U.S. FOOD & DRUG ADMINISTRATION

Human Genetics In Therapeutic Development and Clinical Trials

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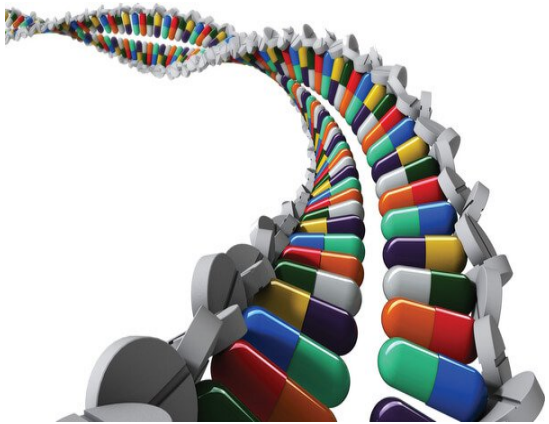
Disclosure:

Alan Shuldiner is an employee of the Regeneron Genetics Center, a subsidiary of Regeneron Pharmaceuticals Inc. and is also the John Whitehurst Professor of Medicine (part-time) at the University of Maryland School of Medicine

Lecture Outline

- Application of human genetics in therapeutic development
  - Identification of new therapeutic targets (efficacy)
  - Derisking therapeutic targets (safety)
  - New indications for therapeutic targets
- Pharmacogenetics in clinical trials
  - Variable drug response (pharmacodynamics)
  - Variable drug metabolism (pharmacokinetics)
  - Adverse events/Safety
  - Understanding disease mechanisms
- Implementation of pharmacogenetics into patient care (Implementation science)



The Reality of Therapeutic Development in 2018

- Despite increased investment in R+D in the pharmaceutical industry, the number of new molecular entities is not increasing
- >90% of molecules that enter Phase I clinical trials fail to demonstrate sufficient safety and efficacy to gain regulatory approval
- Most failures occur in Phase II clinical trials
  - 50% due to lack of efficacy
  - 25% due to toxicity
- Pre-clinical models may be poor predictors of clinical benefit
- *Compounds supported by human genetics evidence are substantially more likely to succeed*

The Potential for Human Genetics to Accelerate Target Identification, Validation and Drug Development

FDA

2003

Mutations in *PCSK9* cause autosomal dominant hypercholesterolemia

Family studies identify *PCSK9* GOF as causing FH

2006

Sequence Variations in *PCSK9*, Low LDL, and Protection against Coronary Heart Disease

Population studies identify *PCSK9* LOF variants conferring ~88% reduction in CHD

2012

Effect of a Monoclonal Antibody to PCSK9 on LDL Cholesterol

Clinical proof of concept

2008

A Null Mutation in Human *APOC3* Confers a Favorable Plasma Lipid Profile and Apparent Cardioprotection

Null *APOC3* mutation enriched in Amish points to cardio-protective effects

2014

Loss-of-Function Mutations in *APOC3* and Risk of Ischemic Vascular Disease

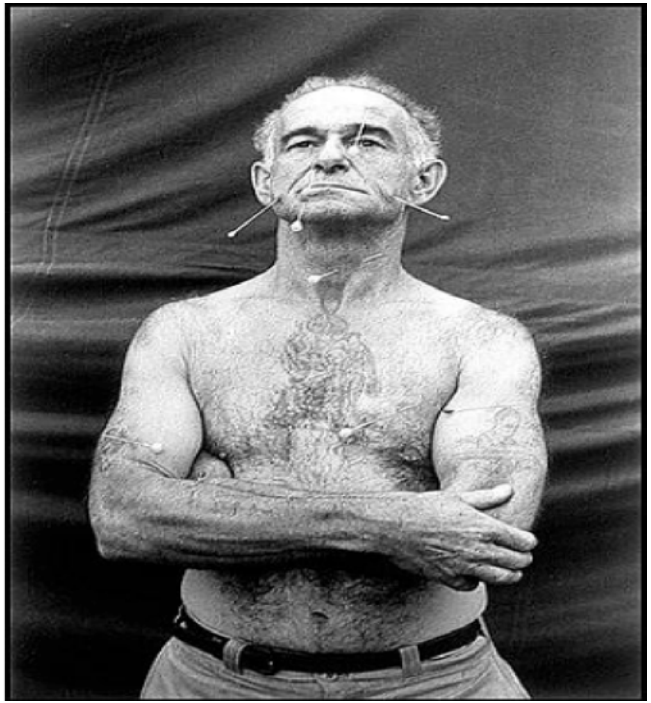
Two population studies identify variants conferring ~40% reduction in CHD

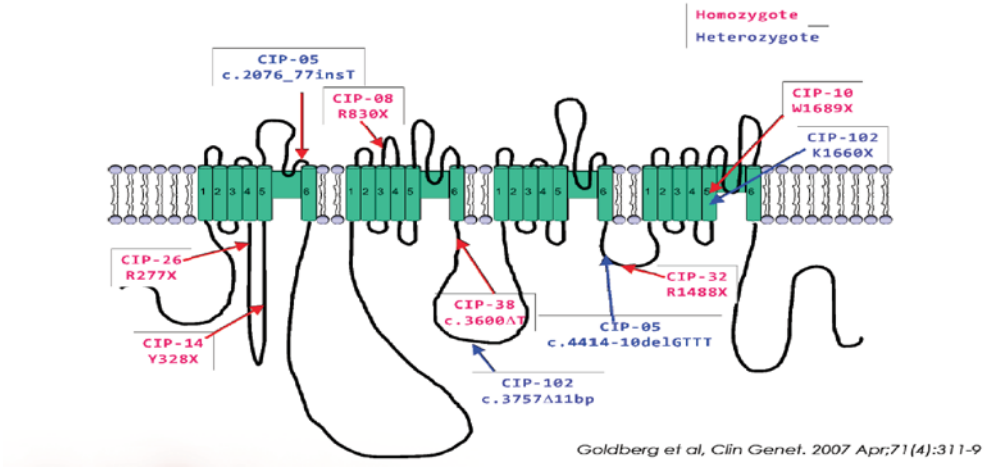
2015

Targeting APOC3 in the Familial Chylomicronemia Syndrome

Clinical proof of concept

Congenital Insensitivity to Pain (CIP) and *SCN9A*: Human Genetics Provides Insights Into New Pain Drug Targets





- CIP → pain free burns, fractures, childbirth, etc
- Extremely rare: <1/1,000,000 prevalence
- Mutations in *SCN9A* cause insensitivity to pain
- Efforts to mimic the effects of pain insensitivity through therapeutics blocking the corresponding protein are being pursued

Application of Human Genetics to Accelerate Novel Target Identification and Clinical Development

The Regeneron Genetics Center applies large-scale, fully-integrated human genetics approaches to advance science, guide the development of therapeutics, and improve patient outcomes.

