Personalized Medicine:
Pharmacogenetics From Bench to Bedside and Beyond

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Disclosure: Conflict of Interest

Pharmacogenomic Resource to Improve Medication Effectiveness (**PRiME**)
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UAB Personalized Medicine Program

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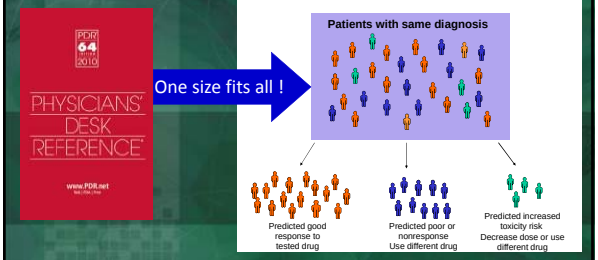
National Institute of Neurological Disorders and Stroke

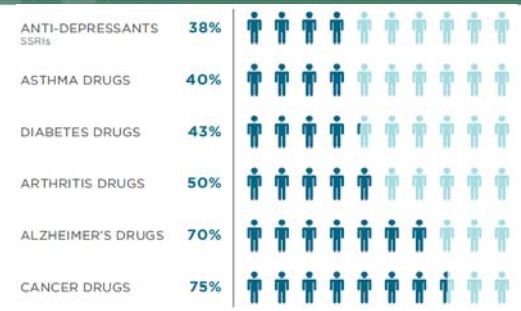
Objectives

1. Understand current drug prescription practice and outcomes
2. Discuss examples of genetic variants and their influence on drug therapy
3. Describe the role of genetics in drug response and potential to tailor drug therapy.
4. Understand barriers to implementing a genotype-guided drug therapy
5. Develop a drug selection strategy according to patient demographics, clinical factors, and genotype

How do we prescribe medications?

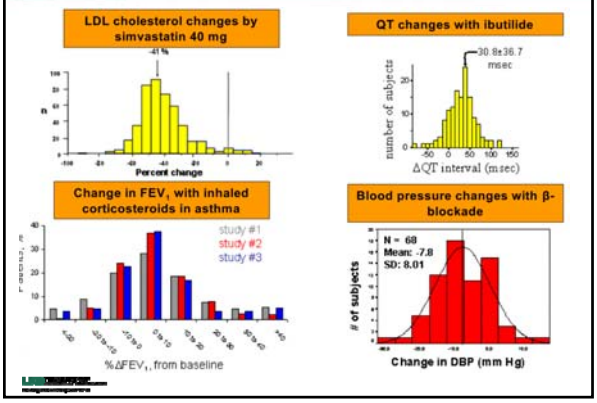


One Size Does Not Fit All !

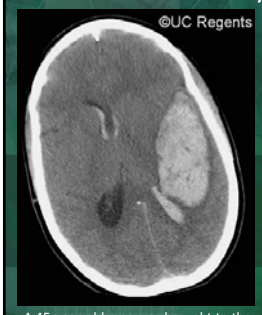


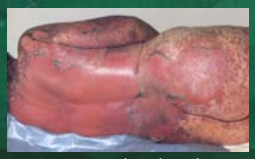
Many patients do not benefit from the first drug they are offered in treatment
For example, 38% of depression patients, 50% of arthritis patients, 40% of asthma patients, and 43% of diabetic patients will not respond to initial tx.

Is variability in response common?



Is variability in a serious problem?

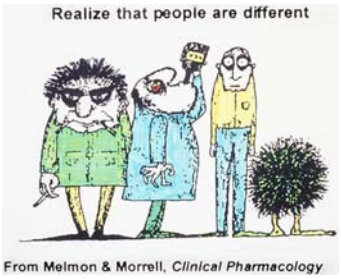




A woman was brought to the emergency department with a mild rash which progressed to Stevens Johnson Syndrome

A 45-year-old man was brought to the emergency department by his friends because of a 1-day history of a severe headache and "bizarre behavior." A computed tomography (CT) scan of his brain revealed acute intracranial hemorrhage with cerebral edema, evidence of midline shift, and increased intracranial pressure. (www.webmm.ahrq.gov)

Why do individuals respond differently?



From Melmon & Morrell, *Clinical Pharmacology*

- Variability in genes:-
  - Drug metabolism genotype
  - Drug transporter genotype
  - Drug receptor genotype
  - Interactions
- Variability in environment:-
  - Medications, Diet, Alcohol,
  - Exercise……

Definitions

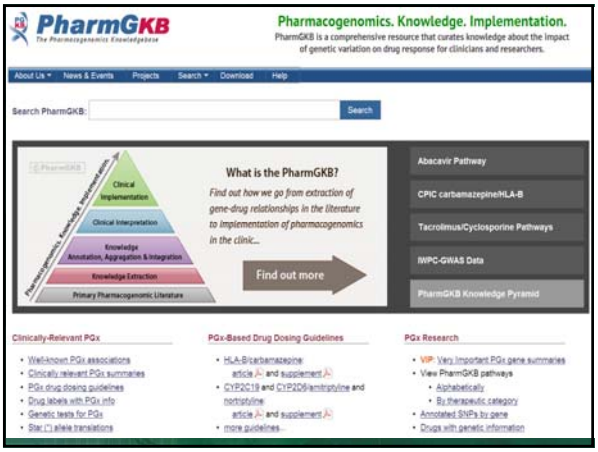
- **Pharmacogenetics:** Effect of genetic variation in response to a drug in terms of therapeutic and adverse effects.
  - Primary candidate genes of interest include those encoding for drug receptors, metabolizing enzymes, and transporters.
- **Pharmacogenomics** more broadly involves genome wide analysis of the genetic determinants of drug efficacy and toxicity.
- **Personalized Medicine** Tailoring treatment for an individual patient based on their genetic makeup and other individual characteristics including clinical, demographics, lifestyles, behavior, and environment to guide disease prediction, prognosis and treatment.

