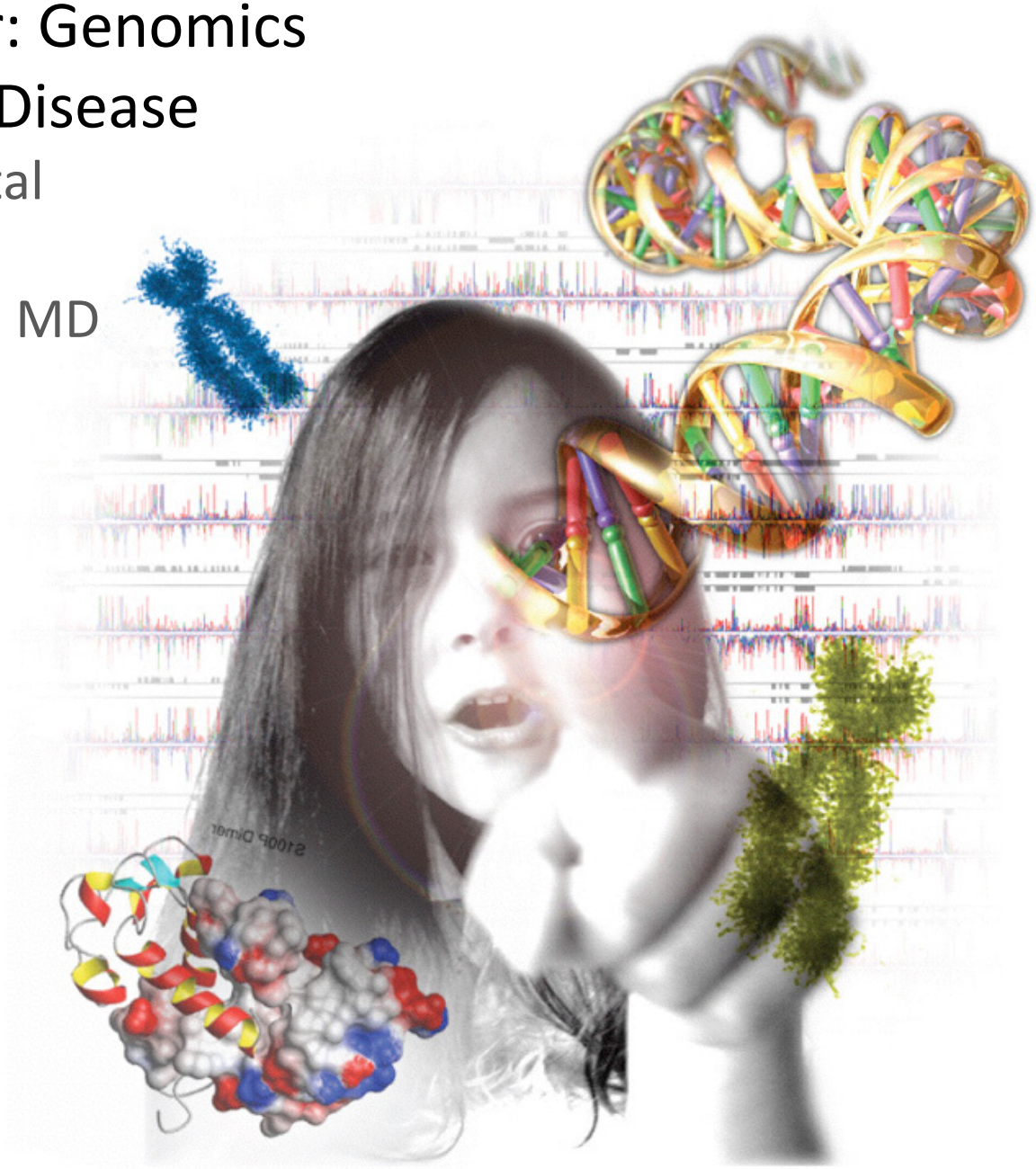
The Heart of the Matter: Genomics and Cardiovascular Disease

Suburban Hospital

July 13, 2012

Leslie G. Biesecker, MD



Individualized Medicine

- The objective is to customize care based on individual risks, not population risks
- Apply treatments that are more likely efficacious and less likely toxic
- Prophylaxis for diseases not yet manifesting
- Suspend futile treatments

ClinSeq™

Individualized Medicine

- The objective is to customize care based on individual risks, not population risks
- 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*

