RETURN OF RESULTS IN GENOMIC RESEARCH: WHY SOMETHING SO SIMPLE IS REALLY SO COMPLICATED
A case to consider

- A person enrolls in a study of the effects of a new statin-like drug on lipid metabolism. They report they are healthy, with no prior medical problems and taking no medication.
- As part of the screening for the study, blood is collected to be analyzed for lipid levels as well as liver function tests, as elevated LFTs are an exclusion criteria. A comprehensive metabolic panel (CMP) is performed with the following results.
CMP results

- Total Cholesterol: 240
- HDL-C: 45
- LDL-C: 190
- LFTS: WNL
- Na: 143
- K: 5.5
- Cl: 103
- HCO3: 20
- Creatinine 4.5
Case #2

- A 21 yo woman enrolls in a study looking for the genetic basis of hyperlipidemia. The investigator is planning to perform whole exome sequencing on affected and control subjects. This participant is in the control arm, and reports no medical problems.
The result....

- Results of sequencing reveal she is heterozygous for a mutation in a gene associated with the long QT syndrome.
- Are these 2 scenarios different?
- Should results be returned in
  - One
  - Both
  - Neither
Incidental findings aren’t usually incidental

- Primary findings
- Secondary findings
- Incidental findings
  - Anticipated
  - Unanticipated
- Discovery finding
Key Question

- Should researchers look for and return secondary findings to research participants?
- Duty to look?
Key Question

- Should researchers look for and return secondary findings to research participants?
- Duty to look?
- Duty to warn?
Fact 7: Research is not clinical medicine
When should results be returned?

- Recommends actively looking for and mandatory reporting of mutations in 56 genes.
ACCE Criteria for Returning Results

- Analytic Validity
- Clinical Validity
- Clinical Utility
- Ethical, Social and Legal Implications

http://www.cdc.gov/genomics/gtesting/ACCE/
ACCE criteria

- Analytic Validity
  - Accuracy and reliability of the test
  - Quality control
ACCE Criteria

- Clinical Validity
  - What is the strength of the relationship between genotype and phenotype?
  - Can false positives be resolved (confirmatory testing)
ACCE criteria

- Clinical Utility
  - Are there actions that can be taken that are important/beneficial to the person?
ACCE

- Ethical, Legal and Social Implications?
  - Does the person want to know?
  - Are there issues around confidentiality, stigmatization etc?
Back to the cases...

- **Case 1:** Incidental finding of renal failure with hyperkalemia
  - Analytically valid, high clinical validity and utility,
  - No ethical barriers to returning result
  - Duty to rescue applies

- **Case 2:** Incidental finding of long QT syndrome
  - Are ACCE criteria met?
    - Maybe...maybe not....
Beware the Incidentalome

- False positive findings lead to unnecessary:
  - Testing
  - Intervention
  - Cost
  - Anxiety
Effect on research

- If there is a duty to look and warn, what would that require?
  - Can a research lab meet ACCE criteria?
- How often would the researcher have to look?
- Kids?
- Biobanks?
- Cost to research?
Research vs Practice

- Distinct obligations of researchers vs clinicians
- Expectations of participants should differ
- Risk of therapeutic misconception
  - Patient/participant
  - Physician/investigator