U.S. Food and Drug Administration

Protecting and Promoting *Your* Health

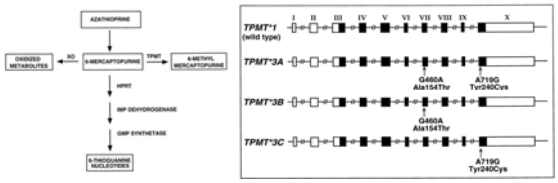
- Pharmacogenomics can play an important role in identifying responders and non-responders to medications, avoiding adverse events, and optimizing drug dose. Drug labels may contain information on genomic biomarkers and can describe:
  - Drug exposure and clinical response variability
  - Risk for adverse events
  - Genotype-specific dosing
  - Mechanisms of drug action
  - Polymorphic drug target and disposition genes

http://www.fda.gov/Drugs/ScienceResearch/ResearchAreas/Pharmacogenetics/ucm083378.htm



Thiopurine methyltransferase: TMPT

- Thiopurine drugs are used to treat patients with neoplasia and autoimmune disease as well as transplant recipients. These agents are metabolized, in part, by *S*-methylation catalyzed by thiopurine methyltransferase (TPMT).



- Patients with inherited very low levels of TPMT activity are at greatly increased risk for thiopurine-induced toxicity such as myelosuppression when treated with standard doses of these drugs, while subjects with very high activity may be undertreated Long-term results of TMPT activity monitoring in azathioprine-treated renal allograft recipients.

Drug Metab Dispos. 2001 Apr;29(4 Pt 2):601-5.

Genotype-phenotype concordance

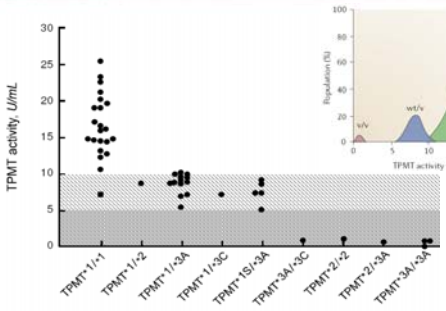
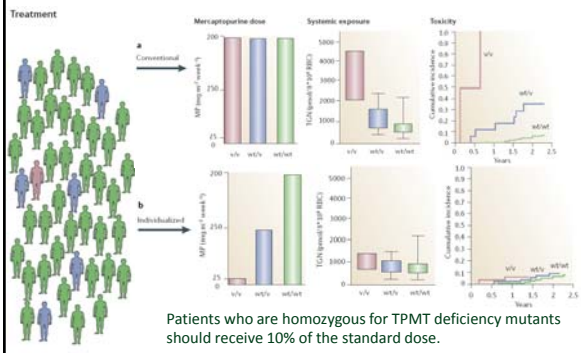


Figure 3. Thiopurine S-methyltransferase *(TPMT)* activity in patients with different TPMT genotypes determined by mutation-specific polymerase chain reaction methods.

Yates et al
Ann Int Med 126(8):608-14, 1997

Dosing 6MP *with* pharmacogenetics



Patients who are homozygous for TPMT deficiency mutants should receive 10% of the standard dose.

Mercaptopurine Label update 2003

metabolite methyl-6-MP. TPMT activity is highly variable in patients because of a genetic polymorphism in the TPMT gene. For Caucasians and African Americans, approximately 0.3% (1:300) of patients have two non-functional alleles (homozygous-deficient) of the TPMT gene and have little or no detectable enzyme activity. Approximately 10% of patients have one TPMT non-functional allele (heterozygous) leading to low or intermediate TPMT activity and 90% of individuals have normal TPMT activity with two functional alleles. Homozygous-deficient patients (two non-functional alleles), if given usual doses of mercaptopurine, accumulate excessive cellular concentrations of active thioguanine nucleotides predisposing them to PURINETHOL toxicity (see WARNINGS and

TPMT Testing

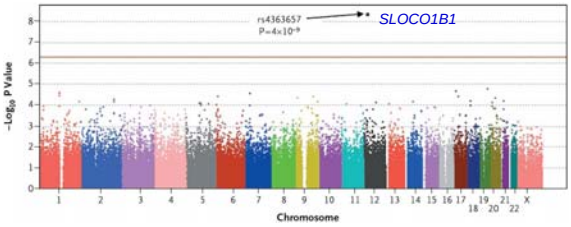
Genotypic and phenotypic testing of TPMT status are available. Genotypic testing can determine the allelic pattern of a patient. Currently, 3 alleles-- TPMT*2, TPMT*3A and TPMT*3C—account for about 95% of individuals with reduced levels of TPMT activity. Individuals homozygous for these alleles are TPMT deficient and those heterozygous for these alleles have variable TPMT (low or intermediate) activity. Phenotypic testing determines the level of thiopurine methyltransferase (TPMT activity in erythrocytes and can also be informative. Caution must be used with phenotyping since some co-administered drugs can influence measurement of TPMT activity in blood, and recent blood transfusions will misrepresent a patient's actual TPMT activity

