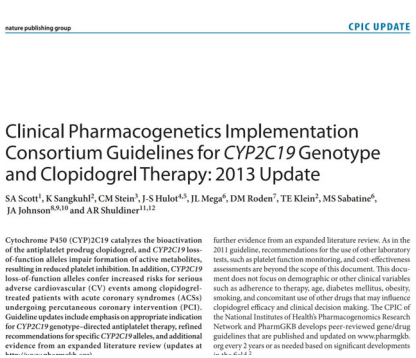
FDA Table of Pharmacogenomic Biomarkers in Drug Labeling
FDA Table of Pharmacogenomic Associations

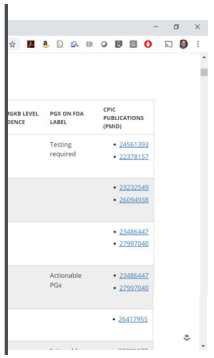
Evidence-based guidelines

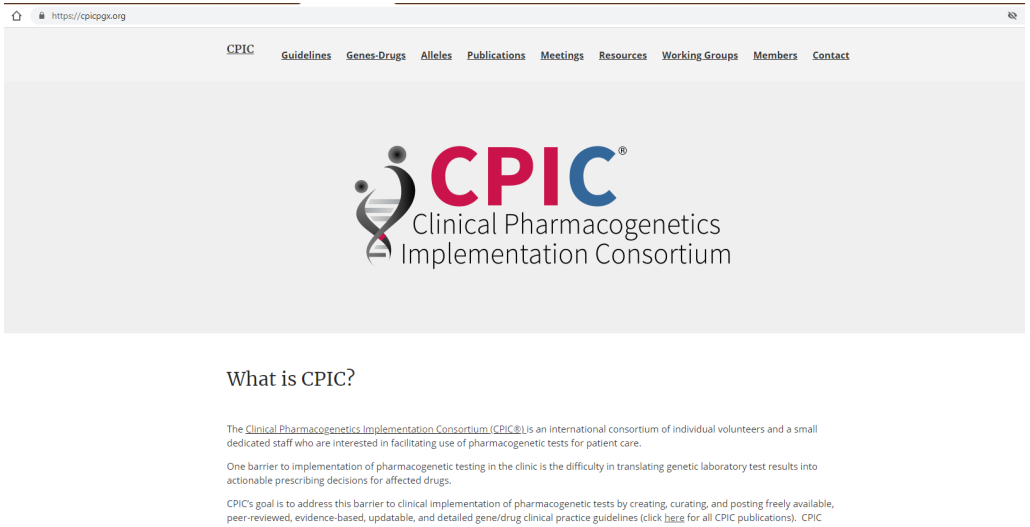
CPIC™ Clinical Pharmacogenetics Implementation Consortium

Freely available, peer-reviewed, evidence-based, updatable, and detailed gene/drug clinical practice guidelines

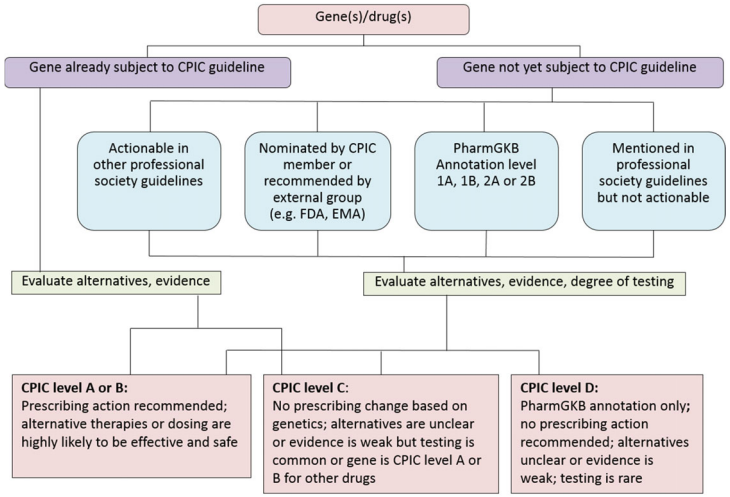








CPIC™
Clinical Pharmacogenetics Implementation Consortium

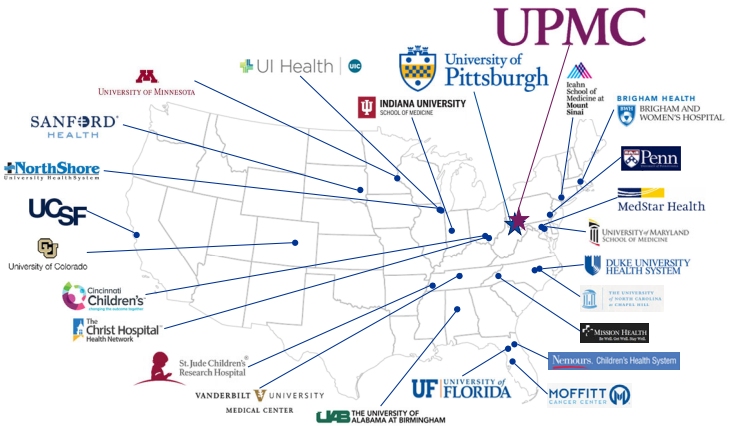


CPIC Guideline Gene-Drug Pairs

- **Cardiology**
  1. *CYP2C19* - clopidogrel
  2. *CYP2C9, VKORC1* - warfarin
  3. *SLCO1B1* - simvastatin
- **Psychiatry**
  4. *CYP2D6, CYP2C19* - SSRIs
  5. *CYP2D6, CYP2C19* - TCAs
  6. *CYP2D6* - atomoxetine
  7. *HLA-A, HLA-B* - carbamazepine and oxcarbazepine
  8. *CYP2C9*, HLA-B/Phenytoin
- **Anesthesiology/Pain management**
  9. *CYP2D6, OPRM1, COMT* - opioids
  10. *RYR1* - anesthetics and succinylcholine
  11. *CYP2C9* - NSAIDs
- **Hematology/oncology**
  12. *CYP2D6* - tamoxifen
  13. *TPMT, NUDT15* - thiopurines
  14. *DPYD* - fluoropyrimidines
- **General/supportive care**
  15. *CYP2C19* - PPIs
  16. *CYP2D6* - ondansetron and tropisetron
  17. *CFTR* - ivacaftor
  18. *HLA-B* - allopurinol
  19. *G6PD* - rasburicase
  20. *CYP3A5* - tacrolimus
- **Infectious disease**
  21. *CYP2C19* - voriconazole
  22. *UGT1A1*- atazanavir
  23. *IFNL3* - peginterferon-alpha-based regimens
  24. *HLA-B* - abacavir
  25. *CYP2B6* - efavirenz

CPICPGx.org

PGx implementation is hitting an inflection point



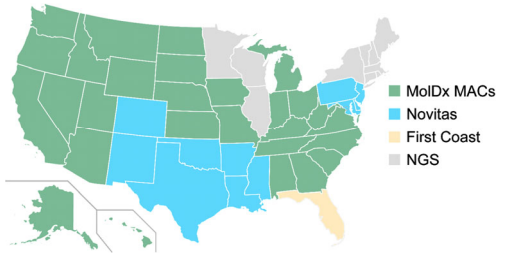
All of Us Research Program

VA | U.S. Department of Veterans Affairs
Veterans Health Administration

Pharmacogenomic testing is currently reimbursed by Medicare

a) True
b) False

Reimbursement is expanding



www.nature.com/gim

Genetics in Medicine

COMMENT

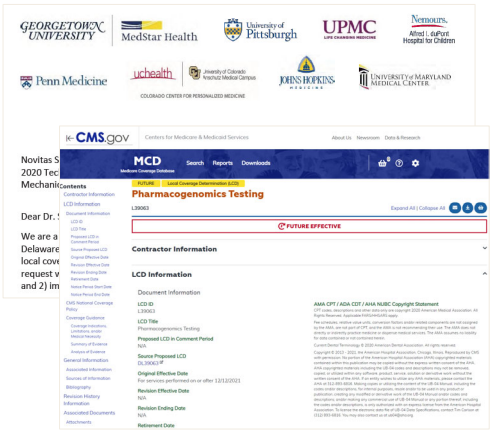
Expanding evidence leads to new pharmacogenomics payer coverage

Philip E. Empey, Victoria M. Pratt, James M. Hoffman, Kelly E. Caudle and Teri E. Klein

Genetics in Medicine (2021) 23:830–832; https://doi.org/10.1038/s41436-021-01117-w

In Dr. Francis Collins' 2001 testimony to Congress, he heralded advances in genetics with the Human Genome Project. He imagined testing "being used to tailor medicines to fit individual genetic profiles, since drugs that are effective in some people

Importantly, the US payer landscape for pharmacogenomic test reimbursement is improving.
In 2012, the American Medical Association (AMA) created unique current procedure terminology codes to facilitate doc-



Empey et al. *Gen Med.* 2021: May: 23(5); 830-832.

