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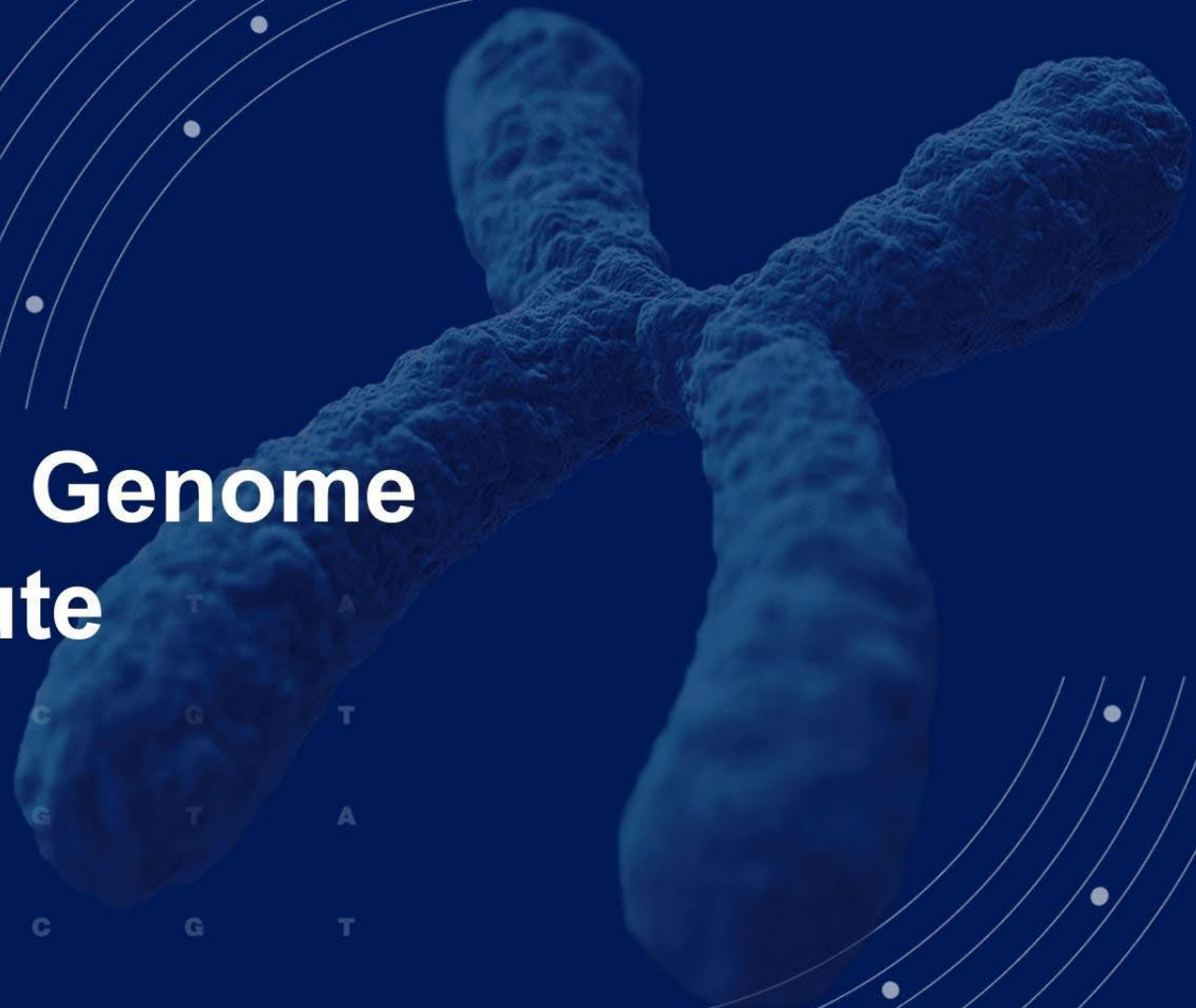

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The Ethics of Genetic Incidental Findings

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National Human Genome Research Institute

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Disclaimer

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

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Roadmap

- Background: next-generation sequencing
- Towards a policy for genetic incidental findings in research
- Unresolved ethical controversies and questions