Common meds with uncommon side effects

- Statins reduce the incidence of heart attacks, strokes, and revascularization procedures by 1/5 for each reduction of 40 mg/dL in LDL cholesterol level
- Rarely, can cause muscle pain or weakness in association with elevated creatine kinase levels (i.e., myopathy), and occasionally, this leads to muscle breakdown and myoglobin release (i.e., rhabdomyolysis), with a risk of renal failure and death
- Incidence of **myopathy** is ~ 1 case per 10,000 patients per year with standard doses of statins
- Mechanisms by which statins cause myopathy remain unknown but appear to be related to statin concentrations in the blood

The SEARCH Collaborative Group NEJM 359:789-799, 2008

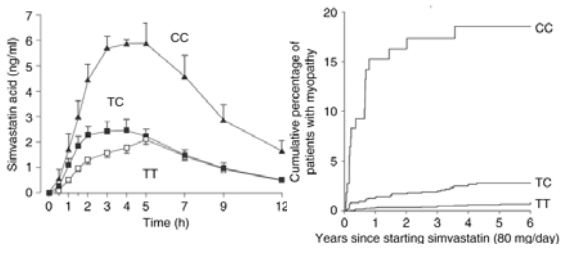
Marker for Statin induced myopathy



- 85 subjects with myopathy and 90 controls, all of whom were taking 80 mg of simvastatin daily as part of a trial involving 12,000 participants. Replication was tested in a trial of 40 mg of simvastatin daily involving 20,000 participants.
- The prevalence of the rs4149056 C allele in the population was 15%. OR=4.5, 95%CI 2.6 to 7.7per copy of the C allele, and 16.9 (95% CI, 4.7 to 61.1) in CC as compared with TT homozygotes. More than 60% of these myopathy cases could be attributed to the C variant.

N Engl J Med 2008;359:789-99.. 2010;87(1):130-3.

SLCO1B1 Variants and Statin-Induced Myopathy — A Genome wide Study



SLCO1B1 encodes the organic anion–transporting polypeptide OATP1B1, which mediates the hepatic uptake of various drugs, including most statins and statin acids.

Maximum statins doses: *SLOCO1B1*

	SLCO1B1 c.521T>C genotype			
	TT	TC	CC	Normal dose range*
Simvastatin	80 mg	40 mg	20 mg	5–80 mg/day
Pitavastatin	4 mg	2 mg	1 mg	1–4 mg/day
Atorvastatin	80 mg	40 mg	20 mg	10–80 mg/day
Pravastatin	80 mg	40 mg	40 mg	10–80 mg/day
Rosuvastatin	40 mg	20 mg	20 mg	5–40 mg/day
Fluvastatin	80 mg	80 mg	80 mg	20–80 mg/day

- Statin therapy should be started with the starting dose recommended by the manufacturer or half of the recommended maximum dose, whichever is lower.
- The dose should be titrated up to the minimum effective dose or the suggested maximum dose on the basis of lipid response and tolerability, and the statin should be changed or discontinued as necessary.
- Other factors known to affect statin pharmacokinetics or myopathy risk should be taken into account when selecting a statin and its dose for an individual patient (interacting drugs, concomitant diseases, age, etc.).

*Based on US Food and Drug Administration–approved maximum doses; lower maximum doses may apply in some countries.

Niemi M. Transporter pharmacogenetics and statin toxicity. Clin Pharmacol Ther. 2010;87(1):130-3.

A marker for Stevens- Johnson syndrome

Table 1 **Frequency of *HLA* alleles in patients with Stevens–Johnson syndrome**

HLA allele	*CBZ-SJS*	*CBZ-tolerant*	*Normal*
*B*1502*	44 (100%)	3 (3%)*	8 (8.6%)†
*Cw*0801*	41 (93.2%)	17 (16.8%)	13 (14%)
*A*1101*	36 (81.8%)	51 (50.5%)	53 (57%)
*DRB1*1202*	33 (75%)	12 (11.9%)	18 (19.4%)
*B*1502, Cw*0801*	41 (93.2%)	3 (3%)	7 (7.5%)
*B*1502, A*1101*	36 (81.8%)	2 (2%)	6 (6.5%)
*B*1502, DRB1*1202*	33 (75%)	1(1%)	5 (5.4%)
*B*1502, Cw*0801, A*1101, DRB1*1202*	29(66%)	0 (0%)	3 (3.2%)

Frequencies (by number and percentage) of individual or combined loci of the *B*1502* ancestral haplotype are shown in patients with carbamazepine-induced Stevens–Johnson syndrome (CBZ–SJS; *n* = 44), and in carbamazepine-tolerant (*n* = 101) and normal subjects (*n* = 93). For methods, see supplementary information.

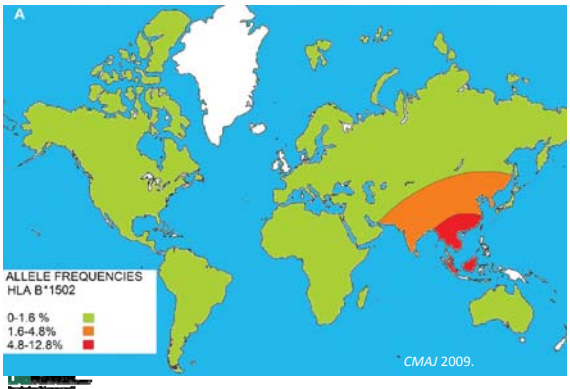
Odds ratio

*CBZ–SJS/CBZ-tolerant: 2,504 (95% CI, 126–49,522); $P = 3.13 \times 10^{-27}$

†CBZ–SJS/normal: 895 (95% CI, 50–15,869); $P = 1.38 \times 10^{-21}$

Nature 2004; 428(6982):486

Ethnicity or Prevalence of HLA-B*1502



CMAJ 2009.

