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

2003
Family studies identify PCSK9 GOF as causing FH

2006
Population studies identify PCSK9 LOF variants conferring ~88% reduction in CHD

2008
Null APOC3 mutation enriched in Amish points to cardio-protective effects

2012
Clinical proof of concept

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

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

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

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

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

**Genetic Classifier**
- Responders
- Non-Responders

**Mouse Genetics**
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 . . .
Geisinger-Regeneron DiscovEHR Collaboration

Two organizations focused on making genomic data medically actionable

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

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

Frederick E. Dewey,1,6 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. Pendergrast,2 Monica A. Giovanni,3 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. Milnaul,1 Lance J. Adams,2 Thomas N. Person,2 Kavita Praveen,1 Anthony Mareketta,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,1 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,1 William A. Faucett,2 Omri Gottesman,3 Marylyn D. Ritchie,7 Alan R. Shuldiner,1 Jeffrey G. Reid,1 David H. Ledbetter,2 Aris Baras,1 David J. Carey2*

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.
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

<table>
<thead>
<tr>
<th>Variant type</th>
<th>All variants</th>
<th>Allele frequency ≤ 1%</th>
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<tr>
<td>Single nucleotide variants</td>
<td>4,028,206</td>
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<td>Insertion/deletion variants</td>
<td>224,100</td>
<td>218,785</td>
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<td>Predicted loss of function variants</td>
<td>176,365</td>
<td>175,393</td>
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<td>Nonsynonymous variants</td>
<td>2,025,800</td>
<td>2,002,912</td>
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<td>Total</td>
<td>4,252,306</td>
<td>4,166,273</td>
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Dewey et al, Science 2016
### Lipid Therapy Targets Table

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<tr>
<th>Target</th>
<th>Agent</th>
<th>Action</th>
<th>Phase</th>
<th>Clinical effect</th>
<th>LOF carriers</th>
<th>LDL-c</th>
<th>HDL-c</th>
<th>Triglycerides</th>
<th>Total cholesterol</th>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>p, effect</td>
<td>p, effect</td>
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<td>p, effect</td>
<td>p, effect</td>
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<tr>
<td>PPARA</td>
<td>Fenofibrate</td>
<td>Agonist</td>
<td>Approved</td>
<td>Decreased triglycerides, increased HDL</td>
<td>2, 0.8</td>
<td>9 mg/dl</td>
<td>0.2</td>
<td>-28%</td>
<td>0.09 113%</td>
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<td>HMGCR</td>
<td>Atorvastatin, rosuvastatin, pravastatin, simvastatin</td>
<td>Antagonist</td>
<td>Approved</td>
<td>Decreased LDL, total cholesterol, increased HDL</td>
<td>12, 0.7</td>
<td>-4 mg/dl</td>
<td>0.3</td>
<td>9%</td>
<td>0.6 -8%</td>
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<td>NPC1L1</td>
<td>Ezetimibe</td>
<td>Antagonist</td>
<td>Approved</td>
<td>Decreased LDL</td>
<td>121, 0.03</td>
<td>-7 mg/dl</td>
<td>0.07</td>
<td>-4%</td>
<td>0.5 -3%</td>
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<td>APOB</td>
<td>mipomersen</td>
<td>Antagonist</td>
<td>Approved</td>
<td>Decreased LDL</td>
<td>80, 0.0003</td>
<td>-15 mg/dl</td>
<td>0.06</td>
<td>6%</td>
<td>0.002 -15%</td>
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<td>MTP</td>
<td>Lomitapide</td>
<td>Antagonist</td>
<td>Approved</td>
<td>Decreased LDL</td>
<td>24, 0.9</td>
<td>1 mg/dl</td>
<td>0.4</td>
<td>4%</td>
<td>0.7 3%</td>
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<td>HCAR3</td>
<td>Niacin</td>
<td>Agonist</td>
<td>Approved</td>
<td>Increased HDL, decreased triglycerides, LDL</td>
<td>107, 0.4</td>
<td>-3 mg/dl</td>
<td>0.4</td>
<td>-2%</td>
<td>0.5 4%</td>
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<td>CETP</td>
<td>anacetrapib, evacetrapib</td>
<td>Antagonist</td>
<td>Phase 3</td>
<td>Increased HDL</td>
<td>37, 0.3</td>
<td>-6 mg/dl</td>
<td>2.0x10^-6</td>
<td>23%</td>
<td>0.6 5%</td>
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<td>PCSK9</td>
<td>Alirocumab, evolocumab, bococizumab</td>
<td>Antagonist</td>
<td>Phase 3</td>
<td>Decreased LDL</td>
<td>52, 8.8x10^-6</td>
<td>-25 mg/dl</td>
<td>0.3</td>
<td>3%</td>
<td>0.03 -12%</td>
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<td>APOC3</td>
<td>APOC3 inhibitors</td>
<td>Antagonist</td>
<td>Phase 2</td>
<td>Decreased triglycerides, increase HDL</td>
<td>226, 0.3</td>
<td>-3 mg/dl</td>
<td>1.5x10^-43</td>
<td>28%</td>
<td>1.5x10^-47 -48%</td>
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<tr>
<td>ACLY</td>
<td>ATP citrate lyase inhibitors</td>
<td>Antagonist</td>
<td>Phase 2</td>
<td>Decreased LDL</td>
<td>13, 0.2</td>
<td>-14 mg/dl</td>
<td>1.0</td>
<td>0%</td>
<td>0.3 -13%</td>
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<tr>
<td>ANGPTL3</td>
<td>ANGPTL3 inhibitors</td>
<td>Antagonist</td>
<td>Phase 2</td>
<td>Decreased triglycerides, LDL, HDL</td>
<td>150, 0.0004</td>
<td>-10 mg/dl</td>
<td>0.0002</td>
<td>-8%</td>
<td>6.4x10^-15 -27%</td>
</tr>
</tbody>
</table>

