Amishomics: Linking Genomes to Phenomes

Alan R. Shuldiner, M.D.

John L. Whitehurst Professor of Medicine
Associate Dean and Director, Personalized Medicine Program
University of Maryland School of Medicine
What is Personalized Medicine?

Personalized 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, Personalized Medicine enables physicians to prescribe the right intervention for the right patient at the right time to prevent or treat disease.

“4 P’s” of Personalized Medicine – predictive, personalized, preemptive, participatory
Mission

To advance discovery in genomics and other “omic” sciences; to accelerate translational research and implementation of these discoveries into more effective and safe individualized health care; and to enhance the training and education of future generations of physicians and scientists.
SOM/UMMS Program in Personalized Medicine

**Evidence-based Medicine**

**Translation**

**Discovery**

**Clinical Research**

**Basic Research**

**Education**

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**PPM Translational Initiatives:**
- Expand clinical genomics services
- Implementation projects – track outcomes
  - Egs., CYP2C19/clopidogrel, cancer, ID, transplant, diabetes, preemptive genotyping in EMR
- Clinical whole genome sequencing
- Executive Personalized Health Program
- Marketing/Branding of UMMS as *The PM Institution*
- Philanthropy

**PPM Discovery Initiatives:**
- CLIA-approved Translational Genomics Lab
- Biobanks linked to EMR and “omics” databases
- BiobankUMD
- Amish Wellness Program
- VA Million Veterans Project
- Faculty Recruitment
- Create synergies (IGS, other UM Schools, FDA)
- Leverage institutional investment for new funding (grants/contracts/philanthropy)

**PPM Education Initiatives:**
- Medical students
- Graduate School (MD/PhD)
- CME
- Seminars/Symposia
- Web-based programs

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Genetics of “Typical” Common Diseases:
A complex 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
Why Study Complex Diseases in the Amish?

- A cultural isolate – traditional dress, no electricity, phones, cars
- Genetically homogeneous closed founder population
  - Complex genetics less complex
- Western/Central European in origin
- Very large extended pedigrees (mean sibship size = 7)
  - Extensive genealogical records (Fisher Book, AGD)
  - Geographically localized
The Old Order Amish:

Ongoing Genetic Studies of Complex Phenotypes at the University of Maryland

N > 5000 (40-45% of adult population)

- Diabetes/Obesity
- Osteoporosis
- OI /OPPG
- Longevity
- CVD
  - Sitosterolemia
  - Hypertension
  - Hyperlipidemia
- Thyroid Disease
- Celiac Disease
- Breast density/cancer
- Pharmacogenomics (CVD, T2D)
- Nutrigenomics
- Gut microbiome
Finding Medically Relevant Complex Disease Genes: 2006-now

Genome-wide Association Analysis

- Genotype >500,000 SNPs genome-wide in cases and controls
- Find SNPs that are more common in disease cases than in controls
- Identify gene and functional consequences of polymorphism
- Predictive testing
- Prevention
- Pharmacogenomics

Exomes/whole genomes, transcriptosomes, and metabolomes too!
Published Genome-Wide Associations
GWA at $p \leq 5 \times 10^{-8}$ for 228 traits

- Adiposity and Obesity
- Age at Menarche
- Aminotransferase Levels
- Arterial Stiffness
- Bone Mineral Density
- Bilirubin Levels
- Carotid IMT
- Coronary calcification
- Glucose Homeostasis
- Heart Rate
- Height
- Hypertension Susceptibility
- Lipid Levels
- Matrix Metalloproteinase
- Metabolic Profile
- Non-alcoholic Fatty Liver Disease
- Platelet Count
- Response to Clopidogrel (Plavix)
- Renal Function
- Type 2 Diabetes
- Uric Acid Levels/Gout
TG Excursion During High Fat Load is Highly Variable Among HAPI Heart Study Subjects
GWAS for Fasting TG and TG Excursion during a High Fat Meal

Pollin (2008) Science
**APOC3 R19X**

*(Carrier Frequency: 5%)*

![Graph showing the relationship between APOC-III and fating TGs.](image)

- **Graph 1:**
  - Points represent different samples.
  - Each point is color-coded by genotype: RR (CC) and RX (CT).
  - A line connects the points to show trends.
  - The correlation coefficient (r) is 0.71, with a p-value of 0.0002.

