Incidental Findings and Next-Generation Genomic Research

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Disclaimer

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

Roadmap

- Background: next-generation sequencing
- Incidental findings in genetic research
- Unresolved ethical controversies and questions

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

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.

Facts

- The study was designed to examine the genetic basis of breast cancer subtypes in an understudied minority population
- It represented a collaboration between X University and NIH researchers
  - Clinical samples would be collected and at the extramural site, but would be sequenced and analyzed at NIH

Facts

- The research team planned to de-identify the samples obtained.
- The relevant consent language read:
  - “Your name and anything else that could identify you will be removed and kept in a separate file. There will be a master list that links the code number to your name. This list will be stored on a secure computer with many levels of password protection.”

Facts

- The original research plans did not intend to inform prospective research participants of their individual research results.
- The relevant consent language read:
  - “You should not expect to get individual results from research done with your blood.”

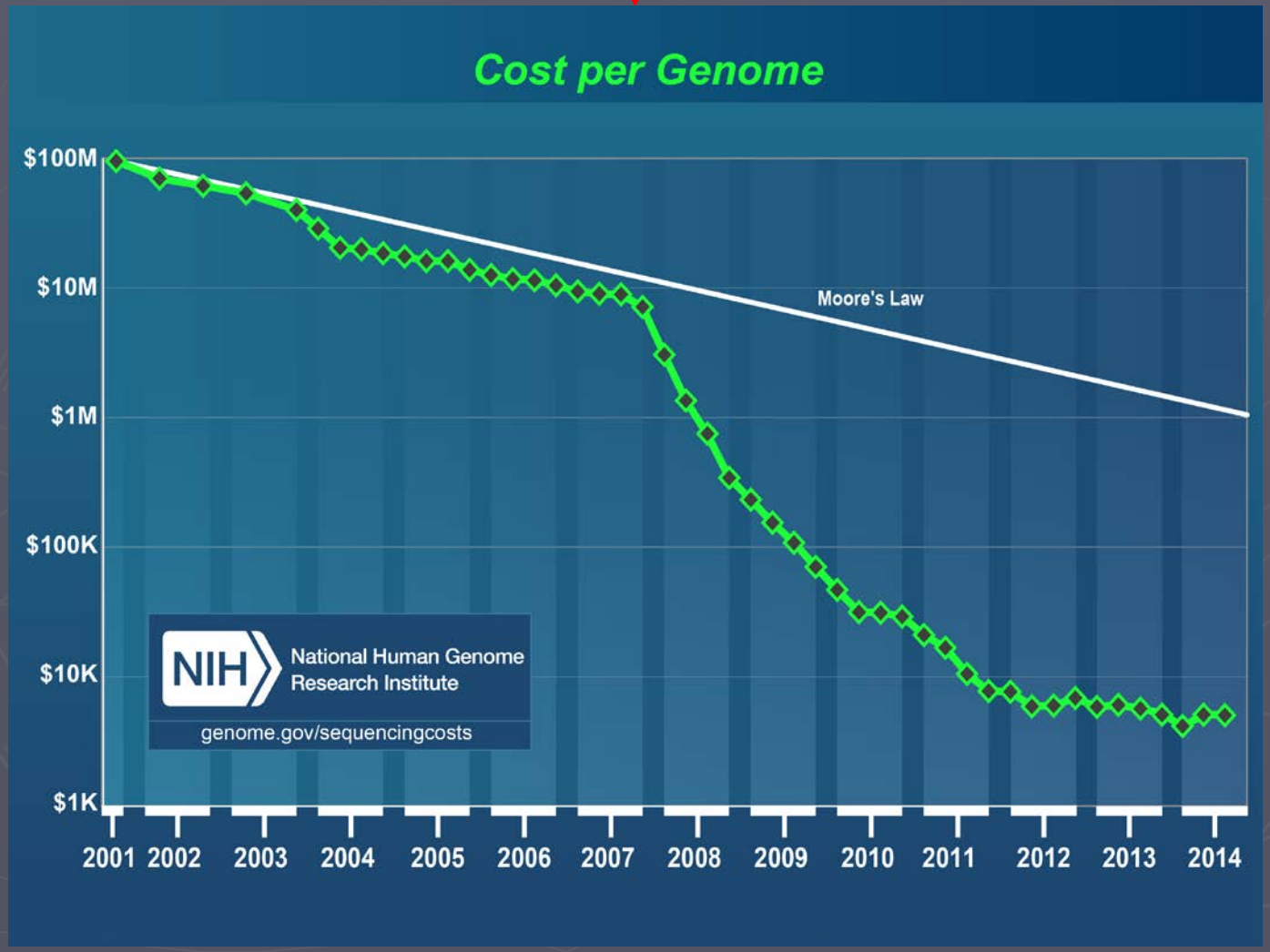
Questions

- Would you approve this protocol as proposed? Why or why not?

