Informed Consent and Returning Results in Whole-Exome Sequencing Protocols

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MEDICAL RECORD	**CONSENT TO PARTICIPATE IN A CLINICAL RESEARCH STUDY** • Adult Patient or • Parent, for Minor Patient

INSTITUTE: National Human Genome Research Institute

STUDY NUMBER: 10-HG-0065 PRINCIPAL INVESTIGATOR: Leslie G. Biesecker, MD

STUDY TITLE: Whole Genome Medical Sequencing for Gene Discovery

Continuing Review Approved by the IRB on 12/02/10
Amendment Approved by the IRB on 06/09/10 (B) Date Posted to Web: 01/07/11
Standard

INTRODUCTION

We invite you to take part in a research study at the National Institutes of Health (NIH).

First, we want you to know that:

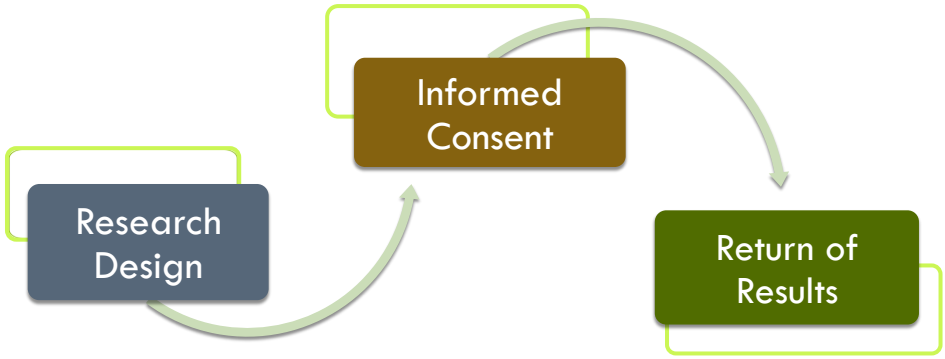
Taking part in NIH research is entirely voluntary.

You may choose not to take part, or you may withdraw from the study at any time. In either case, you will not lose any benefits to which you are otherwise entitled. However, to receive care at the NIH, you must be taking part in a study or be under evaluation for study participation.

You may receive no benefit from taking part. The research may give us knowledge that may help people in the future.

Second, some people have personal, religious or ethical beliefs that may limit the kinds of medical or research treatments they would want to receive (such as blood transfusions). If you have such beliefs, please discuss them with your NIH

