NIH IRB Expectations for Return of Secondary Genomic Findings to Research Participants

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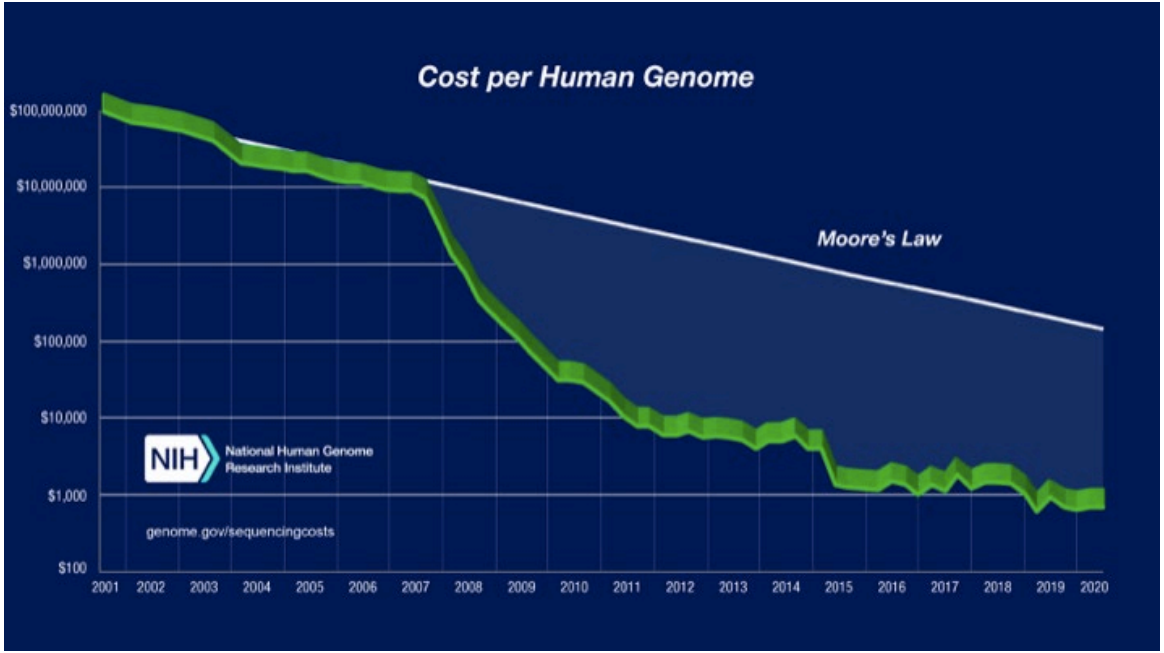
From Targeted Genetic Testing to Next-Generation Sequencing (NGS)

- NGS is a powerful research tool
- Generates massive amounts of data about an individual, beyond that necessary to answer a scientific question
- Can include clinically relevant findings
- What ethical obligations do researchers have with regards to these findings?



Definitions

- Primary research findings
  - Results related to the condition under investigation
- Incidental findings
  - Results that are accidentally found in the course of research analyses
    - Can be research related or not
- Secondary findings
  - Clinical results unrelated to the condition being investigated, but that are actively sought (e.g., ACMG list)

Early Views

- Focused on the type of information that could or should be returned
- No duty to look - “Stumble strategy”
- Little engagement about the kinds of research that should return findings
- Case by case analysis

ACMG

- “Minimum list” of findings to report from any clinical sequence (originally n=53; currently n=78)
  - “unequivocally pathogenic mutations in genes where pathogenic variants lead to disease with very high probability and where evidence strongly supports the benefits of early intervention”
- Variants on the list should be actively sought by the laboratory
  - “Opportunistic Screening”
- Limited to the clinical realm
  - Sporadically transposed to the research setting

Existing ROR Guidance at NIH

- Biesecker working group
  - High-level
  - Requires protocols to explicitly describe their return of results plan (or a plan not to return results)
- Deference to IRBs
  - Study-specific determinations

COMMENTARY

A Clinical Service to Support the Return of Secondary Genomic Findings in Human Research