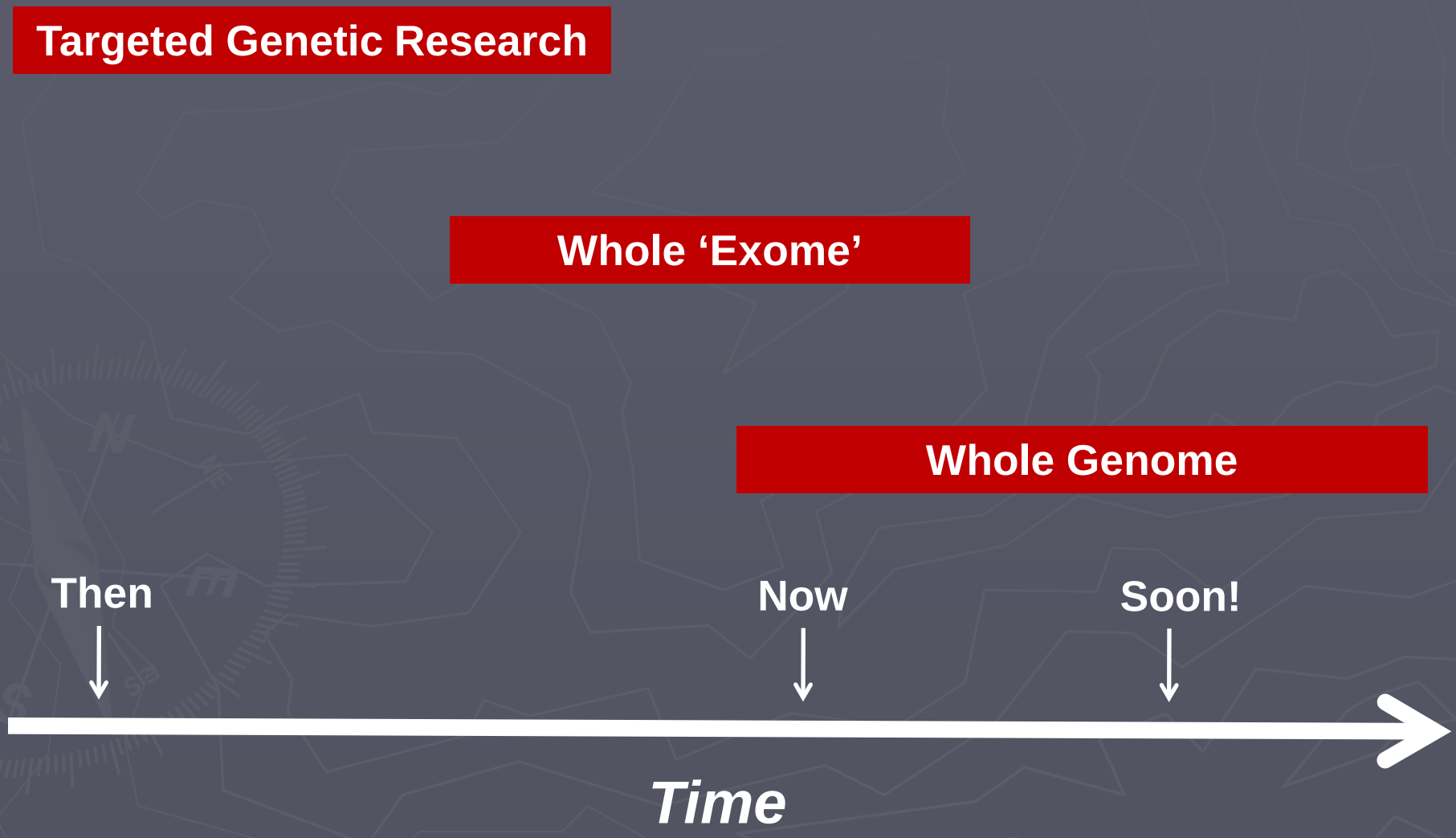
Background: Next-generation sequencing

Advancing Sequencing Capacity

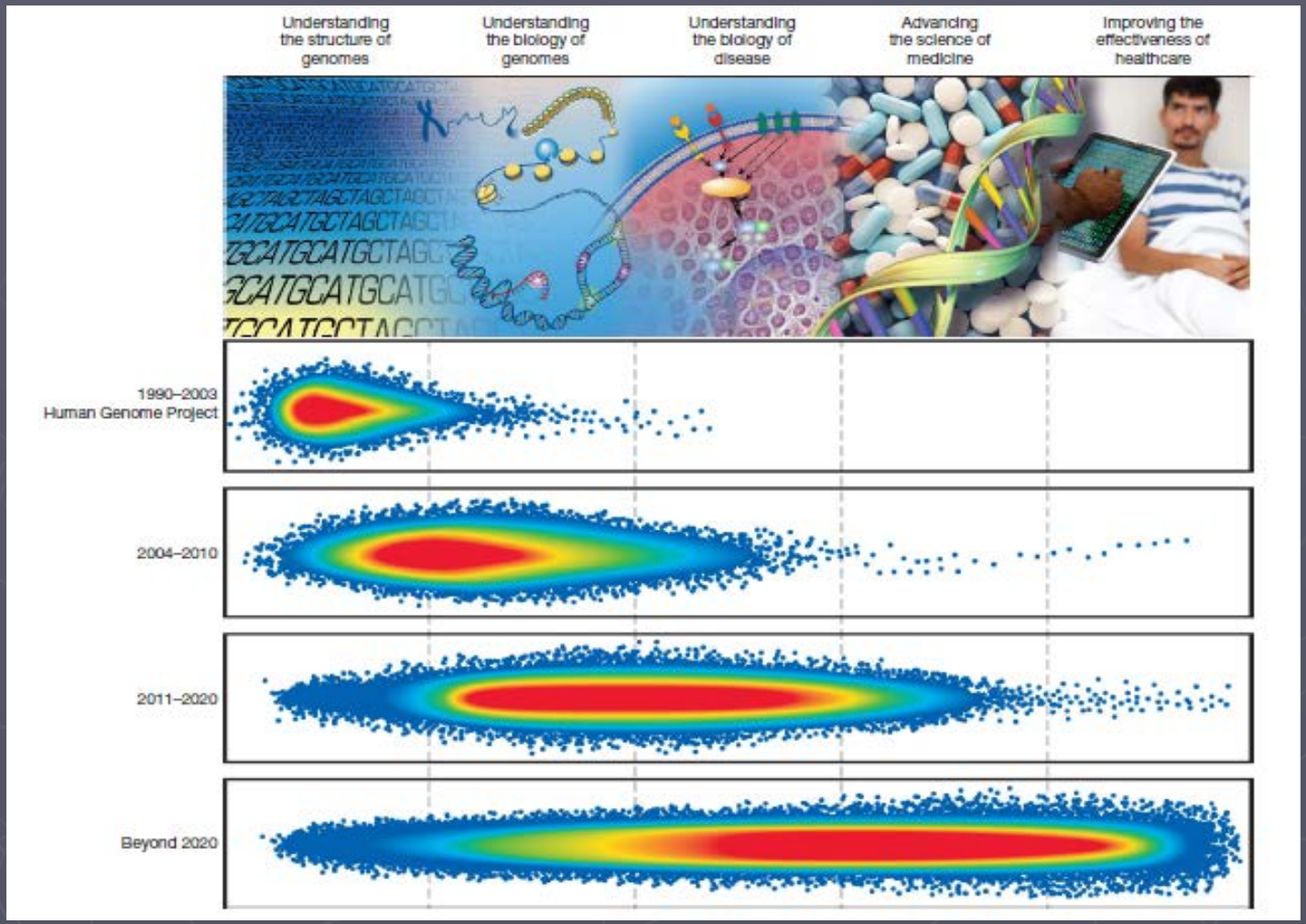
Next-Gen Sequencing



En Route to Routine Whole-Genome Sequencing



The Future of Genomic Medicine



Green, et. al., Nature, 2011, "The Future is Bright".

Incidental Findings in Genetic Research

General Argument

- WES/WGS does not raise novel ethical concerns, but...
- ...it will significantly magnify and make more concrete many of the risks that have been relatively theoretical to this point...
- ...challenging some basic assumptions about how to handle incidental findings in genetic research

Tabor, Berkman, Hull, et. al. How Exome and Whole Genome Sequencing Challenge the Framework of Human Genetics Research. AJMG (2011).

A new way of thinking about returning incidental findings?

- Current assumption #1
  - Traditional genetic research will produce very few clinically significant incidental findings

- Revised assumption #1
  - It is no longer a question of whether or not clinically relevant results will be found in any research participant, but rather how many results will be identified in each participant.