Goal


Informed Consent
Research Design
Return of Results

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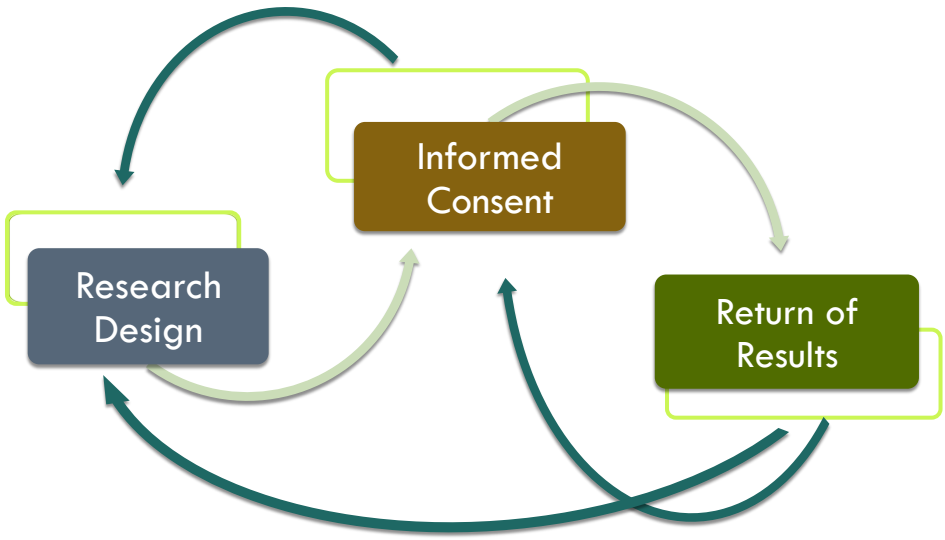
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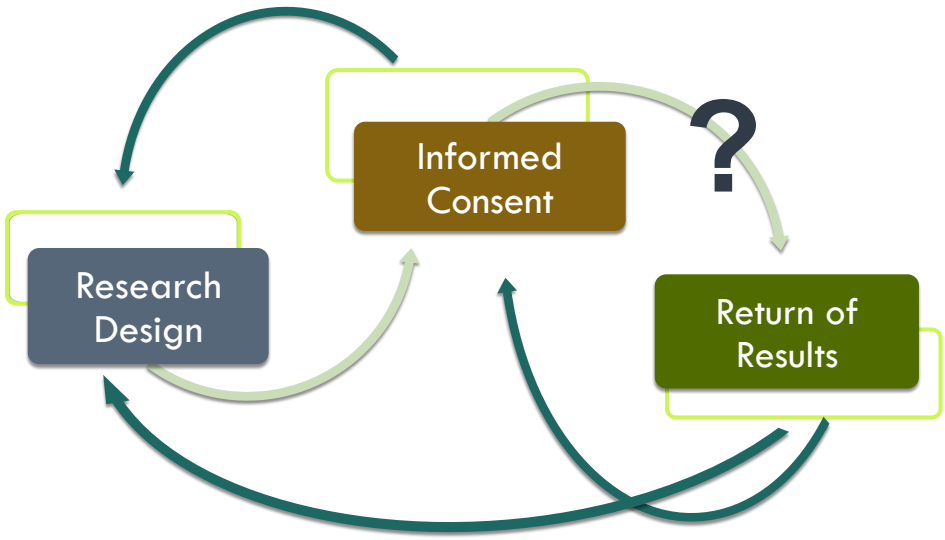

Questions

- "What do I need to keep in mind as I approach (prospective) participants?"
- "How exactly do I go about getting participants' consent?"
- "What about…?
- "How do I return results to participants?"

Outline

- Outline considerations in Whole-Exome Sequencing (**WES**) protocols
- Describe an approach to consent
- Discuss challenging populations and situations
- Explore options for returning results

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Considering Informed Consent

- Informed consent as a process
- An opportunity for researcher-participant dialogue
  - Goals
  - Expectations
  - Plans
- Description of partnership
- Research goals drive informed consent process

Data: inherent challenge

- Volume
  - Immense number of variants per participant
- Nature
  - Continuum from novel to well-characterized
  - Categorization from benign to deleterious
- Iterative generation
  - Downstream use and interrogation

Data: inherent uncertainty

- Data generated are a moving target
- Fully conveying scale and scope is impossible
- Impact on participants varies tremendously
  - Impact on investigators may be non-trivial

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Exome sequencing for gene discovery

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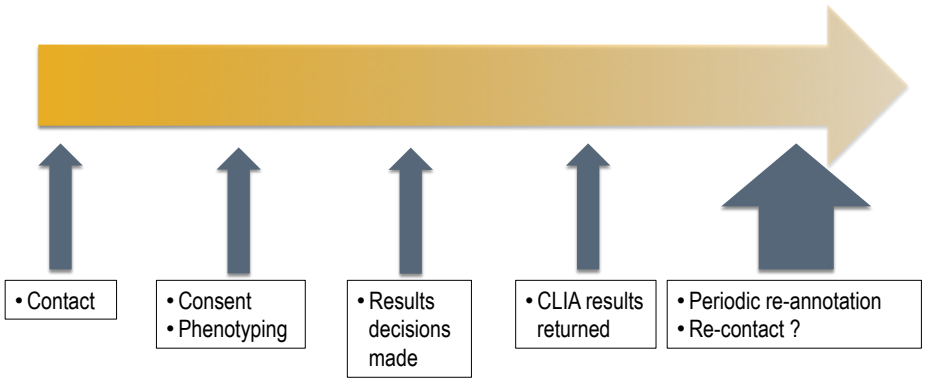
Exome sequencing for gene discovery

