Ethics and IRB Issues Related to Whole-Exome Sequencing

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Disclaimer

The following presentation does not necessarily reflect the official views of the NHGRI, NIH, or DHHS.

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- *Intramural*: Berkman, Chan, Biesecker, Facio, Eidem, Solomon, Porter, Khan, Badgett, Hadley, Wendler, Abdul-Karim, Rid, Bailey-Wilson, Mullikin
- *Extramural*: Wilfond, Lehmann, Tierney, Tabor
- Others…

"How do I get my whole exome sequencing protocol through the IRB???"

Is the wrong question to start with…

From the Mouths of IRBs…

- There is more than one ethically-defensible approach to WES research
  - "It's much more case-by-case. What are the protocols? Who are the people? What's the relationship between the investigators and the people whom they're studying?"

From the Mouths of IRBs…

- IRBs are still figuring out how to review WES protocols
  - "We certainly don't have a policy, and I don't know that we really have come to a firm conclusion. I mean, it gets discussed every time, and there's disagreement every time."

From the Mouths of IRBs…

- "We do not have an institutional policy. I think we've gone through several different discussions in our IRB for each specific protocol, but I think we are still at the stage where we hear from investigators what their approach is, and then we decide at the meeting if that sounds reasonable."

NIH Intramural Policy, Part I

- "Since there are ethically relevant distinctions between traditional genetic research and WES/WGS, the use of these sequencing technologies must be reviewed explicitly by an IRB and/or OHSRP. Existing protocols will need to be amended to include WES/WGS."

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"What if I already have consent to do genetic research on specimens that I collected from subjects?"

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Review Required

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"What if I am not planning to return any incidental genetic research findings?"

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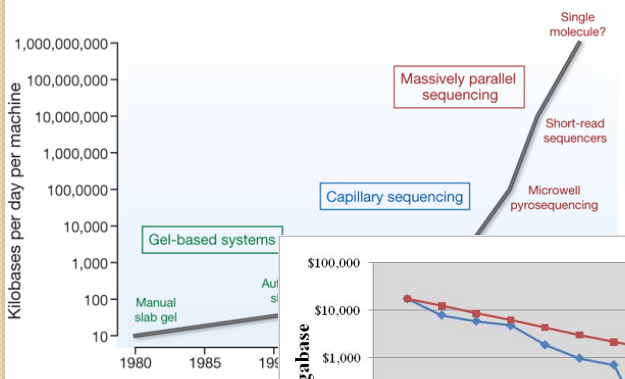
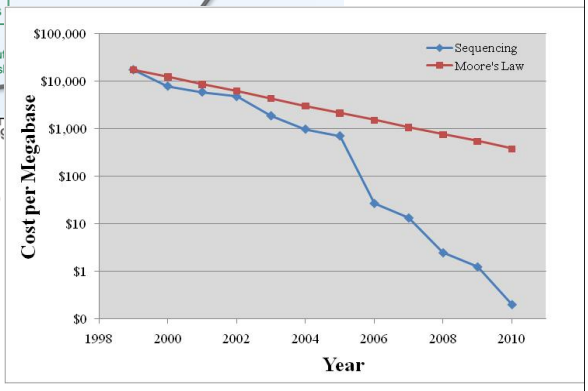
"So…what's *different* about whole exome sequencing?"

Advances in Sequencing Technology



Stratton *et al.* (2009)



Adapted from Eric Lander, Broad Inst. (2009)

General Argument

- WES/WGS does not raise novel ethical concerns, but…
- …it will significantly magnify and make more concrete many of the risks that have been relatively theoretical to this point.
- This has important implications for the way that we conduct ethical review of proposed WES/WGS research, especially given the current regulatory framework

Key Ethical Issues

- Management of Results
  - Research-related (primary)
  - Incidental (secondary)
- Broad Data Sharing
- Adequacy of Consent
  - Potential need for re-consent

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A new way of thinking about returning incidental findings?

- Current assumption #1
  - Traditional genetic research will produce very few clinically significant incidental findings
- Revised assumption #1
  - It is no longer a question of *whether or not* clinically relevant results will be found in any research participant, but rather *how many* results will be identified in each participant.

A new way of thinking about returning incidental findings?

- Current assumption #2
  - A clear distinction exists between so-called "incidental" findings and findings that are explicitly related to the original study hypotheses or disease focus.
- Revised assumption #2
  - For experimental approaches based on WES/WGS, this distinction between incidental and non-incidental findings will become less meaningful.

A new way of thinking about returning incidental findings?

