Incidental Findings & Predictive Medicine

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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, rhabdomyolysis, 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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Niels Bohr

“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

- ACMG Recommendations for Reporting of Incidental Findings in Clinical Exome and Genome Sequencing

- Incidental findings in Clinical Genomics: A Clarification

- ACMG recommendations for standards for interpretation and reporting of sequence variations: Revisions 2007
ACMG Incidental Findings in Clinical Sequencing Working Group

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Univ. Calif. Los Angeles
Univ. Alabama Birmingham
Baylor
Emory Univ.
Univ. Calif. San Francisco
Illumina
Stanford Univ.
Brigham & Women’s; Harvard
Geisinger Health System
Brigham & Women’s
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

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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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  – Expert opinion, thorough process, robust input, open forum at ACMG

“...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