"Do Well by Doing Good"

Target Discovery

Identify new drug targets and pathways

Indication Discovery

Identify new indications for drug targets and programs

Derisking

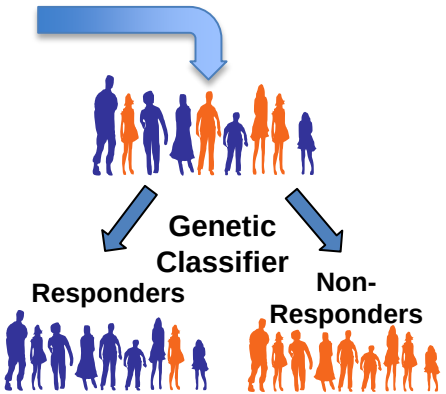
Confirm lack of "on-target adverse side effects" in drug target LOF carriers

Human Genetics

Mouse Genetics

Biomarker

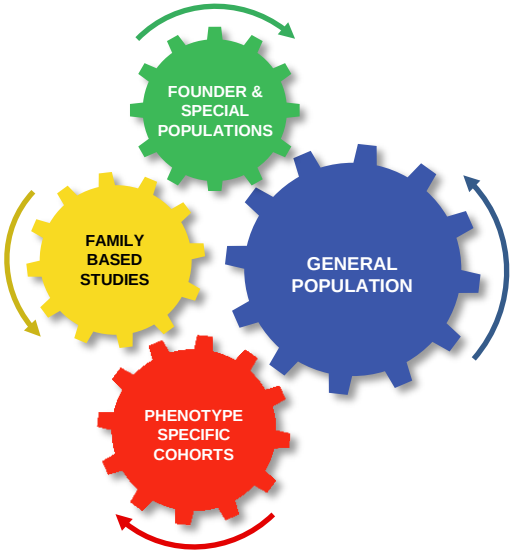
Develop pharmacogenetic markers to predict drug response



Maximizing Discovery Opportunities by Leveraging Human Genetics Resources Across Genetic Trait Architecture and Phenotypes

60+ Academic collaborators – Over 400,000 exomes sequenced

Integrated approaches across genetic trait architectures . . .



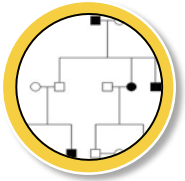
. . . will power genomic discovery

General Population

Geisinger · biobank uk (Improving the health of future generations) · LABioMed · Lund University

Phenotype Specific Cohorts

Mayo Clinic · Duke University · UT Southwestern Medical Center · Feinstein Institute for Medical Research (Northwell Health) · University of Utah Health Care · UConn Health Center · Penn



Family Studies

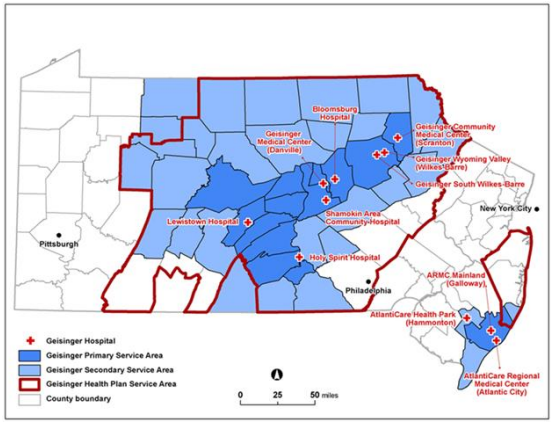
Columbia University Medical Center · BCM Baylor College of Medicine · The University of Iowa · Children's National Medical Center · Mario Negri Istituto di Ricerche Farmacologiche · SickKids · NIH National Institutes of Health · Clinic for Special Children · DDC clinic Center for Special Needs Children · Schneider Children's Medical Center of Israel · Rambam Medical Center

Founder & Special Populations

University of Maryland School of Medicine · Penn · NIH National Institute of Mental Health · NIH National Institute of Diabetes and Digestive and Kidney Diseases · Global Gene Corp · CNCD Center for Non Communicable Diseases · Einstein Albert Einstein College of Medicine · ECOGENE-21 · The University of Edinburgh

Geisinger-Regeneron DiscovEHR Collaboration

Two organizations focused on making genomic data medically actionable



Goal: Build comprehensive genotype-phenotype resource combining de-identified genomic and clinical data from >250,000 people to aid drug development and implementation of genomic medicine into patient care

- Geisinger: Integrated health care system
  - 1.6 million participants (predominantly European Caucasian)
  - Amongst earliest adopters of EHRs (1996) and leaders in clinical informatics
    - Longitudinal EHR data: Median of ~18 outpatient visits per patient over 13.4 years
- Recruitment ongoing
  - >150,000 patients consented into MyCode-DiscovEHR cohort
  - >90,000 sequenced at the Regeneron Genetics Center
  - Large unselected populations as well as targeted efforts in diseases of interest and deeply phenotyped patients
    - Cardiac catheterization lab (~8,000)
    - Bariatric surgery (~4,000) - one of the largest in the world

Science
AAAS

HUMAN GENETICS

Distribution and clinical impact of functional variants in 50,726 whole-exome sequences from the DiscovEHR study

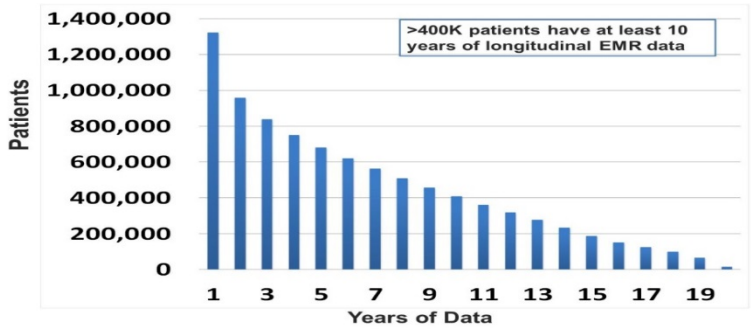
Frederick E. Dewey,[1]* Michael F. Murray,[2] John D. Overton,[1] Lukas Habegger,[1] Joseph B. Leader,[2] Samantha N. Fetterolf,[2] Colm O'Dushlaine,[1] Cristopher V. Van Hout,[1] Jeffrey Staples,[1] Claudia Gonzaga-Jauregui,[1] Raghu Metpally,[2] Sarah A. Pendergrass,[2] Monica A. Giovanni,[2] H. Lester Kirchner,[2] Suganthi Balasubramanian,[1] Noura S. Abul-Husn,[1] Dustin N. Hartzel,[2] Daniel R. Lavage,[2] Korey A. Kost,[2] Jonathan S. Packer,[1] Alexander E. Lopez,[1] John Penn,[1] Semanti Mukherjee,[1] Nehal Gosalia,[1] Manoj Kanagaraj,[1] Alexander H. Li,[1] Lyndon J. Mitnaul,[1] Lance J. Adams,[2] Thomas N. Person,[2] Kavita Praveen,[1] Anthony Marcketta,[1] Matthew S. Lebo,[3] Christina A. Austin-Tse,[3] Heather M. Mason-Suares,[3] Shannon Bruse,[1] Scott Mellis,[4] Robert Phillips,[4] Neil Stahl,[4] Andrew Murphy,[4] Aris Economides,[1] Kimberly A. Skelding,[2] Christopher D. Still,[2] James R. Elmore,[2] Ingrid B. Borecki,[1] George D. Yancopoulos,[4] F. Daniel Davis,[2] William A. Faucett,[2] Omri Gottesman,[1] Marylyn D. Ritchie,[2] Alan R. Shuldiner,[1] Jeffrey G. Reid,[1] David H. Ledbetter,[2] Aris Baras,[1] David J. Carey[2]*