NOVARTIS

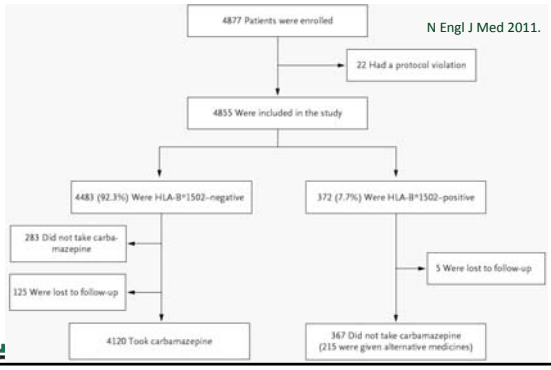
Tegretol®
carbamazepine USP
Chewable Tablets of 100 mg - red-speckled, pink
Tablets of 200 mg – pink
Suspension of 100 mg/5 mL
Tegretol®-XR
(carbamazepine extended-release tablets)
100 mg, 200 mg, 400 mg
Rx only
Prescribing Information

WARNINGS

SERIOUS DERMATOLOGIC REACTIONS AND HLA-B*1502 ALLELE

SERIOUS AND SOMETIMES FATAL DERMATOLOGIC REACTIONS, INCLUDING TOXIC EPIDERMAL NECROLYSIS (TEN) AND STEVENS-JOHNSON SYNDROME (SJS), HAVE BEEN REPORTED DURING TREATMENT WITH TEGRETOL. THESE REACTIONS ARE ESTIMATED TO OCCUR IN 1 TO 6 PER 10,000 NEW USERS IN COUNTRIES WITH MAINLY CAUCASIAN POPULATIONS, BUT THE RISK IN SOME ASIAN COUNTRIES IS ESTIMATED TO BE ABOUT 10 TIMES HIGHER. STUDIES IN PATIENTS OF CHINESE ANCESTRY HAVE FOUND A STRONG ASSOCIATION BETWEEN THE RISK OF DEVELOPING SJS/TEN AND THE PRESENCE OF HLA-B*1502, AN INHERITED ALLELIC VARIANT OF THE HLA-B GENE. HLA-B*1502 IS FOUND ALMOST EXCLUSIVELY IN PATIENTS WITH ANCESTRY ACROSS BROAD AREAS OF ASIA. PATIENTS WITH ANCESTRY IN GENETICALLY AT-RISK POPULATIONS SHOULD BE SCREENED FOR THE PRESENCE OF HLA-B*1502 PRIOR TO INITIATING TREATMENT WITH TEGRETOL. PATIENTS TESTING POSITIVE FOR THE ALLELE SHOULD NOT BE TREATED WITH TEGRETOL UNLESS THE BENEFIT CLEARLY OUTWEIGHS THE RISK (SEE **WARNINGS** AND **PRECAUTIONS, LABORATORY TESTS**).

Prevent carbamazepine-induced SJS–TEN using HLA-B*1502 screening



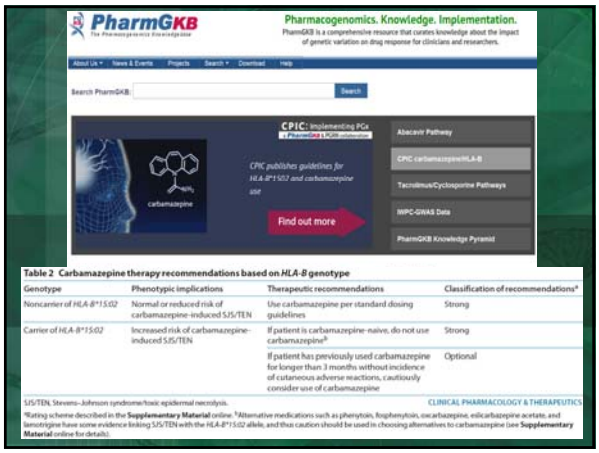
N Engl J Med 2011.

HLA-B*1502 screening Prevents SJS

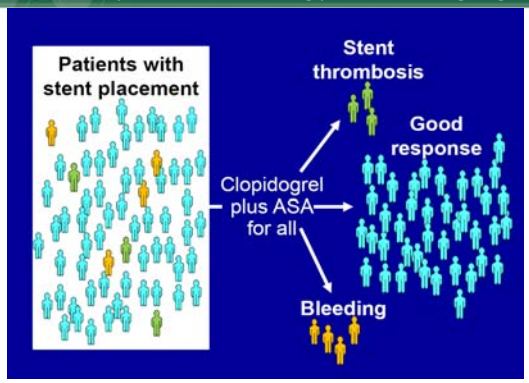
SJS–TEN did not develop in any of the HLA-B*1502–negative subjects receiving carbamazepine (mild transient rash in 4.3% and widespread rash in 0.1%). The estimated historical incidence of carbamazepine-induced SJS–TEN (0.23%) would translate into approximately 10 cases among study subjects (P<0.001).

