The Evolving Ethics of Returning Genetic Research Results

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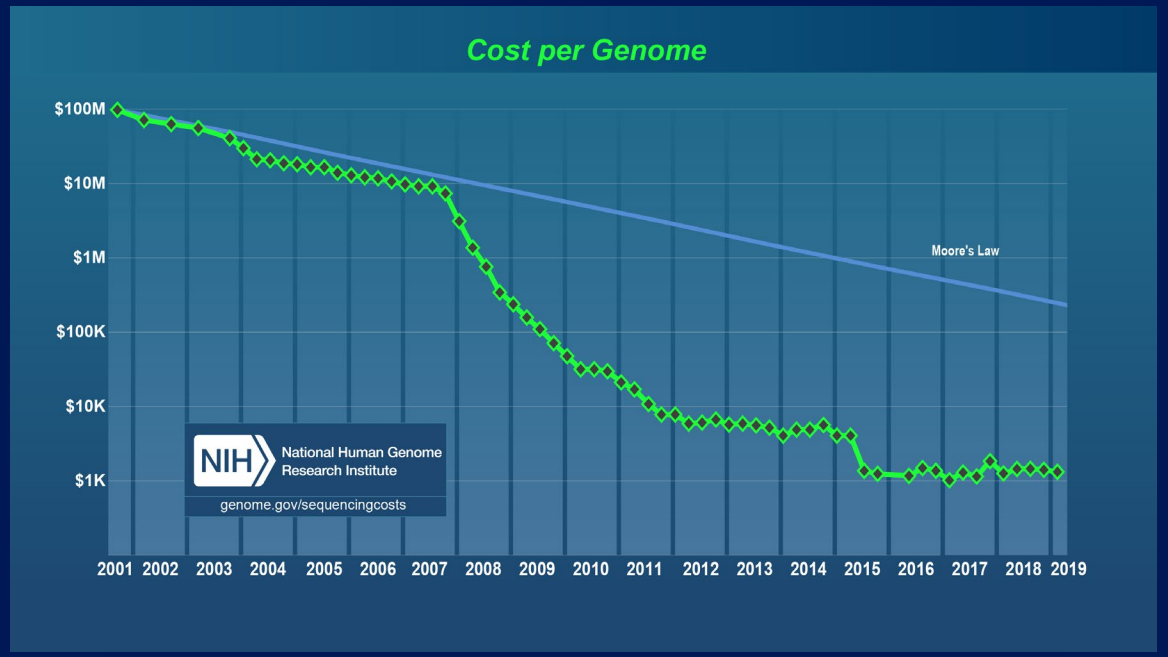
The Forefront of Genomics®

Roadmap

- Background/early views/framing the problem
- Ethical challenges
- NIH intramural policy

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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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).

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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
- Secondary clinical findings
  - Results unrelated to the condition being investigated, but that are actively sought (e.g., ACMG list)

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.

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
  - IRB reluctance to approve return

A Decade Later

- Genomic sequencing is cheap and ubiquitous
- Proliferation of expertise and guidance
- From dangerous to well-established
  - Psychosocial risks seem to be minimal
  - Genomic information = medical information
- Broadly held view that there is some obligation to look for and return a defined set of secondary findings

Why Is There a Duty to Look for Genetic Research Results?

- 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
  - E.g., malaria example

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

Why Is There a Duty to Look for Genetic Research Results (GRR)?

- Duty to rescue/ancillary care seems like a plausible model
  - Specifies conditions when results should be returned
    - High benefit
    - Low burden
    - Unique opportunity
  - 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

Individual vs. Institutional Duty

- The obligation to return results falls to the institution 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)

Ethical Challenges and Unresolved Controversies in Returning Genomic Research Results

Other Ethical Issues

- Legacy Samples and reconsent
- Returning results to relatives of deceased probands
- CLIA/Validation
- Return of pediatric genomic results
- Borderline findings
- 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