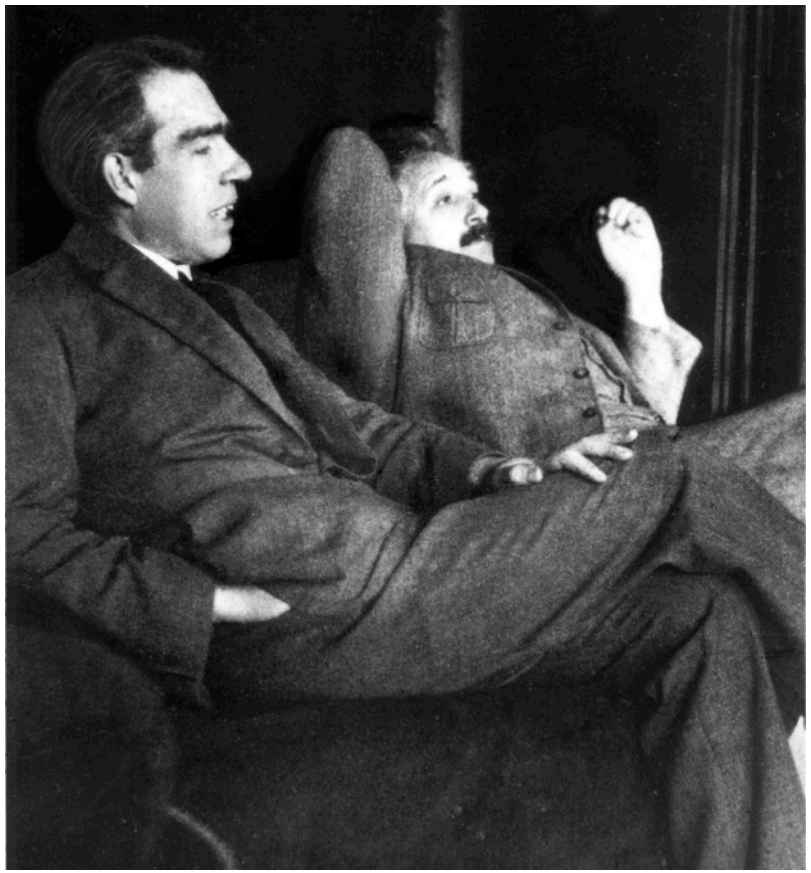
ClinSeq™

Health Predictions

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

ClinSeq™

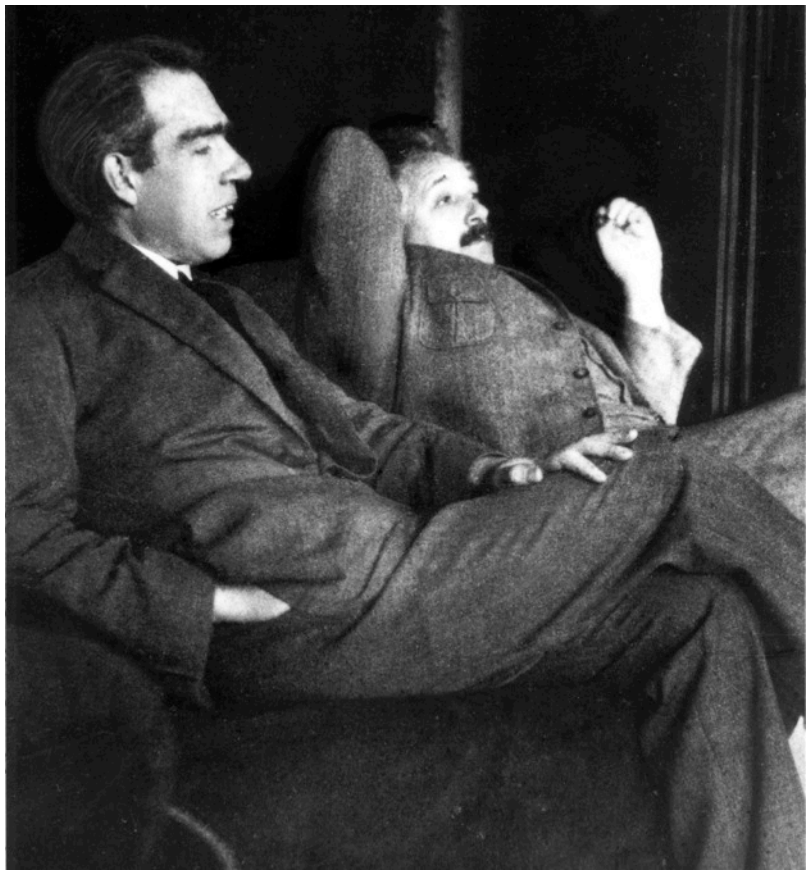
Scientific Predictions



- "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

ClinSeq™

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

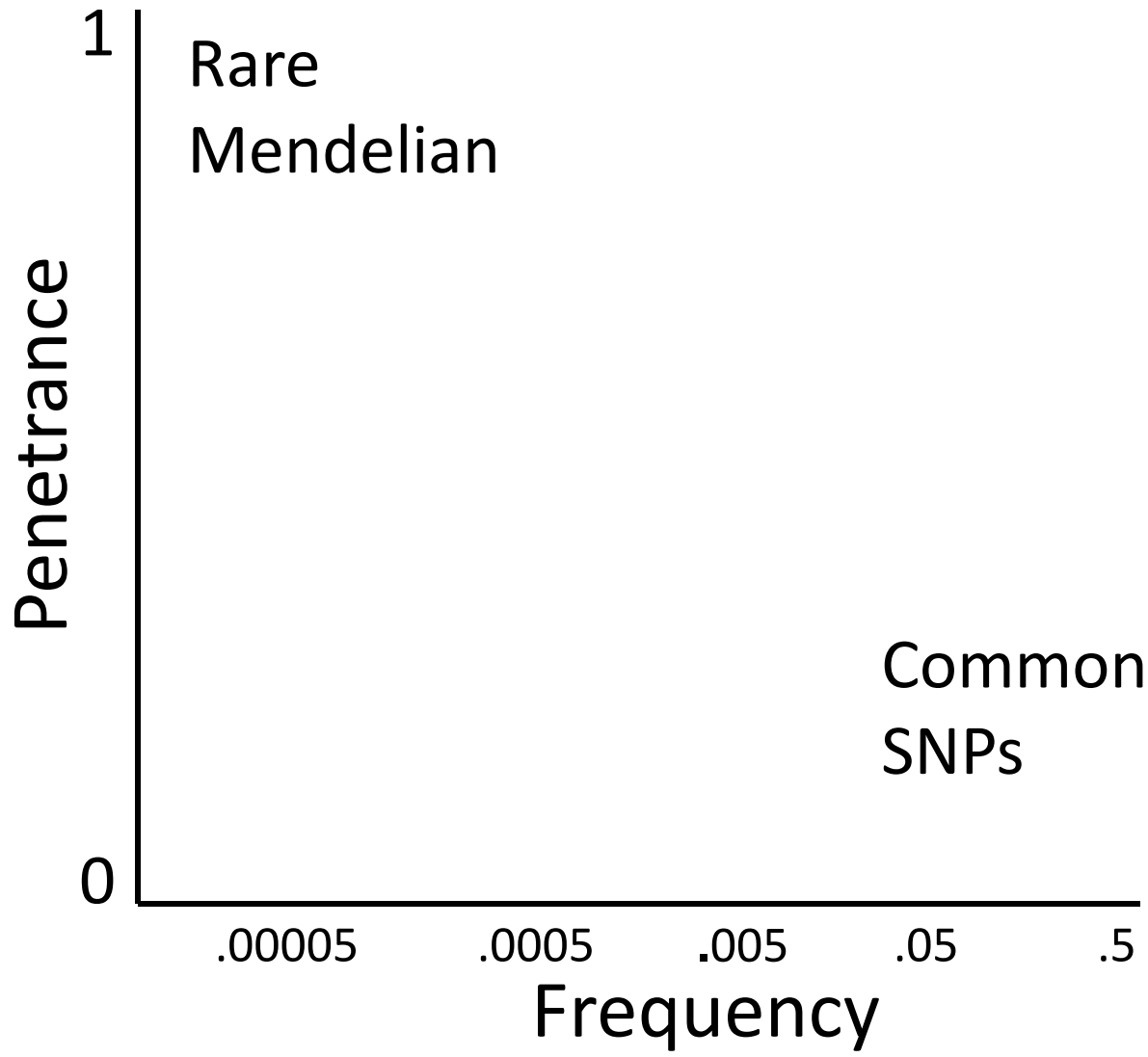
ClinSeq™

Health Predictions

- Need ability to assay an attribute of patient that defines occult disease or future risk
  - Commonly done: physical signs
- Why not for heritable disorders?
  - Need assay to broadly assess risks
  - Until recently it was technically impossible

