U.S. FOOD & DRUG ADMINISTRATION

Personalized/Precision Medicine

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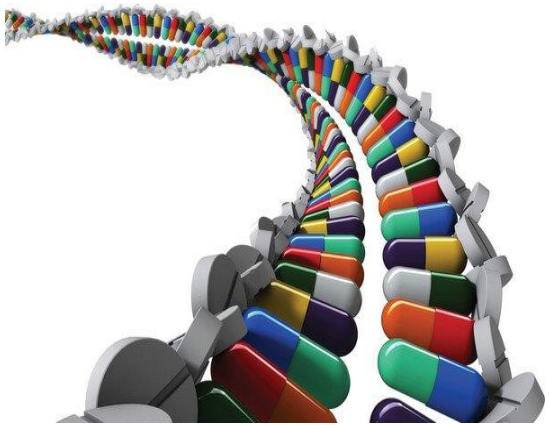
Disclosure:

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

- Precision/Personalized Medicine
  - Definition
  - Genetic architecture of human traits and disease 101
  - Opportunities for prevention, diagnosis and treatment of rare (monogenic) and common (polygenic) disease
  - Pharmacogenetics
    - Variable drug response (pharmacodynamics)
    - Variable drug metabolism (pharmacokinetics)
    - Adverse events/Safety
    - Challenges of implementing evidence-based pharmacogenetics into patient care
  - Application of human genetics in therapeutic development
    - Identification of new therapeutic targets (efficacy)
    - Derisking therapeutic targets (safety)
    - New indications for therapeutic targets



Precision Medicine Initiative

https://www.whitehouse.gov/precision-medicine January 30, 2015

What is Precision Medicine?

Precision medicine is the use of information from a patient's genome or other biomarkers to:

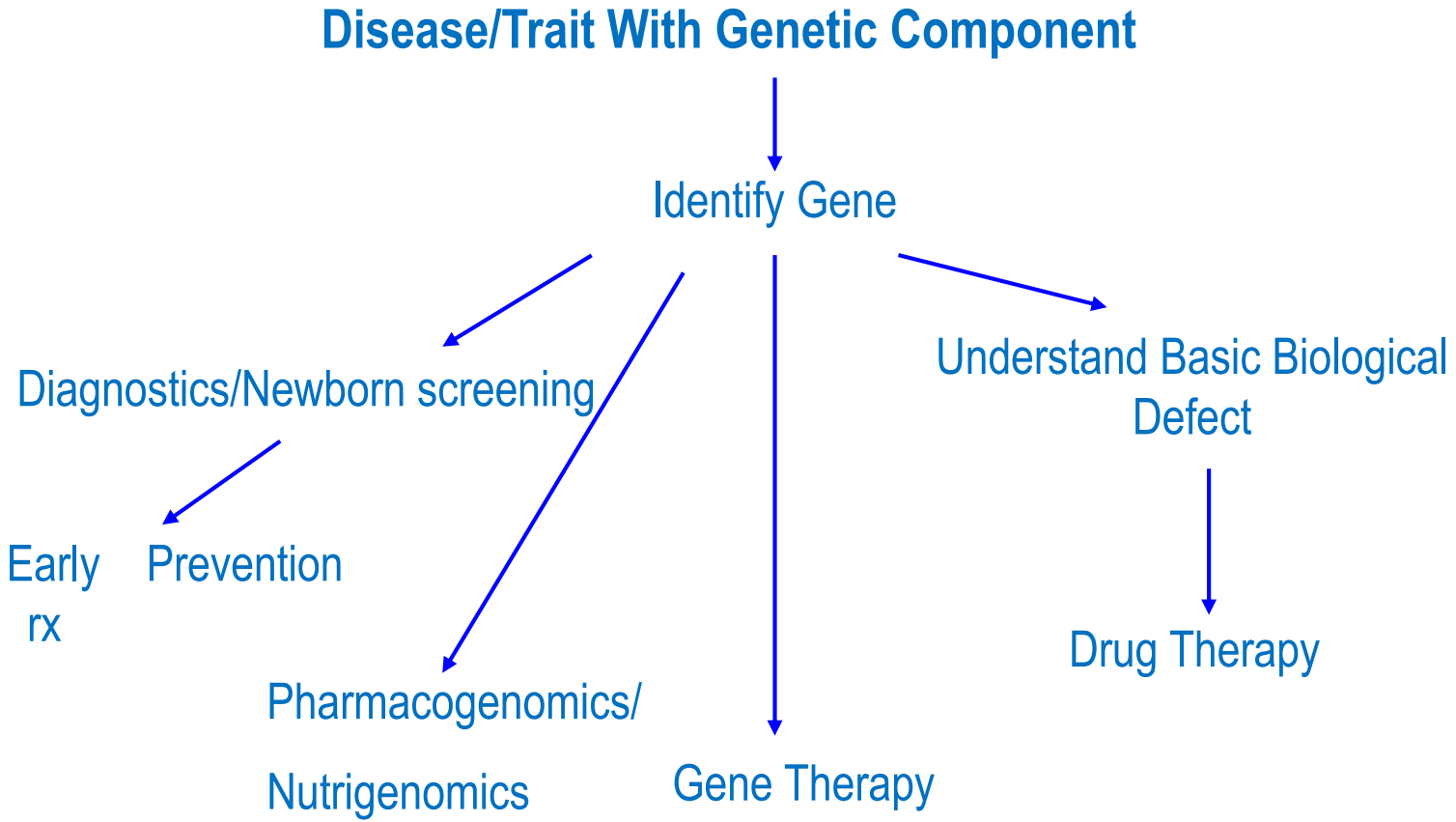
- predict individual disease susceptibility,
- better define disease prognosis,
- tailor medication, medical device use, diet and lifestyle…

…to more effectively prevent or treat disease and minimize adverse treatment effects.

In short, Precision Medicine enables health care providers to prescribe the right intervention for the right patient at the right time to prevent or treat disease.

"4 P's" of Precision Medicine –
predictive, personalized, preemptive, participatory

The Path to Personalized Medicine



How is Genetic Information Used in Medicine Today?

- Diagnostic testing (e.g., factor V Leiden, hemochromotosis)
- Newborn screening (e.g., PKU, MSUD, sickle cell)
- Carrier testing (CF, Tay-Sachs)
- Prenatal testing (e.g., above diseases, chromosomal abnormalities)

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- Rare(ish)
  - Hemochromotosis - 1/200
  - a-1-antitrypsin deficiency - 1/1700
  - Cystic fibrosis - 1/3000
  - Neurofibromatosis 1/3000
- Monogenic
- High penetrance
- High sensitivity and specificity

Whole Exome Sequencing is the Standard of Care for Diagnosis of Rare Genetic Conditions

Total number of monogenic diseases for which the molecular basis is known (11/6/2019) = **6,528**

https://www.omim.org/

The NEW ENGLAND JOURNAL of MEDICINE

FDA

ORIGINAL ARTICLE

Whole-Genome Sequencing in a Patient with Charcot–Marie–Tooth Neuropathy

Clinical assessment incorporating a personal genome

Evan A Ashley, Atu
Alexander A Morga
Katrin Sangkuhl, Jo
Abraham M Rosenl

Summary
Background Th
remains unclea

DIAGNOSTICS

Rapid Whole-Genome Sequencing for Genetic Disease Diagnosis in Neonatal Intensive Care Units