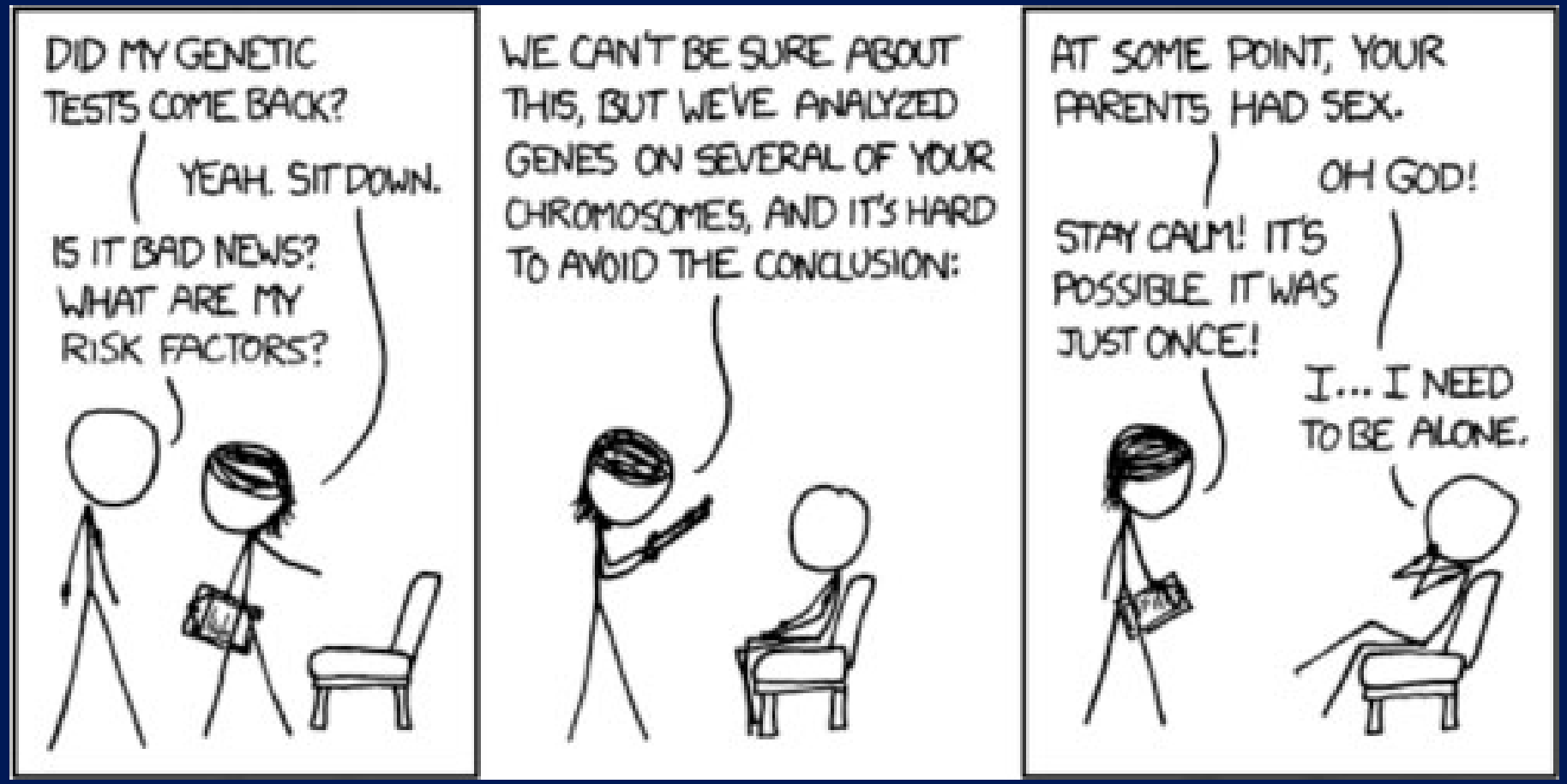
Pediatric Findings

- Right to an open future
  - Evolving guidance
- Reconsent at age of majority
- Misattributed parentage

Borderline Findings

- When should researchers offer to return findings not on a defined list (e.g., ACMG)
- 3V framework
  - Validity
  - Value
  - Volition

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.

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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

NIH policy for genetic incidental findings in research

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
- Existing guidance is very high level, and avoids making specific recommendations

IRBO Charge

- Convene a working group to establish more directive requirements for a consistent, transparent approach across the NIH intramural research program

Our Proposal

- 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 high threshold for what information needs to be returned (i.e., ACMG list)
- Obligation falls to NIH, not individual investigators
  - Centralized resources

Depth of Clinical Relationship

- Define the kinds of research where there is (or is not) a duty to return results
- 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
    - Probably return secondary findings
  - One-time interaction
    - No need to return secondary findings, but…
      - As centralized services are developed, this presumption could evolve

Emerging IRB Expectations

- New and substantially revised studies only
  - Not retroactive
- No need to generate genomic data beyond that necessary to answer research questions
- Distinction between studies based on depth of clinical relationship
  - Expectation will evolve over time, and as centralized resources are expanded/created

Thank You!

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