The DiscovEHR collaboration between the Regeneron Genetics Center and Geisinger Health System couples high-throughput sequencing to an integrated health care system using longitudinal electronic health records (EHRs). We sequenced the exomes of 50,726 adult participants in the DiscovEHR study to identify ~4.2 million rare single-nucleotide variants and insertion/deletion events, of which ~176,000 are predicted to result in a loss of gene function. Linking these data to EHR-derived clinical phenotypes, we find clinical associations supporting therapeutic targets, including genes encoding drug targets for lipid lowering, and identify previously unidentified rare alleles associated with lipid levels and other blood level traits. About 3.5% of individuals harbor deleterious variants in 76 clinically actionable genes. The DiscovEHR data set provides a blueprint for large-scale precision medicine initiatives and genomics-guided therapeutic discovery.

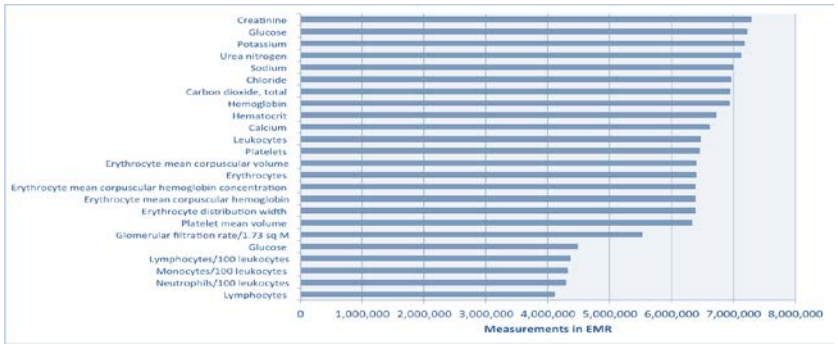
23 DECEMBER 2016 • VOL 354 ISSUE 6319

GHS: In-Depth, Longitudinal Health Records Enriched for Age-Related Diseases and Phenotypes

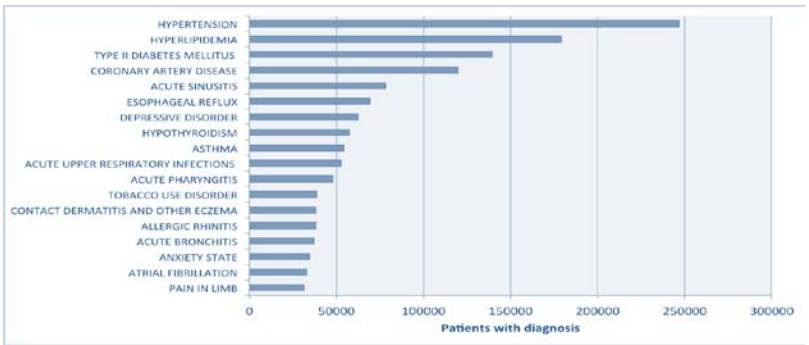
Patients by Years of Clinical Data



Most Prevalent Labs in GHS EHR

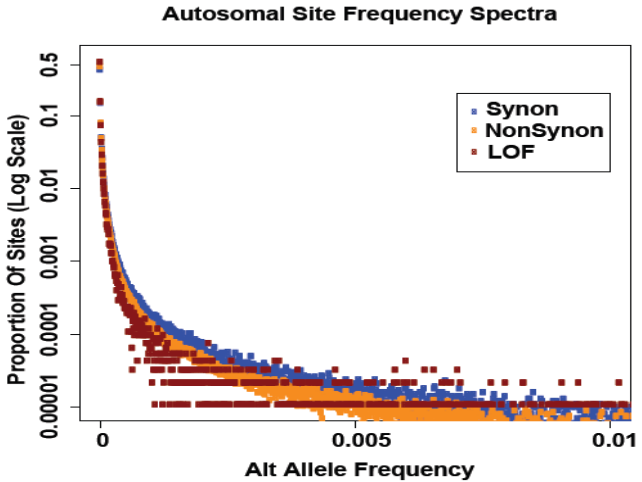


Most Prevalent Office Visit Dx in GHS EHR



Dewey et al, Science 2016

Sequence Variants Identified Using Whole Exome Sequencing of 50,726 DiscovEHR Participants



In 50K Exomes:

- *92% (n=17,409) of genes with at least 1 heterozygous pLOF*
- *7% (n=1,313) of genes with at least 1 homozygous pLOF*

Each individual :

- *Heterozygous pLOF for ~21 genes*
- *Homozygous pLOF for ~1 gene*

Variant type	All variants	Allele frequency ≤ 1%
Single nucleotide variants	4,028,206	3,947,488
Insertion/deletion variants	224,100	218,785
Predicted loss of function variants	176,365	175,393
Nonsynonymous variants	2,025,800	2,002,912
Total	4,252,306	4,166,273

Dewey et al, Science 2016

Proof-of-principle: DiscovEHR Genetics Predict Efficacy of Established Targets for Hyperlipidemia