Looking for Incidental findings in a Whole Genome

- WGS was performed on 2 monozygotic twins
- **44,270** variants detected initially
  - Exclude bad data
  - Exclude known non-pathogenic variants and variants in untranslated regions, noncoding regions, synonymous changes
- **1,407** possibly pathogenic variants
  - Excluding clearly false positive data
- **430** variants

Incidental Findings and WGS

- Looking at raw data, cross reference each of the 430 variants with existing databases and published literature to determine which variants occur in genes connected to any human disease or condition.
- Results
  - 8 likely pathogenic variants that definitely need to be confirmed;
  - 30 potentially pathogenic variants that might be clinically relevant and will be discussed by a group of clinicians, medical geneticists, genetic counselors and ethicists to determine whether they meet the protocol's threshold reporting criteria in our protocol

A new way of thinking about returning incidental findings?

- Current assumption #2
  - A clear distinction exists between so-called “incidental” findings and findings that are explicitly related to the original study hypotheses or disease focus.

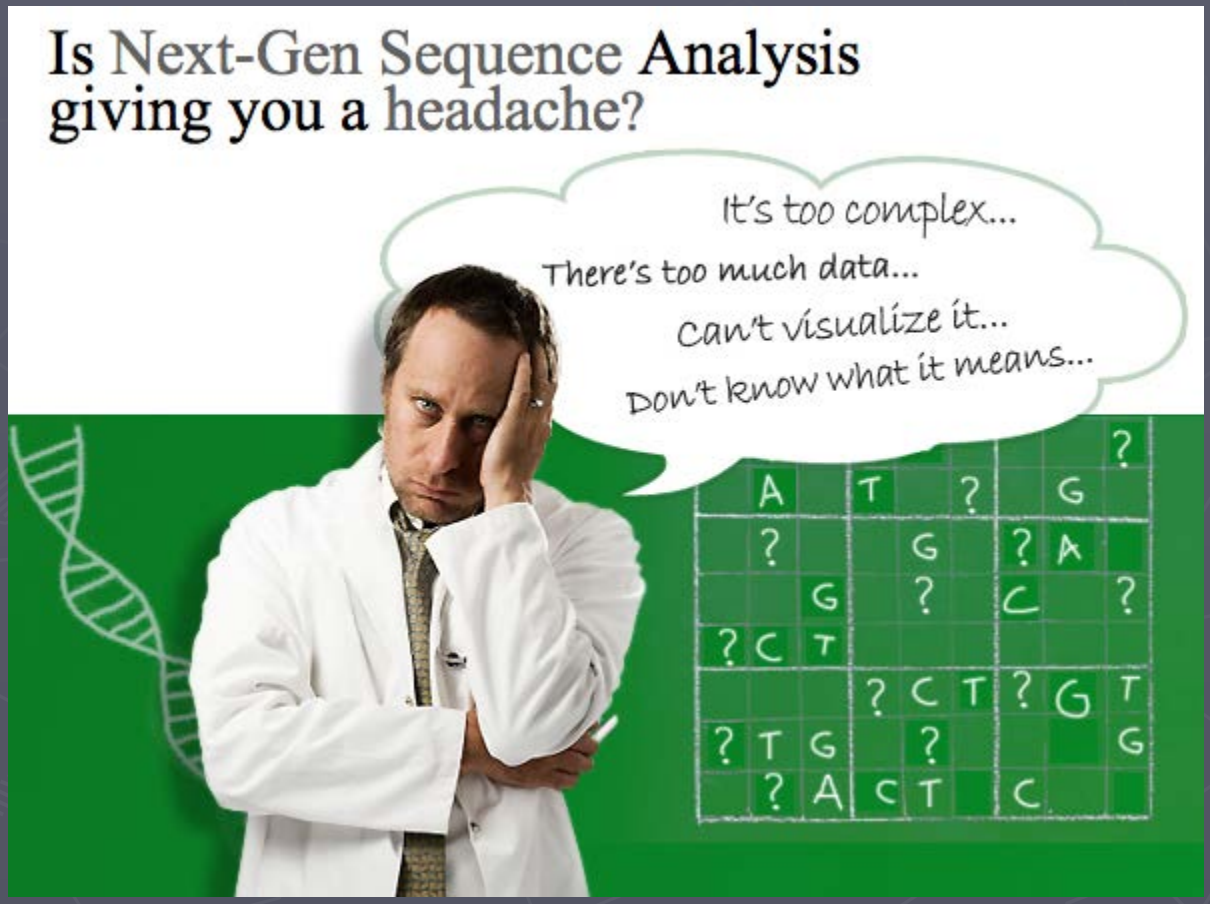
- Revised assumption #2
  - For experimental approaches based on WES/WGS, this distinction between incidental and non-incidental findings will become less meaningful.