Provider status for pharmacists providing PGx services (?!)

Draft
CURES 2.0
legislation

SEC. 408. MEDICARE COVERAGE FOR CONSULTATIONS.

(a) INCLUSION OF CONSULTATIONS AS A MEDICARE BENEFIT.—Section 1861 of the Social Security Act (42 U.S.C. 1395x) is amended—

(1) in subsection (s)(2)—

(A) by striking "and" at the end of subparagraph (GG);

(B) by striking the period at the end of subparagraph (HH) and inserting "; and"; and

(C) by adding at the end the following new subparagraph:

"(II) pharmacogenetic consultations provided by a qualified clinical pharmacist, genetic counselor, or pathologist (as such terms are defined in subsection (lll)).''; and

(2) by adding at the end the following new subsection:

"(lll) DEFINITIONS.—In this section:

"(1) PHARMACOGENETIC CONSULTATION.—The term 'pharmacogenetic consultation' means, with respect to a genetic or genomic test furnished to an individual, a consultation with respect to such test requested by the physician treating such individual to provide such physician with advice and recommendations regarding the dosage, safety, and efficacy of particular drugs, biologicals, and other treatments based on the individual's pharmacogenetic result.

"(2) GENETIC COUNSELOR.—The term 'genetic counselor' means an individual who—

"(A) is licensed as a genetic counselor by the State in which the individual furnishes genetic counseling services; or

"(B) in the case of an individual practicing in a State that does not license genetic counselors, meets such other criteria as the Secretary establishes.

"(3) QUALIFIED CLINICAL PHARMACIST.—The term 'qualified clinical pharmacist' means an individual—

"(A) with a doctoral degree in pharmacy;

"(B) who is licensed as a pharmacist in the State in which such individual furnishes consultations;

"(C) has appropriate pharmacy specialty certifications or appropriate training, as determined by the Secretary; and

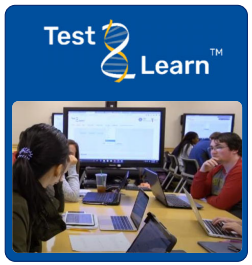
"(D) meets other qualifications as specified by the Secretary.''.

(b) PAYMENT FOR PHARMACOGENETIC CONSULTATION.—Section 1832(a)(2) of the Social Security Act (42 U.S.C. 1395k(a)(2)) is amended—

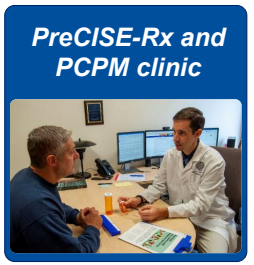
HR 6000 – Cures 2.0 Act, 117th Congress, introduced 11/17/2022

Pittsburgh Pharmacogenomics (@PittPGx)

Research → Clinical



Education



Clinical → Research

University of Pittsburgh | School of Pharmacy

PGx PITTSBURGH PHARMACOGENOMICS

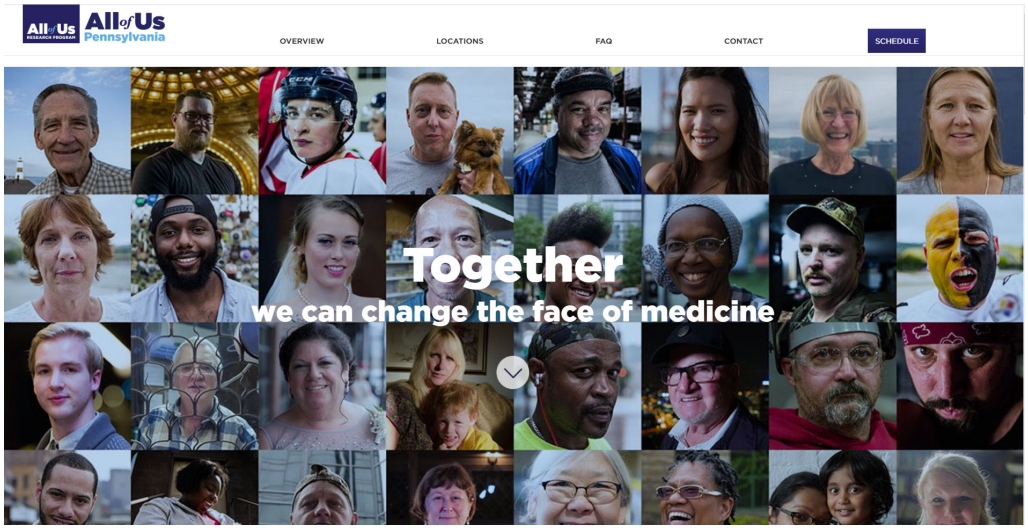
Barriers to "standard of care" PGx

Testing	❖ Complexity and lack of penetration of new technology/arrays ❖ Lack of academic/industry partnerships ❖ Slow turnaround time for results
Clinical	❖ Few drug or dose selection algorithms ❖ Lack of real-world/RCT data on outcomes (utility) and value ❖ Poor reimbursement for pre-emptive testing
Informatics	❖ Poorly-designed clinical informatics systems and decision support ❖ Inadequate analytics and point-of-care tools
Research	❖ Complicated consent and data sharing processes ❖ No population bio-banking for genotype-phenotype discovery ❖ Systematic capture of med use and phenotyping for drug response
Education	❖ Training of current and future health professionals in PGx and PGx communication
ELSI	❖ Ethics (privacy, equity, incidental findings, decision making) ❖ Privacy issues (informed consent) ❖ Legal issues (eg. discrimination, patents)

The field is transitioning rapidly

- One gene → many
- Reactive → preemptive
- Standardization, computable phenotypes
- Pragmatic trials/real world data
- Utility studies, analytics to prove value
- Implementation science
- De-risking results return to patients
- Education
- Data portability

Focused on solving scaling challenges; proving value

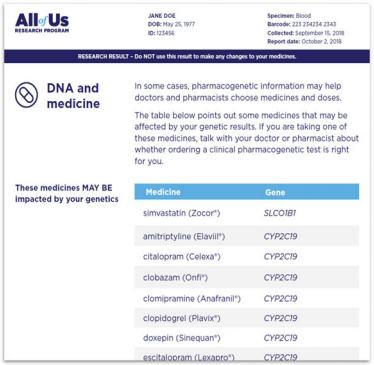


Joinallofuspa.org

The All of Us research program will return PGx results

Pharmacogenes in initial return

CYP2C19	Cytochrome p450 2C19
DPYD	Dihydropyrimidine dehydrogenase
G6PD	Glucose-6-phosphate dehydrogenase
NUDT15	Nudix hydrolase 15
SLCO1B1	Organic anion transporting polypeptide 1B1
TPMT	Thiopurine methyltransferase
UGT1A1	UDP Glucuronosyltransferase 1A1


All of Us RESEARCH PROGRAM

JANE DOE
DOB: May 25, 1977
ID: 123456

Specimen: Blood
Barcode: 223 234234 2343
Collected: September 15, 2018
Report date: October 2, 2018

RESEARCH RESULT – Do NOT use this result to make any changes to your medicines.

DNA and medicine

In some cases, pharmacogenetic information may help doctors and pharmacists choose medicines and doses.