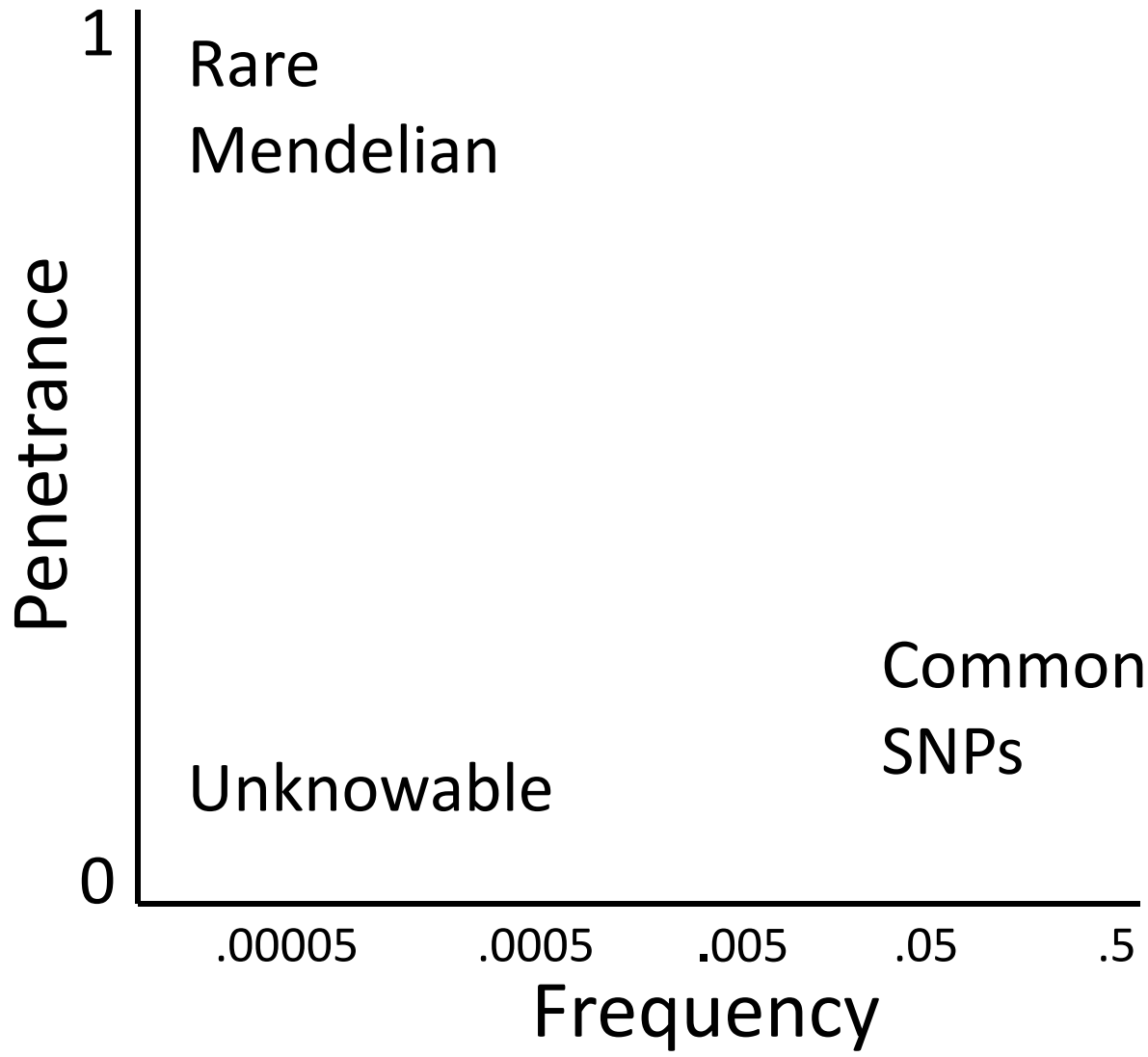
ClinSeq™

Genetic Variation & Penetrance



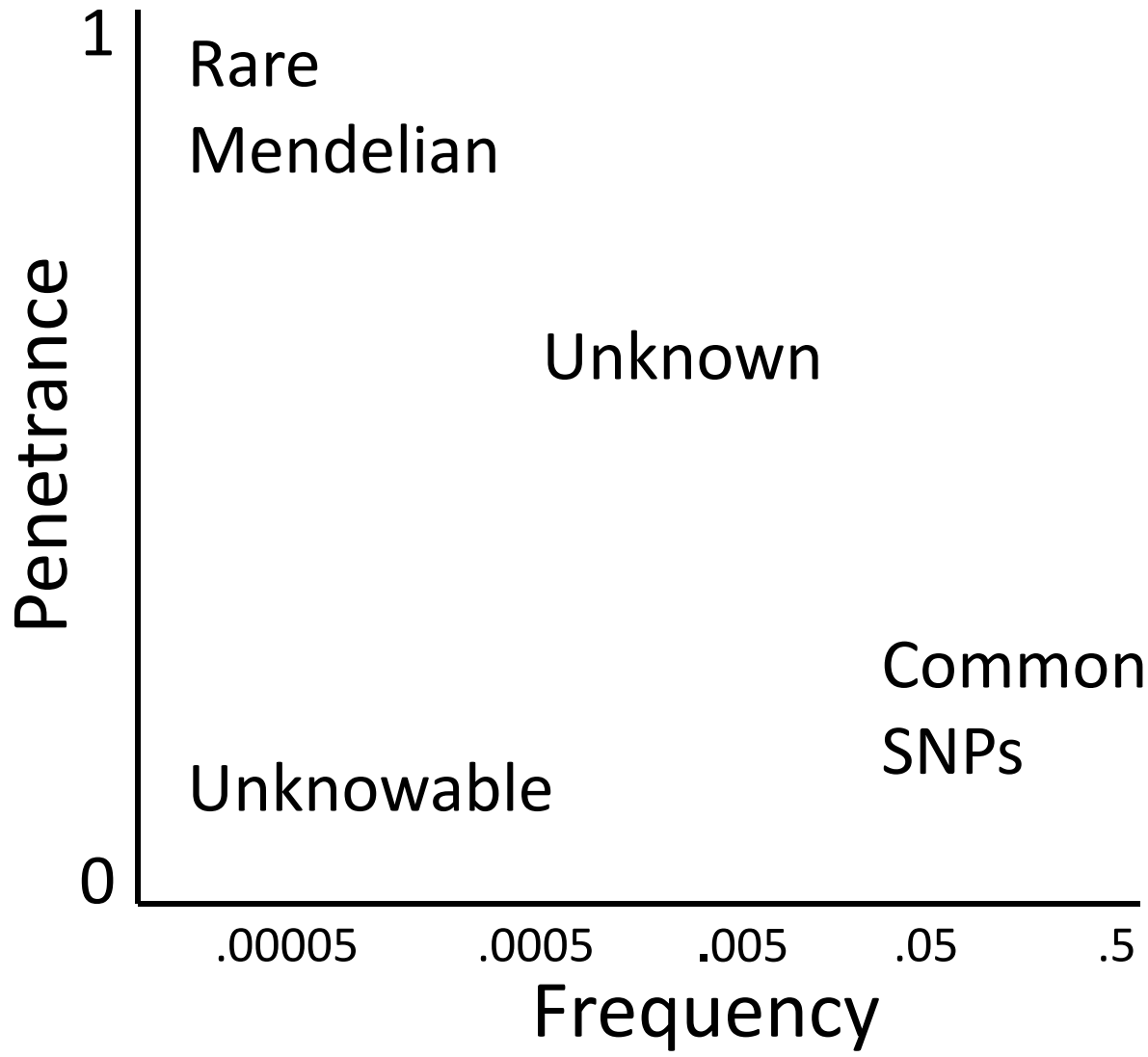
ClinSeq™

Genetic Variation & Penetrance



ClinSeq™

Genetic Variation & Penetrance