Carol Jean Saunders,[1,2,3,4,5*] Neil Andrew Miller,[1,2,4*] Sarah Elizabeth Soden,[1,2,4*] Darrell Lee Dinwiddie,[1,2,3,4,5*] Aaron Noll,[1] Noor Abu Alnadi,[4] Nevene Andraws,[3] Melanie LeAnn Patterson,[1,3] Lisa Ann Krivohlavek,[1,3] Joel Fellis,[6] Sean Humphray,[6] Peter Saffrey,[6] Zoya Kingsbury,[6] Jacqueline Claire Weir,[6] Jason Betley,[6] Russell James Grocock,[6] Elliott Harrison Margulies,[6] Emily Gwendolyn Farrow,[1] Michael Artman,[2,4] Nicole Pauline Safina,[1,4] Joshua Erin Petrikin,[2,3] Kevin Peter Hall,[6] Stephen Francis Kingsmore[1,2,3,4,5†]

ORIGINAL ARTICLE

Clinical application of exome sequencing in undiagnosed genetic conditions

Anna C Need,[1] Vandana Shashi,[2] Yuki Hitomi,[1] Kelly Schoch,[2] Kevin V Shianna,[1] Marie T McDonald,[2] Miriam H Meisler,[3] David B Goldstein[1,4]

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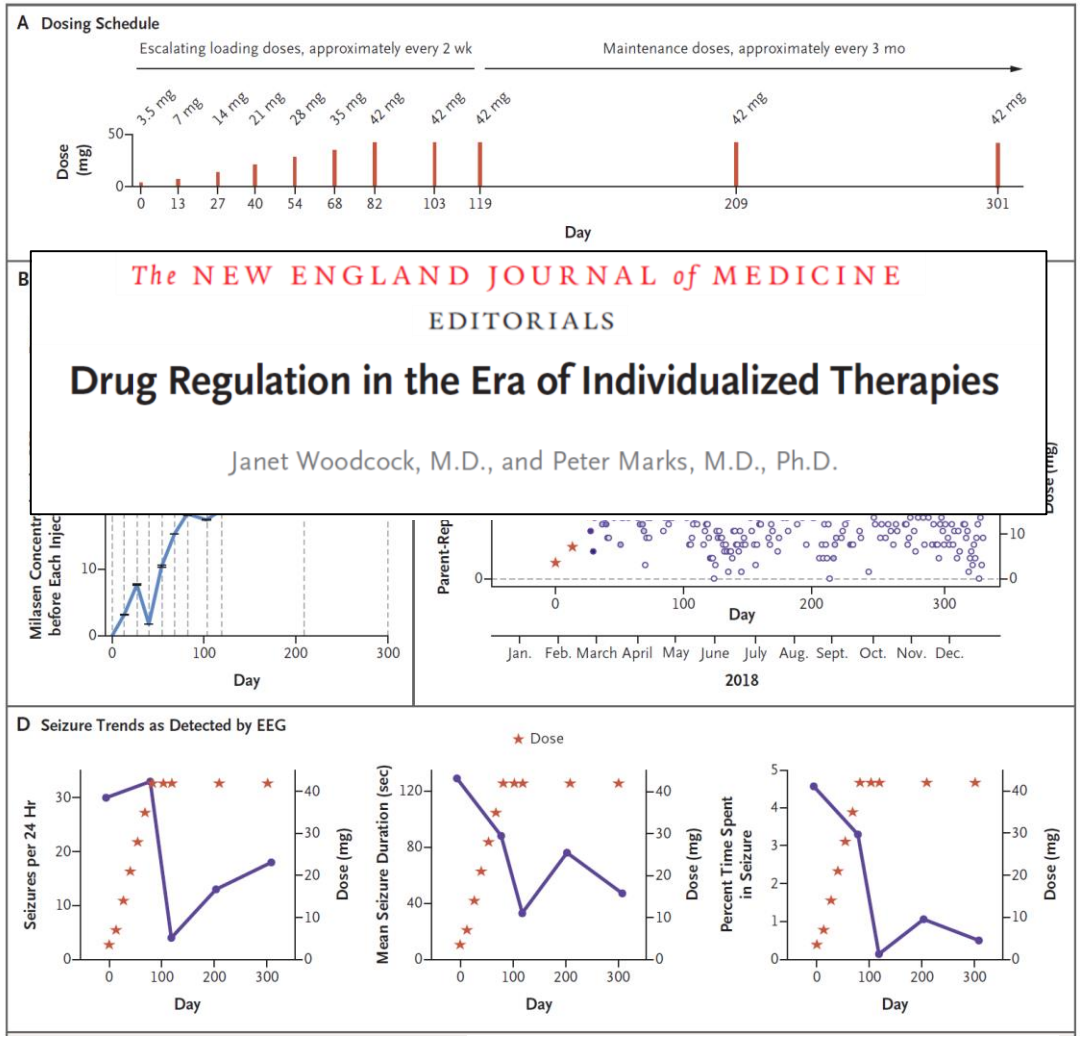
BRIEF REPORT

October 24, 2019

Patient-Customized Oligonucleotide Therapy for a Rare Genetic Disease

J. Kim, C. Hu, C. Moufawad El Achkar, L.E. Black, J. Douville, A. Larson, M.K. Pendergast, S.F. Goldkind, E.A. Lee, A. Kuniholm, A. Soucy, J. Vaze, N.R. Belur, K. Fredriksen, I. Stojkovska, A. Tsytsykova, M. Armant, R.L. DiDonato, J. Choi, L. Cornelissen, L.M. Pereira, E.F. Augustine, C.A. Genetti, K. Dies, B. Barton, L. Williams, B.D. Goodlett, B.L. Riley, A. Pasternak, E.R. Berry, K.A. Pflock, S. Chu, C. Reed, K. Tyndall, P.B. Agrawal, A.H. Beggs, P.E. Grant, D.K. Urion, R.O. Snyder, S.E. Waisbren, A. Poduri, P.J. Park, A. Patterson, A. Biffi, J.R. Mazzulli, O. Bodamer, C.B. Berde, and T.W. Yu

- 6-year old girl with insidious onset of blindness, ataxia, seizures and developmental regression
- Work-up revealed Batten's disease due to mutations in *MFSD8,* a rare neurodegenerative disease with very poor prognosis.
- An allele-specific oligonucleotide (ASO) was designed to correct missplicing caused by the mutation Successful in correcting splicing in the patient's cells
- Toxicity tested in rats
- N of 1 human clinical trial initiated (escalating doses)



Genetics of “Typical” Common Diseases:

Interaction between genetic susceptibility, the environment, and time

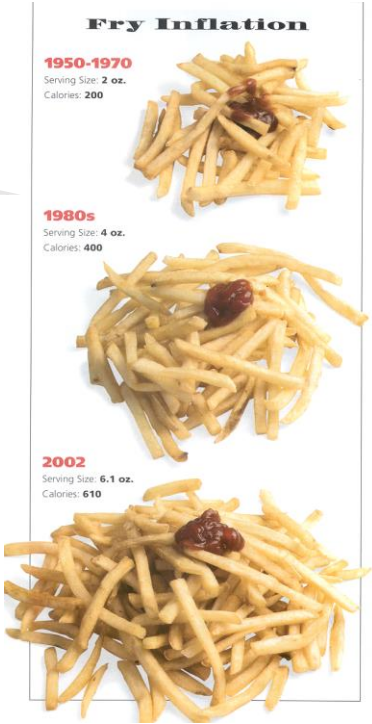
Aging

Environment

Genetic Susceptibility

Polygenes for complex diseases will be
- **predictive (not diagnostic)**
- **provide insights into biology and mechanism(s) of disease**

families/populations



Some Common Diseases with a Known Genetic Component

- Diabetes
- Cancer
- CVD (coronary disease, stroke, heart failure)
- Osteoporosis
- Pulmonary disease (asthma, COPD)
- Eye diseases (glaucoma, macular degeneration)
- Neurodegenerative disorders (Alzheimer, Parkinsons)
- Psychiatric diseases (bipolar, schizophrenia)
- Immune diseases (asthma, rheumatoid arthritis, SLE, MS)

Examples of Diseases and Traits for which GWAS has Identified Associated Variants

159,202 unique SNP-trait associations (Nov 1, 2019)

- Macular Degen.
- Glaucoma
- Myopia
- Optic Disc Size
- Corneal Thickness
- Corneal Dystrophy
- Retinal Vessel Size
- Iris Characteristics
- Lung Cancer
- SCLC Treatment Rsp.
- NSCLC Treatment Rsp.
- Prostate Cancer
- Breast Cancer
- Aromatase Inh. Rsp.
- Mammographic Dens.
- Colorectal Cancer
- Bladder Cancer
- Neuroblastoma
- Melanoma
- Cutaneous Nevi
- Basal Cell Cancer
- TP53 Cancer Pred'n
- Ac/Ch Lymph. Leuk.
- Asparaginase Hypers.
- Follicular Lymphoma
- Lg. B-Cell Lymphoma
- Thyroid Cancer
- Myeloprolif. Syn.
- Testic. Germ Cell Ca.
- Glioma
- Ovarian Cancer
- Pancreatic Cancer
- Esophageal Cancer
- Nasopharyngeal Ca
- Hepatocellular Ca
- Renal Cell Ca
- Endometrial Ca
- Meningioma
- Bleomycin Sens.

- MTX Pharmacokin.
- Platinum Rsp.
- Chemorx Suscept.
- Epirubicin Leukopenia
- Cleft Palate
- Periodo
- Tooth
- Quinin
- Eosino
- Infl. Bo
- Celiac
- Hirschs
- Ileal C
- Biliiubi
- Gallsto
- 1° Scle
- Biliary
- Non-Al
- Cirrhos
- Drug-Ir
- Acetan
- Hepati
- Hepati
- Chroni
- Hep B

- ECG In
- Corona
- Corona
- Coronary Restenosis
- Sudden Cardiac Dth
- Heart Failure
- Peripart. Cardiomyop.
- Atrial Fibrill'n/Flutter
- Ventricular Fibrillation
- Resting Heart Rate
- Stroke
- Intracranial Aneurysm
- Carotid Athero. AIDS

- Migraine
- Angiogenic Activity
- Kawasaki Disease
- Moyamoya Disease
- Hypertension

- Brain Cytoarch.
- Amygdala Activation
- Partial Epillepsy
- EEG Traits
- Hearing, Otoscler.
- Restless Legs Synd.
- Essential Tremor
- Coffee Consumption
- Nicotine Depend.
- Cannabis Depend.

- Alcohol Depend.
- Methamphet. Dep
- Heroin Addiction
- Pain
- Pain Disorder

- Behçet's Disease
- Dupuytren's Cont.
- Osteoarthritis
- Osteoporosis
- Idiopathic Scoliosis
- Paget's Dis. Bone
- Psoriasis
- Sarcoidosis
- Pulmonary Fibrosis
- COPD/Lung Funct.

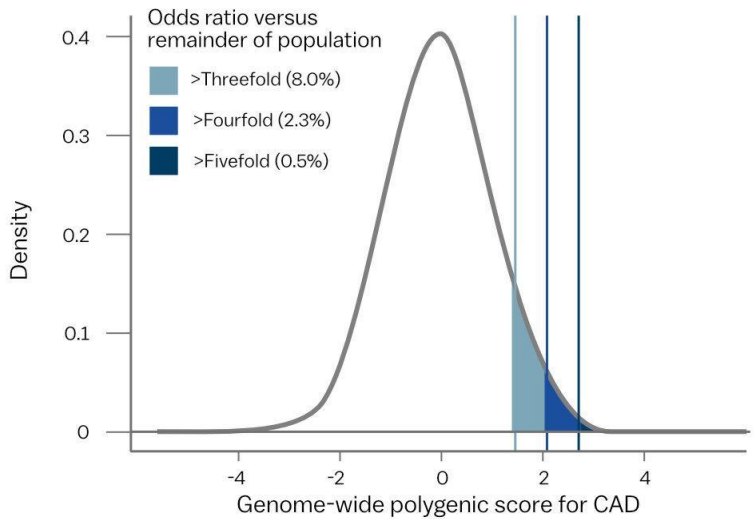
- Interstitial Lung Dis.
- CF Severity
- Asthma
- Chr. Rhinosinusitis
- topy
- tevens-Johnson
- IV Setpoint/Prog.
- IV Mother/Child
- IV Replication
- D4:CD8 Ratio
- ibavirin Adv. Rsp.
- evirapine Adv. Rsp.
- evere Malaria
- eprosy
- uberculosis
- leningococcal Dis.
- accine Adv. Rsp.
- om Var Immunodef.
- ype 1 Diabetes
- ype 2 Diabetes
- iabetic Nephrop.
- iabetic Retinop.
- letformin Trt. Rsp.
- nd-St. Renal Dis.
- idney Stones
- ephrotic Syndrome
- besity, BMI, Waist
- , MetabolicTraits
- Butyrylcholinesterase
- Adipokine Levels
- Anorexia nervosa
- Exercise Behavior
- Fetal Growth
- Height
- Digit Length Ratio
- Thyroid Function
- Menarche
- Menopause/Ov. Fail.

- Polycystic Ovary Syn
- Endometriosis
- Uterine Fibroids
- Alopecia
- Male Infertility
- Erectile Dysfunction
- Hypospadias
- High Altitude Adapt.
- Fetal Hemoglobin
- Iron Status
- Hem/Thromb Levels
- C-Reactive Protein
- Adhesion Molecules
- Eosinophil Numbers
- Total IgE Levels
- Urate Levels, Gout
- Protein Levels
- N-Glycan Levels
- PSA Levels
- DHEAS Levels
- Folate Path. Vita.
- β-Carotene Levels
- Retinol Levels
- Vitamin D Levels
- Phosphorus Levels
- Sphyngolipid Levels
- Recombination Rate
- Telomere Length
- Longevity
- Radiation Response
- Self-Rated Health
- Constitut. Med. Type
- Hair Color/Morphol.
- Pigmentation
- Vitiligo
- Keloid
- Recessive Diseases
- Post Op Nausea

https://www.ebi.ac.uk/gwas/

Polygenic Risk Score (PRS):