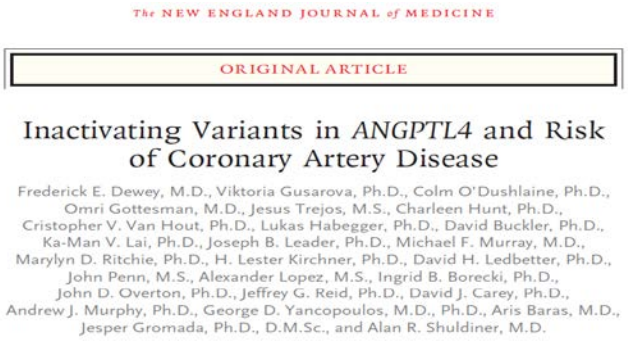
						LDL-c		HDL-c		Triglycerides		Total cholesterol	
Target	Agent	Action	Phase	Clinical effect	LOF carriers	p	effect	p	effect	p	Effect	p	effect
PPARA	Fenofibrate	Agonist	Approved	Decreased triglycerides, increased HDL	2	0.8	9 mg/dl	0.2	-28%	0.09	113%	0.4	27 mg/dl
HMGCR	Atorvastatin, rosuvastatin, pravastatin, simvastatin	Antagonist	Approved	Decreased LDL, total cholesterol, increased HDL	12	0.7	-4 mg/dl	0.3	9%	0.6	-8%	0.7	-4 mg/dl
NPC1L1	Ezetemibe	Antagonist	Approved	Decreased LDL	121	0.03	-7 mg/dl	0.07	-4%	0.5	-3%	0.0004	-12 mg/dl
APOB	Mipomersen	Antagonist	Approved	Decreased LDL	80	0.0003	-15 mg/dl	0.06	6%	0.002	-15%	$8.x10^{-7}$	-21 mg/dl
MTTP	Lomitapide	Antagonist	Approved	Decreased LDL	24	0.9	1 mg/dl	0.4	4%	0.7	3%	1.0	0.2 mg/dl
HCAR3	Niacin	Agonist	Approved	Increased HDL, decreased triglycerides, LDL	107	0.4	-3 mg/dl	0.4	-2%	0.5	4%	0.3	-4 mg/d;
CETP	Anacetrapib, evacetrapib	Antagonist	Phase 3	Increased HDL	37	0.3	-6 mg/dl	$2.0x10^{-6}$	23%	0.6	5%	0.1	9 mg/dl
PCSK9	Alirocumab, evolocumab, bococizumab	Antagonist	Phase 3	Decreased LDL	52	$8.8x10^{-9}$	-25 mg/dl	0.3	3%	0.03	-12%	$6.4x10^{-6}$	-21 mg/dl
APOC3	APOC3 inhibitors	Antagonist	Phase 2	Decreased triglycerides, increase HDL	226	0.3	-3 mg/dl	$1.5x10^{-43}$	28%	$1.5x10^{-87}$	-48%	0.2	-4 mg/dl
ACLY	ATP citrate lyase inhibitors	Antagonist	Phase 2	Decreased LDL	13	0.2	-14 mg/dl	1.0	0%	0.3	-13%	0.4	-10 mg/dl
ANGPTL3	ANGPTL3 inhibitors	Antagonist	Phase 2	Decreased triglycerides, LDL, HDL	150	0.0004	-10 mg/dl	0.0002	-8%	$6.4x10^{-15}$	-27%	$1.6x10^{-10}$	-19 mg/dl

8/11 Lipid therapy targets harbor LOFs with nominally significant or directionally consistent clinical associations that recapitulate drug effects.

Dewey et al, Science 2016

Human Genetics Validation and Derisking of New Lipid Lowering Targets

…and T2D as a potential new indication for ANGPTL4 inhibition

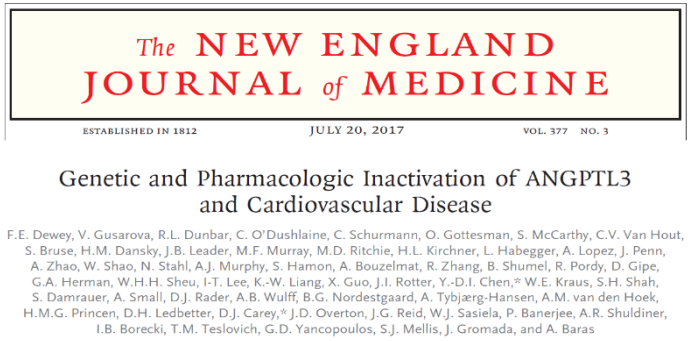


The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Inactivating Variants in *ANGPTL4* and Risk of Coronary Artery Disease

Frederick E. Dewey, M.D., Viktoria Gusarova, Ph.D., Colm O'Dushlaine, Ph.D., Omri Gottesman, M.D., Jesus Trejos, M.S., Charleen Hunt, Ph.D., Cristopher V. Van Hout, Ph.D., Lukas Habegger, Ph.D., David Buckler, Ph.D., Ka-Man V. Lai, Ph.D., Joseph B. Leader, Ph.D., Michael F. Murray, M.D., Marylyn D. Ritchie, Ph.D., H. Lester Kirchner, Ph.D., David H. Ledbetter, Ph.D., John Penn, M.S., Alexander Lopez, M.S., Ingrid B. Borecki, Ph.D., John D. Overton, Ph.D., Jeffrey G. Reid, Ph.D., David J. Carey, Ph.D., Andrew J. Murphy, Ph.D., George D. Yancopoulos, M.D., Ph.D., Aris Baras, M.D., Jesper Gromada, Ph.D., D.M.Sc., and Alan R. Shuldiner, M.D.

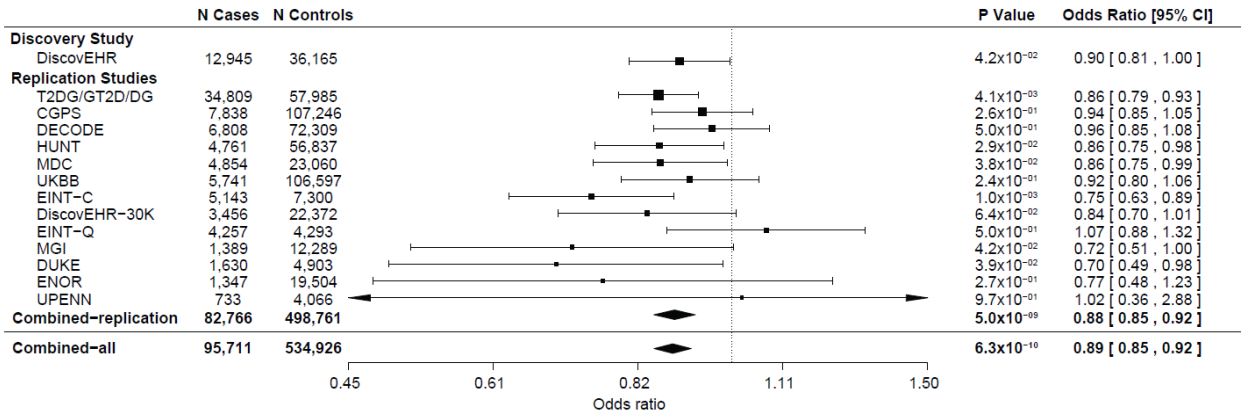


The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JULY 20, 2017 VOL. 377 NO. 3

Genetic and Pharmacologic Inactivation of ANGPTL3 and Cardiovascular Disease

F.E. Dewey, V. Gusarova, R.L. Dunbar, C. O'Dushlaine, C. Schurmann, O. Gottesman, S. McCarthy, C.V. Van Hout, S. Bruse, H.M. Dansky, J.B. Leader, M.F. Murray, M.D. Ritchie, H.L. Kirchner, L. Habegger, A. Lopez, J. Penn, A. Zhao, W. Shao, N. Stahl, A.J. Murphy, S. Hamon, A. Bouzelmat, R. Zhang, B. Shumel, R. Pordy, D. Gipe, G.A. Herman, W.H.H. Sheu, I-T. Lee, K.-W. Liang, X. Guo, J.I. Rotter, Y.-D.I. Chen,* W.E. Kraus, S.H. Shah, S. Damrauer, A. Small, D.J. Rader, A.B. Wulff, B.G. Nordestgaard, A. Tybjærg-Hansen, A.M. van den Hoek, H.M.G. Princen, D.H. Ledbetter, D.J. Carey,* J.D. Overton, J.G. Reid, W.J. Sasiela, P. Banerjee, A.R. Shuldiner, I.B. Borecki, T.M. Teslovich, G.D. Yancopoulos, S.J. Mellis, J. Gromada, and A. Baras