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Glossary of Terms/Acronyms

- GWAS = genome-wide association studies
- SNP = single nucleotide polymorphism
- dbGaP = database of Genotypes and Phenotypes
- WES = whole exome sequencing
- WGS = whole genome sequencing
- NGS = next generation sequencing
- IF = incidental findings

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Definition

- An incidental result is:
  - "[A] finding concerning an individual research participant *that has potential health or reproductive importance* and is discovered in the course of conducting research *but is beyond the aims of the study*"

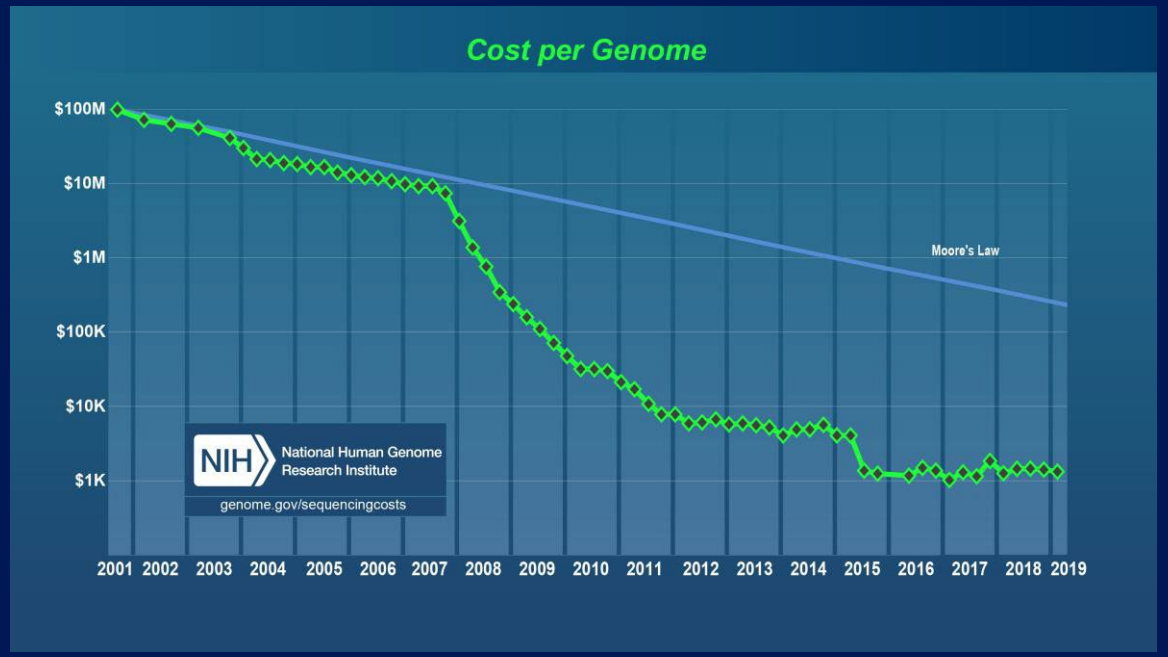
Wolf, et. al. Managing Incidental Findings in Human Subjects Research. JLME (2008).

Warm-up Case

- A clinical researcher is studying the genetic etiology of breast cancer in a group of subjects that present for treatment at an academic medical center. After obtaining research-specific informed consent, the study team generates sequences data from surplus tumor tissue that had been removed for clinical purposes. They are interrogating the BRCA region to search for novel disease-associated variants. They propose to de-identify their sequence data, and do not plan to return any results. Although they are not searching for known disease-associated variants, it is likely that they will occasionally discover known BRCA variants that could be clinically relevant, particularly for near-term treatment decisions.

The Incidental Findings Problem

From Targeting 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 obligation do researchers have with regards to these findings?

