The Heart of the Matter: Genomics and Cardiovascular Disease
Suburban Hospital
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Leslie G. Biesecker, MD
Individualized Medicine

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• Apply treatments that are more likely efficacious and less likely toxic
• Prophylaxis for diseases not yet manifesting
• Suspend futile treatments
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• Apply treatments that are more likely efficacious and less likely toxic
• Prophylaxis for diseases not yet manifesting
• Suspend futile treatments
• Requires ability to make predictions at the level of the individual
Health Predictions

• Need ability to assay an attribute of patient that defines occult disease or future risk
  – Commonly done: physical signs
Scientific Predictions

“Occurrences in this domain are beyond the reach of exact prediction because of the variety of factors in operation, not because of any lack of order in nature.”

*Albert Einstein*
Scientific Predictions

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• “Prediction is very difficult, especially if it's about the future.”
  
  *Niels Bohr*
Health Predictions

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• Why not for heritable disorders?
  – Need assay to broadly assess risks
  – Until recently it was technically impossible
Genetic Variation & Penetrance

Penetrance vs Frequency

- Common SNPs
- Rare Mendelian
Genetic Variation & Penetrance

Penetrance

Frequency

0

.00005

.0005

.005

.05

.5

Common SNPs

Unknowable

Mendelian

Rare

1
Genetic Variation & Penetrance

- **Penetrance**
  - Rare
  - Mendelian
  - Unknown
  - Common SNPs

- **Frequency**
  - Unknowable
  - .00005
  - .0005
  - .005
  - .05
  - .5
Common vs Rare Variants

• Common variants
  – Relatively easy to assay & analyze
  – Associations require huge cohort sizes
  – Useful for understanding pathophysiology

• Rare variants
  – Recently easier to assay – tricky to analyze
  – Associations require smaller cohorts
  – Useful for individual predictions
Anatomy of a Gene

- Common variants not in genes
- Rare, high penetrance variants: 80-90% mutations in coding exons of genes
- ~20,000 genes
- 300,000 exons: exome
- Coding exons of genes 1-2% of DNA
Genome/Exome Sequencing

SureSelect™ Target Enrichment System Capture Process

NGS Kit

Genomic Sample (Set of chromosomes)

SureSelect HYB BUFFER

Genomic Sample (PREPPEd)

Biotinylated RNA Library "Baits"

Hybridization

Streptavidin Coated Magnetic Beads

Unbound Fraction Discarded

Wash Beads and Digest RNA

Bead Capture

Amplify

Sequencing

ClonSeq™
• Good news!
• Sequence whole genome or 6-8 exomes in ~ 3 days
• Cost falling
  – $10,000 genome
  – < $1,000 exome
• Can evaluate nearly all genes
Sequencing Instruments

- *Bad* news!
- Generates huge amounts of variants
  - ~3,000,000 per genome
  - ~30,000 per exome
- Interpretation
  - Currently small fraction can be interpreted
ClinSeq™: A Translational Research Project in Clinical Genomics

Medical & Statistical Genetics

NIH Clinical Center

Suburban

NHLBI

NIH Intramural Sequencing Center
Approach

• Phenotype 1,000 subjects
• Bin by Framingham score (250 each)
  – (<5%, 5-10%, >10%, disease)
• Sequence exome/genome
• Follow-up studies
• Interpret variants and validate some
• Return results
Eligibility – Phase I

- Age 45-65 years
- Any race, ethnicity, both sexes
- Non-smoker
- Have primary care physician
- Willing to consider follow-up ~ 10 years
- Does **not** have access to genetic data
Clinical Evaluations

- Brief history
- Family history
- Ht, Wt, BP, HR, Abd circ
- ECG
- ECHO
- CT coronary calcium
- Chemistries
Clinical and Research Testing

Fasting lipid panel: LIPI2 (Total Chol, Trigl, HDL Chol, LDL Chol)
Direct LDL: LDLD1
Chem20: CH20
Fasting insulin: INSUL
Lipoprotein electrophoresis: LIPOE
C-peptide: CPEPT
IGF-1: SOMC2
Estradiol: ESTS1
Progesterone: PGSN1
Testosterone: TTST1
ApoA1 and ApoB: APOAB
Homocysteine: HCYSP
HbA1C: A1C
Fibrinogen: FIBGA

CBC: CBC
Pro-BNP: BNP1
Troponin I: TROP1
C-reactive protein: CRPHS (high sensitivity CRP)
Factor 7: FVIIS
Plasminogen activator inhibitor-1 (send out)
Thyroid panel: THYR2
DNA isolation (CLIA)
Urinalysis
Urine microalbumin
Research bloods:
DNA isolation (40 ml)
RNA isolation
LCL line
Plasma for research archiving (plasma from DNA tubes)
How do you Practice Predictive Cardiology?