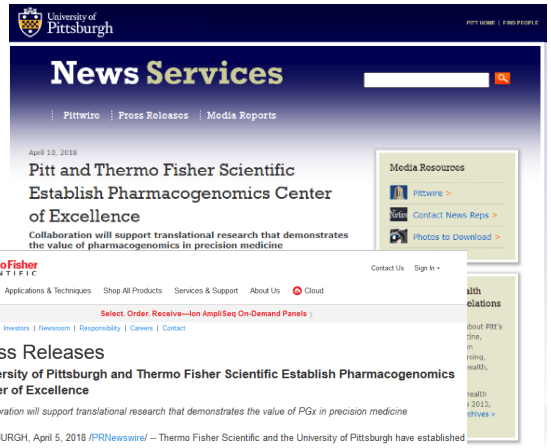
The table below points out some medicines that may be affected by your genetic results. If you are taking one of these medicines, talk with your doctor or pharmacist about whether ordering a clinical pharmacogenetic test is right for you.

These medicines MAY BE impacted by your genetics

Medicine	Gene
simvastatin (Zocor®)	SLCO1B1
amitriptyline (Elavil®)	CYP2C19
citalopram (Celexa®)	CYP2C19
clobazam (Onfi®)	CYP2C19
clomipramine (Anafranil®)	CYP2C19
clopidogrel (Plavix®)	CYP2C19
doxepin (Sinequan®)	CYP2C19
escitalopram (Lexapro®)	CYP2C19

Unpublished data

Population-scale preemptive PGx in Pittsburgh



April 2018

Population-scale preemptive PGx at Pitt/UPMC

University of Pittsburgh School of Pharmacy ····· ThermoFisher SCIENTIFIC

The Pharmacogenomics Center of Excellence

Industry-academic partnership to advance PGx

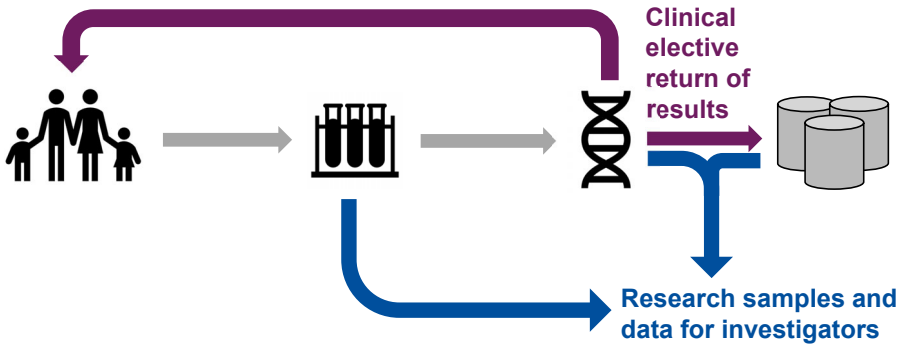
Research

- Cohort discovery
- Drug response phenotyping
- Genotype-phenotype discovery
- Machine learning/predictions
- Commercialization

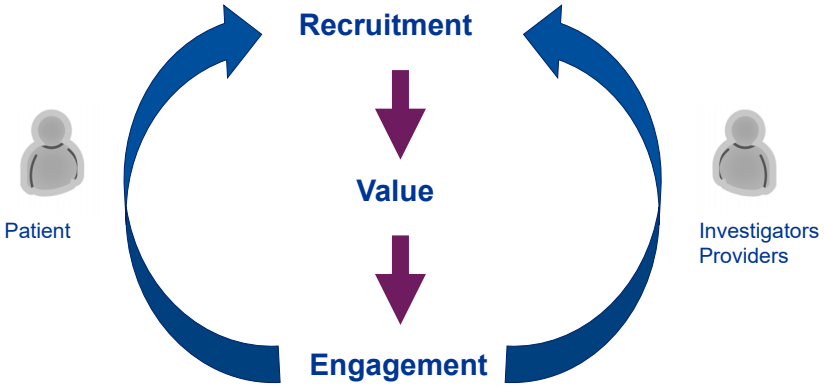
Clinical

- UPMC EHR deposit (14 genes)
- Alerting (100+ drugs)
- Return of results to patients
- Clinical utility analytics
- Value ($) modeling

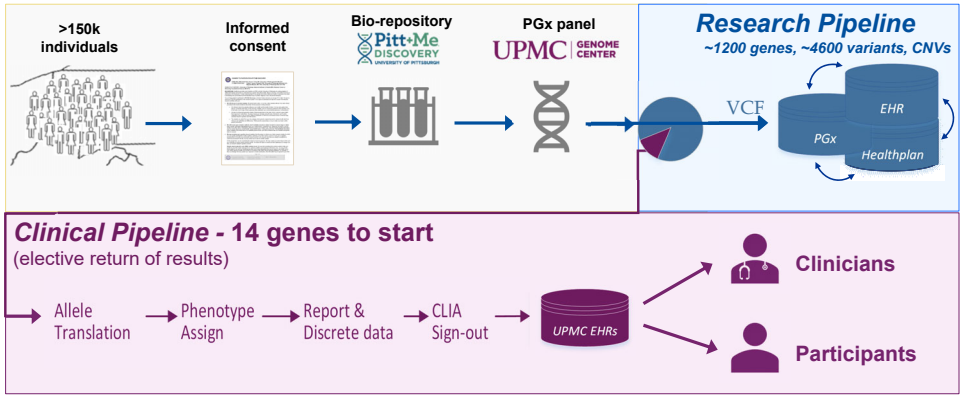
Translational Research ↔ Clinical Model



Sustainability for clinical and research ROI



Pitt/UPMC enterprise PGx workflow



Innovative Testing Platform (CAP/CLIA)

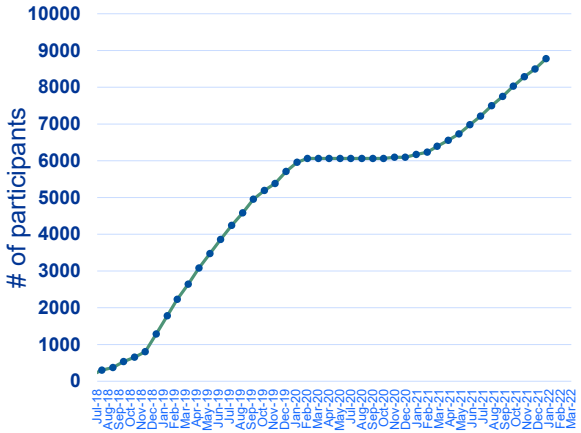
Bio-banking
~100ug DNA/sample

CONTEMPORARY ARRAY
1200 genes; 4600 variants,
CNV → Research

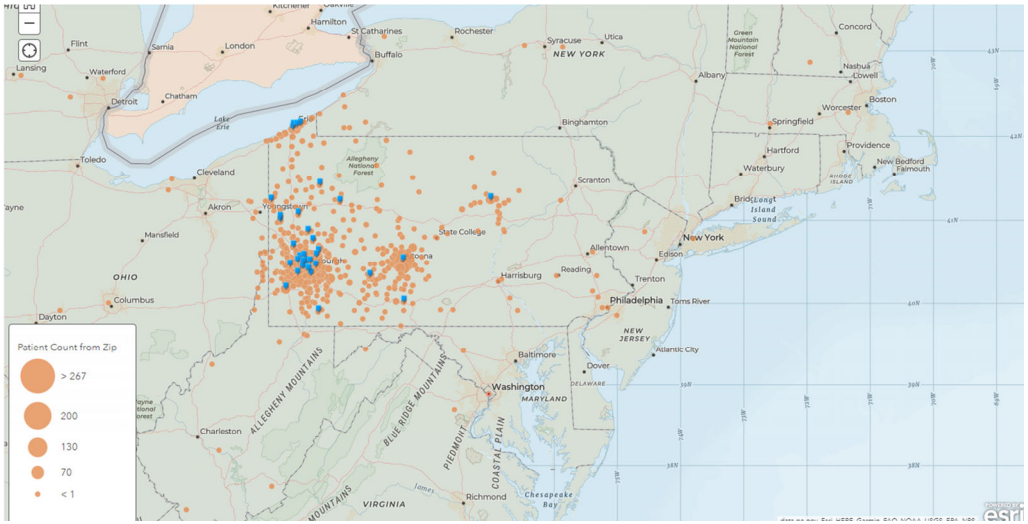
"UPMC Comprehensive PGx panel"
14 genes → Clinical

UPMC | GENOME CENTER

Recruitment metrics



Recruitment metrics



Current enrollment data

92.9% of participants

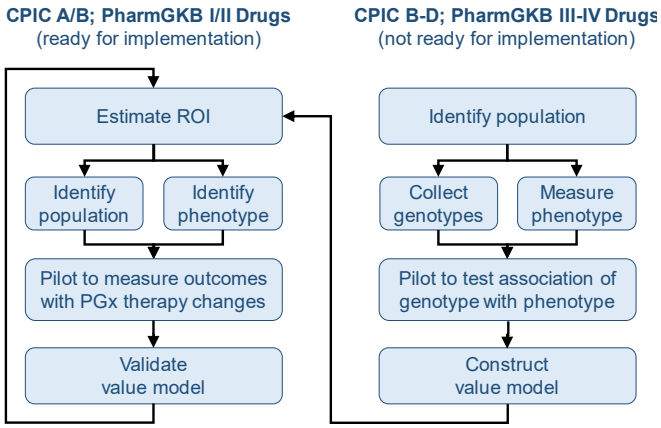
Elected to receive PGx results!