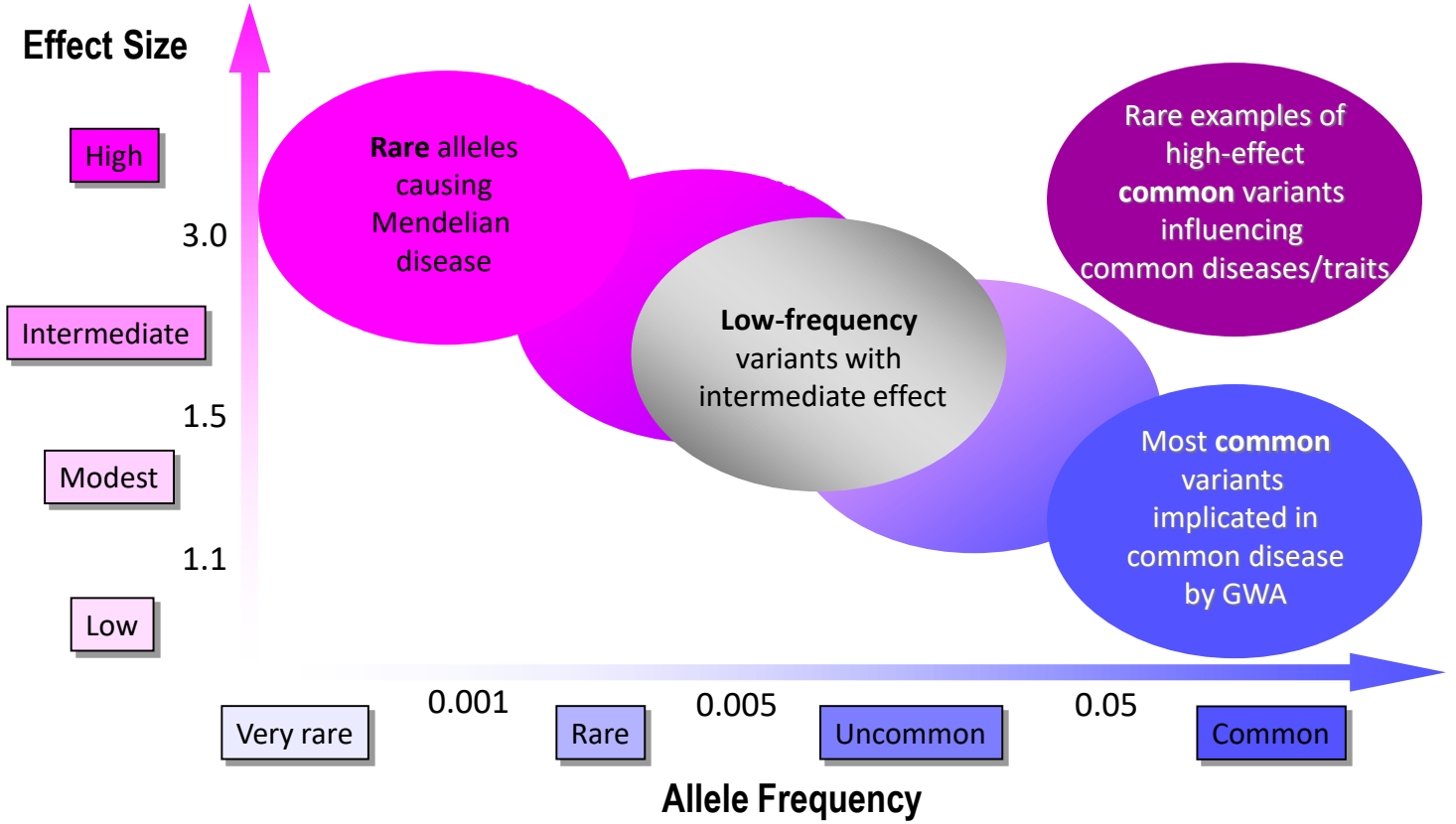
Combining hundreds/thousands of genetic variants, each with small effect on risk for a given disease



Source: Nature Genetics

- To predict disease risk in individual patients
  - More aggressive preventive care
  - Inform actuary tables for health/life insurance
- To select high-risk patients for clinical trials
- Generalizable across populations?

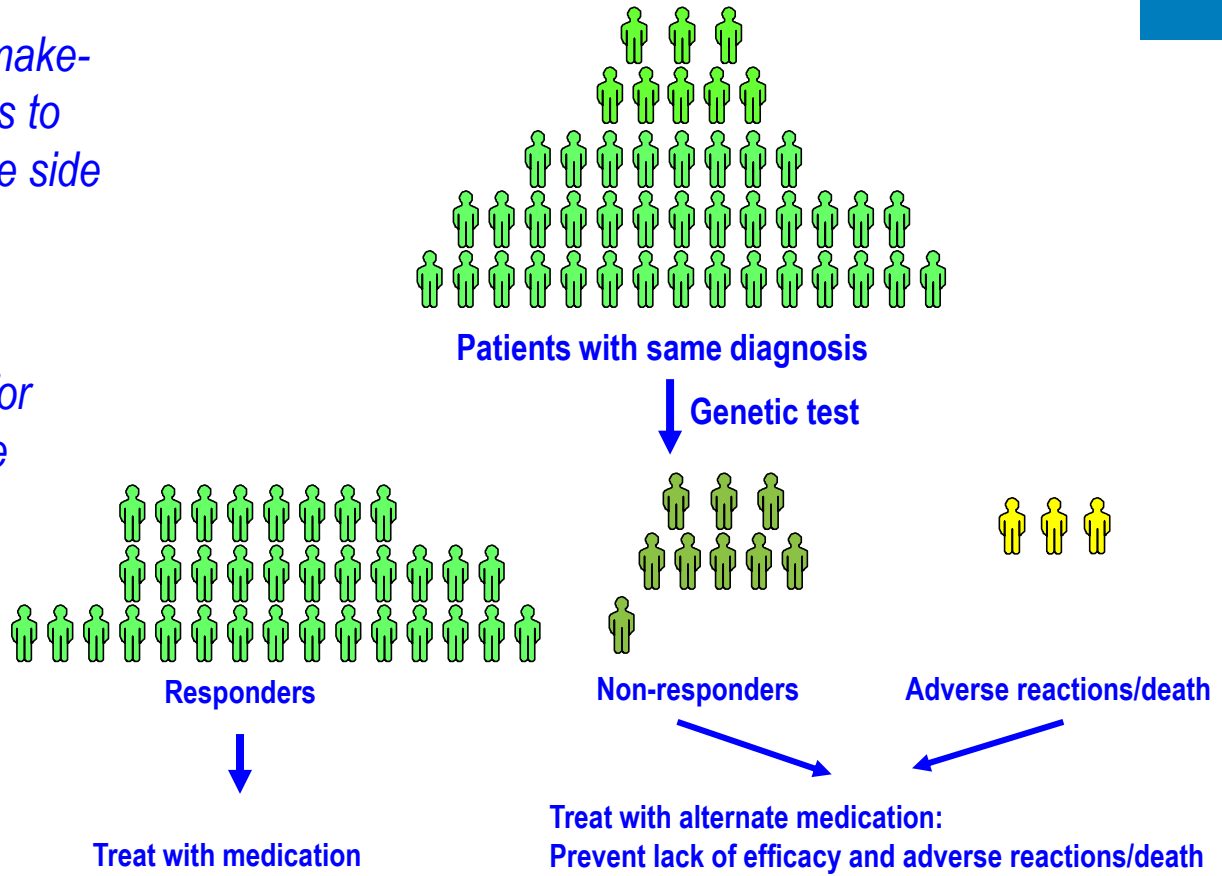
Genetic Architecture of Human Diseases and Traits