• Pilot project – screen 572 exomes for:
  – 41 genes for cardiomyopathy
    • Arrhythmogenic right ventricular cardiomyopathy/dysplasia
    • Dilated cardiomyopathy
    • Hypertrophic cardiomyopathy
    • Left ventricular noncompaction
  – 22 genes for rhythm disorders
    • Atrial fibrillation
    • Brugada syndrome
    • Catecholaminergic polymorphic ventricular tachycardia
    • Long-QT syndrome
    • Short-QT syndrome
Variant Filtering

- 950 cardiomyopathy gene variants
- 245 rhythm gene variants

Filtering/exclusion based on
- Sequence quality
- Frequency
- Mutation types
- Publications
Six Pathogenic Variants

• Dilated cardiomyopathy
  – PLN p.Leu39X

• Hypertrophic cardiomyopathy
  – MYBPC3 IVS16+1G>A & MYH7 p.Arg787Cys

• Long QT syndrome
  – KCNE1 p.Arg98Trp
  – KCNE1 p.Thr10Met
  – SCN3B p.Leu10Pro
Clinical Correlates

- No current evidence cardiomyopathy
- Several with family history unexplained cardiac death
- SCN3B p.Leu10Pro
  - Late 40’s female with unexplained syncope
  - LBBB s CAD or other cardiac disease
  - QTc 493 ms
  - Child with unexplained palpitations
What is Going on Here?

• An cohort *unselected for cardiomyopathy, dysrhythmia, family history of sudden death*

• Sequenced all genes for these traits without a clinical indication

• >1% have a pathogenic mutation in 1 of 63 genes
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• Ordered test for every known gene
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  - Why do we demand that people die before we test?
Dyslipidemias

- 65 yo female
- High cholesterol diagnosed at 25 years
- RX: atorvastatin, ezetimibe, hctz, lisinopril, niacin
- Coro Ca⁺⁺ 1,726
- Chol 172, Trig 50, HDL 75
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- Coro Ca++ 1,726
- Chol 172, Trig 50, HDL 75
- LDLR known pathogenic mutation
- Family members diagnosed & treatment started
Leveraging Genomics

- Exome unnecessary to manage proband
- 4-8 undiagnosed relatives per proband
- Years of life added at small marginal cost
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- Need to move toward this practice
- Policy implication – lowers effective cost of sequencing
Total Results To Date

- 8 high penetrance cancer syndromes
- 6 cardiomyopathy/dysrhythmias
- 9 dyslipidemias
- 2 malignant hyperthermia
- 3 neuropathies
- 1 occult metabolic disorder
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• Just scratching surface - 5% have a ‘rare’ mendelian disorder
What Else is There to be Found?

- Other dominant traits – hundreds
- Pharmacogenetics
- Carrier states
It Looks Easy
Individualized Medicine Criticisms

• Heredity not great at predicting...

• Penetrance wildly overestimated...
Multiple Testing Problem

• High probability of false positive test results
  – Sequencing: ~1,000 variants in cardiomyopathy/rhythm genes
  – Clin Pathology: 5th to 95th centile norms
  – Imaging: High frequency of incidentals
Are Patients Ready for This?

- Genome generates enormous results
- Managing information overload essential
- Will need to develop new practices for this
- To develop these, we need to know what the patients think, want & use
Motivations Study (322)

- Qualitatively assessed motivations to join ClinSeq™
- A desire to further research (altruism)
- To learn about one’s health (personal gain)
- *Not* an analog study

Facio F, et al EJHG 2011
Preferences to Learn Results (311)

• Assessed preferences to learn results from WES/WGS in ClinSeq™ at baseline and following consent
• Divided results into 4 broad categories
• Qualitative & Quantitative approaches
Qualitative

• 294 said they wished to learn results and six were uncertain

• Most expressed an interest in prevention, stating they may be better equipped to prevent the onset of a disease

• Some were specific about a prevention related intent to alter their medical management or improve their diet/exercise
Qualitative (cont.)

• About 1/3 had general health information curiosity, “all knowledge is positive”
• Another 1/3 wanted results to inform family
• Most had a specific condition in mind, predominantly heart disease – this is a big issue
Quantitative

- ClinSeq™ participants enthusiastic about learning all four types of results
- Yet they differentiate among the types
- Most eager to learn actionable results for their health and relatives
- Interest in uncertain results suggest they view utility in having the information
Knowledge: N=311

- Adapted a validated genetics knowledge tool for genomics
- Assessment tool pre & post counseling
  - Unsurprising: Knowledge correl with educ, income, race/ethnicity. Surprising: low CVD risk
  - Knowledge incr sign post consent for 10/11 items
    - 11th item ceiling effect
Big Picture

- Diagnostic abilities less than perceived
- Trial and error medicine
- Prediction at individual level poor
  - Disease susceptibility
  - Disease severity & course
  - Treatment efficacy
  - Treatment side effects
- A little improvement > a big advance
Going Forward

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  – Tighten relationship genotype – phenotype
  – Develop & test approaches to presymptomatic management
  – Build infrastructure and methods for managing information
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• Genomes & exomes being done clinically
  – You will soon begin seeing patients who have had this
The groundhog is like most other prophets; it delivers its prediction and then disappears. *Bill Vaughan*