Genomic and Genetic Medicine in the Clinical Setting
Objectives

- Define genomic and genetic medicine
- Introduce molecular genetic testing
- Outline clinical applications including those for:
  - Mendelian disease
  - Common complex disease
  - Pharmacogenetics
What does it mean to say genomic or genetic medicine?

“an emerging medical discipline that involves using genomic information about an individual as part of their clinical care (e.g., for diagnostic or therapeutic decision-making)”
THE PRECISION MEDICINE INITIATIVE
**WHAT IS IT?**

**Precision medicine** is an emerging approach for disease prevention and treatment that takes into account people’s individual variations in genes, environment, and lifestyle.

The Precision Medicine Initiative will generate the scientific evidence needed to **move the concept of precision medicine into clinical practice.**
Precision medicine is not a new concept

• Tailor anti-hypertension therapy to the individual

• Prescribe the appropriate antibiotic for a given infection (or choose not to prescribe)

• Vaccinate based on an individual’s age and risk factors

• Screen for cancer based on age, family history and risk factors
Precision Medicine

- Clinical history
- Physical Exam
- Data collection through laboratory or imaging studies
- Family history

- Evaluate for variation in drug metabolism
- Evaluate for mendelian conditions
- Genomic risk assessment for common disease

Pharmaco-genomics

Genomic profile

Medicine

SANFORD ImageGenetics
Why Now?

- Human genome has been sequenced
- Biomedical analytics have improved
- Management of large datasets is feasible
Costs declining

**Cost per Genome**

- $100M
- $10M
- $1M
- $100K
- $10K
- $1K

Moore's Law

NIH National Human Genome Research Institute

genome.gov/sequencingcosts

SANFORD imagenetics
How can we get genomic information?

• Genotyping

• Sequencing
  – Single Gene Sequencing
  – Panel-based Sequencing
  – Whole exome sequencing
  – Whole genome sequencing
Genotyping vs Sequencing

• Genotyping
  – detection of genetic variants at specific locations in the genome
  – “comparing difference between two books”

• Sequencing
  – determines exact sequence of a given length of DNA
  – “reading the entire book”
Whole exome vs. whole genome

• Whole exome sequencing
  – Evaluates only the protein coding regions of the genome (exons)

• Whole genome sequencing
  – Evaluates entire genetic code (introns and exons)
Variant Interpretation

• Evaluation of peer-reviewed literature related to variant

• Comprehensive review of available databases

• Application of in-silico prediction models
Databases reviewed

Population databases:
- 1000 Genomes (http://browser.1000genomes.org)
- NHLBI GO Exome Sequencing Project (ESP) (http://evs.gs.washington.edu/EVS)

Disease databases:
- ClinVitae (http://clinvitae.invitae.com)
- Online Mendelian Inheritance in Man (OMIM) (http://www.omim.org)
- Human Gene Mutation Database (HGMD) (http://www.hgmd.org)
- Human Genome Variation Society (HGVS) (http://www.hgvs.org)
- Leiden Open Variation Database (LOVD) (http://www.lovd.nl)
- DECIPHER (http://decipher.sanger.ac.uk)