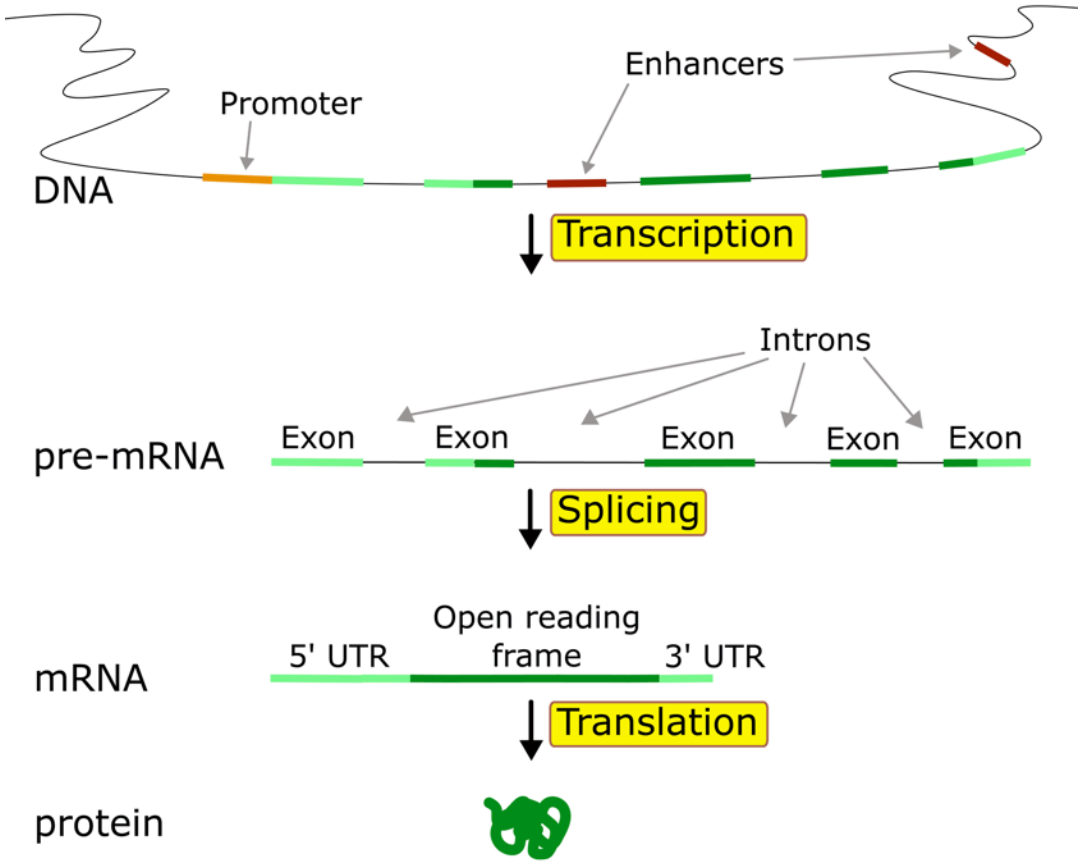


ClinSeq™

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

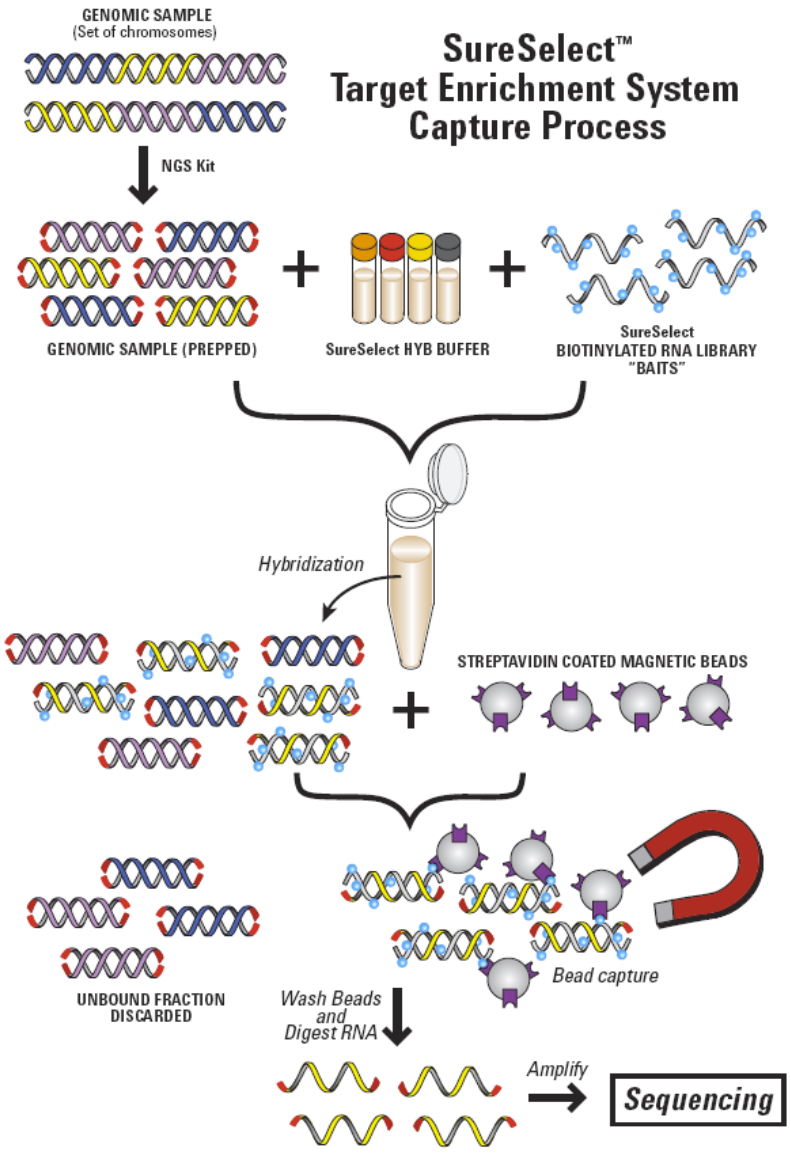
Anatomy of a Gene

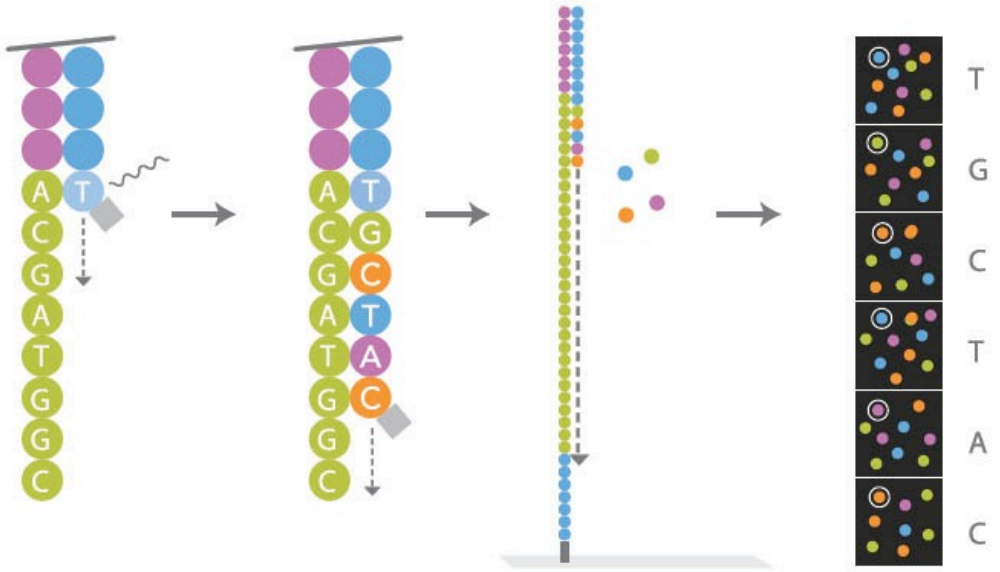