A new way of thinking about returning incidental findings?

- Current assumption #3
  - Don’t look, don’t tell:
    - “Researchers generally have no obligation to act as clinicians and affirmatively search for IFs” (Wolf et al.)

- Revised assumption #3
  - With WGS technology, the act of “looking” for all possible results becomes much more practical and indeed is a fundamental component of the analytical approach

The Problem with Technological Advances



Guidelines and Frameworks

- NHLBI (2004)
- NHLBI (2009)
- Result-evaluation approach (Ravitsky and Wilfond, 2006)
- Net-benefit approach (Wolf, et al., 2008)
- Ancillary care framework (e.g., Beskow and Burke, 2010)
- Tiered-consent model (Rothstein, 2006)
- Etc.

Conflicting Guidance

Table 5

Recommended Classification of Incidental Findings

Category	Relevant IFs	Recommended Action
Strong Net Benefit	• information revealing a **condition likely to be life-threatening** • information revealing a **condition likely to be grave that can be avoided or ameliorated** • genetic information revealing significant risk of a condition likely to be life-threatening • genetic information that can be used to avoid or ameliorate a condition likely to be grave • genetic information that can be used in reproductive decision-making: (1) to avoid significant risk for offspring of a condition likely to be life-threatening or grave or (2) to ameliorate a condition likely to be life-threatening or grave	• **Disclose** to research participant as an incidental finding, unless s/he elected not to know.
Possible Net Benefit	• information revealing a nonfatal **condition that is likely to be grave or serious but that cannot be avoided or ameliorated, when a research participant is likely to deem that information important** • genetic information revealing significant risk of a condition likely to be grave or serious, when that risk cannot be modified but a research participant is likely to deem that information important • genetic information that is likely to be deemed important by a research participant and can be used in reproductive decision-making: (1) to avoid significant risk for offspring of a condition likely to be serious or (2) to ameliorate a condition likely to be serious	• **May disclose** to research participant as an incidental findings, unless s/he elected not to know.
Unlikely Net Benefit	• information revealing a **condition that is not likely to be of serious health or reproductive importance** • information whose **likely health or reproductive importance cannot be ascertained**	• **Do not disclose** to research participant as an incidental finding.

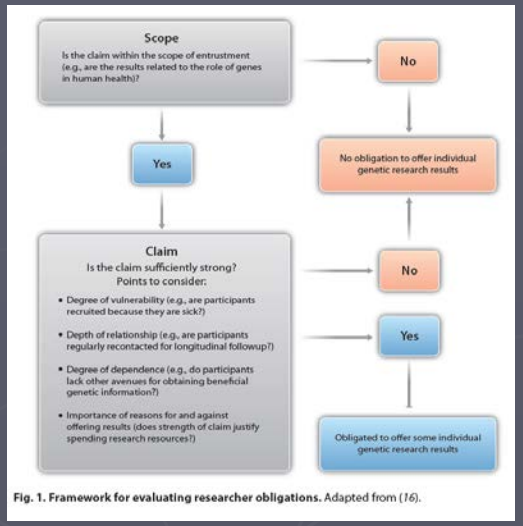
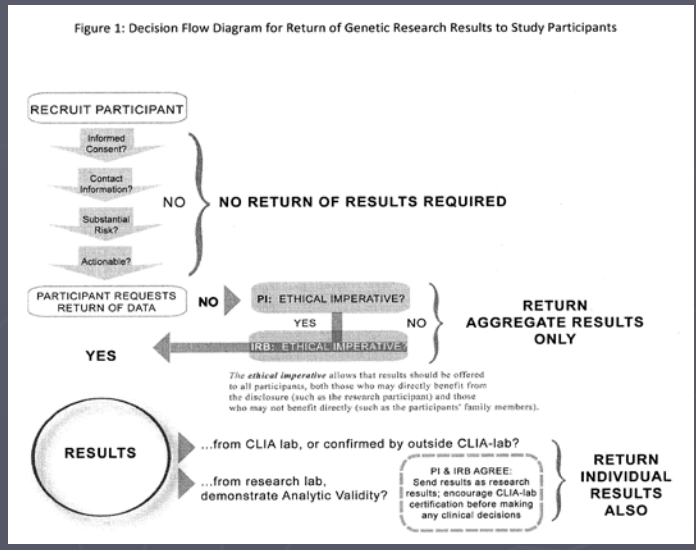
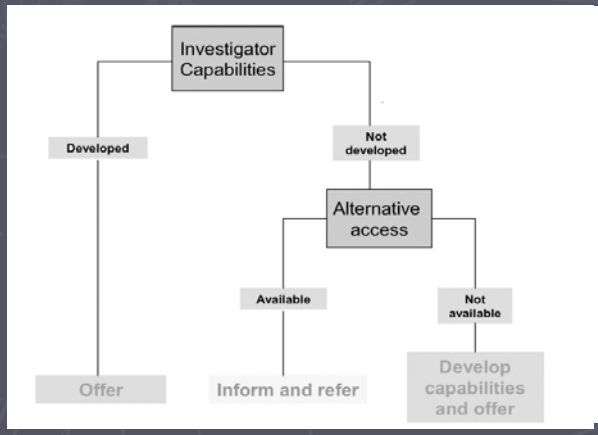
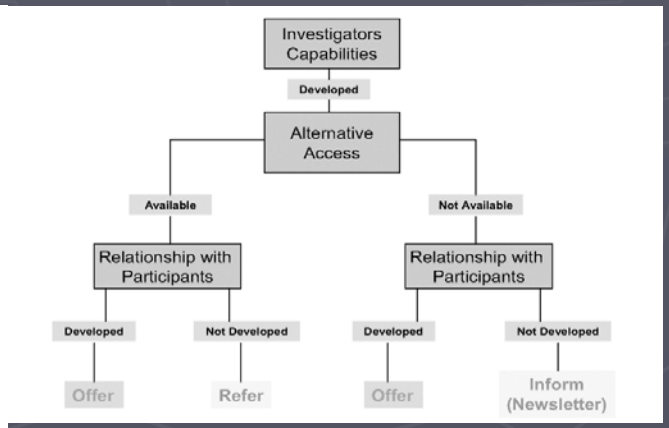