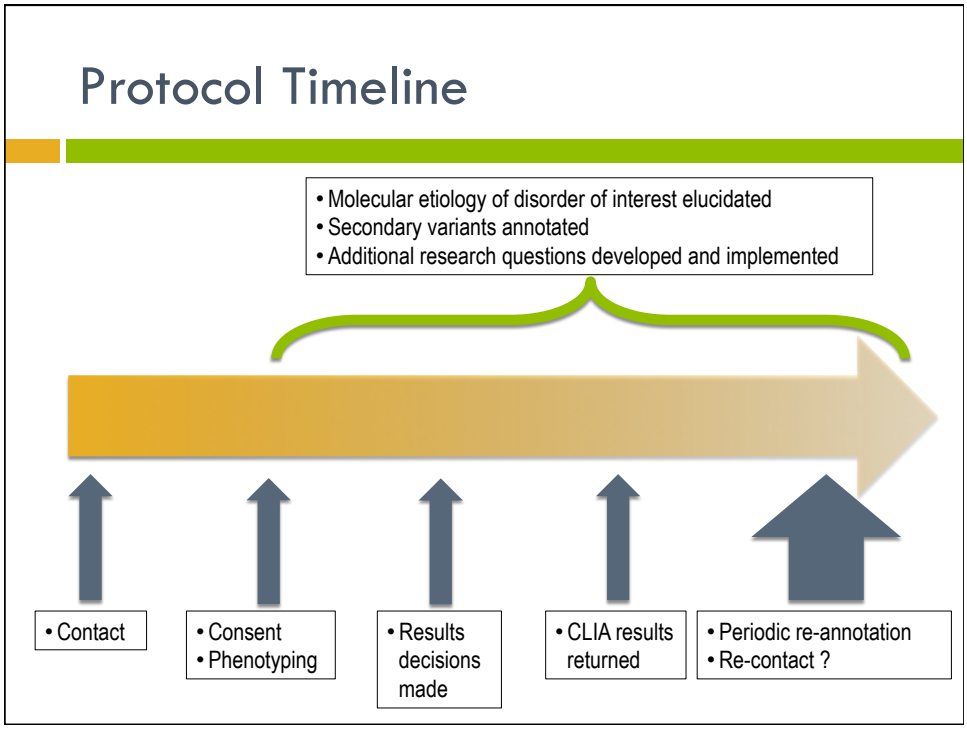
- Protocol enrolls probands with rare disorders
- Broad eligibility criteria
- Trio approach **often** employed
  - But not always
- Comparisons made across probands
  - When possible
- Qualified results disclosure policy

Consent Timeline

- Participant contact initiated
- Phone conversation describing study
- Consent form and one-page summary sent
- Follow-up phone call
- NIH visit for phenotyping and informed consent