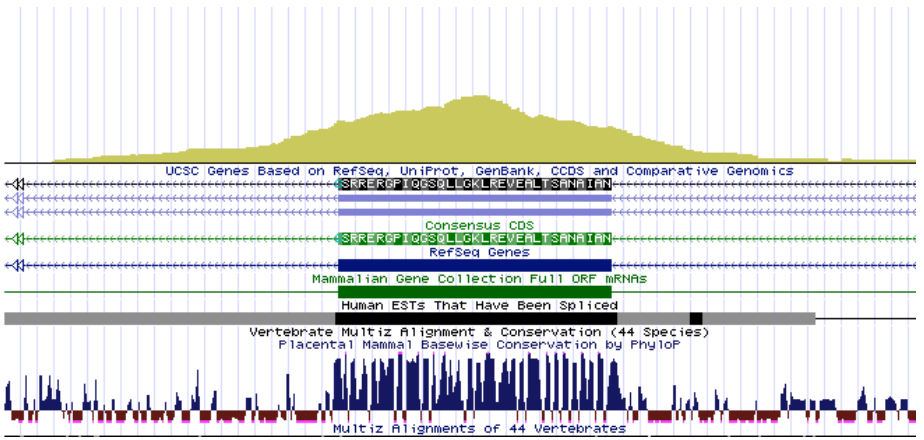
- Common variants not in genes
- Rare, high penetrance variants: 80-90% mutations in coding exons of genes
- ~20,000 genes
- 300,000 exons: exome
- Coding exons of genes 1-2% of DNA