Fig. 1. Framework for evaluating researcher obligations. Adapted from (*16*).







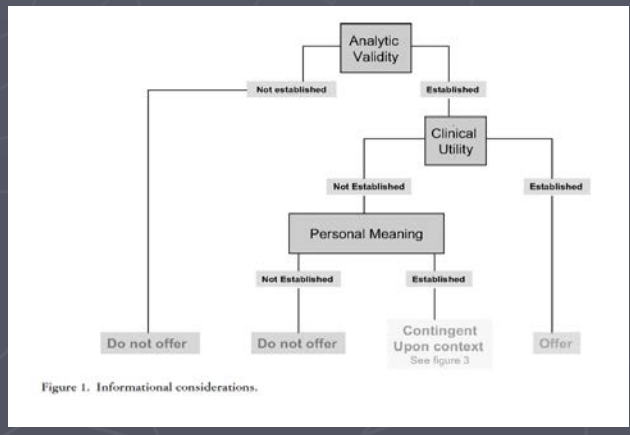


Figure 1. Informational considerations.

Three Emerging Models at NIH

Design	(Re)consent Covers:
No incidental findings to be disclosed	• Nature and scope of analysis • Datasharing plans • That results will NOT be disclosed • even though they might be generated
Limited incidental findings to be disclosed	• Nature and scope of analysis • Datasharing plans • That results might be disclosed under carefully defined circumstances • Though unlikely

More robust plans for disclosure of findings	• Nature and scope of analysis
	• Datasharing plans
	• That results might be disclosed under carefully defined circumstances
	  • How preferences will be solicited
	  • Any "mandatory disclosure" provisions

NIH Policy

- Draft guidance has been written and will be disseminated in the near future.
- CCGO experiment perhaps paving the way for a shared approach

Unresolved Ethical Controversies and Questions

Lurking disagreements and controversial issues

- **What is the principle on which an obligation to disclose rests?**
- Why can't we agree on a set of common definitions?
- How much does the research context matter?
- When is reconsent required?
- Do researchers have a duty to look for incidental findings?
- When is it appropriate to disclose genetic information to relatives of the proband?
- Is the right not to know absolute?

Why is there an obligation to disclise GIFs?

- **Beneficence:** the idea that researchers should have the welfare of the research participant as a goal.
- **Respect for autonomy:** the recognition that all individuals have the right to make their own decisions.
- **Duty to warn:** obligation to warn participants if they are in significant, imminent danger.
- **Right to know:** research participants have an inherent right to obtain genetic information about themselves.

Why is there an obligation to disclise GIFs?