- Current assumption #3
  - Don't look, don't tell:
    - "Researchers generally have no obligation to act as clinicians and affirmatively search for IFs" (*Wolf et al.*)
- Revised assumption #3
  - With WGS technology, the act of "looking" for all possible results becomes much more practical and indeed is a fundamental component of the analytical approach

Questions

- Do current sequencing technologies change the extent to which investigators have an obligation to return incidental genetic research findings?
  - *Yes (sometimes, to some extent)*
- Given new sequencing technologies, what framework should IRBs use to think about whether an investigator's approach to managing incidental findings is ethically appropriate?

The Case of the Well-Intended Investigator, Part I

- A bench scientist studying a common, complex disorder wants to collect samples prospectively for whole exome sequencing.
- The protocol involves a one-time blood draw
  - No ongoing clinical relationship between researcher and subjects.
- The investigator does not have access to genetic counseling resources.
- She "wants to do the right thing"
  - But is conflicted about disclosing results

IRB Issue #1(a): *Whether or Not to Disclose Incidental Findings*

- *The IRB felt that:*
  - The submitted protocol did not clearly and consistently address the study procedures and — most importantly — the plan for providing genetic findings to subjects.
  - It is the decision of the Investigator to determine which genetic findings will be returned to subjects.

IRB Issue #1(b): *Informed Consent*

- The Investigator has a duty to inform subjects clearly during the consent process about the possibility that:
  - the study may identify relevant genetic variants
    - only some of which will be of known clinical significance
  - results will, or will not, be provided to them (or that they will have the option to decide).

IRB Issue #1(C): *Confirmation and Counseling*

- If results are to be returned:
  - Would need to be confirmed in a CLIA-approved lab.
  - Appropriate genetic counseling should be provided to subjects.
    - The Investigator should look into whether genetic counseling resources are available through IC and/ or the Clinical Center.

"The Case of the Well-Intended Investigator, Part II"

- Investigator submits a revised protocol to the IRB
- Proposes that she will indeed determine which incidental findings are clinically relevant
  - and therefore disclosed to subjects
- Expects this # to be small

IRB Issue #2(a): *Process for Determining Which Incidental Findings to Disclose*

- *Stipulation*
  - "Revise the description of the process that will be used to review incidental findings to determine which ones may be clinically relevant."

IRB Issue #2(b):
Process for Determining Which Incidental Findings to Disclose

- *Recommendation*
  - "A multi-disciplinary committee should be used to review these variants and determine whether a variant is considered 'actionable'
    - and the subject should be contacted and offered the option of learning of this finding.
  - The committee should include expertise in medical genetics, genetic counseling, ethics, and the IRB's perspective.
  - This review should occur prior to CLIA-approved laboratory confirmation."

IRB Issue #2(c)
Anticipated Volume of Incidental Findings

- "The IRB also felt that the Investigator might benefit from speaking with Investigators involved with other IRB-approved protocols under which exome sequencing is being conducted, and clinically-significant variant results are being returned to subjects.
- The experience of these protocols indicates that a larger number of incidental variants will be identified than projected by the Investigator."

Unresolved Ethical Controversies and Questions about Return of Incidental Genetic Research Findings

(or "Why This is All So Challenging")

An argument for returning results

- Shalowitz and Miller:
  - Respect for persons
    - "It would be disrespectful to treat research volunteers as conduits for generating scientific data without giving due consideration to their interest in receiving information about themselves derived from their participation in research."
  - Genetic information is important and when incorporated into decision-making can enhance autonomy
  - Returning results recognizes a participant's contribution to research

Other arguments for an obligation to return genetic research results

- Beneficence
- Reciprocity
- Justice
- Investigator integrity and professional responsibility

Some arguments against an obligation to return incidental research findings

- Challenges to the notion that beneficence, respect for persons, reciprocity, justice are violated by lack of disclosure
- The purpose of research is not to benefit the individual research participant but rather to produce generalizable knowledge
- Risks associated with conflating research and clinical care
  - Therapeutic (diagnostic) misconception
- Resource limitations

Guidelines and Frameworks

- NHLBI (2004)
- NHLBI (2009)
- Result-evaluation approach (Ravitsky and Wilfond, 2006)
- Net-benefit approach (Wolf, et al., 2008)
- Ancillary care framework (e.g., Beskow and Burke, 2010)
- Tiered-consent model (Rothstein, 2006)
- etc.

What kind of genetic information generates an obligation?

- Some general agreement about the relevant factors:
  - Analytic validity
  - Clinical relevance
  - Actionable
  - Desired

What kind of genetic information generates an obligation?