Table 2. Adverse Events during the 2-Month Follow-up. N Engl J Med 2011;364:1126-33.

Adverse Event	HLA-B*1502–Positive with Alternative Medication (N=215)	HLA-B*1502–Negative with Carbamazepine (N=4120)	Total
	number of events		
Mild cutaneous events			
Rash and itching	5*	206	211
Rash, itching, and blisters	1†	20	21
Rash, itching, and oral ulcers	0	14	14
Rash, itching, blisters, and oral ulcers	0	7	7
Itching, blisters, and oral ulcers	0	2	2
Blisters and oral ulcers	0	3	3
Severe cutaneous events			
Maculopapular eruption	0	3	3
Hypersensitivity syndrome	0	2	2
Urticaria	1†	1	2
Stevens–Johnson syndrome or toxic epidermal necrolysis	0	0	0

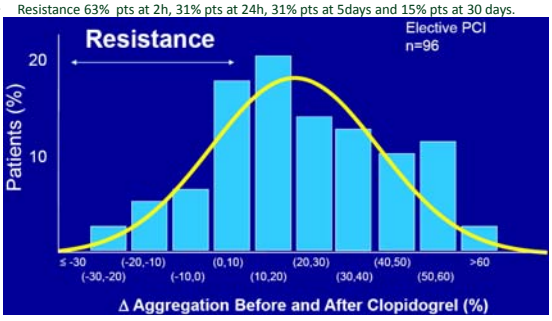


Variability in outcomes among patients undergoing PCI



Variability in Clopidogrel effects

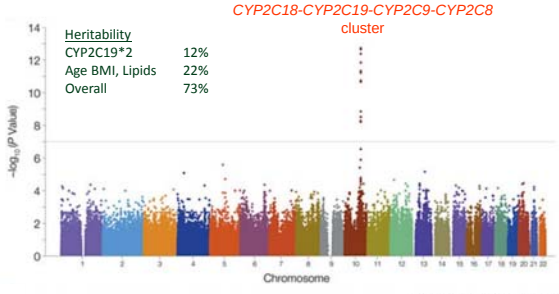
- 96 pts- elective PCI, Rx: aspirin (325 mg) + Clopidogrel (300 mg load then 75mg daily)
- Platelet aggregation (baseline-post-tx. <=10%; 0,2h, 24h, 5 days, and 30 days).
- Resistance 63% pts at 2h, 31% pts at 24h, 31% pts at 5days and 15% pts at 30 days.



Gurbel PA, et al. *Circulation.* 2003;107: 2908-2913.

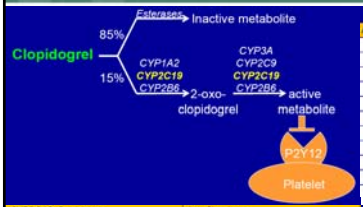
Genome-wide association

Clopidogrel inhibition of ADP-stimulated platelet aggregation



Shuldiner et al., JAMA 2009

Clopidogrel: Pharmacokinetics and Pharmacogenetics



CYP2C19 Gene Alleles

Allele	Variant	CYP2C19 Function
*1	N/A	Normal function
*2	Splicing defect	Loss-of-function
*3	Stop codon	Loss-of-function
*4	1A>G	Loss-of-function
*5	Nonsynonymous SNP	Loss-of-function
*6	Nonsynonymous SNP	Loss-of-function
*7	Splicing defect	Loss-of-function
*8	Nonsynonymous SNP	Loss-of-function
*9	Nonsynonymous SNP	Loss-of-function
*10	Nonsynonymous SNP	Loss-of-function
*17	-806C>T	Gain-of-function

CYP2C19 Genotype	Implications
Extensive metabolizer (EM; *1/*1)	Normal platelet inhibition; normal residual platelet aggregation
Intermediate metabolizer (IM; *1/*2 and *1/*3)	Reduced platelet inhibition; increased residual platelet aggregation; increased risk for adverse cardiovascular events
Poor metabolizer (PM; *2/*2 and *3/*3)	Significantly reduced platelet inhibition; increased residual platelet aggregation; increased risk for adverse cardiovascular events
Ultra-rapid metabolizer (UM; *1/*17 and *17/*17)	Increased platelet inhibition; decreased residual platelet aggregation

Race	PMs	IMs	UM
Caucasian	2%	25%	40%
African American	4%	30%	45%
Asian	14%	50%	<5%

Momary et al. *Pharmacotherapy* 2010;30:265-74; Sibbing et al. *Circulation* 2010;121:512-8.

Clopidogrel - Reduced-Function *CYP2C19* and Clinical Outcomes

- Mega et al (JAMA. 2010;304(16):1821-1830) used consistent end-point definition, investigators from each of the primary studies provided additional data - standardized CV end point (CV death, MI, or stroke)
- Hypothesis: CYP2C19 loss-of-function variant (*2 is the most common) confers an increased risks for major adverse cardiovascular events (MACE)
- Meta-analyses of 9685 patients (91.3% PCI; 54.5% ACS) from 9 trials
- 863 experienced the composite end point of cardiovascular death, myocardial infarction, or stroke; 84 patients had stent thrombosis

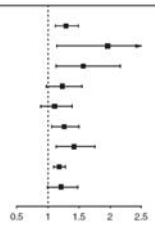
CYP2C19 Genotype	Prevalence	Risk for MACE
*1/*1	71.5%	Reference
*1/*2	26.3%	1.55; 95% CI, 1.11-2.17; *P*=.01
*2/*2	2.2%	1.76; 95% CI, 1.24-2.50; *P*=.002
≥ 1 variant		1.57; 95% CI, 1.13-2.16; *P* = .006