Pharmacogenomics

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

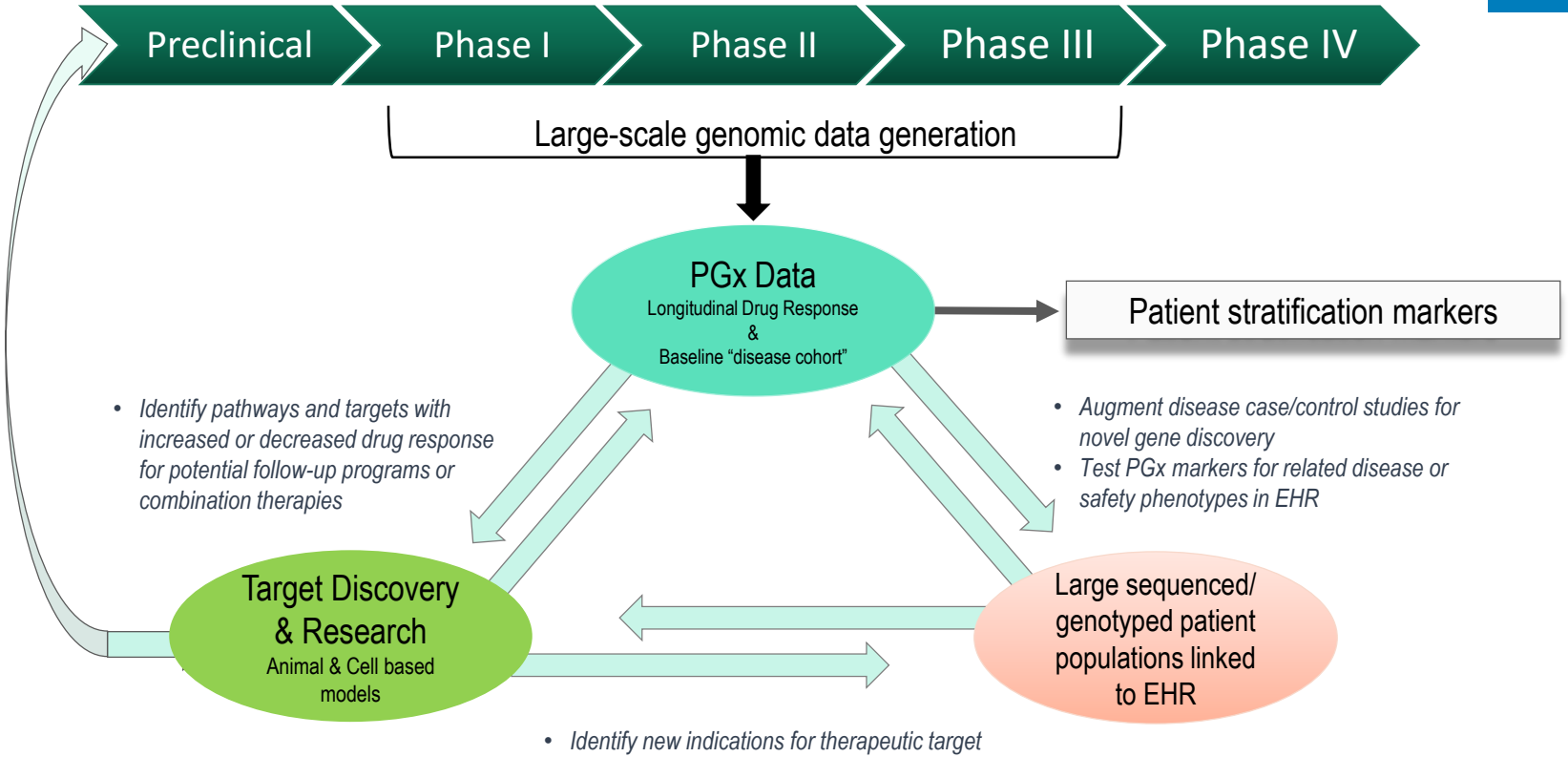
"The right medication for the right patient at the right time."



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



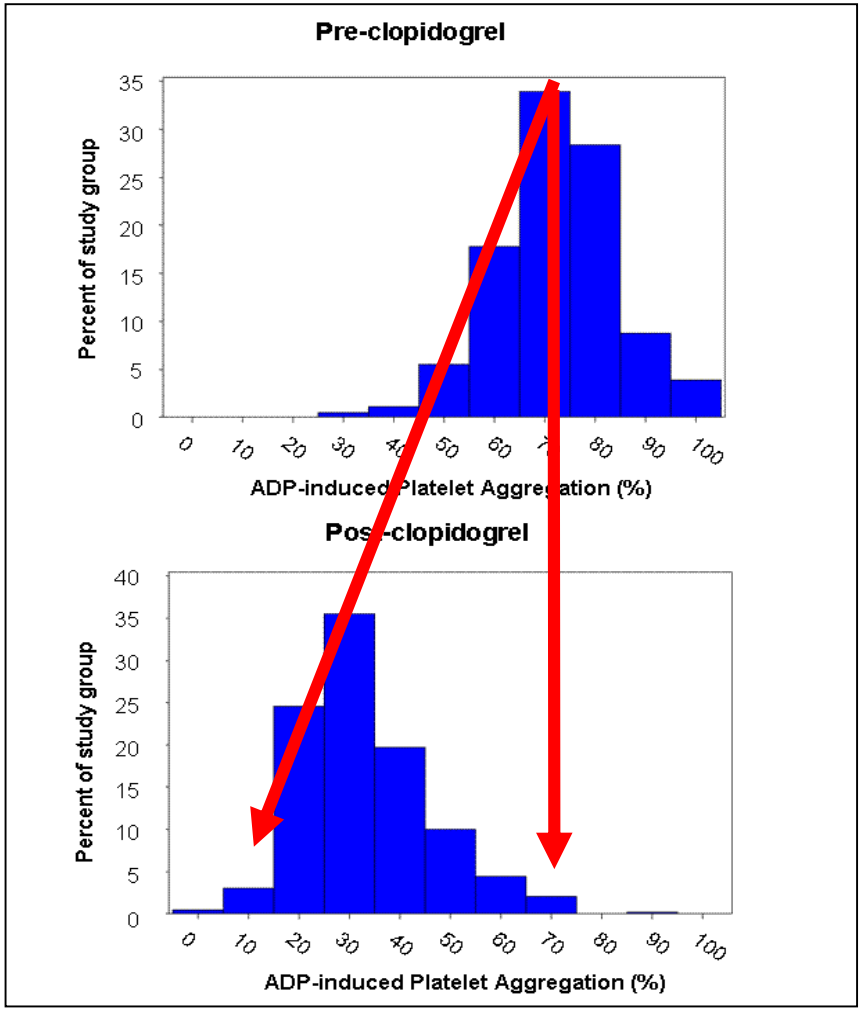
Variability of Clopidogrel Response:

The Amish Pharmacogenomics of Antiplatelet Intervention (PAPI) Study

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

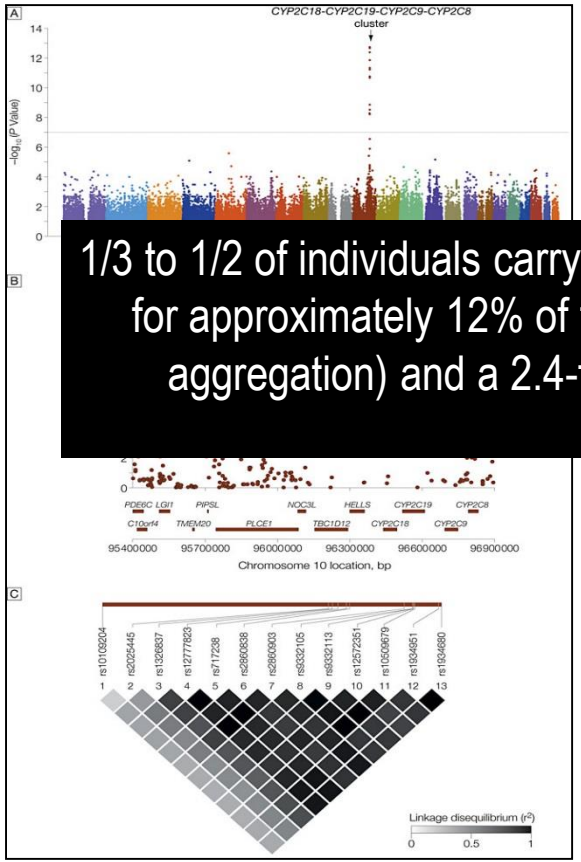
The population “responds” to clopidogrel but there is great inter-individual variation in response

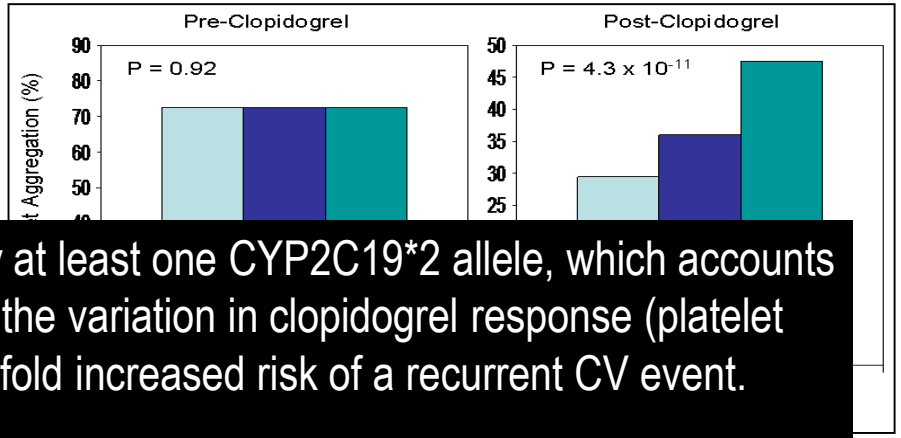
Heritability of clopidogrel response = 0.7 → GENETICS !



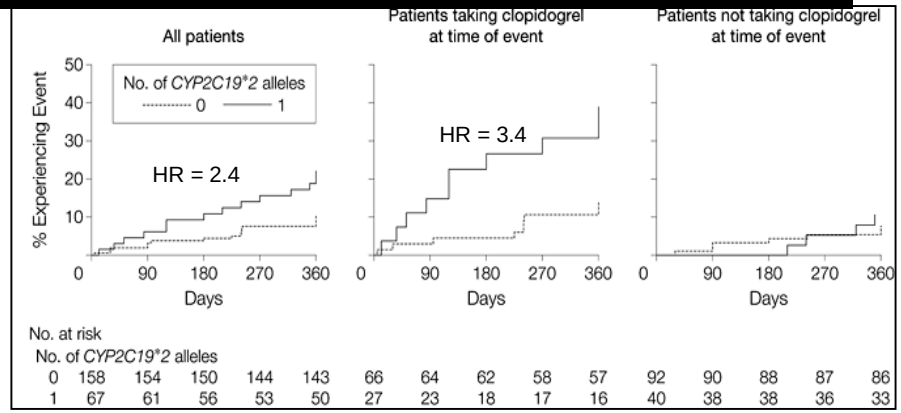
Shuldiner et al (2009) JAMA

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; updated 5/2019):

WARNING: DIMINISHED ANTIPLATELET EFFECT IN PATIENTS WITH TWO LOSS-OF-FUNCTION ALLELES OF THE CYP2C19 GENE

The effectiveness of Plavix results from its antiplatelet activity, which is dependent on its conversion to an active metabolite by the cytochrome P450 (CYP) system, principally CYP2C19 *[see Warnings and Precautions (5.1), Clinical Pharmacology (12.3)]*. Plavix at recommended doses forms less of the active metabolite and so has a reduced effect on platelet activity in patients who are homozygous for nonfunctional alleles of the CYP2C19 gene, (termed "CYP2C19 poor metabolizers"). Tests are available to identify patients who are CYP2C19 poor metabolizers *[see Clinical Pharmacology (12.5)]*. Consider use of another platelet $P2Y_{12}$ inhibitor in patients identified as CYP2C19 poor metabolizers.

Clopidogrel Pharmacogenomics

The perfect storm for individualized anti-platelet therapy?

- Plavix (clopidogrel) off patent (inexpensive)
- Progeny of clopidogrel - prasagrel, ticagrelor - FDA approved (expensive; higher bleeding risk)
- Cyp2C19 *1*1 → clopidogrel
  - Cyp2C19 *2/*2 → prasugrel, ticagrelor (or other alternatives)
  - *1/*2 (intermediate metabolizers)?

Why aren't most cardiologists performing genetic testing?

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

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

A Genotype-Guided Strategy for Oral $P2Y_{12}$ Inhibitors in Primary PCI

Daniel M.F. Claassens, M.D., Gerrit J.A. Vos, M.D., Thomas O. Bergmeijer, M.D., Renicus S. Hermanides, M.D., Ph.D., Arnoud W.J. van 't Hof, M.D., Ph.D., Pim van der Harst, M.D., Ph.D., Emanuele Barbato, M.D., Ph.D., Carmine Morisco, M.D., Ph.D., Richard M. Tjon Joe Gin, M.D., Folkert W. Asselbergs, M.D., Ph.D., Arend Mosterd, M.D., Ph.D., Jean-Paul R. Herrman, M.D., Ph.D., Willem J.M. Dewilde, M.D., Ph.D., Paul W.A. Janssen, M.D., Ph.D., Johannes C. Kelder, M.D., Ph.D., Maarten J. Postma, Ph.D., Anthonius de Boer, M.D., Ph.D., Cornelis Boersma, Pharm.D., Ph.D., Vera H.M. Deneer, Pharm.D., Ph.D., and Jurriën M. ten Berg, M.D., Ph.D.

October 24, 2019

ABSTRACT

BACKGROUND

It is unknown whether patients undergoing primary percutaneous coronary intervention (PCI) benefit from genotype-guided selection of oral $P2Y_{12}$ inhibitors.

METHODS

We conducted a randomized, open-label, assessor-blinded trial in which patients undergoing primary PCI with stent implantation were assigned in a 1:1 ratio to receive either a $P2Y_{12}$ inhibitor on the basis of early *CYP2C19* genetic testing (genotype group) or standard treatment with either ticagrelor or prasugrel (standard group) for 12 months. In the genotype-guided group, carriers of *CYP2C19**3 loss-of-function alleles received ticagrelor or prasugrel, and others received clopidogrel. The two primary outcomes were net adverse clinical events — defined as death from any cause, myocardial infarction, definite stent thrombosis, stroke, or major bleeding defined according to Platelet Inhibition and Patient Outcomes (PLATO) criteria — at 12 months (primary combined outcome) and tested for noninferiority, with a noninferiority margin of 2 percentage points (the absolute difference) and PLATO major or minor bleeding at 12 months (primary bleeding outcome).