Andrew J. Darnell,[1] Howard Austin,[2] David A. Bluemke,[3] Richard O. Cannon III,[4] Kenneth Fischbeck,[5] William Gahl,[6] David Goldman,[7] Christine Grady,[8] Mark H. Greene,[9] Steven M. Holland,[10] Sara Chandros Hull,[8,11] Forbes D. Porter,[12] David Resnik,[13] Wendy S. Rubinstein,[14] and Leslie G. Biesecker[15,*]

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Time for Specificity

- Genomic sequencing is everywhere
- Set of genetic information that can help people keeps growing
- As a genomic SOC emerges, the “Wild West” scattershot approach is increasingly unjustifiable
- Blanket deference to IRBs has led to inconsistent and inequitable outcome

Time for Specificity (at NIH)

- Increasing adoption of genomic methodologies
  - CCGO, SGFS, CSP (NIAID), NCI, NHGRI
- Centralization of IRB review
- Opportunity for systematic data collection
  - Understanding phenotypic variation and penetrance
- NIH role as a leader in the field

IRBO Charge

- Convene a working group to establish requirements for a consistent, transparent approach across the IRP to the management and return of of secondary genomic findings

Working Group Process

- Co-Chairs: Sara Chandros Hull, Ben Berkman
- Members
  - Representatives from programs that are actively returning results
    - Secondary Genomic Findings Service
    - NIAID Centralized Sequencing Program
  - Range of roles
    - Investigators, clinical directors, genetic counselors, molecular geneticists, DLM
- Building on previous NIAID return of results working group

Working Group Members

- Kathy Calzone (NCI)
- Luis Franco (NIAMS)
- Karen Frank (DLM)
- Megan Frone (NCI)
- Nicole Grant (OHSRP)
- Leila Jamal (NCI)
- Jennifer Johnston (NHGRI)
- Julie Sapp (NHGRI)
- Morgan Similuk (NIAID)
- Ben Solomon (NHGRI)

* *Jeffrey Menzer (NHGRI)*

Emerging Expectations

- Clinically significant, actionable findings can be important for a subject's health...but, research ≠ clinical care
- Secondary findings are a kind of ancillary care
- Ancillary care is medical care that arises during research, but that is unrelated to the research, where:
  - There is high benefit to participant
  - The research enterprise is uniquely situated to help
  - There are relatively low costs to the research enterprise
- Malaria example

Emerging Expectations

- Current IRB position: Any protocol that involves sequencing must have a plan about secondary findings (even if that plan is to not return them)

- New IRB position: There will be an expectation that certain studies will return secondary findings

Emerging Expectations

- Which studies will be expected to return secondary findings?
  - Only new studies
  - Only studies generating data that can easily be interrogated for secondary findings
    - No need to generate genomic data beyond that necessary to answer research questions
  - Only studies where there is a significant clinical relationship
    - Deeper clinical relationship → Stronger presumption in favor of disclosure

Depth of Clinical Relationship: Some Examples

- Genomic studies that involve extensive, repeat workups at the Clinical Center
  - Probably will return secondary findings
- Secondary research with samples collected elsewhere
  - No need to return secondary findings
- One-time interaction
  - No need to return secondary findings, but…
    - As ICs develop centralized services, this presumption could evolve

Miscellaneous Issues

- Only applies prospectively
- One-time analysis is sufficient
  - ACMG list
- No negative reports required
  - ~3-4% expected positive result rate

Miscellaneous Issues

- Distinct cohorts within a protocol can be treated differently
- Rebuttable presumption
- Setting a floor
- Right not to know

CLIA

- Do researchers have to get positive findings CLIA-validated before returning them?
  - Yes.
- HIPAA and CLIA create conflicting legal (and ethical) obligations
- Whenever feasible, collect a second sample at the initial sample collection timepoint so that findings can be confirmed without asking for another sample

Existing Resources

- Secondary Genomics Findings Service
- NIAID Centralized Sequencing Program
- NISC
- Commercial Services
- Other emerging shared intramural resources

Feasibility and Cost

Cost estimates for a Secondary Genomics Findings Consultation service in the Intramural Research Program of the National Institutes of Health.