CYP2C19 Genotype	Prevalence	Risk of stent thrombosis
*1/*1	71.5%	Reference
*1/*2	26.3%	2.67; 95% CI, 1.69-4.22; *P*=.0001
*2/*2	2.2%	3.97; 95% CI, 1.75-9.02; *P*=.001
≥ 1 variant		2.81; 95% CI, 1.81-4.37; *P* <.00001

CYP2C19 LoF alleles and outcomes

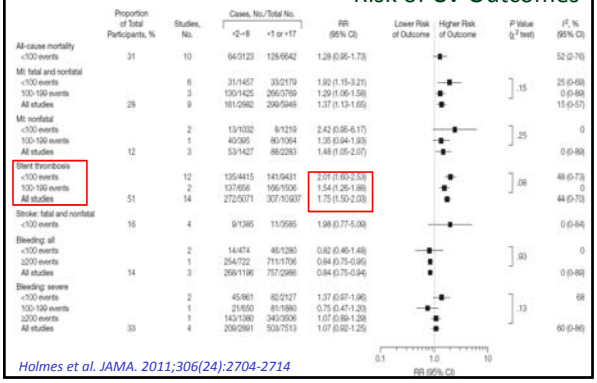
- Nine systematic review with meta-analysis have been published from 2010 to 2012 ranging from a highly significant effect of the *CYP2C19* genotype (RR=1.96 ; 95% CI= 1.14–3.37), to a modest and non-statistically significant effect (RR of 1.11; 95% CI; 0.89–1.39)

Systematic review	Search date	*N* studies	*N* participants	Relative risk (95% CI)
Hulot	Oct 2009	10	11,959	1.29 (1.12, 1.49)
Sofi	Jan 2010	7	8,043	1.96 (1.14, 3.37)
Mega	Aug 2010	9	9,685	1.57 (1.13, 2.16)
Zabalza	Oct 2010	11	16,360	1.23 (0.97, 1.55)
Bauer	Dec 2010	12	18,529	1.11 (0.89, 1.39)
Liu	May 2011	18	21,441	1.26 (1.06, 1.50)
Jang	Sep 2011	16	20,785	1.42 (1.13, 1.76)
Holmes	Oct 2011	26	26,251	1.18 (1.09, 1.28)
Yang	Nov 2011	12	17,339	1.21 (0.99, 1.48)



CPT. 2013;94(3):376-382.

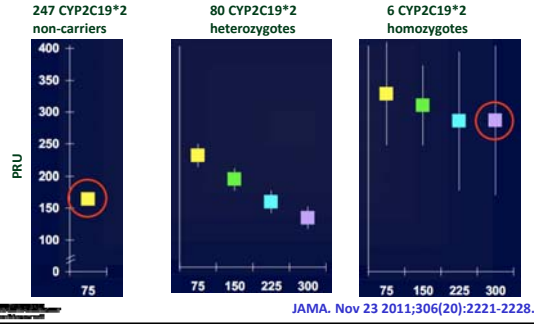
CYP2C19 Genotype (*2 to*8 vs *1 or *17) and Risk of CV Outcomes



Holmes et al. JAMA. 2011;306(24):2704-2714

Clopidogrel Dose Escalation

- 335 patients with stable CAD on clopidogrel 75 mg daily (ELEVATE-TIMI)
- 4 x 14d treatment period based on CYP2C19. Verifynow platelet function testing



JAMA. Nov 23 2011;306(20):2221-2228.

Strategies for *CYP2C19* intermediate /poor metabolizers

Mega et al. *Circulation* 119, 2553-2560 (2009)

Wiviott, S.D. *NEJM* 357, 2001-2015 (2007).

Prasugrel

- Provides greater protection against CV events, but increases bleeding risk compared to clopidogrel.
- Like clopidogrel, undergoes biotransformation to an active metabolite:

Prasugrel —(Esterases)→ Inactive metabolite —(CYP3A, CYP2B6, CYP2C9, CYP2C19)→ Active metabolite

- Efficacy is not affected by *CYP2C19* genotype
- Contraindicated in patients with h/o TIA or stroke

Wallentin et al. *NEJM* 361, 1045-1057 (2009)

Wallentin et al. *Lancet* 376, 1320-1328 (2010)

Ticagrelor

- Ticagrelor superior to clopidogrel in reducing death from vascular causes, MI, or stroke (HR 0.84, 95% CI 0.77-0.92).
- Ticagrelor associated with higher rate of non-CABG major bleeding (4.5% vs 3.8%, p=0.03).

