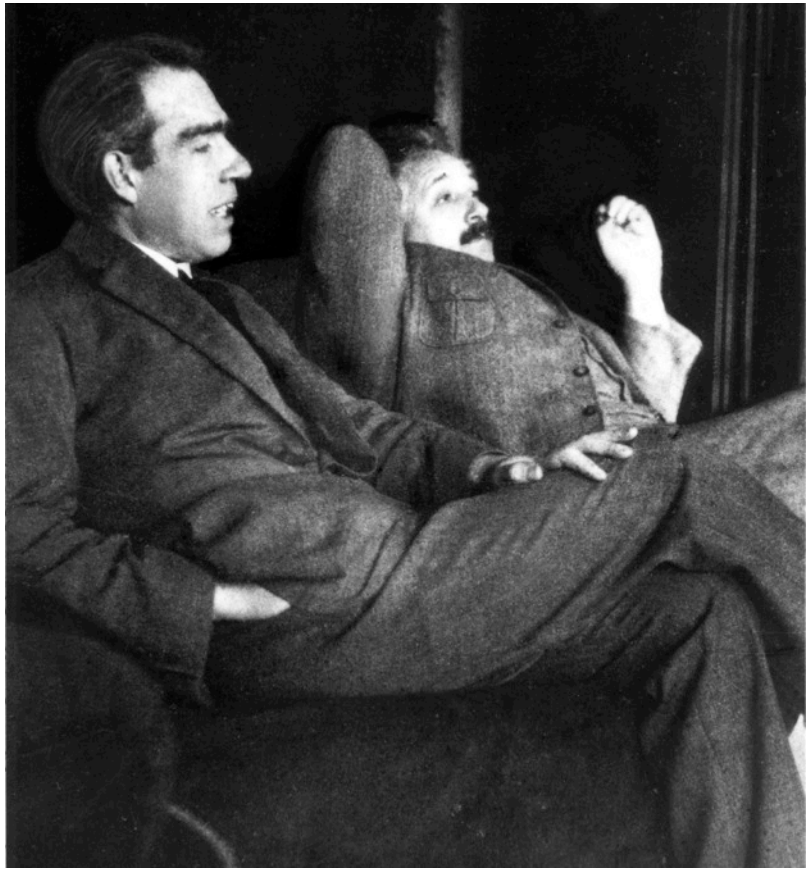
Incidental Findings & Predictive Medicine

Leslie G. Biesecker

NHGRI

Predictions



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

Niels Bohr

ClinSeq® & Predictive Medicine

- Started in 2006
- 1,000 patients
- 45-65 yo
- Selected & phenotyped for atherosclerosis
  - All other disorders 'incidental'
- Consented for all 'omic interrogations
- Consented for iterative phenotyping
- Opportunity to pilot IFs / Predictive medicine

Eight Pathogenic Variants Among 12 Subjects

- *BRCA1* or *BRCA2:* six variants among eight participants
  - BRCA1 p.Glu23ValfsX17 (c.del185AG) (x3)
  - *BRCA1* c.547+2T>A
  - BRCA2 p.Ser1982ArgfsX22 (c.6174delT) (x3)
  - BRCA2 p.Lys1828ValfsX4
  - BRCA2 p.Thr2766AsnfsX11
  - BRCA2 p.Arg3052Trp
- SDHC: p.Arg15X
- MSH6: p.Gln244X

Malignant Hyperthermia Susceptibility

- Hypermetabolism, fever, rhabdomyolosis, hypertonicity, arrhythmia
- 1/2,000 – 1/10,000 prevalence
- RYR1 p.Arg614Cys - among 30 mutations in Eur. MH Group & 17 Amer. MH consensus panel list
  - No family or personal history, exposed x3

Cardiomyopathy & Dysrhythmias

- *MYH7* IVS8+1G>A
  - Reinterpretation MRI > L ventricular non-compaction
- MYBPC3 p.Arg495Gln
  - Echo mild concentric L ventricular hypertrophy
  - Afib (+ FH Afib)
- MYBPC3 p.Gly490Arg
  - Echo: Asymm septal hypertrophy
- All w positive FH