Protocol Timeline

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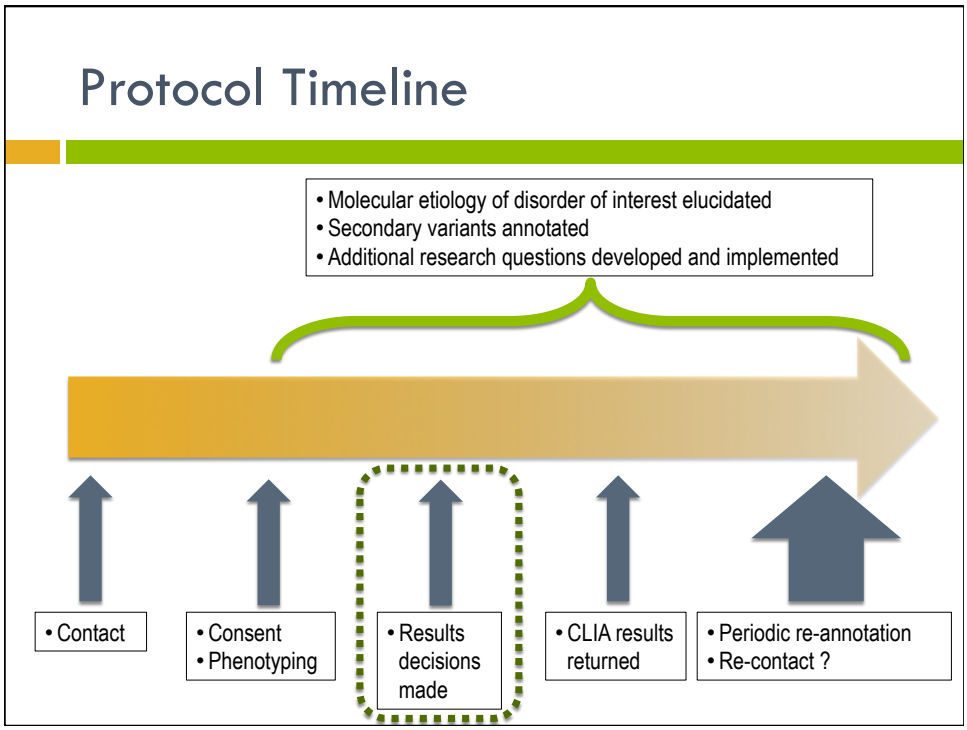
• Molecular etiology of disorder of interest elucidated
• Secondary variants annotated
• Additional research questions developed and implemented
• Contact
• Consent
• Phenotyping
• Results decisions made
• CLIA results returned
• Periodic re-annotation
• Re-contact ?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Results framed in terms of goal

- Broad categorization of results

Primary Variant

- Genetic cause of disorder under investigation

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Primary Variant	Secondary Variants

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Results framed in terms of goal

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Primary Variant	Secondary Variants
Genetic cause of disorder under investigation	Everything else Not goal of study Inherent to methodology

Secondary Variants

- Autosomal recessive disorders
- Disease-causing mutations
  - Current/Future Onset
  - Treatment/Prevention
  - Surprising/Expected
- Uncertain significance
- Normal variation

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- Ancillary to research goal
- Annotation is time-consuming
- Annotation is ongoing
- Represents departure from traditional paradigms
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- May not even be generated!

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Defy complete *a priori* delineation and categorization

Choices about results

- Participants may elect to receive results (or not)
  - Primary variant
  - Secondary variants by category
- Each participant is independent actor
- Duty-to-warn exception explained

Duty-to-warn

- Variants of this type are rare overall
- Not our intent to discover
- Research primacy explained

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Most participants identify with our intent

Familial implications

- Not all family members may undergo same interrogation
- Concerns regarding extended family
- Some approaches requires communication among family members
- Minor children may undergo testing

Why so much detail?

- Return meaningful results to participants
- Enable participants to make informed decisions about results

Once you choose to know something, it is impossible to return to a state of ignorance

Alternatives and withdrawal

- Not like other genetic testing
- Exome sequencing clinically available
- Withdrawal from protocol may not be simple
- Will play role in clinical practice in future

Outline

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Minor probands

- A parent may consent on behalf of child
  - Specific consent form
- Some results may be returned
  - Actionable in childhood
  - Carrier status
  - Actionable in adulthood
    - Very specific circumstances
- Asked to re-contact at age of majority

Intellectual impairment

- Legal guardian/surrogate decision-maker
- Proof required prior to consent
- May require ethics consult

Intellectually impaired minors

- Thorough discussion at time of consent
- Current and future decision-making capacity discussed
- Any results may be returned per family's preference

Not appropriate for some

- Research is not appropriate for everyone
  - Willing to engage over period of years
  - Stable/known family structure
  - Medical and social resources