	TICAG	CLOP	HR (95% CI)	P value
CV death, MI, or CVA event rate				
No loss-of-fxn	8.8%	10.0%	0.86 (0.74-1.01)	0.06
Any loss-of-fxn	8.6%	11.2%	0.77 (0.60-0.99)	0.04

FDA Clopidogrel Label Revised March 2010

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)**

2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention: executive summary

5.1.2. Clopidogrel Genetic Testing

CLASS IIb

1. Genetic testing might be considered to identify whether a patient at high risk for poor clinical outcomes is predisposed to inadequate platelet inhibition with clopidogrel (434). *(Level of Evidence: C)*
2. When a patient predisposed to inadequate platelet inhibition with clopidogrel is identified by genetic testing, treatment with an alternate $P2Y_{12}$ inhibitor (e.g., prasugrel or ticagrelor) might be considered (434). *(Level of Evidence: C)*

CLASS III: NO BENEFIT

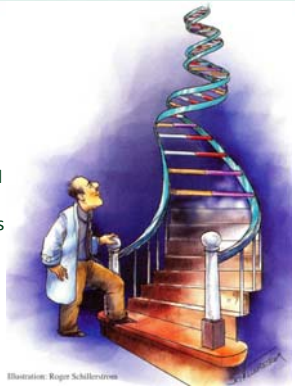
1. The routine clinical use of genetic testing to screen patients treated with clopidogrel who are undergoing PCI is not recommended (434). *(Level of Evidence: C)*

Summary of Evidence for CYP2C19 guided antiplatelet therapy

- *CYP2C19* genotype associated with clinical outcomes, especially stent thrombosis
- Clopidogrel labeling now contains a boxed warning regarding reduced effectiveness in *CYP2C19 poor-metabolizers*.
- CPIC guidelines are available to assist with clinical decisions regarding *CYP2C19* genotype.
- Recommend alternative antiplatelet therapy (prasugrel or ticagrelor) in PMs (strong recommendation) and IMs (moderate recommendation) in ACS/ high risk PCI patients.

Challenges and Opportunities

- Limited of evidence of efficacy
- Lack on knowledge of harms
- Lack of genotyping capability
- Lack of guidelines on genotype-guided therapy
- Lack of provider education
- Lack of institutional support and infrastructure
- Lack of (prospective) Informatics support
- Lack of reimbursement
- Legal/ ethical issues



UAB Personalized Medicine Institute

Nita A. Limdi, Pharm.D, PhD, MSPH
Professor, Department of Neurology
Interim Director, Personalized Medicine Institute

THE UNIVERSITY OF ALABAMA AT BIRMINGHAM

PMI- Strategic Initiatives

1. Fuel discovery through research: Conduct and support innovative and collaborative research in basic, clinical, population, and translational science focused on identifying the genetic basis of disease and drug response, specifically where UAB has unique populations such as cancer, cardiovascular, cerebrovascular, endocrine and immunologic disorders, and transplantation.
   - Identify and respond to research opportunities
   - Biobank (information and biologic samples)
2. Improve patient care through implementation: Deliver personalized health care
   - facilitate diagnosis/ prognosis of disease (include genetic markers)
   - integrating genetic information along with clinical and demographic information to guide selection of medications and their doses.
     - identify drug/ disease targets for which genomics can potentially improve patient outcomes
3. Educate and engage stakeholders: Develop an innovative curriculum to educate current and future practitioners, payors and the community at large in the field of genomics, pharmacogenomics and personalized medicine.

Pharmacogenomic Resource to improve Medication Effectiveness: Genotype-Guided Antiplatelet therapy

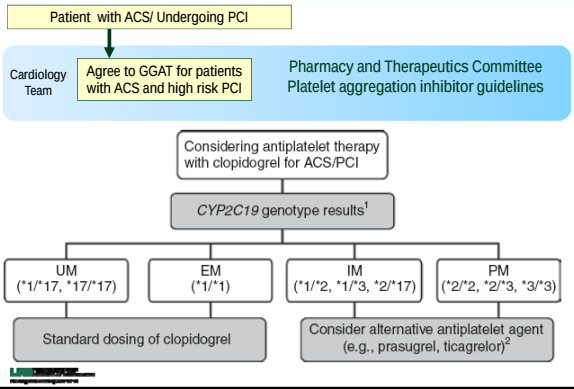
- **Aim 1**: Build genotyping capability within the Molecular Diagnostic laboratory within UAB hospital that can perform candidate gene assessment within the timeline conducive to the delivery of care.
  - We selected implementation of CYP2C19 genotype-guided antiplatelet therapy as there is sufficient evidence of justify its use in clinical practice and a patient volume (~1000 PCI/year) at UAB to support assessment of outcomes.
- **Aim 2**: Build clinical decision making algorithms (CDMAs) within our EMR (CERNER- IMPACT) and enable automated integration of patient-specific clinical, demographic and genetic information into these CDMAs to guide drug therapy.
  - We will develop clinical decision support based on for published guidelines.
- **Aim 3**: Generate evidence of capability by demonstrating feasibility of genotype-guided drug therapy and measure outcomes to demonstrate impact (effectiveness, cost-effectiveness) on clinically meaningful outcomes.
  - We will assess effect of CYP2C19 genotype-intervention on outcomes (30 day readmissions, major adverse cardiovascular events, stent thrombosis, bleeding).
  - We will also assess process outcomes (e.g. assay validation, turnaround time for genotype results, adoption of testing and recommendations, etc.)