ClinSeq™

Genome/Exome Sequencing



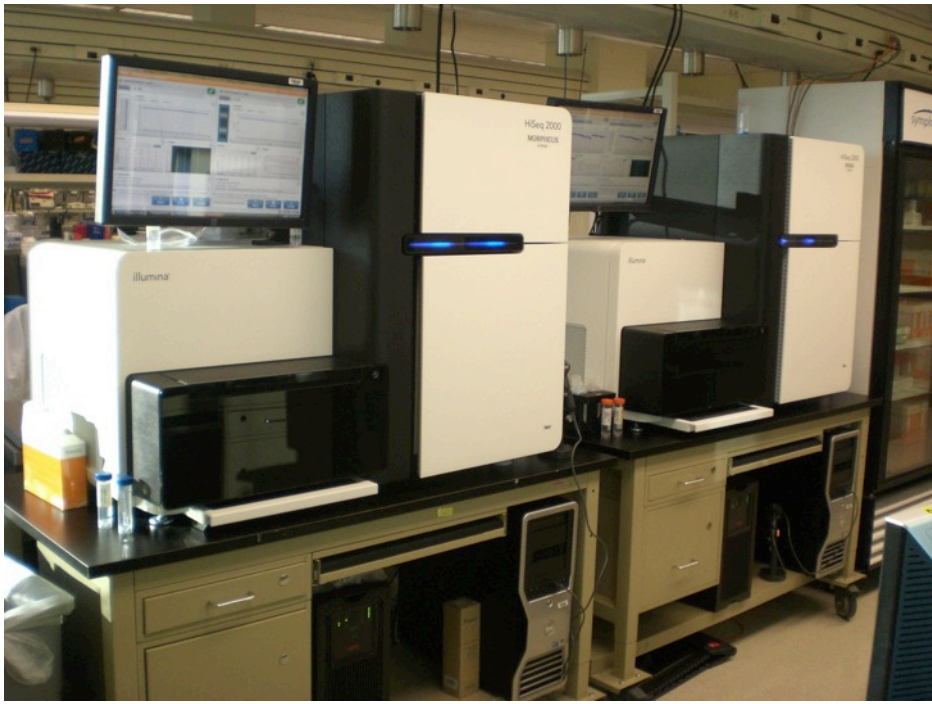




ClinSeq™

Sequencing Instruments

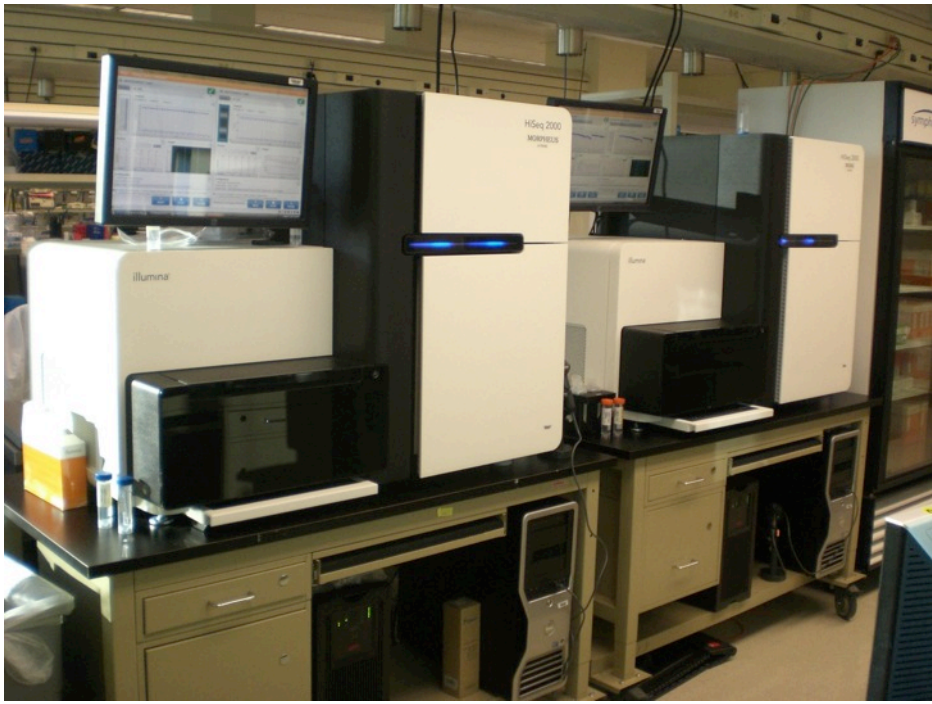
- Good news!
- Sequence whole genome or 6-8 exomes in ~ 3 days
- Cost falling
  - $10,000 genome
  - < $1,000 exome
- Can evaluate nearly all genes



ClinSeq™

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™

ClinSeq™: A Translational Research Project in Clinical Genomics

Medical & Statistical Genetics

NHLBI

?

ClinSeq

TGCTGATCG

NIH Clinical Center

NIH Intramural Sequencing Center

Suburban

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

<u>Research bloods</u>:

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

ClinSeq™

Variant Filtering

- 950 cardiomyopathy gene variants
- 245 rhythm gene variants

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

ClinSeq™

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

ClinSeq™

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

ClinSeq™

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

ClinSeq™

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
- No CC, history, exam, clinical test, family history
- Ordered test for every known gene

ClinSeq™

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
- No CC, history, exam, clinical test, family history
- Ordered test for every known gene
  - *This is contrary to everything we were taught!*