- **Reciprocity:** the idea that investigators owe participants something in exchange for their contribution to the research endeavor.
- **Autonomy:** Genetic information is important and when incorporated into decision-making can enhance autonomy
- **Doctor-Patient relationship:** participants should be treated like patients, and clinicians would disclose these results to their patients.
- **Professional responsibility** to inform their subjects

Why is there an obligation to disclise GIFs?

- **Legal liability:** fears about law suits if a participant later develops a condition that could have been prevented.
- **Public trust in research**
- **Institution's professional reputation**

Some arguments against an obligation to return incidental research findings

- Challenges to the notion that beneficence, respect for persons, reciprocity, justice are violated by lack of disclosure
- The purpose of research is not to benefit the individual research participant but rather to produce generalizable knowledge
- Risks associated with conflating research and clinical care
  - Therapeutic (diagnostic) misconception
- Resource limitations

Initial Views on Whether There is an Obligation to Disclose GIFs

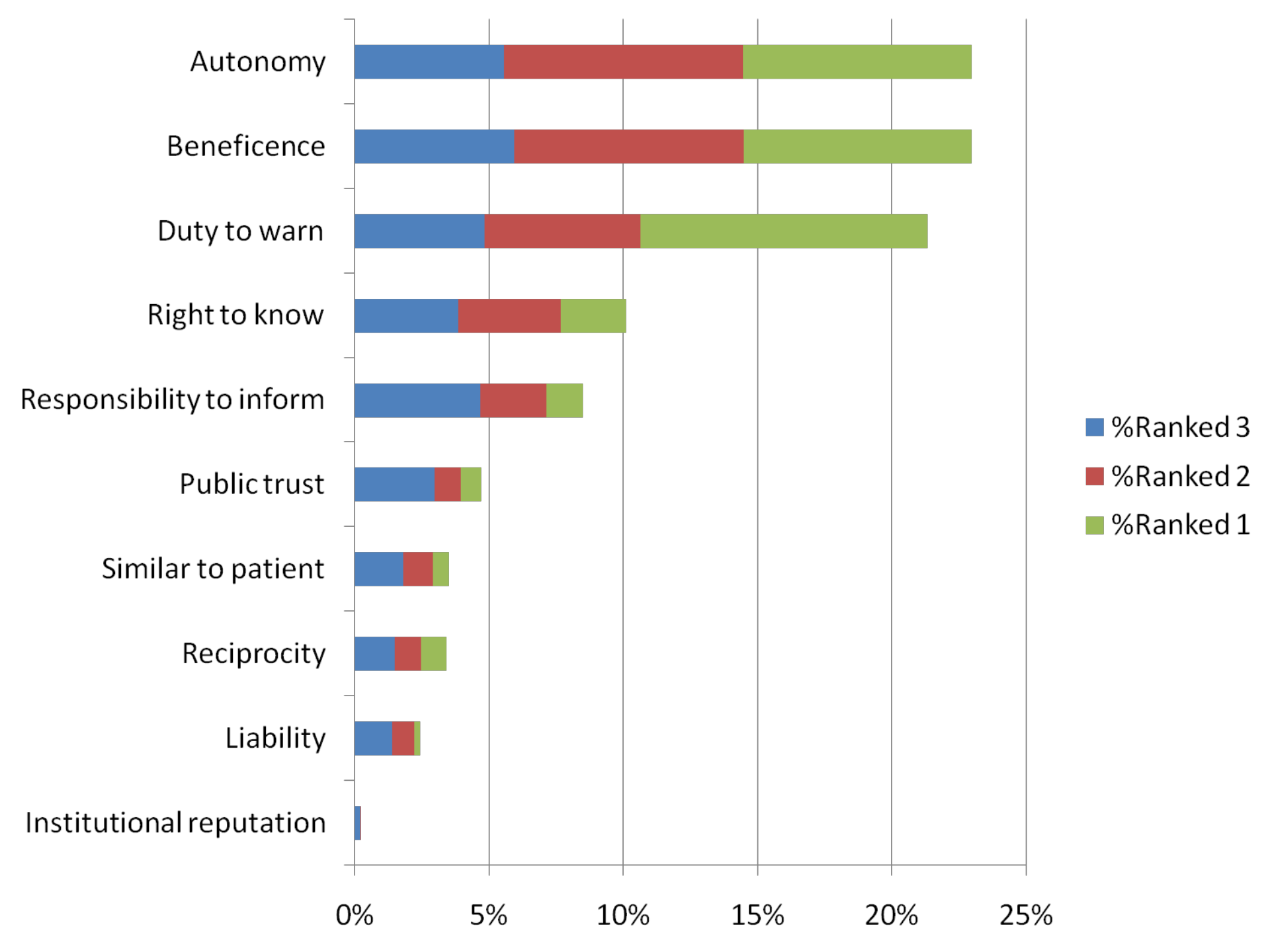
Do you believe that researchers have an obligation to disclose genetic incidental findings to participants?