Sequence databases:
- Locus Reference Genomic (LRG) (http://www.lrg-sequence.org)
- MitoMap (http://www.mitomap.org/MITOMAP/HumanMitoSeq)
<table>
<thead>
<tr>
<th>Population data</th>
<th>Supporting</th>
<th>Supporting</th>
<th>Moderate</th>
<th>Strong</th>
<th>Very strong</th>
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<tbody>
<tr>
<td>MAF is too high for disorder BA1/BS1 OR observation in controls inconsistent with disease penetrance BS2</td>
<td>Absent in population databases PM2</td>
<td>Novel missense change at an amino acid residue with a different pathogenic missense change has been seen before PM5</td>
<td>Protein length changing variant PM4</td>
<td>Same amino acid change as an established pathogenic variant PS1</td>
<td>Predicted null variant in a gene where LOF is a known mechanism of disease PVS1</td>
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<tr>
<th>Computational and predictive data</th>
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<tr>
<td>Multiple lines of computational evidence suggest no impact on gene/gene product BP4</td>
<td>Multiple lines of computational evidence support a deleterious effect on the gene/gene product PP3</td>
<td>Novel missense change at an amino acid residue with a different pathogenic missense change has been seen before PM5</td>
<td>Protein length changing variant PM4</td>
<td>Same amino acid change as an established pathogenic variant PS1</td>
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<td>Well-established functional studies show no deleterious effect BS3</td>
<td>Missense in gene with low rate of benign missense variants and path. missenses common PP2</td>
<td>Mutational hot spot or well-studied functional domain without benign variation PM1</td>
<td>Well-established functional studies show a deleterious effect PS3</td>
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<tbody>
<tr>
<td>Nonsagregation with disease BS4</td>
<td>Cosagregation with disease in multiple affected family members PP1</td>
<td>Increased segregation data</td>
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<table>
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<tbody>
<tr>
<td>De novo (without paternity &amp; maternity confirmed) PM6</td>
<td>De novo (paternity and maternity confirmed) PS2</td>
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<tr>
<td>Observed in trans with a dominant variant BP2</td>
<td>Observed in cis with a pathogenic variant BP2</td>
<td>For recessive disorders, detected in trans with a pathogenic variant PM3</td>
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<tr>
<td>Reputable source w/o shared data = benign BP6</td>
<td>Reputable source = pathogenic PP5</td>
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<th>Strong</th>
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</thead>
<tbody>
<tr>
<td>Found in case with an alternate cause BP6</td>
<td>Patient’s phenotype or FH highly specific for gene PP4</td>
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</table>

**Figure 1 Evidence framework.** This chart organizes each of the criteria by the type of evidence as well as the strength of the criteria for a benign (left side) or pathogenic (right side) assertion. Evidence code descriptions can be found in Tables 3 and 4. BS, benign strong; BP, benign supporting; FH, family history; LOF, loss of function; MAF, minor allele frequency; path., pathogenic; PM, pathogenic moderate; PP, pathogenic supporting; PS, pathogenic strong; PVS, pathogenic very strong.
Five-tier classification system

**Pathogenic:** This sequence change directly contributes to the development of disease.

**Likely pathogenic:** This sequence change is very likely to contribute to the development of disease; however, the scientific evidence is currently insufficient to prove this conclusively.

**Uncertain significance:** There is not enough information at this time to support a more definitive classification of this sequence change.

**Likely benign:** This sequence change is not expected to have a major effect on disease; however, the scientific evidence is currently insufficient to prove this conclusively.

**Benign:** This sequence change does not cause disease.
Categories of Genomic Medicine

- Mendelian conditions
  - Single Mendelian variants of large effect

- Polygenic complex conditions
  - Multiple risk variants each with small effect

- Pharmacogenetic variation
  - Genetic variants of drug metabolism

- Cancer genomics
  - Sequence variation between tumor and normal cells
Spectrum of Genetic Disease

Variant Frequency

Effect Size

- Large
  - Mendelian disease
  - Carrier testing
- Small

Variant Frequency

- Very rare
- Common

Targeting testing, sequencing

Genotyping, GWAS

Coronary Artery Disease

- Three known genes PCSK9, APOB, LDLR
- Early onset CAD
- May be resistant to typical lipid therapy
- Genetic testing can identify affected, inform:
  - Screening
  - Treatment
  - Testing of at-risk family members

- ~ 60 genetic risk variants known
  - PCSK9 included
- Later onset CAD
- Lifestyle significant contributor
- Genomic risk may inform:
  - Screening
  - Treatment

Categories of Genetic Medicine

• Mendelian conditions

• Polygenic complex conditions

• Pharmacogenetic variation
MENDELIAN CONDITIONS
Rare Disease in the U.S.