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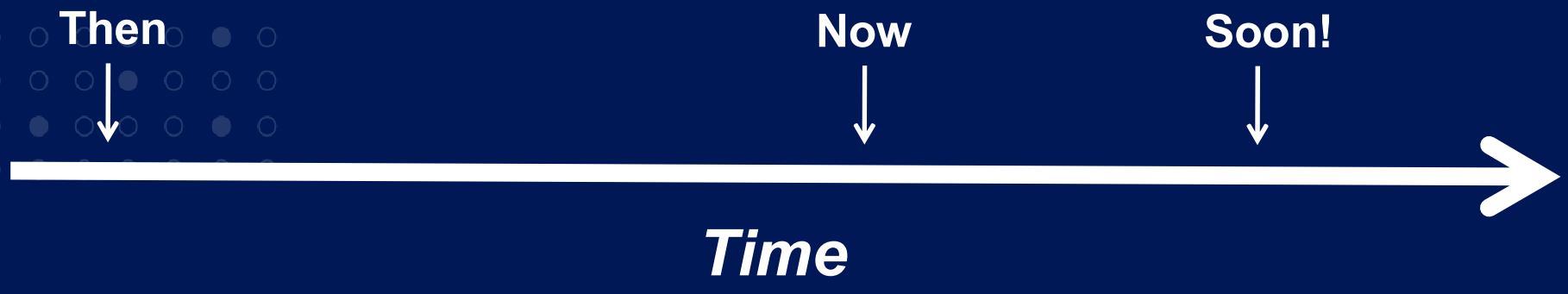
En Route to Routine Whole-Genome Sequencing

Targeted Genetic Research

Whole ‘Exome’

Whole Genome



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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 clinical findings
  - 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
- “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

Towards a policy for genetic incidental findings in research

Existing ROR Guidance

- Very high-level
  - Avoid making specific recommendations
- Deference to IRBs
  - Study-specific determinations
- Punt on controversial issues

Time for Specificity?

- Genomic sequencing is everywhere
- Set of genetic information that can help people keeps growing
- As a genomic SOC is established, the Wild West scattershot approach is increasingly unjustifiable
- Deference to IRBs leads to inconsistent and inequitable outcomes

Initial Views on Whether There is an Obligation to Disclose GIFs

Do you believe that researchers have an obligation to disclose genetic incidental findings to participants?

Always	13%
Sometimes	65%
Rarely	13%
Never	2%
Don’t know	7%

Gliwa C, Yurkiewicz I, Lehmann LS, Hull SC, Jones N, Berkman BE. IRB Perspectives on Obligations to Disclose Genetic Incidental Findings to Research Participants. *Genetics in Medicine* 18(7): 705-711 2016.

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Factors that can diminish an obligation to disclose GIFs

	Strongly agree or agree
Inadequate clinical or analytic validity	71%
Inadequately demonstrated clinical utility	66%
Lack of funding, resources or infrastructure	29%
Adverse psychological impact	23%
Participants won't understand	22%
Investigators ≠ clinicians	18%
Time and effort required	7%

#1 (validity) and #2 (utility) > #3, #4, #5, #6, #7 ($p<0.05$)

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An Emerging View?

- Beneficence
  - Some genetic information can be very clinically important
- But research ≠ clinical care
  - Researchers cannot be responsible for the entire medical care of the subject
- Duty to rescue/ancillary care

Duty to Rescue

- General duty to rescue
  - Applies to everyone
  - Operative when
    - Benefit of rescue is very high
    - Burden of rescue is relatively low

Ancillary Care

- Ancillary care obligations are a related role-specific obligation for researchers
- "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
- But…
  - Makes ROR dependent on researcher expertise and protocol specific resources
    - Inefficient
    - Justice concerns

Institutional Duty of Easy Rescue

- Some have argued that the duty to rescue applies to institutions rather than individuals (Rulli and Millum; MacKay and Rulli; Garrett)
  - Limits scope of duty (to research subjects)
  - Provides framework to balance rescue obligations with institutional goals
- Related to a professional duty to rescue

My Claim

- There is a broad but shallow obligation to return genetic results generated in research
  - Broad in the sense that it applies to most research protocols
  - Shallow in the sense that it employs a fairly high threshold for what information needs to be returned

My Initial Claim

- This obligation falls to the institution (e.g., NHGRI, NIAID, NIH) rather than individual researchers, because:
  - Individual researchers will often lack the right expertise to analyze and return non-primary (i.e., non-immunological) findings
  - A centralized resource can be created/expanded to more efficiently and effectively provide support to investigators
  - Creates a uniform policy that solves the fairness problem that plagues most institutions (intramurally and extramurally)

Are There Limits on the Scope of ROR Obligations?

Do All Studies Have to Return Incidental Findings?

