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
• 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

Disease/Trait With Genetic Component

- Identify Gene
  - Diagnostics/Newborn screening
  - Early Prevention
  - Pharmacogenomics/Nutrigenomics

- Understand Basic Biological Defect
- Gene Therapy
- Drug Therapy
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/
Patient-Customized Oligonucleotide Therapy for a Rare Genetic Disease


- 6-year old girl with insidious onset of blindness, ataxia, seizures and developmental regression
- Work-up revealed Batten's disease due to mutations in \textit{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

- Polygenic (several genes)
  - The effect of any single gene variant is modest
- Genetic heterogeneity
  - Different or overlapping sets of genes in different families/populations

Polygenes for complex diseases will be:
- predictive (not diagnostic)
- provide insights into biology and mechanism(s) of disease
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 Resp.
- NSCLC Treatment Resp.
- Prostate Cancer
- Breast Cancer
- Aromatase Inh. Resp.
- Mammographic Dens.
- Colorectal Cancer
- Bladder Cancer
- Neuroblastoma
- Melanoma
- Cutaneous Nevi
- Basal Cell Cancer
- TPS3 Cancer Pred’n
- Ac/Ch Lymph. Leuk.
- Asparaginase Hypers.
- Follicular Lymphoma
- Lg. B-Cell Lymphoma
- Thyroid Cancer
- Glioma
- Ovarian Cancer
- Pancreatic Cancer
- Esophageal Cancer
- Nasopharyngeal Ca
- Hepatocellular Ca
- Renal Cell Ca
- Endometrial Ca
- Meningioma
- Bleomycin Sens.

- Migraine
- Angiogenic Activity
- Kawasaki Disease
- Moyamoya Disease
- Thrombosis

- MTX Pharmacokin.
- Platinum Resp.
- Chemox Suscep.
- Epirubicin Leukopenia
- Ceft Palate
- Peripat. Tooth I
- Quinrin
- Esinino
- Infl. Bc
- Celiac
- Hirsch
- Ileal C
- Bilub
- Gallistic
- 1° Scle
- Biliary
- Non-Al
- Cirhosis
- Drug I
- Acetal
- Hepati
- Hepati
- Chronic
- Hep B

- EGG In
- Coron
- Coronary Renostens
- Sudden Cardiac Dth
- Heart Failure
- Peripart. Cardiomyop.
- Atrial Fibril/”n/Flutter
- Ventricular Fibrillation
- Resting Heart Rate
- Stroke
- Intracranial Aneurysm
- Carotid Athero.

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

- Alcohol Depend.
- Methamphetamine, Dep
- Heroin Addiction
- Pain
- Pain

- Intestinal Lung Dis.
- CF Severity
- Asthma
- Chr. Rhinosinusitis
- topy
- Ivers-Johnson
- IV Setpoint/Prog.
- IV Mother/Child
- IV Replication
- D4: CDB Ratio
- Tolvirim Adv.
- Resp.
- evirine Malaria
- sprosy
- Abereulliosis
- Ieningoccocal Dis.
- gm Var Immunodef.
- 1 Diabetes
- 2 Diabetes
- iabetic Nephrop.
- iabetic Retinop.
- Letformin Trt. Resp.
- ml-St. Renal Dis.
- idney Stones
- Phosphoric Syndrome
- BMI, Waist
- 1, MetabolicTraits
- Butylcholinesterase
- Adipokine Levels
- Anorexia nervosa
- Exercise Behavior
- Fetal Growth
- Height
- Digh 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
- Hrnx/Thromb Levels
- C-Reactive Protein
- Adhesion Molecules
- Esaiophin Numbers
- Total IgG Levels
- Urine Levels, Gout
- Protein Levels
- N-Glcan Levels
- PSA Levels
- DHEAS Levels
- Folse Path. Vita.
- B-Carotene Levels
- Retinol Levels
- Vitamin D Levels
- Phosphorus Levels
- Sphingolipid Levels
- Recombination Rate
- Telomere Length
- Longevity
- Radiation Response
- Self-Rated Health
- Constit. 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

• 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?

Source: Nature Genetics
Genetic Architecture of Human Diseases and Traits

**Allele Frequency**
- Very rare: \( \leq 0.001 \)
- Rare: \( > 0.001 \) to \( < 0.005 \)
- Uncommon: \( > 0.005 \) to \( < 0.05 \)
- Common: \( \geq 0.05 \)

**Effect Size**
- Low: \( \leq 1.1 \)
- Modest: \( > 1.1 \) to \( < 1.5 \)
- Intermediate: \( > 1.5 \) to \( < 3.0 \)
- High: \( \geq 3.0 \)

- **Rare alleles causing Mendelian disease**
- **Low-frequency variants with intermediate effect**
- **Most common variants implicated in common disease by GWA**
- **Rare examples of high-effect common variants influencing common diseases/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.”

Patients with same diagnosis

Genetic test

Responders

Treat with medication

Non-responders

Adverse reactions/death

Treat with alternate medication:
Prevent lack of efficacy and adverse reactions/death
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

Preclinical Phase I Phase II Phase III Phase IV

Large-scale genomic data generation

PGx Data
Longitudinal Drug Response & Baseline "disease cohort"

Patient stratification markers

• Identify pathways and targets with increased or decreased drug response for potential follow-up programs or combination therapies

• Augment disease case/control studies for novel gene discovery
• Test PGx markers for related disease or safety phenotypes in EHR

Target Discovery & Research
Animal & Cell based models

• Identify new indications for therapeutic target

Large sequenced/genotyped patient populations linked to EHR
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 \( \rightarrow \) GENETICS!
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
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 P2Y₁₂ 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!
A Genotype-Guided Strategy for Oral P2Y$_{12}$ Inhibitors in Primary PCI

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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 either a P2Y$_{12}$ inhibitor on the basis of early CYP2C19 genotyping (genotype-guided group) or standard treatment with ticagrelor or prasugrel (standard-treatment group) for 12 months. In the genotype-guided group, carriers of 2 common CYP2C19*3 loss-of-function alleles received ticagrelor or prasugrel received clopidogrel. The two primary outcomes were net adverse clinical outcomes — defined as death from any cause, myocardial infarction, definite stent thrombosis, stroke, or major bleeding defined according to the Platelet Inhibition and patient Outcomes (PLATO) criteria — at 12 months (primary combined outcome defined for noninferiority; with a noninferiority margin of 2 percentage points or absolute difference) and PLATO major or minor bleeding at 12 months (primary bleeding outcome).

RESULTS

For the primary analysis, 2,488 patients were included: 1,242 in the genotype-guided group and 1,246 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 differences -0.7%; 95% CI, -2.0 to 0.7; P<0.001 for noninferiority).

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 respect 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, Tamoxifen
- 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

Family studies identify PCSK9 GOF as causing FH

2006

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

2012

Clinical proof of concept

2008

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

2014

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

2015

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

**Indication Discovery**
Identify new indications for drug targets and programs

**Target Discovery**
Identify new drug targets and pathways

**Biomarker**
Develop pharmacogenetic markers to predict drug response

**Derisking**
Confirm lack of “on-target adverse side effects” in drug target LOF carriers

**Human Genetics**

**Mouse Genetics**
Human Genetics Validation and Derisking of New Lipid Lowering Targets

...and T2D as a potential new indication for ANGPTL4 inhibition

- 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 ANGPTL4 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.
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 ENGL J MED 378;12 NEJM.ORG MARCH 22, 2018
"Here's my sequence..."

Summary and Conclusions

- “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