- 30 million people in the United States are living with rare diseases

- ~1 in 10 Americans or 10% of the U.S. population
  - 80% of rare diseases are genetic
  - 50% are adults

Global genes: Allies in Rare Disease, https://globalgenes.org/rare-diseases-facts-statistics/
Genetic conditions with common phenotype

- Familial Hypercholesterolemia: 1 in 200
- Lynch Syndrome: 1 in 440
  - Individuals with colon cancer: 1 in 30
- BRCA Mutation: 1 in 400
  - Women with breast cancer (any age): 1 in 50
  - Women with breast cancer (< 40 years): 1 in 10 (10%)
  - Men with breast cancer (any age): 1 in 20 (5%)
  - Women with ovarian cancer (any age): 1 in 8 to 1 in 10 (10%–15%)
FAMILIAL HYPERCHOLESTEROLEMIA

- Inherited disorder characterized by markedly elevated LDL cholesterol leading to premature cardiovascular disease
- Multiple genes with both homozygous and heterozygous disease states

- Largely under recognized in the United States
- Presentation can vary depending on whether an individual is homozygous or heterozygous for a mutation in LDLR, APOB, or PCSK9

Untreated FH leads to 20X increase in heart disease risk

- LDL levels can vary widely in people with same mutation
- Cascade screening may reveal carriers of mutation who don’t meet clinical criteria
  - Treatment still appropriate due to lifetime exposure to LDL

1:200 estimated prevalence in the US:
- 90% are undiagnosed
Approach to genetic testing

1. Consider retesting the person who best meets diagnostic criteria when new genes are known.
2. Provide feedback to genetic testing laboratory when segregation testing results are available.
3. See screening guidelines for healthy at-risk individuals.

From GeneReviews Hypertrophic Cardiomyopathy 2016.
How do we find these people?

- **Family history**
  - Early onset conditions
  - Multiple generations affected with similar condition

- **Individuals who present with**
  - Early onset conditions
  - Multisystemic condition
Referrals to Adult Genetics Clinic

- **Cancer**
  - Breast, ovarian, endometrial, colorectal, pancreatic, kidney
- **Neurological disorders**
  - Ataxia, myopathy, muscular dystrophy, sensory and/or motor neuropathy, motor neuron disease, dementia
- **Gastrointestinal disorders**
  - Polyposis, pancreatitis
- **Cardiovascular disorders**
  - Connective tissue, cardiomyopathy, hyperlipidemia
- **Reproductive concerns**
  - Miscarriage, infertility, pre-conception, pre-natal
- **Other**
  - PM&RS, Nephrology, Pulmonology, Eye, Pharmacy, Dermatology, Dental, Pathology, Radiology
COMMON COMPLEX DISEASE
Common Disease Complexity

Elevated Risk

Environment
- Pathogens
- Chemicals
- Smoking
- Diet
- Sun exposure

Elevated Risk

Epigenetic, post-genomic and regulatory events
- Gene rearrangements
- Somatic mutations
- Messenger RNA splicing
- Methylation
- Retroviral Signals
- MicroRNAs

Elevated Risk

Genome variants
- Single nucleotide polymorphism
- Copy number variation
- Insertion-deletion polymorphisms
- Disease modifier genes
- Disease susceptibility genes

Greatest Risk

Genetics of common disease

• Substantial heritable components exist for common disease (eg. CHD)

• Identifying genetic variants that quantify that heritability could help with screening and prevention

• Genome wide association (GWA) studies have identified many of these variants
What is GWA?

• **Genome Wide Association** – analysis of the entire genome at one time with fine resolution, VERY fast

• Technology makes available the ability to genotype 700,000 to 2,500,000 SNPs per subject at $50-$175

• Computer methods to analyze a dataset of this size have become available
The Genomewide Association Study

A

Chromosome 9

SNP1

SNP2

Person1

Person2

Person3

G-C → T-A

A-T → G-C

B

Cases

Initial discovery study
P=1×10^{-12}

Controls

Cases

Initial discovery study
P=1×10^{-8}

Controls

Common homozygote
Heterozygote
Variant homozygote

C

-Log_{10} P Value

Chromosome

0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22

SNP1

SNP2

-Log_{10} P Value

0 2 4 6 8 10 12 14

Position on chromosome 9

0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22
Meta-Analysis of Genomewide Association Studies

Replications: Study 1
Replications: Study 2
Replications: Study 3

Meta-analysis

Why does finding the genes help?