Outline

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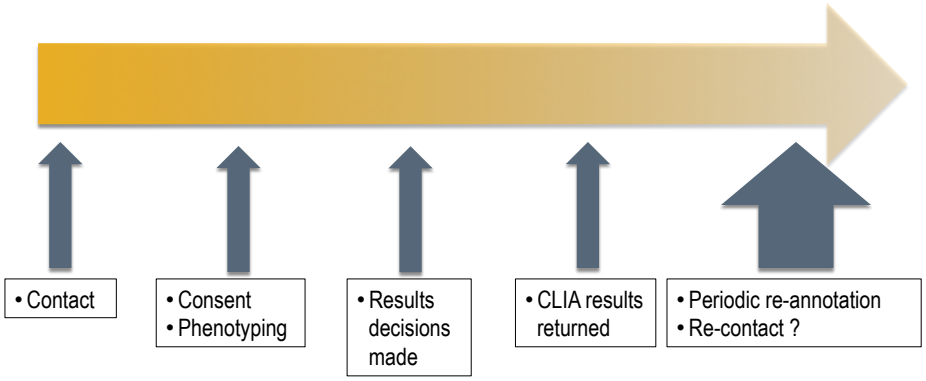
Results disclosure policies

- No results returned
- All results returned
- Some results returned
  - Limited or qualified disclosure

Protocol Timeline



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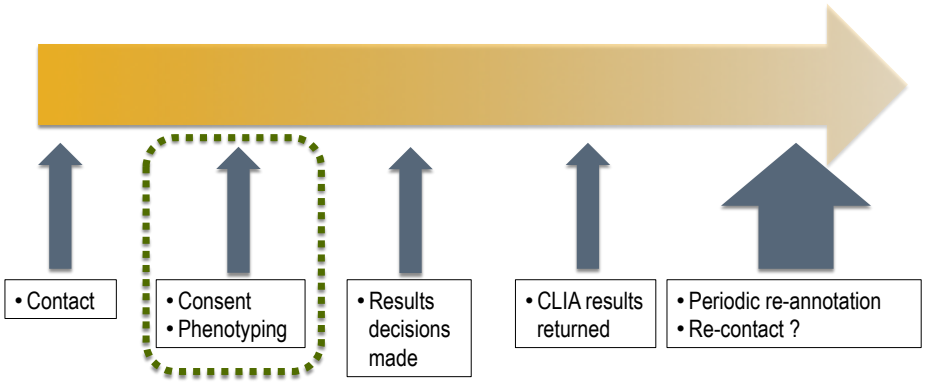

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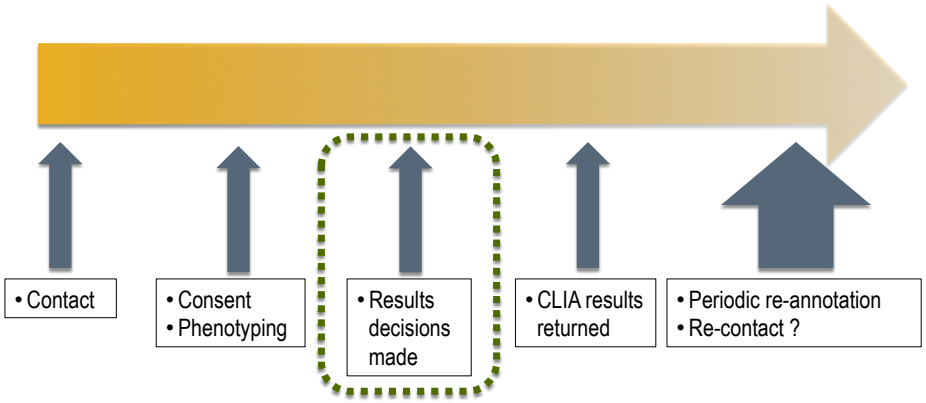


Process

- Results possibilities reviewed, noted
- No commitment to preference at time of consent
- Annotation proceeds per study goal
- Participants re-contacted when available
- Categories reviewed and discussed
- Election made
- CLIA Validation
- Return to NIH for in-person review
  - May happen more than once

Results

I think knowing is better than not knowing. I absolutely want to know whatever you find.