- In 95,711 T2D cases and 534,926 controls, carriers of p.E40K carriers have a ~11% reduced odds of diabetes per allele (OR 0.89, 95%CI 0.85-0.92, $p=6.3x10^{-10}$)
- In 32,015 T2D cases and 84,006 controls, carriers of rare pLOFs of *ANGPLT4 have a 29% reduced OR of T2D (OR 0.81, 95%CI 0.49-0.99 , p = 0.04)*
- *pE40K non-diabetic carriers have lower glucose and increased insulin sensitivity*

Gusarova et al, Nat Commun 2018

DiscovEHRy of a New Drug Target for Chronic Liver Disease

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

A Protein-Truncating *HSD17B13* Variant and Protection from Chronic Liver Disease

N.S. Abul-Husn, X. Cheng, A.H. Li, Y. Xin, C. Schurmann, P. Stevis, Y. Liu, J. Kozlitina, S. Stender, G.C. Wood, A.N. Stepanchick, M.D. Still, S. McCarthy, C. O'Dushlaine, J.S. Packer, S. Balasubramanian, N. Gosalia, D. Esopi, S.Y. Kim, S. Mukherjee, A.E. Lopez, E.D. Fuller, J. Penn, X. Chu, J.Z. Luo, U.L. Mirshahi, D.J. Carey, C.D. Still, M.D. Feldman, A. Small, S.M. Damrauer, D.J. Rader, B. Zambrowicz, W. Olson, A.J. Murphy, I.B. Borecki, A.R. Shuldiner, J.G. Reid, J.D. Overton, G.D. Yancopoulos, H.H. Hobbs, J.C. Cohen, O. Gottesman, T.M. Teslovich, A. Baras, T. Mirshahi, J. Gromada, and F.E. Dewey

N ENGL J MED 378;12 NEJM.ORG MARCH 22, 2018

Pharmacogenomics

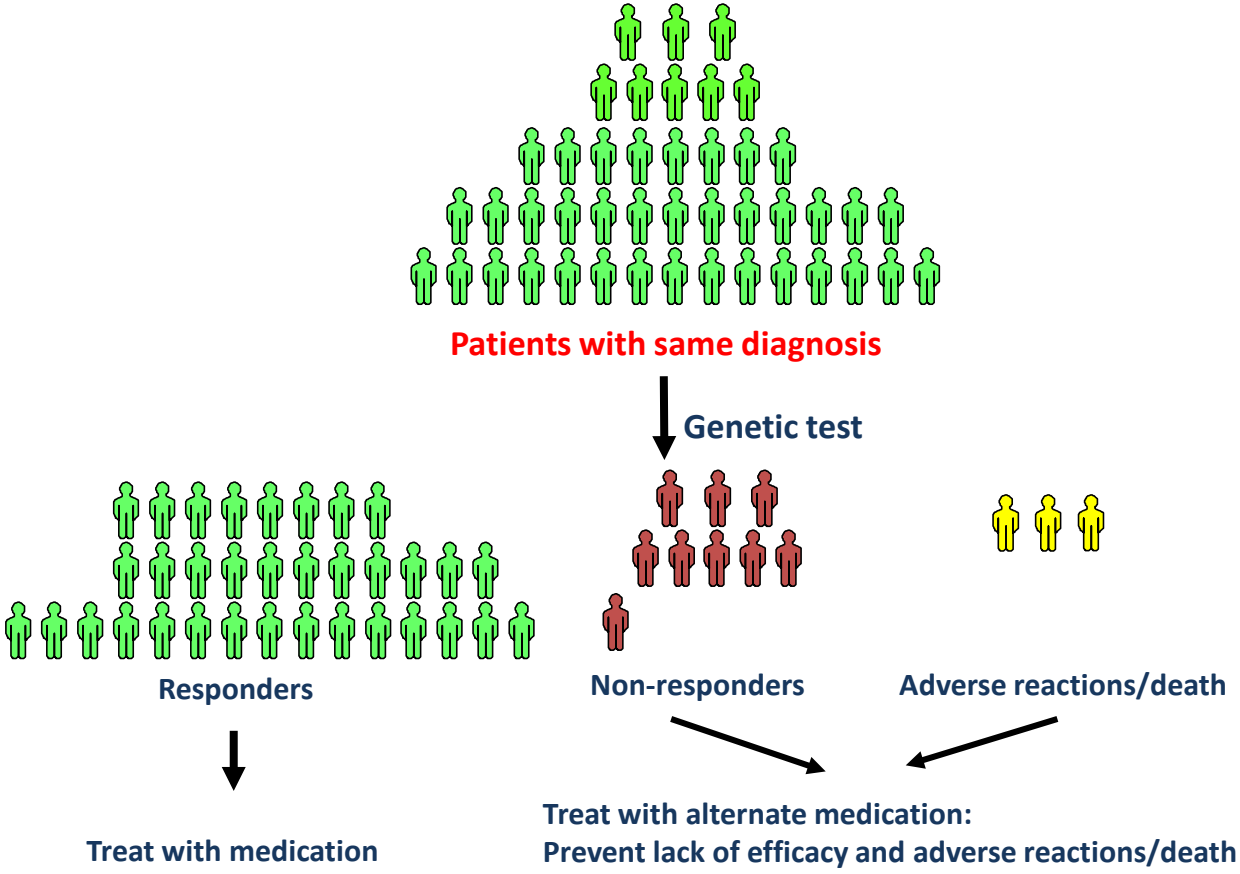
From New Yorker

"Here's my sequence..."

The study of how genetic make-up affects responsiveness to drugs (efficacy) and adverse side effects

"The right medication for the right patient at the right time."