- Developing specific therapies
- Understanding mechanisms
- Genetic screening to identify high risk individuals
- Identify prevention approaches
Coronary heart disease

- Family history is a well-established independent risk factor for CHD
  - Framingham:
    - Men: 2.4x increased risk for heart disease
    - Women: 2.2x increased risk for heart disease
  - Interheart: 1.5x increased risk for heart disease

- Twin and family studies have proven 40-50% of susceptibility to CHD is heritable
  - The frequency of CHD in monozygotic twins is ~ 44% vs 14% in dizygotic twins based on the Danish twin registry study

GWAS have led to success in identification of CHD SNPs

CHD-related SNPs by Mechanism

- LDL
- HDL
- TG
- MI
- HTN
- Unknown

CHD-related SNPs by Year

- 2007
- 2009
- 2010
- 2011
- 2012
- 2015

Quantifying Genomic Risk

- Genetic risk score
  - Genotype for known risk SNPs
  - Calculate a score based on the presence of the risk SNP weighted by associated risk
CHD genomic variants as additional screening tool

• 15-20% of myocardial infarctions occur in individuals considered to be at low risk based on conventional risk factors

• Improved screening with genomic variants has the potential to improve risk prediction

Genetic risk, coronary heart disease events, and the clinical benefit of statin therapy: an analysis of primary and secondary prevention trials.

Meghji J1,2, Stitziel NO2, Smith JG3,4, Chasman DI5, Caulfield M6, Devlin J7, Nordio F1, Hyde C8, Cannon CP1, Sacks F5, Poulter NR10, Sever PS10, Ridker PM11, Braunwald E1, Melander O12, Kathiresan S4, Sabatine MS3.

Abstract

BACKGROUND: Genetic variants have been associated with the risk of coronary heart disease. In this study, we tested whether or not a composite of these variants could ascertain the risk of both incident and recurrent coronary heart disease events and identify those individuals who derive greater clinical benefit from statin therapy.

METHODS: A community-based cohort study (the Malmö Diet and Cancer Study) and four randomised controlled trials of both primary prevention (JUPITER and ASCOT) and secondary prevention (CARE and PROVE IT-TIMI 22) with statin therapy, comprising a total of 48,421 individuals and 3477 events, were included in these analyses. We studied the association of a genetic risk score based on 27 genetic variants with incident or recurrent coronary heart disease, adjusting for traditional clinical risk factors. We then investigated the relative and absolute risk reductions in coronary heart disease events with statin therapy stratified by genetic risk. We combined data from the different studies using a meta-analysis.

FINDINGS: When individuals were divided into low (quintile 1), intermediate (quintiles 2-4), and high (quintile 5) genetic risk categories, a significant gradient in risk for incident or recurrent coronary heart disease was shown. Compared with the low genetic risk category, the multivariable-adjusted hazard ratio for coronary heart disease for the intermediate genetic risk category was 1.34 (95% CI 1.22-1.47, p < 0.001) and for the high genetic risk category was 1.72 (1.55-1.92, p < 0.001). In terms of the benefit of statin therapy in the four randomised trials, we noted a significant gradient (p = 0.0277) of increasing relative risk reductions across the low (13%), intermediate (29%), and high (48%) genetic risk categories. Similarly, we noted greater absolute risk reductions in those individuals in higher genetic risk categories (p = 0.0101), resulting in a roughly threefold decrease in the number needed to treat to prevent one coronary heart disease event in the primary prevention trials. Specifically, in the primary prevention trials, the number needed to treat to prevent one such event in 10 years was 66 in people at low genetic risk, 42 in those at intermediate genetic risk, and 25 in those at high genetic risk in JUPITER, and 57, 47, and 20, respectively, in ASCOT.

INTERPRETATION: A genetic risk score identified individuals at increased risk for both incident and recurrent coronary heart disease events. People with the highest burden of genetic risk derived the largest relative and absolute clinical benefit from statin therapy.

FUNDING: National Institutes of Health.