ClinSeq™

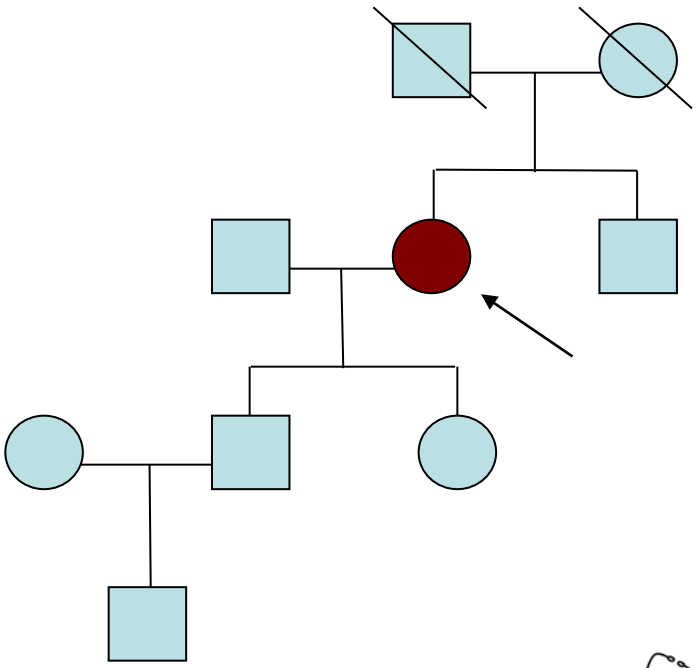
What is Going on Here?

- 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
- No CC, history, exam, clinical test, family history
- Ordered test for every known gene
  - *This is contrary to everything we were taught!*
  - *Why do we demand that people die before we test?*

ClinSeq™

Dyslipidemias

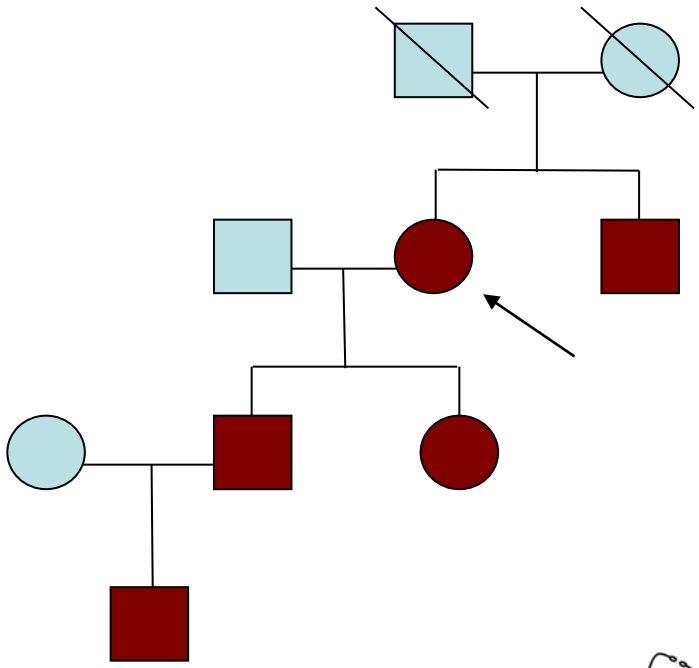
- 65 yo female
- High cholesterol diagnosed at 25 years
- RX: atorvastatin, ezetimibe, hctz, lisinopril, niacin
- Coro Ca^{++} 1,726
- Chol 172, Trig 50, HDL 75



ClinSeq™

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
- LDLR known pathogenic mutation
- Family members diagnosed & treatment started



ClinSeq™

Leveraging Genomics

- Exome unnecessary to manage proband
- 4-8 undiagnosed relatives per proband
- Years of life added at small marginal cost

ClinSeq™

Leveraging Genomics

- Exome unnecessary to manage proband
- 4-8 undiagnosed relatives per proband
- Years of life added at small marginal cost
- Genomic result forces question – neither the doc nor patient can ignore genetics

ClinSeq™

Leveraging Genomics

- Exome unnecessary to manage proband
- 4-8 undiagnosed relatives per proband
- Years of life added at small marginal cost
- Genomic result forces question – neither the doc nor patient can ignore genetics
- Need to move toward this practice

ClinSeq™

Leveraging Genomics

- Exome unnecessary to manage proband
- 4-8 undiagnosed relatives per proband
- Years of life added at small marginal cost
- Genomic result forces question – neither the doc nor patient can ignore genetics
- Need to move toward this practice
- Policy implication – lowers effective cost of sequencing

ClinSeq™

Total Results To Date

- 8 high penetrance cancer syndromes
- 6 cardiomyopathy/dysrhythmias
- 9 dyslipidemias
- 2 malignant hyperthermia
- 3 neuropathies
- 1 occult metabolic disorder

Total Results To Date

- 8 high penetrance cancer syndromes
- 6 cardiomyopathy/dysrhythmias
- 9 dyslipidemias
- 2 malignant hyperthermia
- 3 neuropathies
- 1 occult metabolic disorder
- Just scratching surface - 5% have a ‘rare’ mendelian disorder

What Else is There to be Found?