50% of participants are taking **≥1 PGx drug with CDS alerts**

19.4% have been exposed to **5+ clinically actionable PGx drugs**

10.1% have been exposed to **10+ clinically actionable PGx drugs**

Our goal is to prove value



Overcoming education barriers

- **Clinicians, feel responsible but are <u>not confident</u> with PGx data:**
  - 57% of pharmacists agreed that their role should include PGx counseling
  - 83% rated their PGx understanding as fair/poor.
  - 10-20% felt "comfortable" or "competent" to discuss PGx results with patients/other providers

- **Participatory education models demonstrated <u>superior learning outcomes,</u> is <u>feasible to be deployed in an ethically responsible framework</u>, and can be integrated into diverse educational formats (classroom, CE, certificate programs)**

De Denus et al, *Pharmacogneomics*. 2013
Roederer et al. *Per Med*. 2011
Tuteja et al. *Per Med*. 2013

Krynetskiy et al. *AJPE*. 2009
Knoell et al. *AJPE. 2009*
Salari et al. *Academic Medicine*. 2011
Salari et al. PLoS One. 2013

Adams et al. *AJPE*. 2016
Frick et al. *Front Pharmacol*. 2016
Weitzel et al. *AJPE*. 2016
Surofchy et al. *Innovations in Pharmacy. 2017*

What it means to achieve PGx competency

30 competency statements

- Mapped to *Pharmacist Patient Care Process*
- Ethical, legal, social implications integrated throughout

Emphasis on pharmacists as practice-based leaders in PGx (vs genomics competency statements for other HCPs)

All pharmacists should be "practice-ready" for PGx with acknowledgement of need for advanced training for specialists.

Gammal et al., *AJPE*, 2022 Apr;86(4):8634.

Pitt/UPMC Advancing PGx through innovative education

- Personal genome testing to learn genomics
- Trained >4k learners through modular competency-based, continuing education, micro-credentialing
- Integrated in pharmacy/medicine curricula and nationally at multiple universities

Test2Learn™ test2learn.org

Personal Genomic Testing + Emerging trends in educational innovation + Expert Instruction = High Level Learning Outcomes

Experience testing like your patients

Short, web-delivered; competency-based

Meeting G2C2 and discipline learning objectives and standards

Gain practical knowledge to improve your practice

University of Pittsburgh School of Pharmacy — 4 invention disclosures — 23andMe — AACP Innovations in Education Award — Pitt Advisory Council on Instructional Excellence Grant Award — NACDS National Association of Chain Drug Stores — Richard King Mellon Foundation — NIH NHGRI

Test2Learn genomics learning management system

Key Takeaways

- PGx is a leading use case for precision medicine and has a wealth of data.
- Pharmacists can lead implementations and professional organizations emphasize our key roles
- Resources exists from CPIC, PharmGKB, FDA to guide decision making
- PGx reimbursement landscape is expanding.

Katsanis et al. *Science* 2008;320(5872):53-54.

Clinical Applications of PGx in the Hospital Setting

James Coons, PharmD, FCCP, FACC, BCCP
Professor, Pharmacy & Therapeutics
University of Pittsburgh School of Pharmacy
Clinical Pharmacist, Cardiology
UPMC Presbyterian Hospital

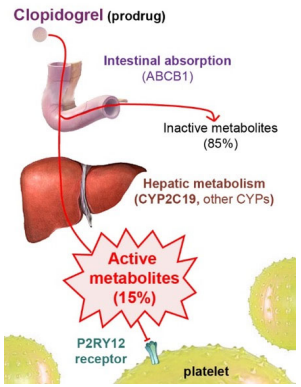
University of Pittsburgh School of Pharmacy

PGx PITTSBURGH PHARMACOGENOMICS

Learning Objectives

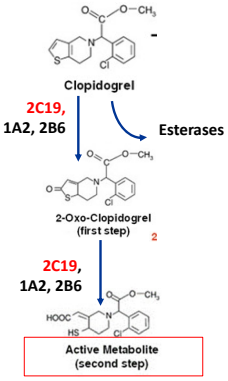
- Describe an example of clinical pharmacogenomics (PGx) implementation program in the acute care setting.
- Explain the role of a pharmacist in a hospital-based PGx implementation program.
- Highlight the impact of an inpatient PGx program on patient outcomes.

Clopidogrel: A Leading PGx Use Case



An enzyme *CYP2C19* plays a key role in drug activation

↓ active metabolite
↓ antiplatelet effect
↑ MACE, stent thrombosis



JAMA 2010;304:1821-30.

FDA - Approved Clopidogrel Labeling

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.
- 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.
- Tests are available to identify a patient's CYP2C19 genotype and can be used as an aid in determining therapeutic strategy.
- Consider alternative treatment or treatment strategies in patients identified as CYP2C19 poor metabolizers.

https://www.fda.gov/drugs/postmarket-drug-safety-information-patients-and-providers/fda-drug-safety-communication-reduced-effectiveness-plavix-clopidogrel-patients-who-are-poor

CPIC Guideline

CPIC UPDATE

Clinical Pharmacogenetics Implementation Consortium Guideline for *CYP2C19* Genotype and Clopidogrel Therapy: 2022 Update

Craig R. Lee[1], Jasmine A. Luzum[2], Katrin Sangkuhl[3], Roseann S. Gammal[4,5], Marc S. Sabatine[6], Charles Michael Stein[7], David F. Kisor[8], Nita A. Limdi[9], Yee Ming Lee[10], Stuart A. Scott[11,12], Jean-Sébastien Hulot[13], Dan M. Roden[14], Andrea Gaedigk[15], Kelly E. Caudle[5], Teri E. Klein[3], Julie A. Johnson[16] and Alan R. Shuldiner[17,*]

CYP2C19 catalyzes the bioactivation of the antiplatelet prodrug clopidogrel, and CYP2C19 genotype impacts clopidogrel active metabolite formation. CYP2C19 intermediate and poor metabolizers who receive clopidogrel experience reduced platelet inhibition and increased risk for major adverse cardiovascular and cerebrovascular events. This guideline is an update to the 2013 Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline for the use of clopidogrel based on *CYP2C19* genotype and includes expanded indications for *CYP2C19* genotype-guided antiplatelet therapy, increased strength of recommendation for CYP2C19 intermediate metabolizers, updated *CYP2C19* genotype to phenotype translation, and evidence from an expanded literature review (updates at www.cpicpgx.org).

Clin Pharmacol Ther 2022 Jan 16. doi: 10.1002/cpt.2526.