- 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

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Incorporating Factors Relating to the Research Characteristics

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

Incorporating Factors Relating to Subject Characteristics

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

Scope of Obligation

- How can we delineate the kinds of research where there is no duty to return results?
- Richardson's "partial entrustment model"
  - When subjects enroll in a study, they entrust limited aspects of their health to researchers
  - Ancillary care obligations only attach to "entrusted" aspects of health
- Four cases

Case 1

- A medical geneticist wants to add WES to his existing natural history study of a rare genetic disease. This would include analyzing specimens that were already collected under this protocol.
- Subjects enrolled in the study have ongoing contact with the research team, participating in quarterly follow-up visits and receiving standard of care treatment as needed.
- The original consent describes genetic analysis and a general plan not to return incidental findings unless clinically relevant to the management of the disease being investigated.

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Scope of Obligation – Case 1

- Patients seen at the Clinical Center by intramural investigators where there is a substantial clinical relationship, including sequencing
  - Clear broad entrustment of medical care and specific entrustment of genetic information
  - Definitely return

Case 2

- NIH investigators are collecting WGS and identifiable clinical data from populations in low-resource African countries. Based on experience with similar studies in the US, they propose to analyze the data for the ACMG list of 56 high-value incidental findings. Given the lack of health care resources available to their African participants, it is unlikely that they will be able to access treatment for any positive findings.

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Scope of Obligation – Case 2

- International genetic research projects conducted by intramural investigators where there is a substantial clinical relationship, but when patients do not come to the CC
  - Similar to Case 1; clear entrustment
  - Default to return findings, just like for CC patients

Scope of Obligation – Case 2

- Caveat #1: First ask local representatives if returning results makes sense in their context
  - Consideration of unintended negative consequences in specific local contexts
- Caveat #2: Actionability problem
  - Solicit preferences about RNTK

Case 4

- An NIH researcher has identified a source of clinical samples from patients at a biobank.
- The samples were collected with written informed consent and IRB approval.
- The NIH researcher will have access to deidentified/coded information about these patients.
- The NIH researcher wants to proceed with whole genome sequencing.

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Scope of Obligation – Case 4

- Secondary research on deidentified samples/data not collected by NIH intramural researchers
  - No entrustment to secondary researchers, so no obligation to return findings (primary or secondary)
  - [Contra Richardson]
- Caveat: We want to discourage projects from deidentifying samples/data solely to avoid having to return results (i.e., only when there is a strong scientific justification for deidentification)

Case 3

- A bench scientist studying a common, complex disorder wants to initiate a protocol to collect samples prospectively for WES.
- The protocol involves a one-time blood draw. Subjects will be recruited from sites across the country.
- There is no ongoing clinical relationship between researcher and subjects (but assume that recontact is feasible).

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Scope of Obligation – Case 3

- Subjects seen by intramural investigators where there is only minimal contact (e.g., one-time blood draw) or research on identified secondary samples
- Even if one accepts the partial-entrustment model, it isn't always obvious whether there has been sufficient entrustment in these marginal cases to derive an obligation to return

Unresolved Controversies

Unresolved Controversies

- Legacy samples and reconsent
- Returning results to relatives of deceased probands
- CLIA
- Right not to know

Legacy Samples and Reconsent

- “Freezer problem”
- General consent language (e.g., “genetic research”) that hasn’t anticipated new sequencing technologies
- Is it ethical to allow researchers to sequence these samples?
  - Should incidental findings be sought and returned?
  - Only with prior consent?

ROR to relatives of (deceased) probands?

- While the obligation to relatives with whom there is no relationship has to be less than the obligation to a proband, findings should be returned in some circumstances
  - Although it is acceptable to set a higher bar for severity, i.e., only return findings to relatives when they can have potential direct implications for their health