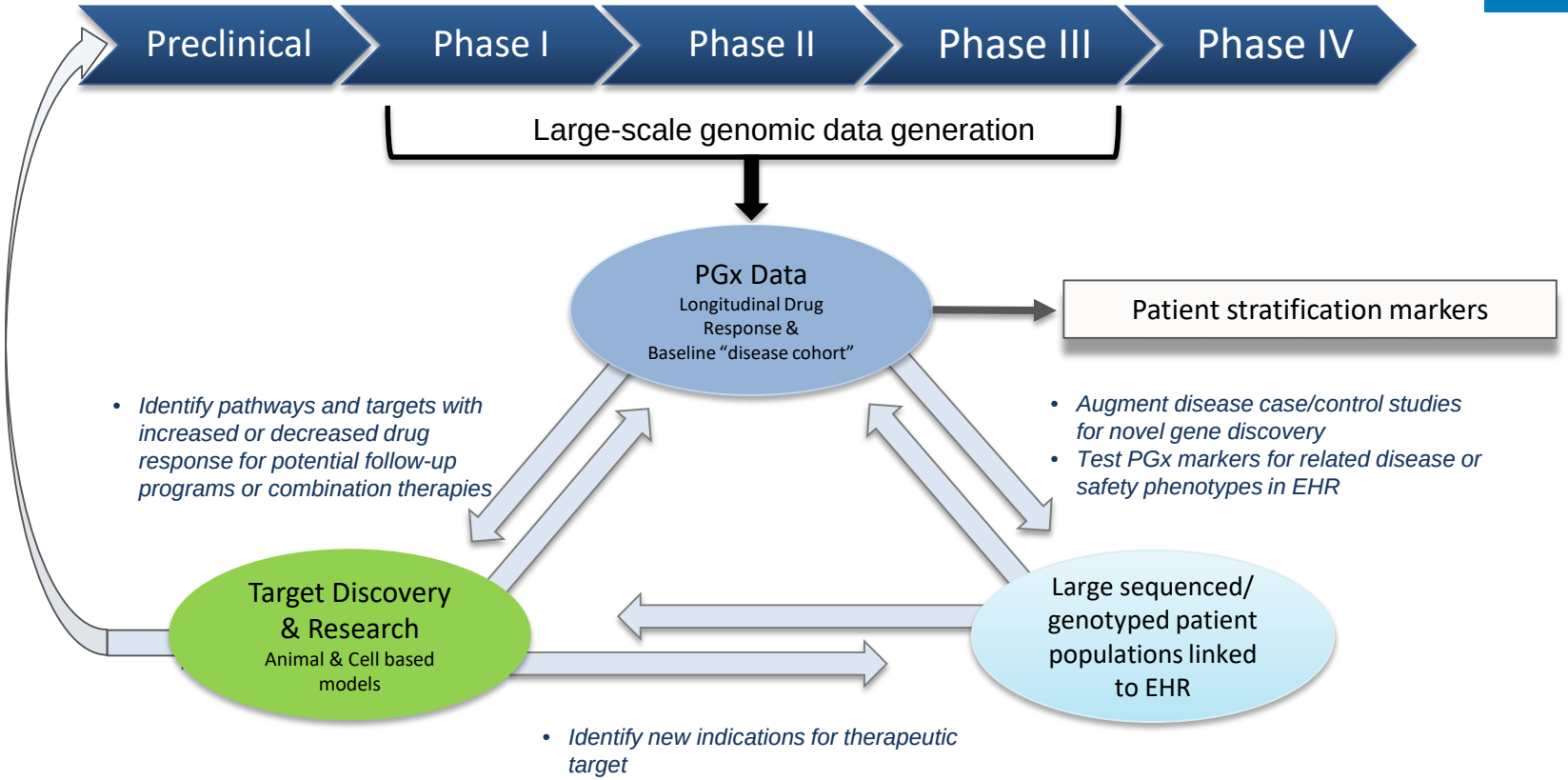
Pharmacogenomics



Goals for Pharmacogenomic Studies for Clinical Trials

- Provide a molecular understanding of drug response in patients
  - » Inform patient stratification strategies for enrichment of clinical studies or diagnostic development
  - » Identify targets/pathways associated with non-responders
  - » Inform follow-up programs or identify potential drug combinations to explore
- Provide a molecular understanding of drug safety for patients
  - » Identify patients at risk for developing AE's
- Provide a molecular understanding of PK variability for patients
- Understand disease pathogenesis:
  - » Understand baseline patient subgroups with differential progression and disease pathology, may use this information to stratify future clinical studies
  - » Inform target discovery
- Development of a program database of genotyped/sequenced patients as a resource for novel disease gene discovery

Maximizing the Use of Genetic Data from Clinical Trials



Pharmacogenomic Approaches: Understanding Patient Variability

- Produce comprehensive sequencing/genotyping datasets (exome sequencing, genotyping arrays, and imputation): producing 5-6 million variants per study dataset
- Analysis can be targeted (e.g drug target or candidate gene) or genome-wide
- Going forward, **all patients** enrolled in clinical studies that are consented for PGx studies will be directly exome sequenced and genotyped
- Perform genetic analysis broadly across development programs, multiple indications, and phases of development
- Analysis being performed for all efficacy, baseline, biomarker variables collected in clinical trials
- Focus on late stage trials with the largest sample sizes and greatest statistical power

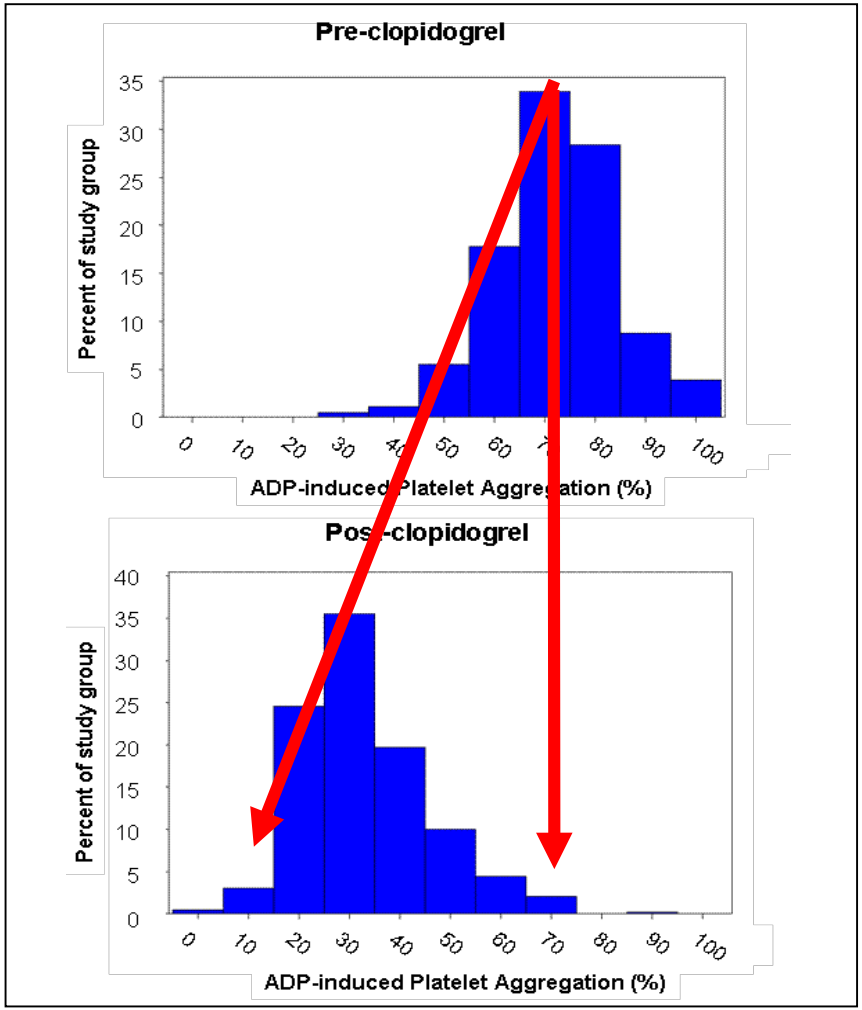
Variability of Clopidogrel Response:

The Amish Pharmacogenomics of Antiplatelet Intervention (PAPI) Study

- 668 healthy subjects treated with clopidogrel for 1 week
- Platelet aggregation measured before and after therapy

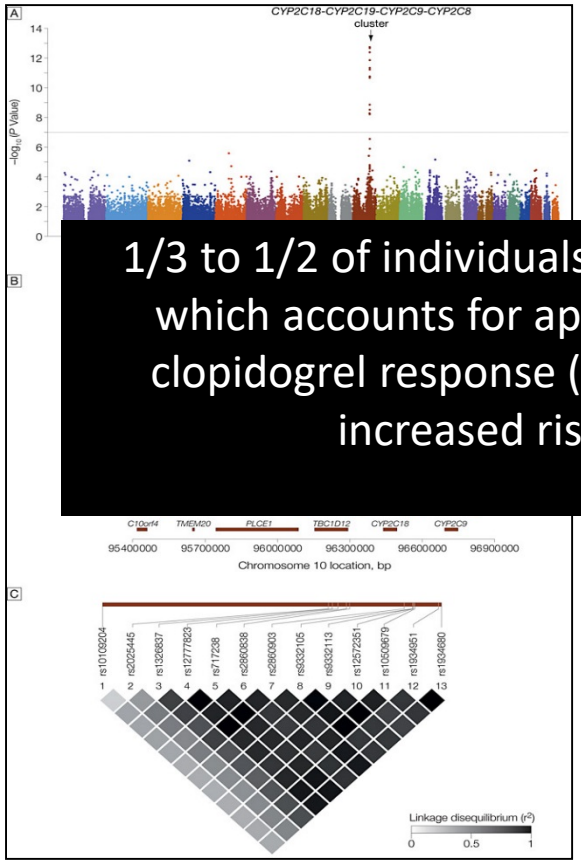
The population “responds” to clopidogrel but there is great inter-individual variation in response

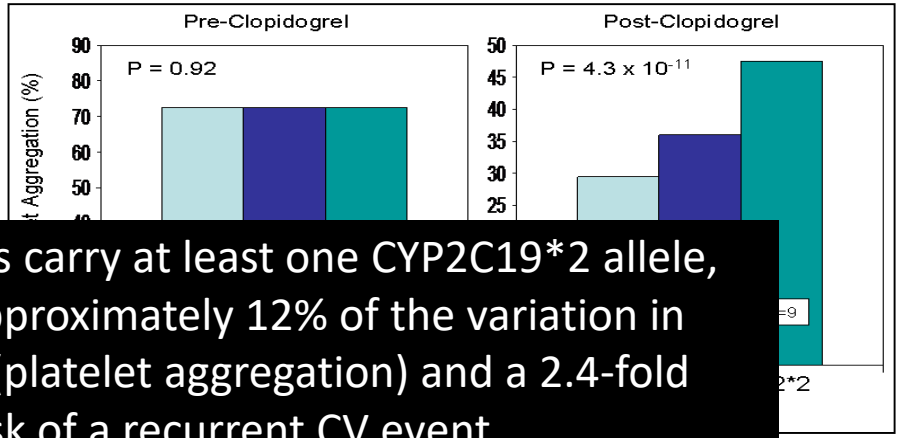
Heritability of clopidogrel response = 0.7
→ GENETICS !



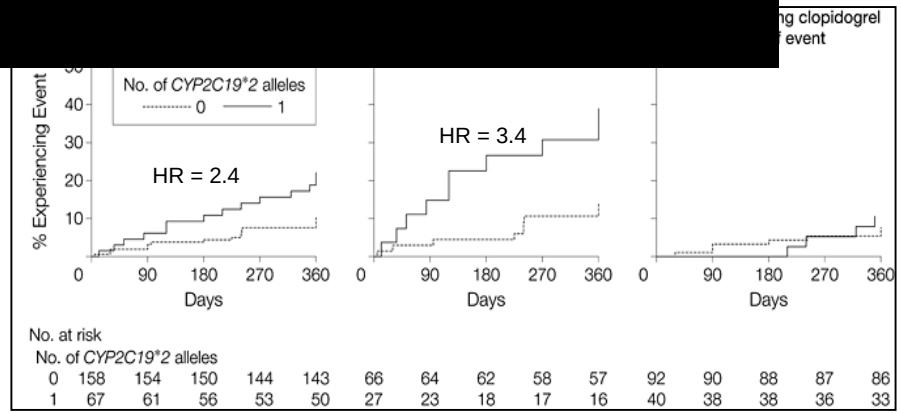
Shuldiner et al (2009) JAMA

PAPI-1: Clopidogrel Response GWAS to Functional Variant to Clinical Outcome





1/3 to 1/2 of individuals carry at least one CYP2C19*2 allele, which accounts for approximately 12% of the variation in clopidogrel response (platelet aggregation) and a 2.4-fold increased risk of a recurrent CV event.



Shuldiner et al (2009) JAMA

FDA Boxed Warning: Plavix (3/20/2010):

WARNING: DIMINISHED EFFECTIVENESS IN POOR METABOLIZERS

See full prescribing information for complete boxed warning.

