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

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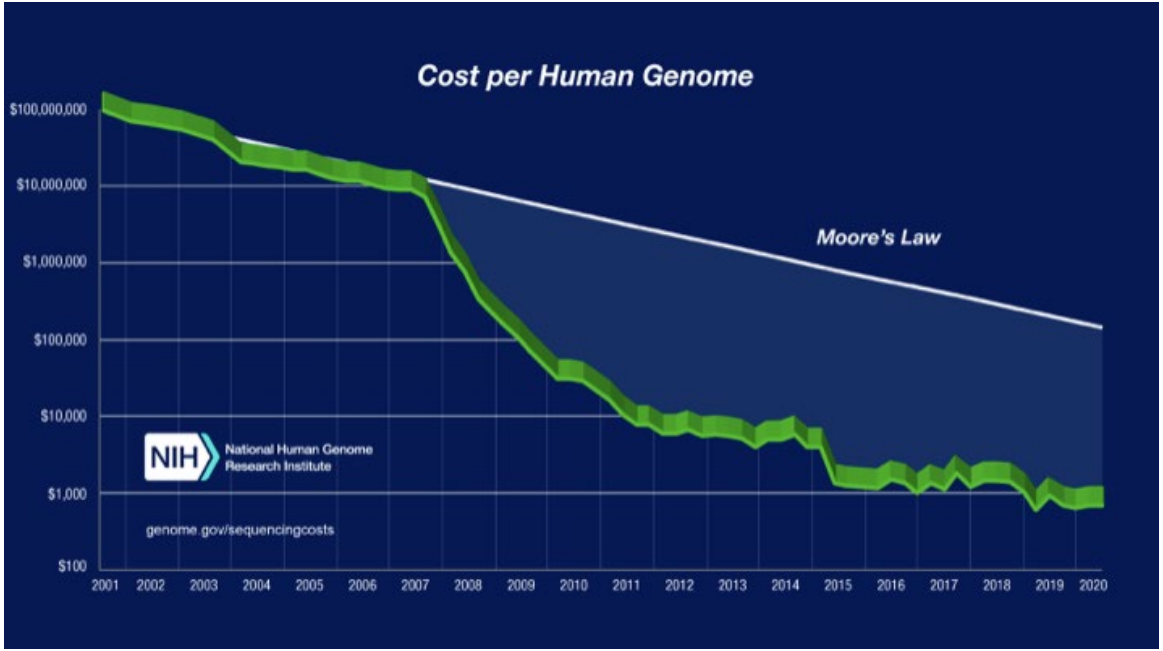
From Targeted Genetic Testing to Next-Generation Sequencing (NGS)

- 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

A Decade Later

- Genomes are cheap (~$1000)
- Increasingly ubiquitous
  - 2003 – 1
  - 2015 – 50,000
  - 2018 – 1.5M
- Research is a large driver of this sequencing
  - UK Biobank + AOU = millions subjects

A Decade Later

- Increasing clinical utility
  - 75,000 genetic tests actively available
  - 5,210 new tests per year (2017) – 14.3 per day
  - 3% of FDA approved drugs have pharmacogenomic recommendations
- Improving quality and reliability
  - Regular increases in coverage/resolution of sequencing

A Decade Later

- Proliferation of expertise and guidance
  - e.g, ClinVar, gnomAD, ClinGen
  - Clinical molecular genetics - new area of expertise straddling pathology and medicine
- From dangerous to consistent and fairly well-established
  - Psychosocial risks seem to be minimal
  - Genomic information = medical information

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 outcomes

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
- General duty of rescue
  - Beneficence based
  - Applies to everyone

Emerging Expectations

- Ancillary care obligations are like the duty to rescue, but specifically for researchers
  - Malaria example
- Secondary findings are a kind of ancillary care
- "Ancillary care is that which goes beyond the requirements of scientific validity, safety, keeping promises, or rectifying injuries.” (Belsky and Richardson)
- Situations where there is a **significant need** that the researcher is **uniquely** able to address at **little cost** to the research enterprise

Ancillary Care

- Incidental findings have been conceptually linked to ancillary care
  - General (Bredenoord; Ulrich; Beskow and Burke)
  - Partial entrustment model (Richardson)
  - Duty to look (Gliwa and Berkman; Savulescu)
  - IFs in low-resource settings (Sullivan and Berkman)

- Ancillary care seems like a plausible model
  - Specifies conditions when results should be returned
  - Balances benefit to participant and burden to research enterprise