Table S1: Overall Costs

Number of Analyzed Exomes or genomes per year	Number of secondary findings per year	Salaries & Benefits (Table 2)	Sample intake costs	ABI Arrays	PCR Validations	Office & Computer Expenses	Fixed Costs*	Total Projected Cost	Cost per Exome
1,000	50	$82,600	$500	$1,000	$3,000	$2,500	$50,000	$139,600	$140
5,000	250	$188,000	$2,500	$1,000	$15,000	$5,000	$50,000	$261,500	$52
10,000	500	$327,600	$5,000	$1,000	$30,000	$10,000	$50,000	$423,600	$42
20,000	1,000	$516,00	$10,000	$2,000	$60,000	$15,000	$50,000	$653,000	$33

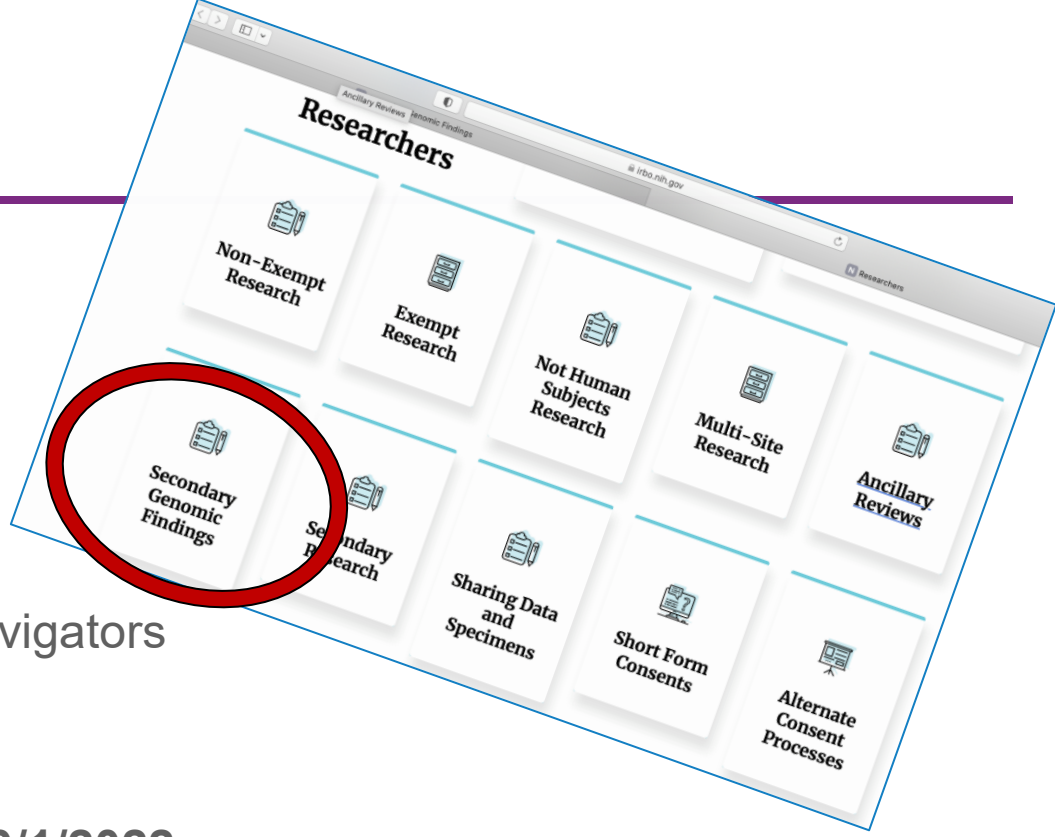
Fixed costs include software licensing, sequencer service contract and amortization, etc.

Table S2: Staffing Costs

Darnell et al. (2016)

Next Steps

- IRBO Website
  - Protocol template and consent library language
  - Additional resources
- Education
  - Research teams and protocol navigators
  - IRB members and staff
- Implementation
  - New protocols submitted **after 10/1/2022**
- Evaluation (ongoing)



Questions?

- https://irbo.nih.gov/confluence/display/ohsrp/Researchers
- IRB@OD.nih.gov