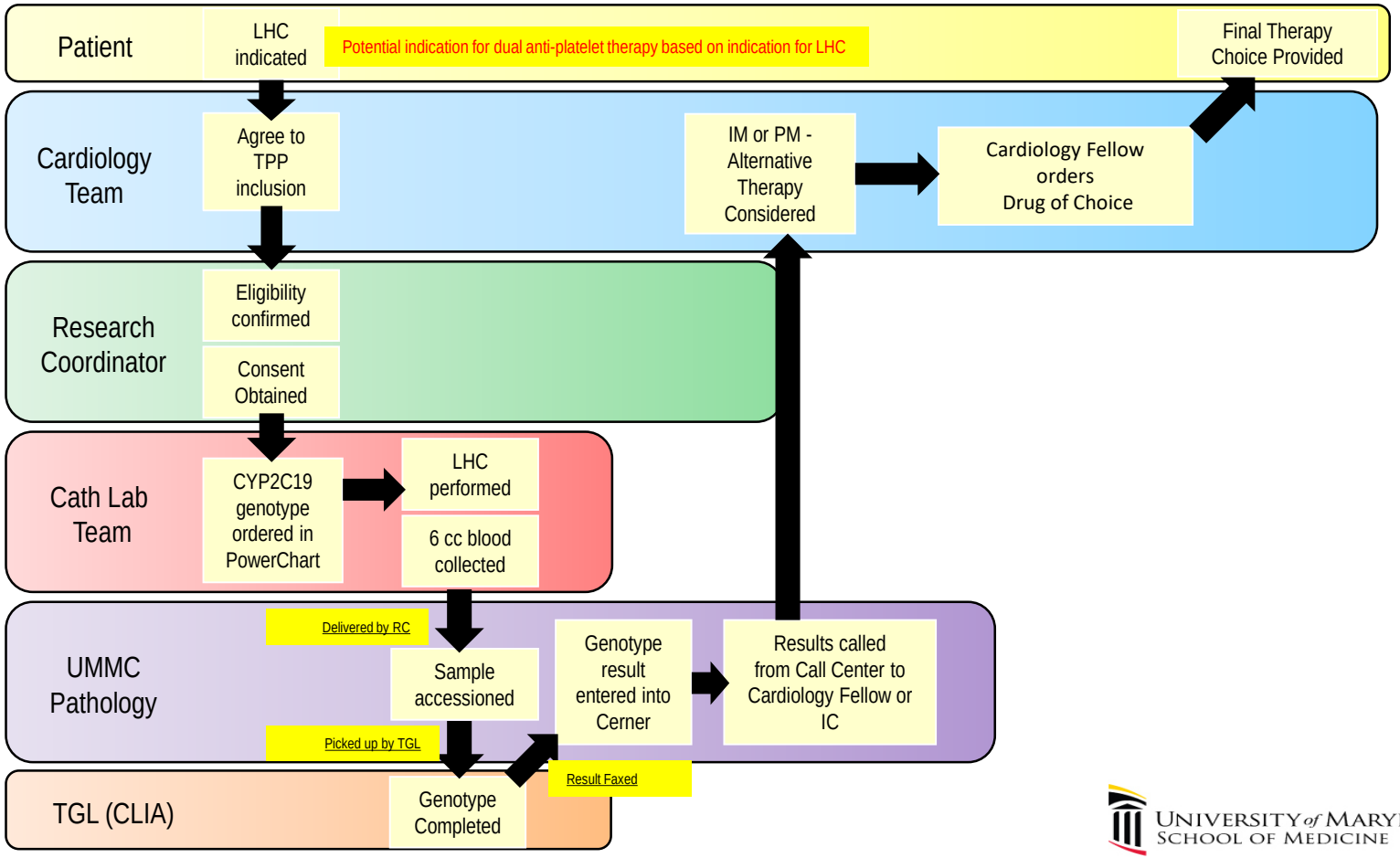
- Effectiveness of Plavix depends on activation to an active metabolite by the cytochrome P450 (CYP) system, principally CYP2C19. (5.1)
- Poor metabolizers treated with Plavix at recommended doses exhibit higher cardiovascular event rates following acute coronary syndrome (ACS) or percutaneous coronary 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)

Why Aren't Most Cardiologists Performing Genetic Testing?

- Lack of prospective randomized clinical trials (evidence base)
  - Does pgx improve outcomes?
  - What is the optimal clinical algorithm for its application?
  - Is it cost effective?
  - Who will pay for a RCT?
- Conservative (and litigious) nature of professional society clinical recommendations
- Health care provider education (and expectations)
- Logistics of genetic testing
  - Point-of-care, CLIA, etc.
- Reimbursement
- Ethical and legal considerations
  - FDA
- Despite above: Patients 'get it' and want it!

Personalized DAPT - CYP2C19 - UMMC Workflow

(5-hour turnaround)



University of Maryland *CYP2C19* Clinical Implementation Project

	VA	UMMC	Total No. (%)
No. Screened	52	697	749
No. Enrolled	39	571	610 (81.4%)
No. of IM/PM	17	176	193 (31.6%)
No. Actionable Genotypes (IM/PM w/PCI)	7	83	90 (14.8%)
No. of Patients w/ Actionable Genotypes Prescribed Alternate Treatment	6	43	49 (54.4%)

Might Pragmatic Clinical Trials be a Pragmatic way to Build the Evidence Base for Implementation of Pgx?

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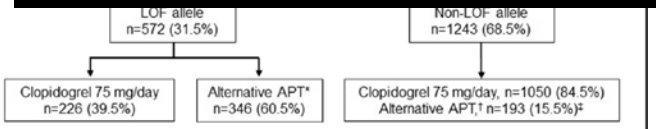
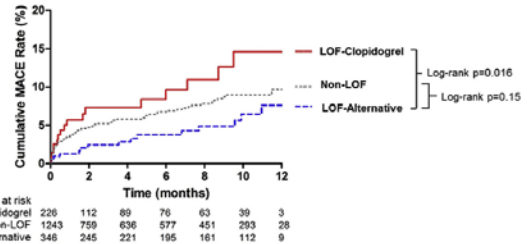
Multisite Investigation of Outcomes With Implementation of *CYP2C19* Genotype-Guided Antiplatelet Therapy After Percutaneous Coronary Intervention

CYP2C19 genetic testing now standard of care at UMMC!



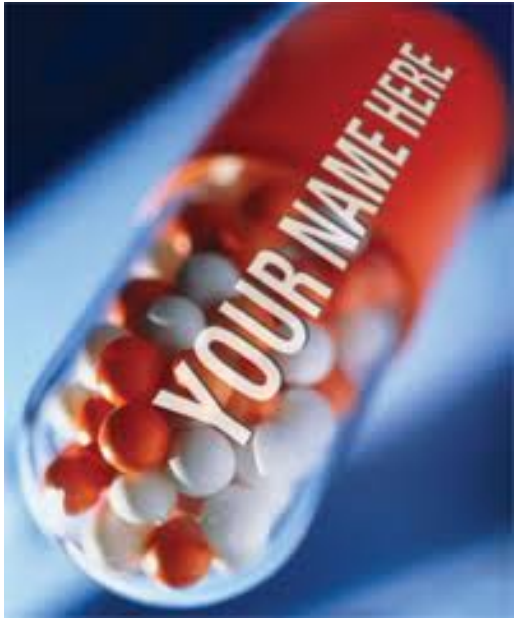
*Alternative therapy in patients with 1 or 2 loss-of-function (LOF) alleles consisted of prasugrel (n = 222), ticagrelor (n = 116), or high-dose clopidogrel (150 mg/day, n = 2; 225 mg/day, n = 6). †Alternative therapy in the non-LOF group consisted of prasugrel (n = 125) or ticagrelor (n = 68). ‡$p < 0.001$ for use of alternative therapy in the non-LOF group compared with the LOF group. APT = antiplatelet therapy; PCI = percutaneous coronary intervention.



Data are shown for patients with a *CYP2C19* loss-of-function (LOF) allele treated with clopidogrel (LOF-clopidogrel), patients with an LOF allele treated with alternative antiplatelet drug therapy (LOF-alternative), and patients without an LOF allele treated with either clopidogrel or alternative therapy (non-LOF). The unadjusted log-rank p values for the LOF-clopidogrel group compared with the LOF-alternative group and for the non-LOF group compared with the LOF-alternative group are provided. MACE = major adverse cardiovascular event.

Lesson Learned: Implementation of Pharmacogenetics

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