CYP2C19 Genotype-Phenotype Pairs

CYP2C19 Genotype – Phenotype Pairs

	*1	*2	*3	*4	*5	*6	*7	*8	*9	*10	*17
*1	*1/*1	*1/*2	*1/*3	*1/*4	*1/*5	*1/*6	*1/*7	*1/*8	*1/*9	*1/*10	*1/*17
*2		*2/*2	*2/*3	*2/*4	*2/*5	*2/*6	*2/*7	*2/*8	*2/*9	*2/*10	*2/*17
*3			*3/*3	*3/*4	*3/*5	*3/*6	*3/*7	*3/*8	*3/*9	*3/*10	*3/*17
*4				*4/*4	*4/*5	*4/*6	*4/*7	*4/*8	*4/*9	*4/*10	*4/*17
*5					*5/*5	*5/*6	*5/*7	*5/*8	*5/*9	*5/*10	*5/*17
*6						*6/*6	*6/*7	*6/*8	*6/*9	*6/*10	*6/*17
*7							*7/*7	*7/*8	*7/*9	*7/*10	*7/*17
*8								*8/*8	*8/*9	*8/*10	*8/*17
*9									*9/*9	*9/*10	*9/*17
*10										*10/*10	*10/*17
*17											*17/*17

Ultra-rapid Metabolizers (UM)
Rapid Metabolizers (RM)
Normal Metabolizers (NM)
Intermediate Metabolizers (IM)
Poor Metabolizers (PM)

*Likely IM (*1/*9, *9/*17, *9/*9)
*Likely PM (*2/*9, *3/*9)

No function alleles	*2, *3, *4, *5, *6, *7, *8
Decreased function alleles	*9, *10
Wildtype allele	*1
Increased function allele	*17

Clin Pharmacol Ther 2022 Jan 16. doi: 10.1002/cpt.2526.

CPIC Recommendations

Phenotype	Recommendation	Classification
UM, RM, NM	Clopidogrel standard dose	ACS/PCI: Strong Other: NR (UM/RM); Strong (NM)
IM, likely IM, PM, likely PM	Prasugrel or Ticagrelor	ACS/PCI: Strong Other: NR (IM/likely IM); Moderate (PM/likely PM)

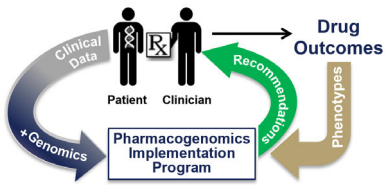
NR – no recommendation

Clin Pharmacol Ther 2022 Jan 16. doi: 10.1002/cpt.2526.

Clinical Implementation of *CYP2C19*-Clopidogrel: Program Overview

Pharmacogenomic Guided Care

- ***PreCISE-Rx***: Pharmacogenomics-guided Care to Improve the Safety and Effectiveness of Medications



Goal: ***Prediction of patient medication outcomes by integrating PGx and clinical variables to improve the health of the population at reduced cost***

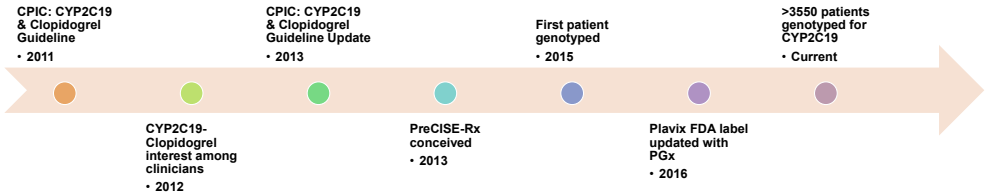
Approach

- Create value-driven genomics-guided pharmacotherapy protocols integrated into clinical pathways
- Make pharmacogenomics testing available
- Configure the EHR and build educational resources necessary efficient implementation

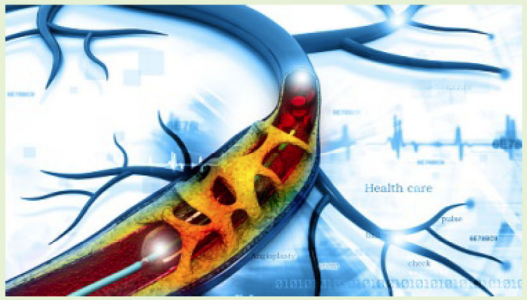
Hypothesis: ***pharmacogenomics-guided therapy individualization is clinically feasible.***

PreCISE-Rx

- Pharmacogenomics-guided Care to Improve the Safety and Effectiveness of Medications
  - To measure the performance and impact of pharmacogenomics-guided drug therapy individualization following PCI
  - Results of CYP2C19 genotyping can be considered when selecting antiplatelet agents for patients with acute coronary syndrome undergoing percutaneous coronary intervention



PreCISE-Rx – PGx Implementation at UPMC

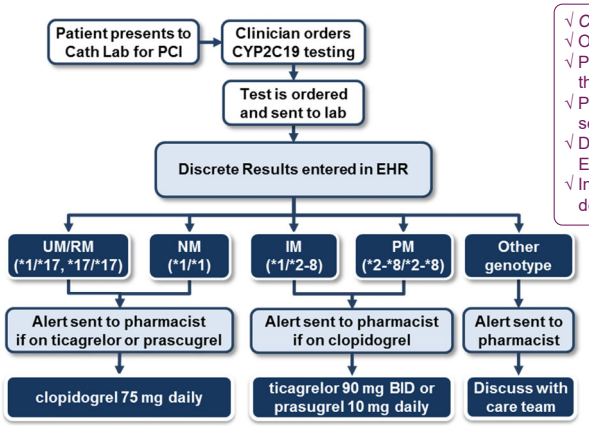


UPMC Uses Gene Test to 'Personalize' Meds for Heart Patients

Test checks for gene variant that limits response to blood thinner used after blood vessel stenting.
Read More>>

University of Pittsburgh School of Pharmacy | INSTITUTE FOR PRECISION MEDICINE A partnership of the University of Pittsburgh and UPMC | ashp pharmacists advancing healthcare | UPMC LIFE CHANGING MEDICINE

PreCISE-Rx Clinical Workflow



√ *Clinical "standard-of-care"*
√ On-site testing
√ Protocolized ordering; therapy modification
√ Pharmacist-led clinical services
√ Discrete results in both Epic & Center
√ Interruptive clinical decision support

Metrics collected and projected outcomes

Research Study
- IRB approved
- Biobank/EHR Data

Clinical Outcomes
- Major adverse events
- Any bleeding

Process Efficiency
- Turnaround time
- Capture rate

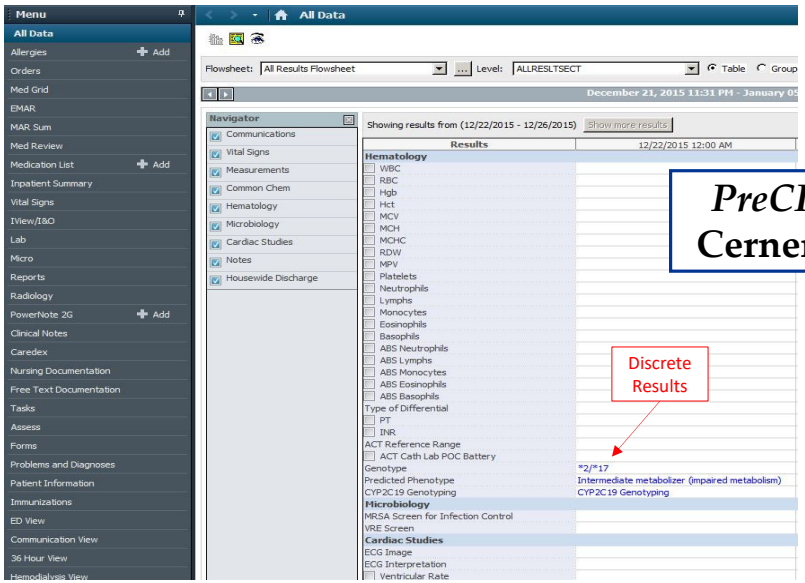
Medication Use
- Adherence
- Conversions