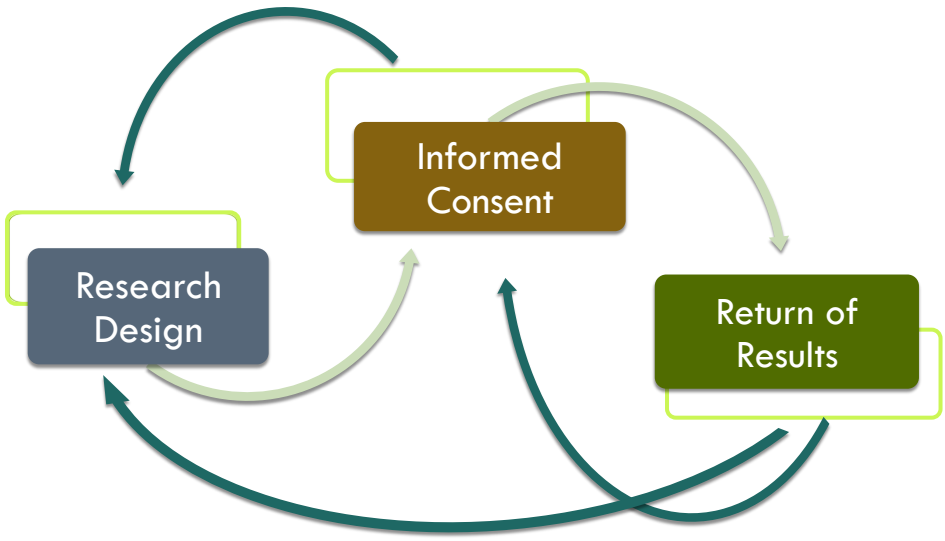
Do you have to look?

I'd probably want to know. I have a great fear of knowing. But I'd want to know.

Conclusions

- Most participants state preference to learn any results
  - Parents want children's results
- Participants align with researchers' goals
- Complexities are understandable
- Participant preferences vary

Conclusion



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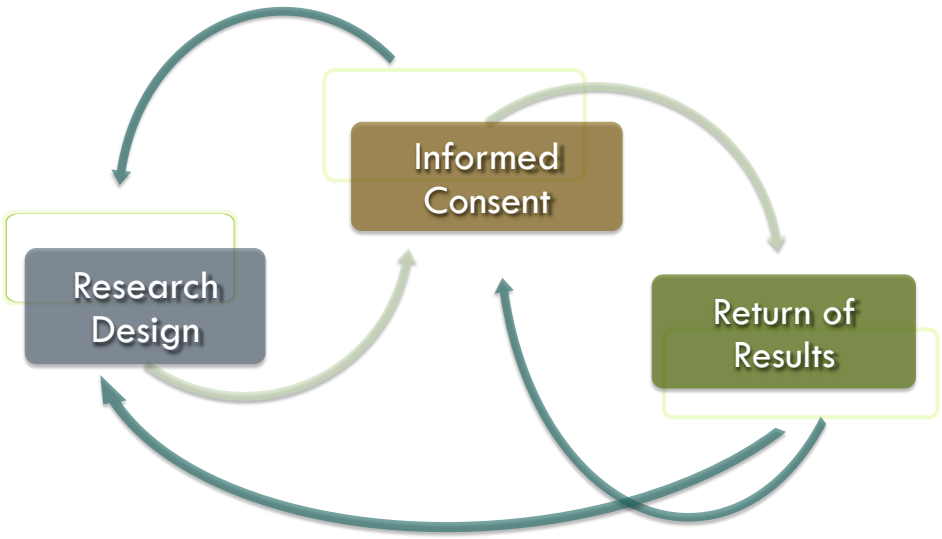

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Thank you!