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

- Cases where there probably is an obligation to return secondary findings
  - Longitudinal studies of rare disorders where the goal is to perform deep phenotyping as well as analysis of exome and/or genome data
  - Mail-in samples obtained from participants with rare disorders where the goal is to perform significant genetic interrogation of exome data to understand their specific disease
  - A study that does not regularly perform large-scale sequencing, but occasionally does so for select subjects, would have an obligation to those specific subjects

Depth of Clinical Relationship: Some Examples

- Cases where there probably is NOT an obligation to return secondary findings
  - A protocol that involves secondary analysis of data collected elsewhere
  - A protocol looking at genetic factors relating to host-susceptibility for COVID-19, where even though there is an extensive health history taken, the participants are being seen only once and do not expect to receive any clinical care or information from the research team
  - A large-scale population health study where participants regularly fill out health related questionnaires, but where there is minimal direct engagement except in select cases where subjects are recruited for specific sub-studies
  - A study that obtains consent and samples up front for genetic analysis, but explicitly does not plan to do that analysis for many years and does not have ongoing interactions with the participants

Depth of Clinical Relationship: Trickier Cases

- How much interaction is sufficient to count as a significant clinical relationship?
  - One-time interaction with significant physical workup and/or advice about disease management
  - Local doctors are AIs on an intramural protocol
  - Send-in samples from relatives of CC patients who are enrolled to help with the interpretation of proband data

- Local context considerations and the actionability problem
  - A study that focuses on the health of particular community and meaningfully engages community members in the development and implementation of the research, also known as community-based participatory research
  - Protocol where the NIH researchers recruit international participants and develop a substantial clinical relationship, but when patients do not come to the CC

Depth of Clinical Relationship: Questions and Discussion

Miscellaneous Issues

- Only applies prospectively
- One-time analysis is sufficient
  - ACMG list is the default
- 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	$516,000	$10,000	$2,000	$60,000	$15,000	$50,000	$653,000	$33

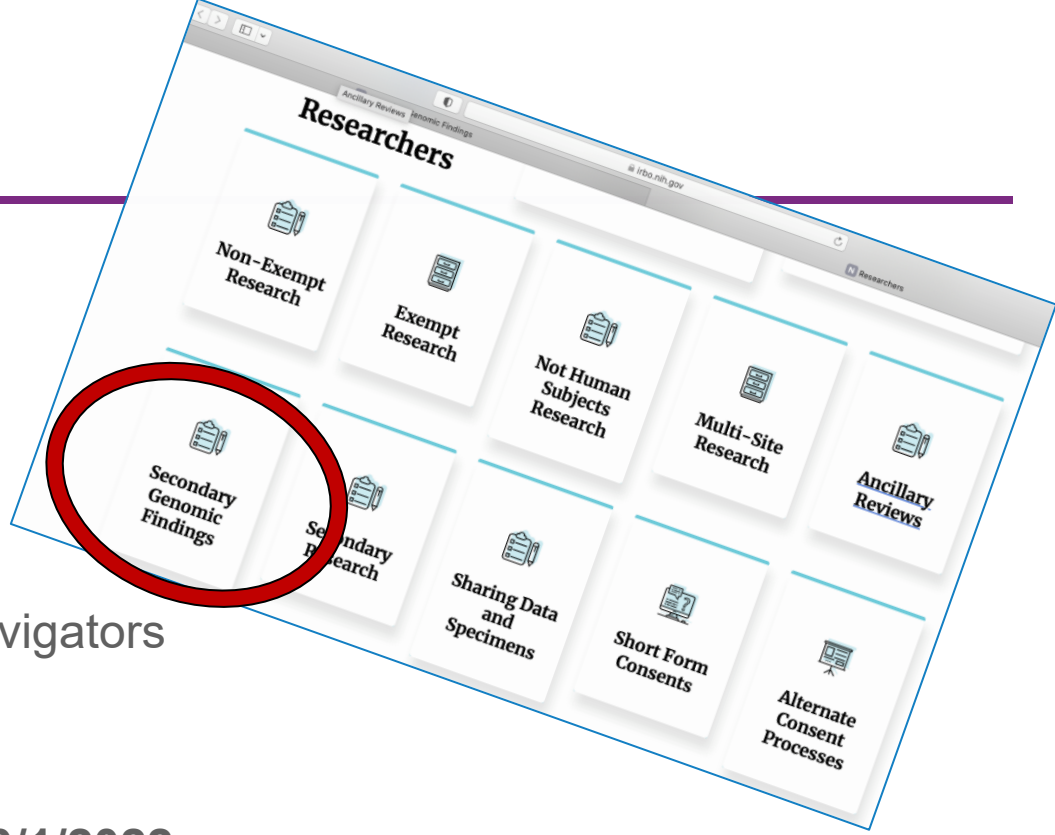
Fixed costs include software licensing, sequencer service contract and amortization, etc.

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