- But disagreements lurk:
  - Clinical relevance
    - Defining the threshold
      - Clear and immediate need vs. important health implication
      - Net benefit (strong, possible, unlikely)
      - Clinical utility, personal utility, general utility
      - Relative risk > X
  - Desired
    - Overriding the right not to know
  - Analytic validity
    - Is CLIA certification required?

Adding a dimension

- Literature and guidelines have focused on defining the *kind* of information that might give rise to an obligation to return results
- Emerging idea that the obligation to return incidental findings could also be a function of the research *context*
  - Study characteristics
  - Population characteristics

Incorporating Factors Relating to the Research Characteristics

- Nature of study
  - Clinical trial, natural history, basic science
- Study resources
  - *e.g.*, genetic counselors, CLIA confirmation
- Investigator expertise
- Specific aims
- Feasibility of recontact

Incorporating Factors Relating to Subject Characteristics

- Alternative access/dependence
- Degree of vulnerability
- Depth of relationship

"What if I am only using coded specimens that were given to me by an extramural collaborator?"

Case Study Involving Coded Samples from Collaborator

- You have identified a source of clinical samples from patients with a rare condition who are being seen at University X Medical Center (UXMC).
- The samples were collected with written informed consent and UXMC IRB approval.
- The samples will be coded, and you will not have access to any identifiable information about these patients.
- You want to proceed with whole exome sequencing and set up a planning meeting with NISC.
- NISC asks: "Do you have appropriate institutional approvals from an NIH IRB or OHSRP?"

Case Study Involving Coded Samples from Collaborator

- If using coded, de-identified samples, IRB review might not be required
- This determination must be made by the NIH Office of Human Subjects Research Protections (OHSRP, formerly known as OHSR)
- Form 1 "OHSRP Request for Review"
  - http://ohsr.od.nih.gov/info/info.html

NIH Intramural Policy, Part II

- Investigators requesting OHSR[P] review of WES/WGS research activity will be asked to answer a set of supplemental questions to allow for enhanced OHSR[P] review.

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NIH Intramural Policy, Part II

- Sampling of Supplemental OHSRP Questions
  - Has an IRB or Ethics Committee explicitly approved the conduct of whole exome/genome sequencing with these samples?
  - Is it possible that results from the proposed sequencing analyses will be returned to subjects?
    - ****Do you and your collaborators have a clear plan in place for managing incidental findings****
  - Sequence datasharing plans
  - Level of informed consent

Do NIH Data Sharing Policies Apply to Exome Sequence Data?

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Possibly

NIH GWAS Data Sharing Policy

- Data sharing requirement for all NIH-funded GWAS data
  - Deposition in GWAS repository (dbGaP)
    - Or "alternate" data sharing plan
  - To promote broad sharing of genotypic and phenotypic data with researchers
- Efforts to expand this policy to include broad genomic data are underway

NIH GWAS Data Sharing Policy

- Anticipatory steps
  - Will it be appropriate to deposit WES data in a data repository for dbGaP?
    - Engagement and consent
      - study population
      - individual subjects
    - Risk of identifiability
    - Management of incidental findings from secondary uses of data

Approaches to Informed Consent for Whole Exome Sequencing

- WES-Specific Elements
  - Scope of genomic analyses and potential results
  - Whether results (related, incidental) will be disclosed
    - Choices?
  - Plans for WES data sharing

Consent for Whole Exome Sequencing Using Previously Collected Specimens

- When is re-consent indicated?
  - When scope of genomic analysis was not covered in prior consent
  - Plan for managing incidental findings was not previously described
    - If findings will be disclosed
    - If findings will be generated but not disclosed
  - If data will be shared broadly (e.g., dbGaP)

Three Emerging Models

Design	(Re)consent Covers:
No incidental findings to be disclosed	• Nature and scope of analysis • Datasharing plans • That results will NOT be disclosed • even though they might be generated
Limited incidental findings to be disclosed	• Nature and scope of analysis • Datasharing plans • That results might be disclosed under carefully defined circumstances • Though unlikely

More robust plans for disclosure of findings	• Nature and scope of analysis
	• Datasharing plans
	• That results might be disclosed under carefully defined circumstances
	  • How preferences will be solicited
	  • Any "mandatory disclosure" provisions

Take-Home Messages

Question:

Can I go ahead with WES/WGS based on protocols and consent forms that are already in place?

Answer:

No. Not until you receive some level of institutional approval

-IRB

-OHSRP

Take-Home Messages

Question:

What are the key things that an IRB or OHSRP is going to be looking for?

Answers:

- That you (and collaborators) have thought about a plan for managing incidental findings that is coherent & takes into account expertise, resources, expectations,
- That you are starting to think about datasharing plans
- That the informed consent process reflects these various plans

Managing Expectations

Thank you!