Patient Satisfaction
- Care model
- Education

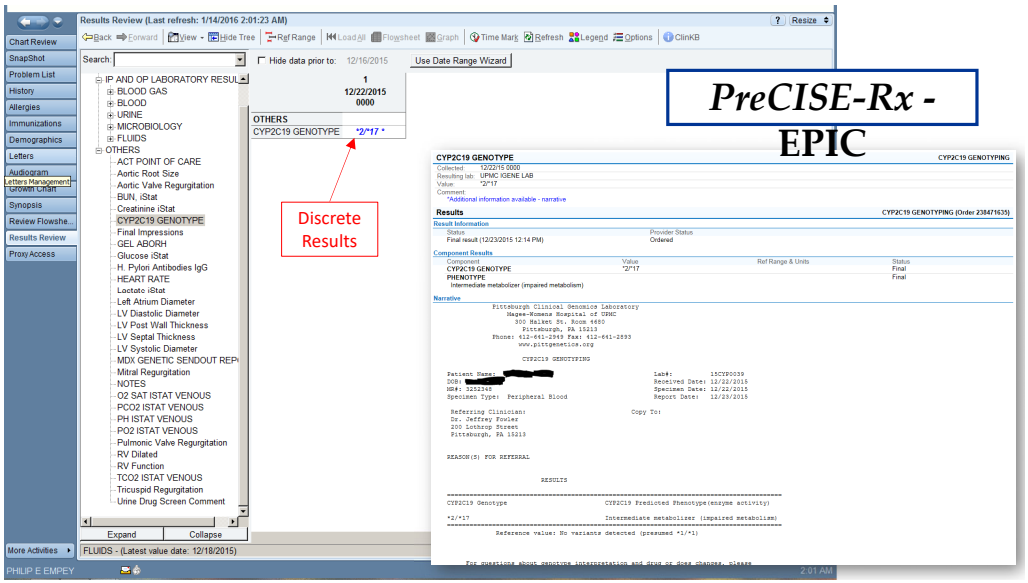
Financial Impact
- Reimbursement
- Business model

Process of ordering *CYP2C19* genotype

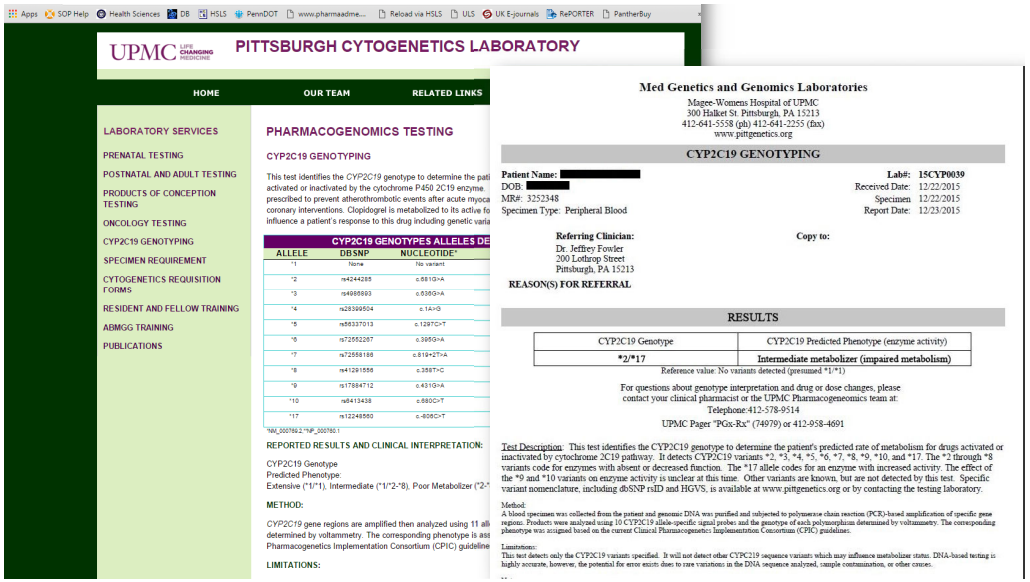
- Available within Cerner order sets that is <u>pre-checked</u> (opt-out process)
  - Cardiac PTCA/ Stent Post Procedure Order Set
  - Radial Artery Post PTCA/ Stent Procedure PowerPlan
  - Cardiac Catheterization Lab Post Procedure Order Set



***PreCISE-RX* – Cerner eRecord**



***PreCISE-Rx* - EPIC**

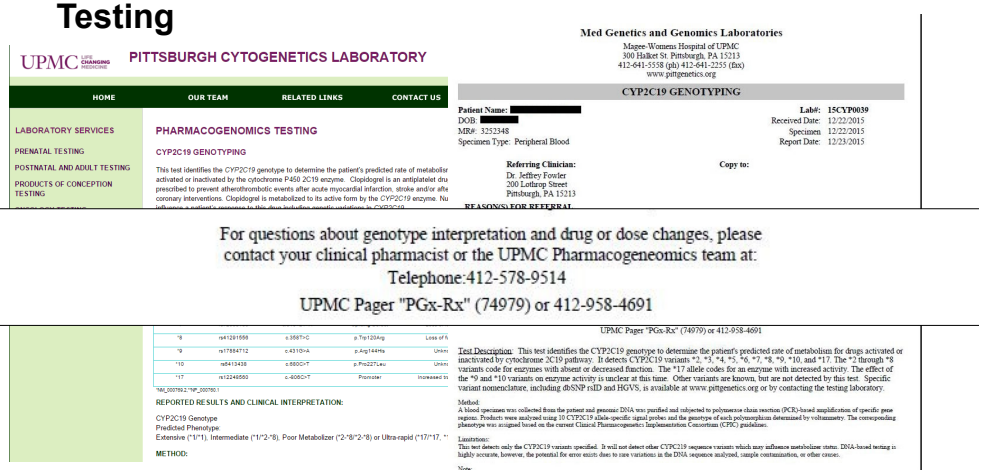


Clinical Implementation of *CYP2C19*-Clopidogrel: Pharmacist Role

Pharmacist's Clinical Role

- Evaluate genotype result ("metabolizer status") in context of clinical data and current antiplatelet medication
- Determine need for clinical intervention and contact prescriber accordingly for change in therapy
- Counsel patient (when available) on antiplatelet medication and genetic result as appropriate
- Document pharmacy consult note in Powerchart

Testing



PreCISE-Rx – PGx Service Notes

1]01/10/2016 IP Consult None

Back | Links

pantoprazole (pantoprazole 40 mg oral delayed release tablet) 40 mg 2 TIMES A DAY By Mouth

thiamine (thiamine 50 mg oral tablet) 50 mg ONCE A DAY By Mouth

ticagrelor (Brilinta (ticagrelor) 90 mg oral tablet) 90 mg 2 TIMES A DAY By Mouth

Results Review

CYP2C19 genotyping results viewable under All Documents>Cytogenetics>CYP2C19 genotyping.
Result: *2/*17
Predicted phenotype: Intermediate (impaired) metabolizer

Assessment and Plan

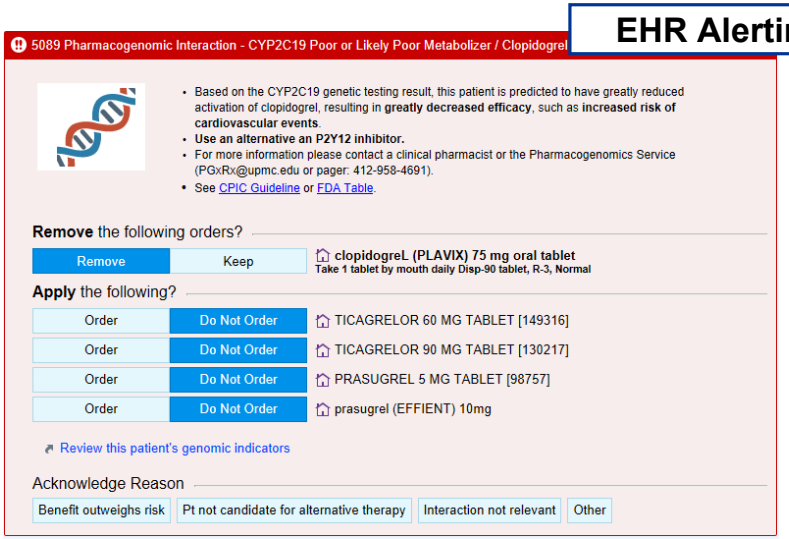
Pt is predicted to have impaired metabolism of clopidogrel (decreased formation of active metabolite). Effectiveness of clopidogrel depends on activation to an active metabolite by the cytochrome P450 (CYP) enzyme system, principally CYP2C19. Intermediate/poor metabolizers treated with clopidogrel at recommended doses exhibit higher cardiovascular event rates following acute coronary syndrome (ACS) or percutaneous coronary intervention (PCI) than patients with normal CYP2C19 function. Other genetic and clinical factors may also influence a patient's risk for secondary cardiovascular events and response to clopidogrel.