RESULTS

For the primary analysis, 2488 patients were included: 1242 in the genotype-guided group and 1246 in the standard-treatment group. The primary combined outcome occurred in 63 patients (5.1%) in the genotype-guided group and in 73 patients (5.9%) in the standard-treatment group (absolute difference, −0.7 percentage points; 95% confidence interval [CI], −2.0 to 0.7; P<0.001 for noninferiority). The primary bleeding outcome occurred in 122 patients (9.8%) in the genotype-guided group and in 156 patients (12.5%) in the standard-treatment group (hazard ratio, 0.78; 95% CI, 0.61 to 0.98; P=0.04).

CONCLUSIONS

In patients undergoing primary PCI, a *CYP2C19* genotype–guided strategy for selection of oral $P2Y_{12}$ inhibitor therapy was noninferior to standard treatment with ticagrelor or prasugrel at 12 months with respect to thrombotic events and resulted in a lower incidence of bleeding. (Funded by the Netherlands Org... and Development; POPular Genetics ClinicalTrials.gov number, NC... Netherlands Trial Register number, NL2872.)

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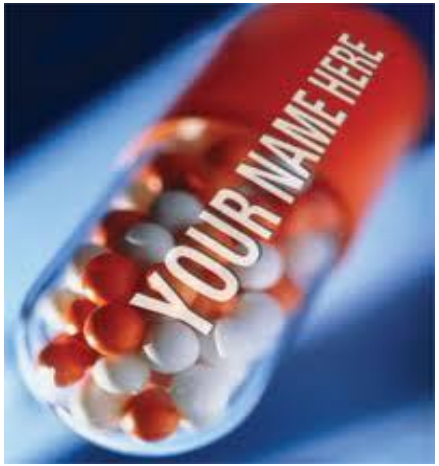
In patients undergoing primary PCI, a CYP2C19 genotype-guided strategy for selection of oral P2Y12 inhibitor therapy was noninferior to standard treatment with ticagrelor or prasugrel at 12 months with result to thrombotic events and resulted in a lower incidence of bleeding.

Examples of Ready for Prime Time PGX:

http://www.pharmgkb.org/page/cpic

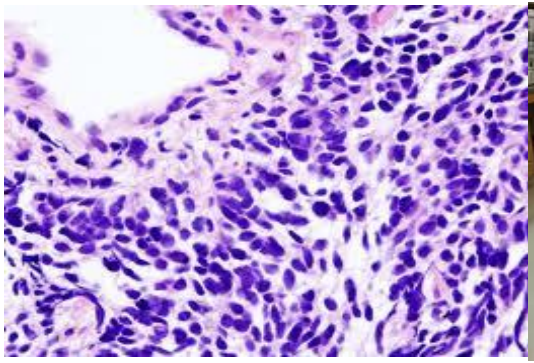
- TPMT/Thiopurines
- CYP2C19/Clopidogrel
- CYP2C9-VKORC1/Warfarin
- HLA-B*5701/Abacavir
- CYP2D6/Codeine, SSRIs, ADHD drugs, Tamoxofen
- SLCO1B1/Simvastatin
- HLA-B/*1502/Carbamazepine
- IL28B/interferon
- CYP2D6/SSRIs
- UGT1A1/irinotecan



Cancer: Leading the Way in Personalized Medicine

(http://www.fda.gov/drugs/scienceresearch/researchareas/pharmacogenetics/ucm083378.htm)

- Her-Neu2/Trastuzumab (Herceptin), everolimus
- ER/tamoxifen
- Brc-Abl-C-Kit/ Imatinib (Gleevac)
- EGFR/gefitinib, cetuximab, erlotinib, panitumumab
- KRAS/cetuximab, panitumumab
- ALK/crizotinib
- BRAF/vemurafenib
- PD1/PDL1 checkpoint inhibitors and tumor neoantigens



The Reality of Therapeutic Development in 2019

- 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

2003

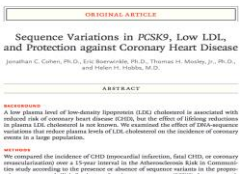
Mutations in *PCSK9* cause autosomal dominant hypercholesterolemia

Marianne Abifadel[1,2], Mathilde Varret[1], Jean-Pierre Rabès[1,3], Delphine Allard[1], Khadija Ouguerram[4], Martine Devillers[5], Corinne Cruaud[3], Suzanne Benjannet[6], Louise Wickham[6], Danièle Erlich[7], Aurélie Derré[1], Ludovic Villéger[1], Michel Farnier[7], Isabel Beucler[8], Eric Bruckert[9], Jean Chambaz[10], Bernard Chanu[11], Jean-Michel Lecerf[12], Gerald Luc[13], Philippe Moulin[13], Jean Weissenbach[3], Annick Prat[6], Michel Krempf[4], Claudine Junien[1,2], Nabil G Seidah[6] & Catherine Boileau[1,3]

Autosomal dominant hypercholesterolemia (ADH; OMIM144400), a risk factor for coronary heart disease, is characterized by an increase in low-density lipoprotein cholesterol levels that is associated with mutations in the genes *LDLR* (encoding low-density lipoprotein receptor) or *APOB* (encoding apolipoprotein B). We mapped a third locus associated with ADH, *HCHOLA3* at 1p32, and now report two mutations in the gene *PCSK9* (encoding proprotein convertase subtilisin/kexin type 9) that cause ADH. *PCSK9* encodes NARC-1 (neural apoptosis regulated convertase), a newly identified human subtilase that is highly expressed in the liver and contributes to cholesterol homeostasis.

Family studies identify *PCSK9* GOF as causing FH

2006



THE NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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

Jonathan C. Cohen, Ph.D., Eric Boerwinkle, Ph.D., Thomas H. Mosley, Jr., Ph.D., and Helen H. Hobbs, M.D.

ABSTRACT

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

2012

THE NEW ENGLAND JOURNAL of MEDICINE

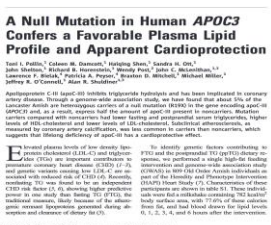
ORIGINAL ARTICLE

Effect of a Monoclonal Antibody to PCSK9 on LDL Cholesterol

ABSTRACT

Clinical proof of concept

2008



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

Toni I. Pollin,[1] Coleen M. Damcott,[1] Haiqing Shen,[1] Sandra K. Ott,[1] John Shelton,[1] Richard B. Horenstein,[1] Wendy Post,[1] John C. McLenithan,[1,2] Lawrence F. Bielak,[3] Patricia A. Peyser,[3] Braxton D. Mitchell,[1] Michael Miller,[1] Jeffrey R. O'Connell,[1] Alan R. Shuldiner[1,2]