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Higher GRS associated with increased risk for coronary heart disease

<table>
<thead>
<tr>
<th>Genetic risk score category</th>
<th>Hazard ratio (95% CI)</th>
<th>p value</th>
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<tr>
<td>Low risk</td>
<td>Reference</td>
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</tr>
<tr>
<td>Intermediate risk</td>
<td>1·34 (1·22–1·47)</td>
<td>&lt;0·0001</td>
</tr>
<tr>
<td>High risk</td>
<td>1·72 (1·55–1·92)</td>
<td>&lt;0·0001</td>
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Number Needed to Treat Declines with Increasing GRS

- NNT declined in individuals with increasing GRS
- Target treatment to those who derive greatest benefit

<table>
<thead>
<tr>
<th>GRS</th>
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<tr>
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<td>57</td>
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<tr>
<td>Intermediate</td>
<td>42</td>
<td>47</td>
</tr>
<tr>
<td>High</td>
<td>25</td>
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Barriers to implementation

- Clinical guidelines do not exist to use this type of screening
- Most variants have been identified in Caucasian males
  - Additional studies in more diverse populations required
- Risk prediction has not exceeded performance of existing clinical predictors
  - Reclassification likely a better measure
PHARMACOGENETICS
PHARMACOGENETICS

= How genes affect a person’s response to drugs
Pharmacogenetics

- Nearly every pathway of drug metabolism, transport and action is influenced by genetic variation
- FDA requires genetic info on package inserts for ~160 medications
- Prescription guidelines based on genetic information exist for ~20 medications
CPIC

• Clinical Pharmacogenetics Implementation Consortium (CPIC)
• Goal is to address some of the barriers to implementation of pharmacogenetic tests into clinical practice
• CPIC guidelines are peer-reviewed and published in a leading journal
• CPIC provides guidelines that enable the translation of genetic laboratory test results into actionable prescribing decisions for specific drugs
• Guidelines center on genes or around drugs
Types of Metabolizers

- Ultra rapid metabolizer (UM)
- Extensive normal metabolizer (EM)
- Intermediate metabolizer (IM)
- Poor metabolizer (PM)

For some antidepressants...

- Ultra rapid metabolizer (UM) → Lack of response
- Extensive normal metabolizer (EM) → Expected response
- Intermediate metabolizer (IM) → Exaggerated response
- Poor metabolizer (PM) → Adverse effects

Genotyping to identify an individual’s metabolism can help to minimize adverse events and increase drug efficacy.
The Plavix Story...

- Bioactivated by cytochrome P450 2C19
- CYP2C19 is the gene encoding this cytochrome
- Variation in this gene can affect how well the enzyme works
- 1 abnormal copy = reduced enzyme activity
- 2 abnormal copies = no enzyme activity
- ~20% have at least one abnormal copy = “Plavix non-responder”

Primary efficacy outcome = death from cardiovascular causes, MI or stroke
Prospective Clinical Implementation of CYP2C19 Genotype Guided Antiplatelet Therapy After PCI: a Multi Site Investigation of MACE Outcomes in a Real-World Setting

IGNITE Pharmacogenetics Interest Group
AIM:

Compare risk for major adverse cardiovascular events (MACE) in post-PCI patients using CYP2C19 guided antiplatelet therapy
Prospective multi-center investigation of clinical CYP2C19 genotype-guided antiplatelet therapy post-PCI

- Alternative antiplatelet therapy recommended in CYP2C19 Loss of function (LOF)
- No genotype-guided recommendations in NON-LOF
- 7 sites contributed data on patients who underwent PCI and genotyping for primary analysis
  - Sanford Health under the leadership of Dr. Russ Wilke and Dr. Eric Larson
MACE stratified by genotype and treatment of choice

Log-rank $p=0.016$

Unadjusted HR: 2.30
CI (1.17–4.52), $p = 0.015$

**LOF = Loss of function**
Genotype-guided approach to antiplatelet therapy in the real world is feasible.

In patients with CYP2C19 LOF, CV outcomes can be improved when clinical genotype made available and alternative therapy prescribed early after PCI.
Barriers to implementation

• Clinical guidelines for many drug-gene interactions are still evolving

• Clinical outcomes data does not yet exist for many drug-gene interactions
Genomic Medicine in the Clinic

- Genomic information is becoming more readily available
- Diagnostic tools have improved our ability to diagnose rare disease
- Several applications to use genomics in the clinical setting are emerging
- There are limitations, thus we need to proceed with caution when using this data
QUESTIONS?