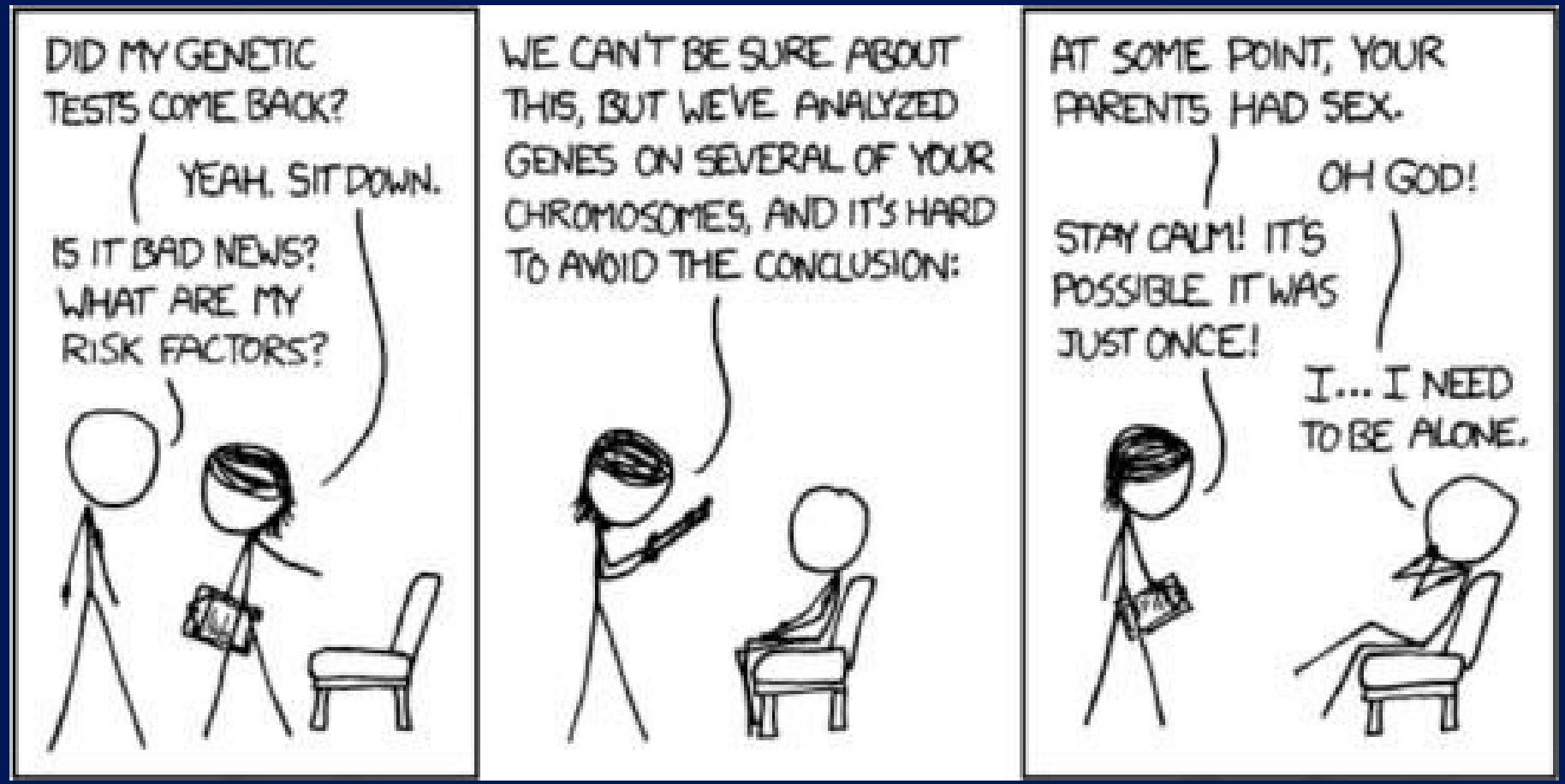
ROR to relatives of (deceased) probands?

- In most circumstances, the obligation can be satisfied by doing the following:
  - If the patient is alive, tell the patient to tell their family
  - If the impacted relative is enrolled in the study, tell them directly
  - In pediatric cases, tell the parents
  - If the patient is deceased, tell the next-of-kin or primary contact person
    - In some situations, the treating physician might have relationships with relatives of the deceased proband and could serve as the conduit for returning the information
- A reasonable effort standard is sufficient to discharge this obligation, but those efforts (and their outcome) should be documented in the chart

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
- Sanger sequencing of the relevant variant is sufficient, although CLIA-compliant sequencing platforms are available
- Data quality thresholds and a centralized genomics service will mitigate this problem

The Right Not to Know?



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A Case

- P is having her genome sequenced and during the informed consent process opts not to receive any incidental results. During their analysis, her physicians find evidence of high genetic risk for Hereditary Non-Polyposis Colon Cancer (HNPCC). They believe that this information will prevent serious disease and perhaps even save P's life. Should they disclose the finding, even though P indicated that she did not want to receive any secondary findings.