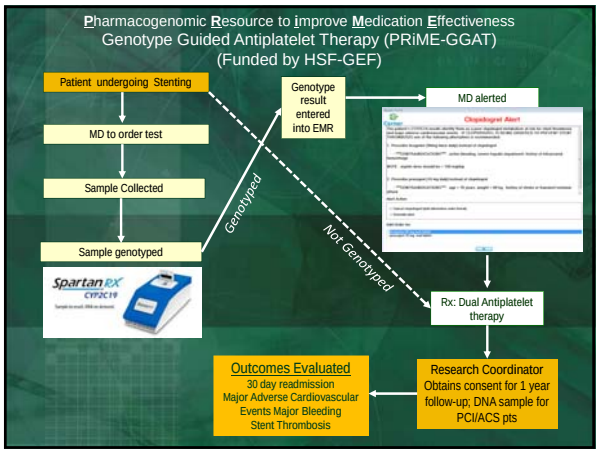
UAB BioBank

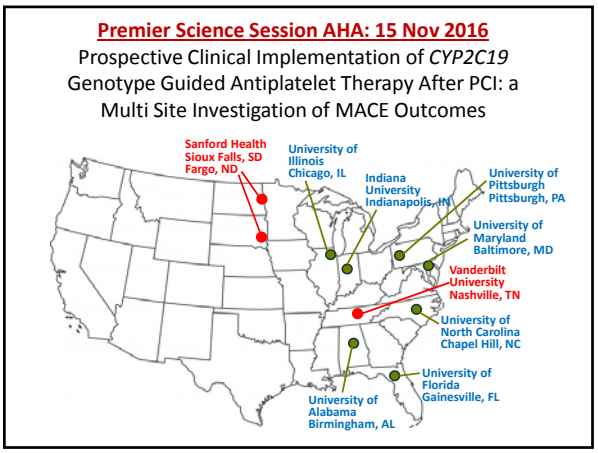
- The University of Alabama at Birmingham Health System (UABHS) provides an ideal setting to identify and address challenges in the delivery of genomic medicine and provide information on clinical validity and utility in racial minorities
- **Racially and socio-economically representative population**: The UAB hospital (UABH; >45,000 admissions/ year; 45% men and 37-40% African Americans) and associated the outpatient clinics (>1.4 million visits/ year; 51% men, 40% African American) have extensive experience in the care of patients

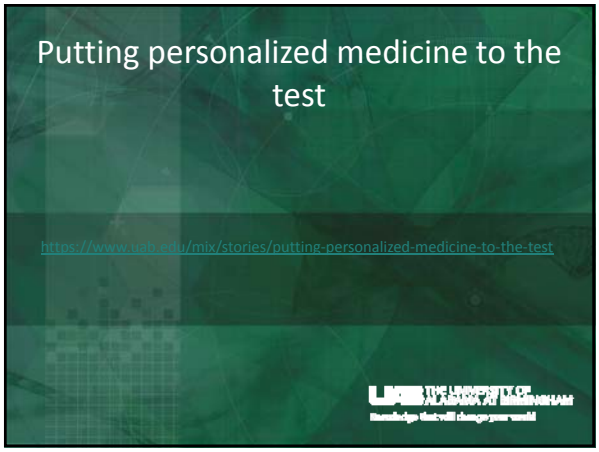
Population reflects socio-demographic		
2010 census	WPg cohort	Jefferson County[1]
Female	52.7%	48.2%
African Americans	43.2%	42.3%
European American	56.2%	54.7%
Education >High School	82.7%	86.6%
Income <15K	19.0%	15.5%
Income 15-25K	14.5%	12.6%
Income 25-50K	34.3%	26.4%
Income 50-100K	27.5%	28.1%
Income >100K	7.6%	17.4%

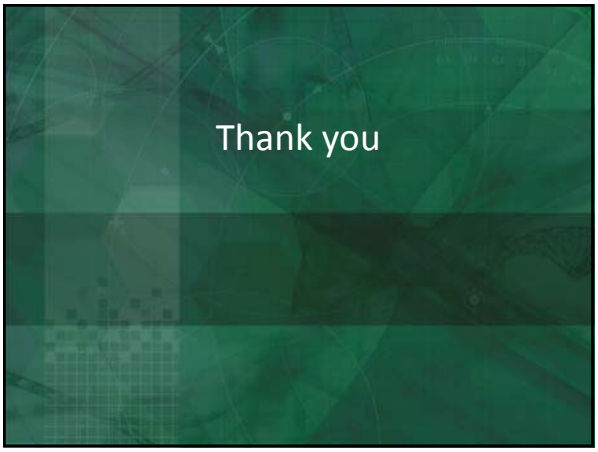
Genotype-guided antiplatelet therapy




Pharmacogenomic Resource to improve Medication Effectiveness
Genotype Guided Antiplatelet Therapy (PRiME-GGAT)
(Funded by HSF-GEF)
Patient undergoing Stenting
MD to order test
Sample Collected
Sample genotyped
Genotyped
Not Genotyped
Genotype result entered into EMR
MD alerted
Rx: Dual Antiplatelet therapy
Research Coordinator
Obtains consent for 1 year follow-up; DNA sample for PCI/ACS pts
Outcomes Evaluated
30 day readmission
Major Adverse Cardiovascular Events Major Bleeding
Stent Thrombosis


Premier Science Session AHA: 15 Nov 2016
Prospective Clinical Implementation of CYP2C19 Genotype Guided Antiplatelet Therapy After PCI: a Multi Site Investigation of MACE Outcomes
Sanford Health Sioux Falls, SD Fargo, ND
University of Illinois Chicago, IL
Indiana University Indianapolis, IN
University of Pittsburgh Pittsburgh, PA
University of Maryland Baltimore, MD
Vanderbilt University Nashville, TN
University of North Carolina Chapel Hill, NC
University of Florida Gainesville, FL
University of Alabama Birmingham, AL


Putting personalized medicine to the test
https://www.uab.edu/mix/stories/putting-personalized-medicine-to-the-test


Thank you