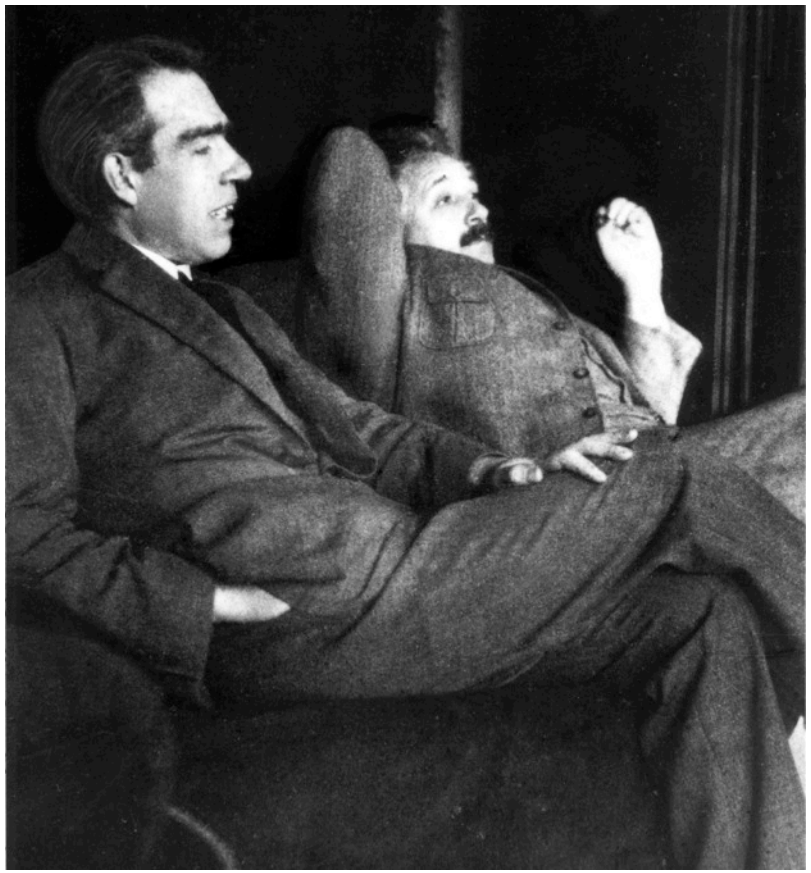
Miscellaneous

- *PPARG*
  - Familial partial lipodystrophy
- *HOX*
  - Limb anomalies
- *FLCN*
  - Birt-Hogg-Dubé syndrome
- *PMP22*
  - 3 patients with deletions > HNPP

Conclusions

- Practical to extract clinically meaningful results from exomes/genomes
- Analytic validity not major challenge
  - Clinical validity needs to be our focus
- Customized, hypothesis-generating clinical research identifies undiagnosed disorders
- Counseling is challenging

Predictions



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"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

Challenges

- Known knowns
  - Clinicians not ready for this
  - Databases a major problem
- Known unknowns
  - Full spectrum of genotype-phenotype unknown
  - Difficult to interpret nearly all novel variants
  - How to cope with sensitivity
- Changing paradigm causes discomfort

Four Documents

- **Points to Consider in the Clinical Application of Genomic Sequencing**
  - **Korf et al. http://www.acmg.net/StaticContent/PPG/Clinical_Application_of_Genomic_Sequencing.pdf**

- **ACMG Recommendations for Reporting of Incidental Findings in Clinical Exome and Genome Sequencing**
  - **Green et al. http://www.acmg.net/docs/ACMG_Releases_Highly-Anticipated_Recommendations_on_Incidental_Findings_in_Clinical_Exome_and_Genome_Sequencing.pdf**

- **Incidental findings in Clinical Genomics: A Clarification**
  - **http://www.acmg.net/docs/Incidental_Findings_in_Clinical_Genomics_A_Clarification.pdf**

- **ACMG recommendations for standards for interpretation and reporting of sequence variations: Revisions 2007**
  - **Richards CS, et al. Genet Med. 2008 10:294-300**

ACMG Incidental Findings in Clinical Sequencing Working Group

Robert Green, MD, MPH (Co-Chair)	Brigham & Women's; Harvard
Leslie Biesecker, MD (Co-Chair)	NHGRI/NIH
Jonathan Berg, MD, PhD	Univ. of North Carolina
Wayne Grody, MD, PhD	Univ. Calif. Los Angeles
Bruce Korf, MD, PhD	Univ. Alabama Birmingham
Amy McGuire, JD, PhD	Baylor
Christa Martin, PhD	Emory Univ.
Robert Nussbaum, MD	Univ. Calif. San Francisco
Julianne O'Daniel, MS	Illumina
Kelly Ormond, MS	Stanford Univ.
Heidi Rehm, PhD	Brigham & Women's; Harvard
Marc Williams, MD	Geisinger Health System
Sarah Kalia, ScM	Brigham & Women's
Michael Watson, MS, PhD	ACMG Staff (*ex-officio*)

Charge to Working Group

- Whether a list should be made
- Generate a *specific* list
- Generate a *minimum* list of variants/conditions that laboratories should look for and return

Inclusion on a Minimum List

- High penetrance or confirmatory testing
- Long asymptomatic period
- Highly efficacious treatment
- Not detected by NBS
- ACMG known pathogenic ± expected pathogenic variants
- Revise the list periodically

ACMG Recommendations Divergence from Current *Genetics* Practice

- Minimum list of medically important conditions/genes/variants should be evaluated & returned to clinicians
- Variants should be returned regardless of the age of the patient
- Estimate 1% of patients will receive result

ACMG Recommendations
Divergence from Current *Genetics* Practice

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Convergence with Current *Medical* Practice

Controversial Elements

- Preferences
  - *Constitutional mutations found in the genes on the minimum list (see Table) should be reported by the laboratory, regardless of the indication for which the clinical sequencing was ordered*
- Children
  - *Incidental (secondary) variants should be reported regardless of the age of the patient.*

Controversial Elements

- Consent
  - "Pre-test counseling should be done by a medical geneticist or an affiliated genetic counselor and should include a formal consent process."
  - "Prior to initiating WGS/WES, participants should be counseled regarding the expected outcomes of testing, the likelihood and type of incidental results that could be generated, and what results will or will not be disclosed."

Controversial Elements

- Evidence
  - Expert opinion, thorough process, robust input, open forum at ACMG

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"…even though evidence is insufficient, the clinician must still provide advice, patients must make choices, and policymakers must establish policies"

US Preventive Services Task Force, 2009