Based on genotype, continuation of ticagrelor is recommended.

Please call: If you wish to discuss further, Solomon Adams, PharmD
Pharmacogenomics Consult Service
Pager 74979

Perform - Completed by ADAMS, SOLOMON M (on 01/10/2016 15:51)
Sign - Completed by ADAMS, SOLOMON M (on 01/10/2016 15:51)
VERIFY - Completed by ADAMS, SOLOMON M (on 01/10/2016 15:51)

EHR Alerting

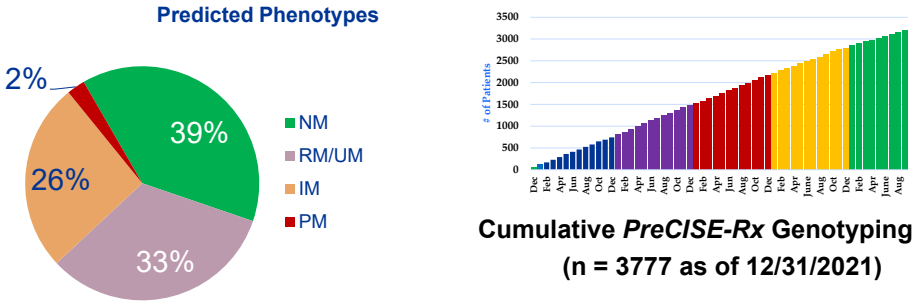


UPMC & Pitt PGx team

- **UPMC PGx service**:
  - "PGx-Rx" (74979) or 412-958-4691
- **Pittsburgh Pharmacogenomics:**
  - Email: pittpgx@pitt.edu

Impact of Clinical Implementation of *CYP2C19*-Clopidogrel on Outcomes

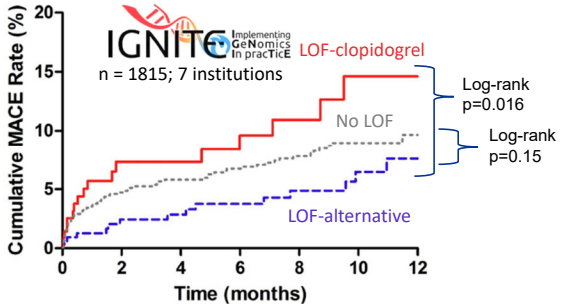
Actionable Genotypes are Common



Cumulative *PreCISE-Rx* Genotyping (n = 3777 as of 12/31/2021)

- 28.6% (n=1081/3777) carry LOF variants
  18.9% (n= 714/3777) with actionable genotypes

PGx Improves Clinical Outcomes



- Composite MACE (death, stroke, MI) were significantly lower in patients with a LOF allele on alternative therapy versus clopidogrel
- 8.7 vs 23.4 events per 100 patient-years; adjusted hazard ratio: 0.44; p=0.013).

JACC Cardiovasc Interv 2018;11:181-91.

Recent Clinical Trials

Trial	Patients (Indication)	Design	Key Outcomes
POPular Genetics	N = 2,488 (STEMI PCI)	Prospective, open-label, non-inferiority, de-escalation ***Genotype-guided*** (CYP2C19 *2 and *3: ticagrelor or prasugrel vs. CYP2C19 *1/*1: clopidogrel) vs. ***control (ticagrelor or prasugrel)***	Composite of death, MI, ST, stroke, PLATO major bleed at 12 mos: 5.1% vs. 5.9%; p<0.001 for non-inferiority PLATO major/minor bleed at 12 mos: 9.8% vs. 12.5%; p=0.04

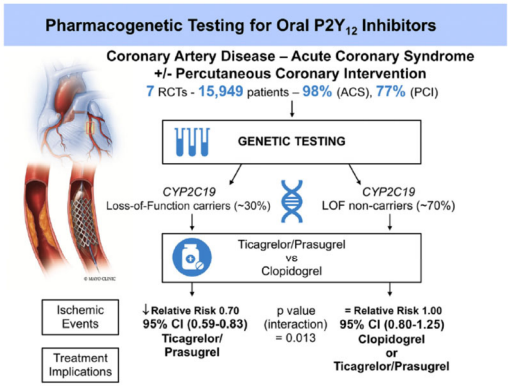
N Engl J Med 2019;381:1621-31.

Recent Clinical Trials

Trial	Patients (Indication)	Design	Key Outcomes
TAILOR-PCI	N = 5,302 (ACS PCI + elective)	Prospective, open-label, superiority, escalation ***Genotype-guided*** (CYP2C19 *2 and *3: ticagrelor vs. CYP2C19 *1/*1: clopidogrel) vs. ***control (clopidogrel)***	Composite of CV death, MI, ST, severe recurrent ischemia at 12 mos: 4% vs. 5.9%; p=0.06

JAMA 2020;324:761-71.

Proposed Algorithm for Use of CYP2C19 Genotyping for P2Y12 Inhibitor Prescribing



JACC Cardiovasc Interv 2021;14:739-50.

Patient Case

- 72 y/o female with PMH significant for CAD, PCI (2014), HFpEF, HTN, and dyslipidemia presents with NSTEMI complicated by acute heart failure
- Patient with multi-vessel CAD by LHC, scheduled for complex PCI
- PCI with DES x 2 to the LAD, staged PCI considered in future for LCx, RCA
- Clinical course complicated by new-onset Afib (CHA_2DS_2-VASc of 5)
- Current medications: clopidogrel 75 mg daily, aspirin 81 mg daily, unfractionated heparin IV infusion, atorvastatin 80 mg daily, metoprolol 25 mg bid

Patient Case

- CYP2C19 genotyping performed as part of clinical care for PCI
- Result returned 24 hours later:
  - Genotype: *1/*2
- Predicted phenotype: Intermediate metabolizer

What would be your antiplatelet recommendation?
Other considerations (i.e., anticoagulation, aspirin)?

What if the patient was on ticagrelor and the genotype result was *1/*17?

Lessons learned

- Creating new PGx services is feasible
- Multidisciplinary collaboration is important
- Timing and communication is critical
- Effective transitions of care with community is a key to success!

Many early adopter institutions have published details about how their programs are designed. For example, for an overview of CYP2C19 implementations strategies of 12 institutions, please see:

Empey et al. *Clin Pharmacol Ther.* 2017 Dec 26. doi: 10.1002/cpt.1006.

Key Takeaways

- Clopidogrel-*CYP2C19* is a leading PGx use case
- Evidence supports clinical actionability
- CPIC guideline is a key resource to help facilitate successful implementation

Clinical Applications of PGx in Primary Care

Lucas A. Berenbrok, PharmD, MS, BCACP, TTS
Associate Professor
School of Pharmacy

University of Pittsburgh School of Pharmacy

PGx PITTSBURGH PHARMACOGENOMICS

Learning Objectives

1. Describe an example clinical pharmacogenomics (PGx) service in primary care.
2. Explain the role of pharmacists in outpatient PGx services.
3. Highlight how preemptive and reactive PGx testing can impact patient outcomes.

Learning Objectives

1. **Describe an example clinical pharmacogenomics (PGx) service in primary care.**
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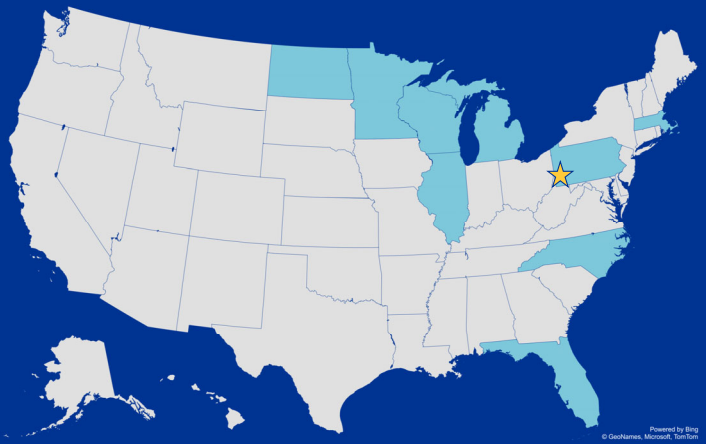
University of Pittsburgh.