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

*Dewey et al, Science 2016*
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, $p=6.3\times10^{-10}$).

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

A Protein-Truncating \textit{HSD17B13} Variant and Protection from Chronic Liver Disease


\textit{N ENGL J MED} 378;12 \textit{NEJM.ORG} MARCH 22, 2018
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.”

“Here’s my sequence...”
Pharmacogenomics

Patients with same diagnosis

Genetic test

Responders

Non-responders

Adverse reactions/death

Treat with medication

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

Target Discovery & Research
Animal & Cell based models

- Identify new indications for therapeutic target

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

Large sequenced/genotyped patient populations linked to EHR
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!
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.
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)

- **Patient**
  - LHC indicated
  - Potential indication for dual anti-platelet therapy based on indication for LHC

- **Cardiology Team**
  - Agree to TPP inclusion
  - IM or PM - Alternative Therapy Considered
  - Cardiology Fellow orders Drug of Choice

- **Research Coordinator**
  - Eligibility confirmed
  - Consent Obtained

- **Cath Lab Team**
  - CYP2C19 genotype ordered in PowerChart
  - LHC performed
  - 6 cc blood collected

- **UMMC Pathology**
  - Sample accessioned
  - Genotype result entered into Cerner
  - Results called from Call Center to Cardiology Fellow or IC

- **TGL (CLIA)**
  - Genotype Completed
  - Result Faxed

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Delivered by RC
Picked up by TGL
### University of Maryland CYP2C19 Clinical Implementation Project

<table>
<thead>
<tr>
<th></th>
<th>VA</th>
<th>UMMC</th>
<th>Total No. (%)</th>
</tr>
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<tbody>
<tr>
<td>No. Screened</td>
<td>52</td>
<td>697</td>
<td>749</td>
</tr>
<tr>
<td>No. Enrolled</td>
<td>39</td>
<td>571</td>
<td>610 (81.4%)</td>
</tr>
<tr>
<td>No. of IM/PM</td>
<td>17</td>
<td>176</td>
<td>193 (31.6%)</td>
</tr>
<tr>
<td>No. Actionable Genotypes (IM/PM w/PCI)</td>
<td>7</td>
<td>83</td>
<td>90 (14.8%)</td>
</tr>
<tr>
<td>No. of Patients w/ Actionable Genotypes Prescribed Alternate Treatment</td>
<td>6</td>
<td>43</td>
<td>49 (54.4%)</td>
</tr>
</tbody>
</table>
Might Pragmatic Clinical Trials be a Pragmatic way to Build the Evidence Base for Implementation of Pgx?

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!
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.