- **Graph 2:**
  - Shows the change in triglycerides (mg/dl) over time (hours).
  - Two lines represent different genotypes: RR (CC) and RX (CT).
  - Time is on the x-axis, and triglycerides are on the y-axis.

- **Graph 3:**
  - Scatter plot showing the relationship between age and CAC.
  - Age is on the x-axis, and CAC is on the y-axis.

*Pollin (2008) Science*
**APOC3 R19X, Cardioprotection and Lifespan**

**Implications:**
- Atkins-like diet “healthy” for 5% of the Amish population?
- APOC3 inhibitors/antagonists will be effective and safe TG lowering agents and may even increase lifespan (reverse pharmacogenomics)

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*All descendants of MRCA (38/409 died ≥ 90 years old)*

*Inferred R19X descendants of MRCA (10/44 died ≥ 90 years old)*

\[ P = 0.01 \]
What areas of Personalized Medicine is ripe for translation to patient care today?

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…”

*From New Yorker*
Pharmacotherapy Today: One size fits all

Patients with same diagnosis

Treat all with the same medication

70% Good response

25% Lack of response: Recurrent disease

5% Adverse reactions

0.01% Death

Increased morbidity, mortality and health care costs

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$\text{University of Maryland}
\text{School of Medicine

PGRN}$
Pharmacogenomics

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
• Anti-platelet agent
• Effective (with aspirin) for prevention of MI and stroke, and thrombosis prevention coronary stent placement and angioplasty
• In 2005, world’s 2nd highest selling drug
  – U.S. sales $5.9 billion
• Acts by binding to ADP receptors on platelets, preventing platelet aggregation and thrombosis
• Great variability in response to clopidogrel
  – 4 - 32% of individuals are resistant
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

Heritability of clopidogrel response = 0.7 \( \rightarrow \) GENETICS!

Shuldiner et al (2009) JAMA
PAPI-1: Clopidogrel Response GWAS to Functional Variant to Clinical Outcome

PLAVIX (clopidogrel bisulfate) tablets
Initial U.S. Approval: 1997

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)
PAPI-2 Study

Consent all potential PCI patients

Cath Lab $\rightarrow$ Stent placed $\rightarrow$ Eligibility confirmed

Randomize

Genotype Directed Arm (n = 3600)

Genotype patient

IMs

PMs

EMs, UMs

Dual anti-platelet therapy agent selected by prescribing physician

DNA

Optional platelet aggregation 10 days after Randomization Visit

Prasugrel 5-10 mg/d plus asa

Clopidogrel 75 mg/d plus asa

Monitor for CV outcomes and AEs at 3, 6, 9 and 12 months

1° CV events

2° Adverse events/bleeding

Post treatment platelet aggregation

Pharmacoeconomic analysis

GWAS and exome sequencing - new gene discovery

Retrospectively genotype after follow up is complete
Team Science!

Jessica Albert
Amber Beitelshees
Y. Christy Chang
Coleen Damcott
Adam Fisch
Susan Fried
Mao Fu
Da-Wei Gong
Nicole Hoppman
Richard Horenstein
Hong Hu
Joshua Lewis
Jie Liu
Patrick McArdle
Daniel McBride
John McLenithan
Braxton Mitchell
Jeffrey O'Connell
Afshin Parsa
Kathleen Palmer
Toni Pollin
Evadnie Rampersaud
Laurie Reinhart
Kathy Ryan

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John Shelton
Haiqing Shen
Julia Shi
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