One Area of Apparent Consensus?

- Findings should only be returned when they are desired by the research participant
- An obligation to *offer* individual findings to research subjects
- Discuss right not to know and solicit subject preferences
  - IFs should only be *offered* when “During the informed consent process or subsequently, the study participant has opted to receive his or her individual genetic results.”

ACMG Recommendations

- “Minimum list” of incidental findings to actively search for and report from any clinical sequence (n=59)
  - “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”
- Controversially, ACMG argued that these variants should be returned **without soliciting patient preferences** about knowing or not knowing
- An uproar ensued; ACMG walked back their recommendations

The Right Not to Know (RNTK)

- Proponents of the RNTK argued that returning information to patients without soliciting their preferences is a violation of patient autonomy
- Even when life-saving, some have argued that autonomy should take priority over concerns of beneficence

RNTK Skeptic

- Philosophically shaky
- RNTK ≠ right to refuse medical treatment
- Opinions are easily shifted
- Strong RNTK would do more harm than good
- Moral distress and genetic exceptionalism

Right Not to Know

- Refusers aren't a monolithic group
  - 42 "strong refusers" (declined at both timepoints)
  - 41 "weak refusers" (declined then accepted)
- Strong refusers demonstrated significantly higher concordance (Fisher's exact, $p < 0.001$)
- 75% of weak refusers incorrectly thought they had agreed to receive SFs

A Normative Question

- Should RNTK policies be constructed to accommodate this very small group, given the significant harms of patients or participants misreporting their preferences on a consent form
  - Whose interests are more important: weak or strong refusers?
  - Is the availability of a clear but passive opt-out mechanism sufficient to respect strong refusers' autonomy?

Right Not to Know

- Don’t explicitly solicit preferences during the consent process
- If a subject raises a concern about not knowing, and clearly understands what they are potentially declining to learn, honor that choice not to know
- When there are subjects for whom genetic findings might not be clinically actionable (e.g., terminally ill patients, low-resource settings) it is appropriate to solicit preferences
- Protocol teams (or the centralized genomics resource) needs to develop a practical mechanism to document and track these rare exceptions

RNTK Articles

- Schupmann W, Miner SA, Sullivan HK, Glover JR, Hall JE, Schurman SH, and Berkman BE. Exploring the Motivations of Research Participants Who Choose Not to Learn Medically Actionable Secondary Genetic Findings about Themselves. *Genetics in Medicine* (2021).
- Berkman BE. Refuting the Right Not to Know. *Journal of Healthcare Law and Policy* 19(1): 1-75 (2017).
- McGrew S, Raskoff, S, Berkman BE. When Not to Even Ask: A Defense of Choice-Masking Nudges in Medical Research. *Journal of Health Care Law and Policy* (2022).
  - Available at: https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3908716
- Gliwa C, Yurkiewicz I, Lehmann LS, Hull SC, Jones N, Berkman BE. IRB Perspectives on Obligations to Disclose Genetic Incidental Findings to Research Participants. *Genetics in Medicine* 18(7): 705-711 (2016).

Emerging NIH IRB Expectations

- Clinically significant, actionable findings can be important for a subject's health
- Research ≠ Clinical care
- Secondary findings are a kind of ancillary care
  - High benefit to participant
  - Research enterprise is uniquely situated to help
  - Relatively low cost to research enterprise

Emerging NIH IRB 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
  - New studies only
  - No need to generate genomic data beyond that necessary to answer research questions
  - Distinction between studies based on depth of clinical relationship

Depth of Clinical Relationship

- Deeper clinical relationship → Stronger presumption in favor of disclosure
  - Secondary research with samples collected elsewhere
    - No need to return secondary findings
  - Genomic studies that involve extensive, repeat workups at the Clinical Center
    - Probably will return secondary findings
  - One-time interaction
    - No need to return secondary findings, but…
      - As centralized services are developed, this presumption could evolve

Miscellaneous Issues

- Only applies prospectively
- One-time analysis sufficient
  - ACMG list
- No negative reports required
  - ~3-4% expected positive result rate
- Distinct cohorts within a protocol can be treated differently
- Rebuttable presumption
- Setting a floor
- Right not to know

Thank You!

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Questions?

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