- Other dominant traits – hundreds
- Pharmacogenetics
- Carrier states

ClinSeq™

It Looks Easy

ClinSeq™

Individualized Medicine Criticisms

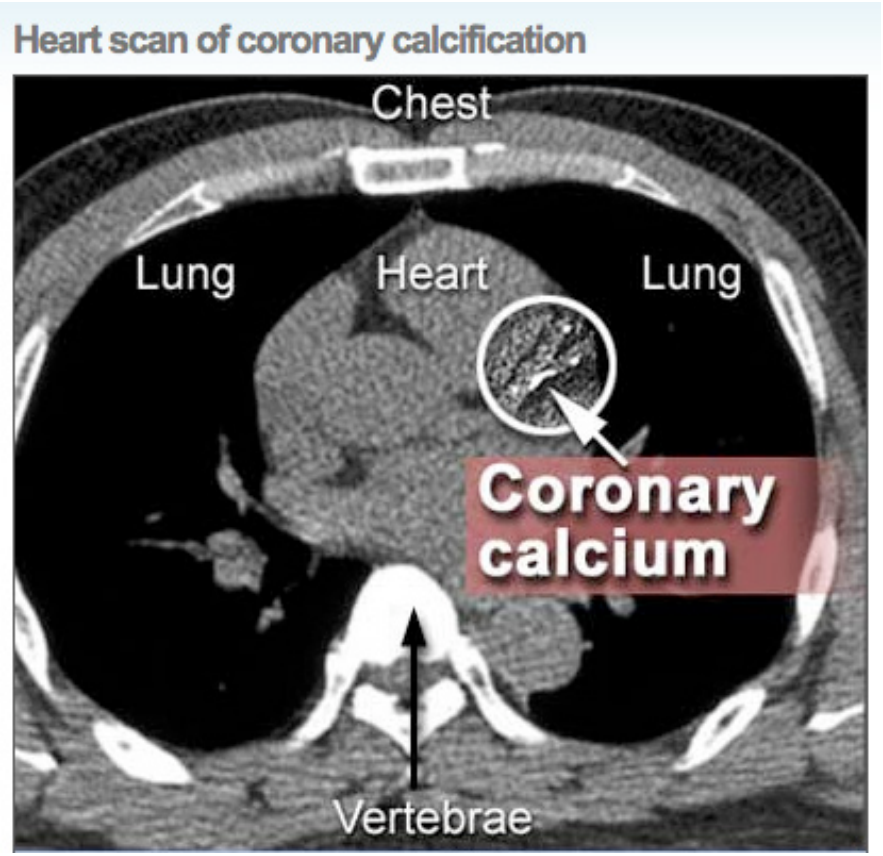
- Heredity not great at predicting…
  - Roberts et al Sci Transl Med 2012

- Penetrance wildly overestimated…
  - Kohane et al Genet Med 2012

ClinSeq™

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



ClinSeq™

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

ClinSeq™

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

ClinSeq™

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

ClinSeq™

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

ClinSeq™

Going Forward

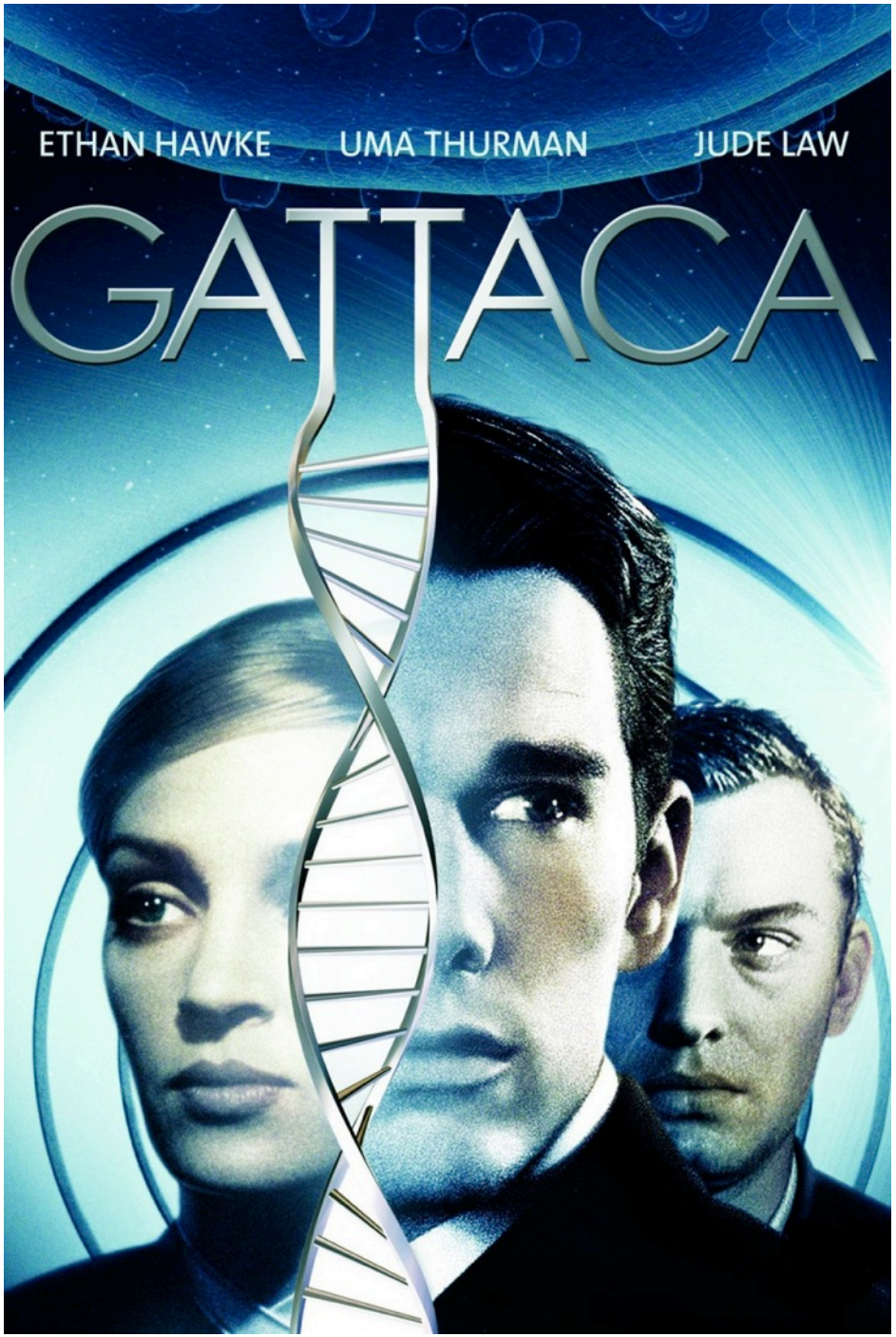
- Much research to be done
  - Tighten relationship genotype – phenotype
  - Develop & test approaches to presymptomatic management
  - Build infrastructure and methods for managing information

ClinSeq™

Going Forward

- Much research to be done
  - Tighten relationship genotype – phenotype
  - Develop & test approaches to presymptomatic management
  - Build infrastructure and methods for managing information
- Genomes & exomes being done clinically
  - You will soon begin seeing patients who have had this

ClinSeq™



ClinSeq™
ATGCTGATCG


The groundhog is like most other prophets; it delivers its prediction and then disappears. *Bill Vaughan*