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

2014

THE NEW ENGLAND JOURNAL of MEDICINE

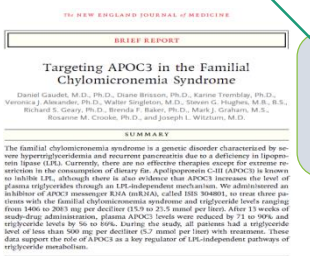
ORIGINAL ARTICLE

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

ABSTRACT

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

2015



THE NEW ENGLAND JOURNAL of MEDICINE

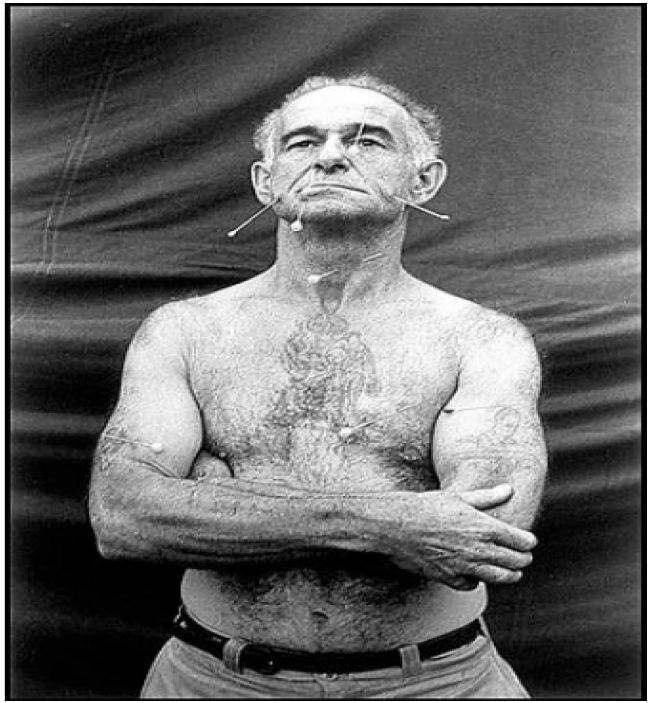
BRIEF REPORT

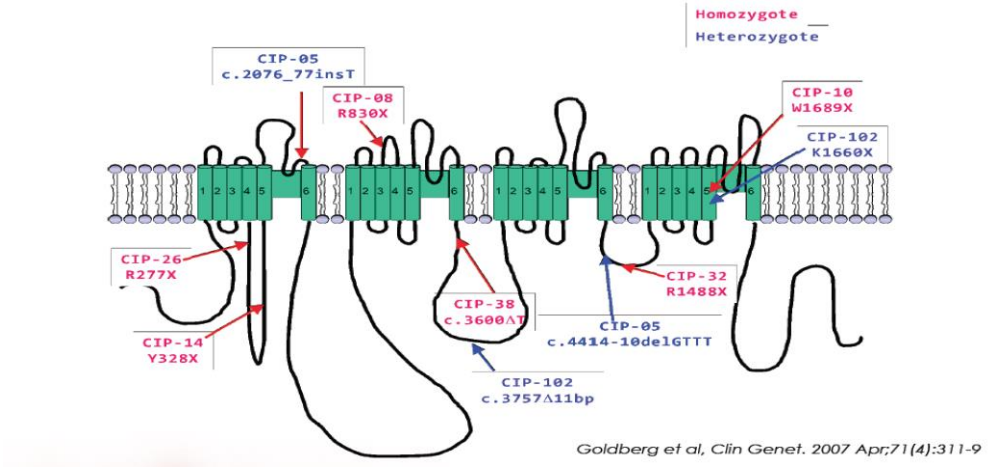
Targeting APOC3 in the Familial Chylomicronemia Syndrome

SUMMARY

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

Target Discovery

Identify new drug targets and pathways

Human Genetics

Mouse Genetics

Indication Discovery

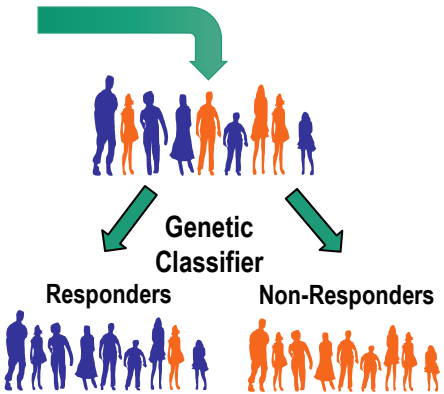
Identify new indications for drug targets and programs

Derisking

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

Biomarker

Develop pharmacogenetic markers to predict drug response



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

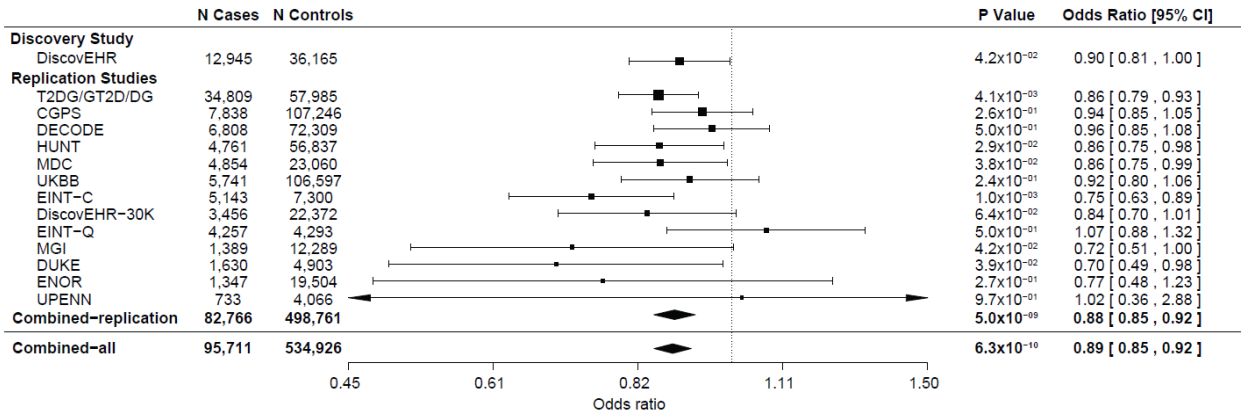
Frederick E. Dewey, M.D., Viktoria Gusarova, Ph.D., Colm O'Dushlaine, Ph.D., Omri Gottesman, M.D., Jesus Trejos, M.S., Charleen Hunt, Ph.D., Cristopher V. Van Hout, Ph.D., Lukas Habegger, Ph.D., David Buckler, Ph.D., Ka-Man V. Lai, Ph.D., Joseph B. Leader, Ph.D., Michael F. Murray, M.D., Marylyn D. Ritchie, 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*

MARCH 3, 2016

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

Summary and Conclusions

From New Yorker

"Here's my sequence..."

- "4 P's" of Precision Medicine – predictive, personalized, preemptive, participatory
- The genomic architecture of human traits and disease is a continuum from rare large effect genetic variants that cause highly penetrant monogenic diseases to many common small effect genetic variants that in aggregate influence susceptibility to common (polygenic) diseases
- A deeper understanding of the genomic architecture of human traits and disease offer opportunities for precision medicine
  - Diagnosis and novel treatments for highly penetrant monogenic diseases
  - Polygenic risk scores (PRS) to stratify patients at risk for common diseases
  - Pharmacogenetics
- Human genetics can identify novel therapeutic targets more likely to be effective and safe in man