PGx in Primary Care



University of Pittsburgh

UPMC Primary Care Precision Medicine Clinic

Family Medicine

Patient

Pharmacy services

Genetic Counseling

University of Pittsburgh

2 visit PGx model

1st

Decision to Test

- Comprehensive medication review
- Complete medication history
- Risks, benefits, limitations of testing

2nd

Return of Results

- Interpretation of results
- Recommendations to optimize pharmacotherapy
- Documentation

University of Pittsburgh

Decision to Test

Actionable Now

Actionable Later

Informative of Past

University of Pittsburgh

2 visit PGx model

1st

Decision to Test

- Comprehensive medication review
- Complete medication history
- Risks, benefits, limitations of testing

2nd

Return of Results

- Interpretation of results
- Recommendations to optimize pharmacotherapy
- Documentation

University of Pittsburgh

Return of Results

Documentation

✓ Precise

✓ Discoverable

✓ Discrete

University of Pittsburgh

Billing

1. Physician bills

-OR

2. Pharmacist bills

99211 "*Incident-to" physician*

University of Pittsburgh

Payers

University of Pittsburgh

Patient 1

1st

Patient is a 19 yo female who presents to the Primary Care Precision Medicine clinic for evaluation of pharmacogenomic testing.

Patient reports surgery in November 2019. Patient reports connective tissue issue, not specified. Prior to surgery, pain was well managed with dronabinol (MARINOL). Following surgery, patient remains in chronic pain. She also reports PTSD following surgery due to incredible pain post-op.

Today we discussed the utility of Pgx testing in the context of pain. We also discussed the limitations of Pgx testing. Patient was informed of the expected out-of-pocket costs. The patient was given opportunities to ask questions about the Pgx test and its expected benefits.

ASSESSMENT/PLAN
Patient may benefit from CYP2D6-guided pain control. Patient to follow-up with physician to determine if/when to test.

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Patient 1

2nd

CYP2D6 *2/*4 Intermediate metabolizer (Gaedigk Activity Score = 1)

This result signifies that this patient has 1 copy of a normal function allele (*2) and 1 copy of a decreased function allele (*4). Based on the genotype result this patient is predicted to be an intermediate metabolizer of CYP2D6 substrates. Drugs with actionable PGx guidance based on these results include:

CODEINE, OXYCODONE, HYDROCODONE, TRAMADOL

The patient's phenotype is associated with reduced formation of active metabolites for opioids metabolized by CYP2D6.

Therefore, the patient is expected to have insufficient pain relief from codeine or tramadol and possibly hydrocodone or oxycodone.

If the patient does not experience adequate pain relief from (codeine, tramadol, oxycodone, or hydrocodone) consider switching to a non-opioid analgesic (e.g. NSAID) and/or an opioid not metabolized by CYP2D6, such as morphine or hydromorphone.

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Assessment Question #1

Which of the following genes must be interpreted by calculating an activity score?

a. CYP2D6
b. SLCO1B1
c. TPMT
d. VKORC1

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Learning Objectives

1. Describe an example clinical pharmacogenomics (PGx) service in primary care.
2. **Explain the role of pharmacists in outpatient PGx services.**
3. Highlight how preemptive and reactive PGx testing can impact patient outcomes.

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Applications of PGx in Primary Care

>300 FDA-approved medications with PGx in their labeling

Adverse Reactions, Boxed Warning, Contraindications, Clinical Pharmacology, Clinical Studies, Dosage and Administration, Indication and Usage, Use in Specific Populations, Warnings and Precautions

95% of individuals carry one or more PGx variants

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American Pharmacists Association (APhA)

2011 *Integrating Pharmacogenomics into Pharmacy Practice via Medication Therapy Management*

"…the pharmacy profession must define a process for the application of pharmacogenomic data into pharmacy clinical practice that is aligned with MTM service delivery…"

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J Am Pharm Assoc. 2011 Nov-Dec;51(6):e64-74.

American Society of Health-System Pharmacists (ASHP)

2014 *ASHP Statement on the Pharmacist's Role in Clinical Pharmacogenomics*

"…all pharmacists should have a basic understanding of pharmacogenomics in order to provide appropriate patient-care recommendations."

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http://www.ashp.org/DocLibrary/BestPractices/SpecificStGenomics.aspx

Accreditation Council for Pharmacy Education

- ACPE Standards 2016
  - Required elements of the Didactic PharmD Curriculum

Pharmacogenomics/genetics

- Genetic basis for disease and individual differences in metabolizing enzymes, transporters, and other biochemicals impacting drug disposition and action that underpin the practice of personalized medicine.

Pharmacotherapy

- Emphasis on patient safety, clinical efficacy, **pharmacogenomic** and pharmacoeconomic considerations, and treatment of patients across the lifespan.

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ACPE. Accreditation standards and key elements for the professional program in pharmacy leading to the doctor of pharmacy degree. Appendix 1. 2015. https://www.acpe-accredit.org/standards/. Accessed Aug 30, 2016.

Assessment Question #2

Pharmacogenomic information can be found in the drug labeling of how many unique FDA approved drugs?

a. 50+
b. 100+
c. 200+
d. 300+

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Learning Objectives

1. Describe an example clinical pharmacogenomics (PGx) service in primary care.
2. Explain the role of pharmacists in outpatient PGx services.
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Applications of PGx in Primary Care

>40 consensus guidelines from the Clinical Pharmacogenetics Implementation Consortium (CPIC)

Antiplatelets
NSAIDs
Opioids
PPIs
SSRIs
Statins
TCAs

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PGx testing in relation to Rx

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Rigter T et al. Front Genet. 2020.

Preemptive vs Reactive

Preemptive

- Multi-gene panel
- Ordered before clinical need
- Future clinical utility/actionable later

Reactive

- Single gene
- Ordered after clinical need
- Current clinical utility/actionable now

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Preemptive Testing

Reasons for Referral

- Patient curiosity
- History of medication intolerances
- Multiple failed trials of medications
- Complex medication regimen
- High likelihood of future utility

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Reactive Testing

Case Use Examples

- Antiplatelet therapy post MI/PCI
- Psychiatric multi-gene panel

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PGx Related Outcomes

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Assessment Question #3

For which of the following classes of medications has the Clinical Pharmacogenetics Implementation Consortium (CPIC) published a clinical pharmacogenomic practice guideline?

a. Antihypertensives
b. Antidiabetic medications
c. Antipsychotics
d. Non-steroidal anti-inflammatory drugs

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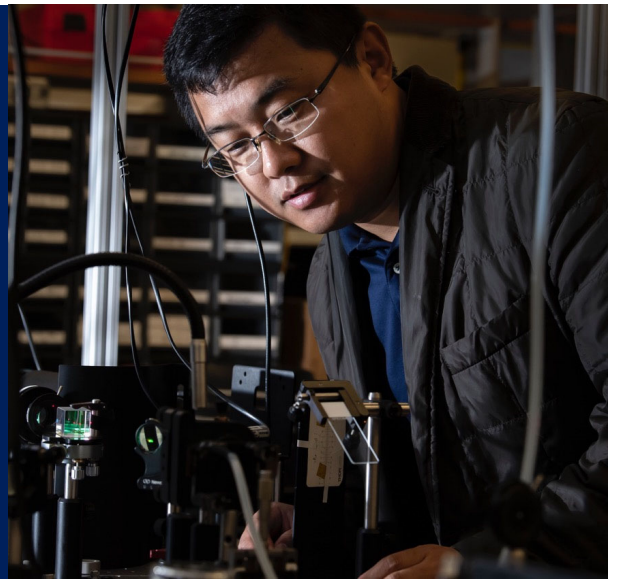
Questions?



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2. Rigter T, Jansen ME, de Groot JM, Janssen SWJ, Rodenburg W, Cornel MC. Implementation of Pharmacogenetics in Primary Care: A Multi-Stakeholder Perspective. Front Genet. 2020 Jan 31;11:10.

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Clinical Applications of PGx in Primary Care

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