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.

Ethical Reasoning

	Strongly agree or agree
Duty to warn	84%
Respect for autonomy	80%
Beneficence	79%
Professional responsibility	67%
Public trust in research	58%
Right to know	54%
Institutional reputation	36%
Legal liability	34%
Participants = patients	34%
Reciprocity	34%


Autonomy
Beneficence
Duty to warn
Right to know
Responsibility to inform
Public trust
Similar to patient
Reciprocity
Liability
Institutional reputation
0%
5%
10%
15%
20%
25%
%Ranked 3
%Ranked 2
%Ranked 1

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 ($p<0.05$)

Lurking disagreements and controversial issues

- What is the principle on which an obligation to disclose rests?
- **Why can’t we agree on a set of common definitions?**
- How much does the research context matter?
- When is reconsent required?
- Do researchers have a duty to look for incidental findings?
- When is it appropriate to disclose genetic information to relatives of the proband?
- Is the right not to know absolute?

What kind of genetic information generates an obligation?

- Some general agreement about the relevant factors:
  - Analytic validity
  - Clinical relevance
  - Actionable
  - Desired

A Lack of Common Definitions

- "Clinical Significance"
  - Defining the threshold
    - Clear and immediate need vs. important health implication
    - Net benefit (strong, possible, unlikely)
    - Clinical utility, personal utility, general utility
    - Relative risk > X
- "Incidental"
  - Aims vs. methods
- "Actionable"
  - Reproductive information
  - Huntington's Disease
  - **Low resource settings**
- "Research Result"
  - Analytic validity - Is CLIA certification required?

(See, e.g. Eckstein L, Garrett JR, Berkman BE. A Framework for Analyzing the Ethics of Disclosing Genetic Research Findings. *Journal of Law, Medicine and Ethics* (2014).

Lurking disagreements and controversial issues

- What is the principle on which an obligation to disclose rests?
- Why can't we agree on a set of common definitions?
- **How much does the research context matter?**
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- Do researchers have a duty to look for incidental findings?
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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

Beskow and Burke. Offering Individual Genetic Research Results: Context Matters. *Science Translational Medicine* (2010).

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

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.

Questions

- Would you approve this amendment as proposed?
- Does it matter whether the investigator already has the infrastructure necessary to return genetic information to subjects?

Case 2

- 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).

- The investigator does not have access to genetic counseling resources.

Questions

- Would you approve this protocol as proposed? Why or why not?

Case 3

- 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 identifiable information about these patients.
- The NIH researcher wants to proceed with whole exome sequencing and set up a planning meeting with the sequencing center.

Question

- Should investigators participating in biobank specimen research have an obligation to return incidental findings?

Case 4

- 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 resourcs available to their African participants, it is unlikely that they will be able to access treatment for any positive findings.

Question

- Should the investigators return these incidental/secondary findings even though they aren't as clearly actionable as they would be in a high-resource setting?
- Is it ethical to have a different standard of care in high and low resource settings?

Lurking disagreements and controversial issues

- What is the principle on which an obligation to disclose rests?
- Why can’t we agree on a set of common definitions?
- How much does the research context matter?
- **When is reconsent required?**
- Do researchers have a duty to look for incidental findings?
- When is it appropriate to disclose genetic information to relatives of the proband?
- Is the right not to know absolute?

When is Reconsent Required?

- A research study on genetic causes of asthma that incorporated targeted genetic tests was initiated several years ago. In the original consent, participants allowed “genetic analysis” of their samples, but next-generation sequencing (NGS) was not explicitly mentioned as it was not an option at the time. Now that NGS is less expensive, researchers would like to use it as part of their study to increase their chances of discovering genes related to asthma. They have submitted an amendment to the IRB describing the alternative sequencing plan, but this amendment does not explicitly mention a plan to obtain re-consent for NGS.

Questions

- Would you require these investigators to obtain reconsent?
- If the investigators make a good faith effort to recontact a participant, but fails to locate them, can their specimen still be sequenced?

Lurking disagreements and controversial issues

- What is the principle on which an obligation to disclose rests?
- Why can’t we agree on a set of common definitions?
- How much does the research context matter?
- When is reconsent required?
- **Do researchers have a duty to look for incidental findings?**
- When is it appropriate to disclose genetic information to relatives of the proband?
- Is the right not to know absolute?

Re-examining the Stumble Strategy

- Assuming there is a duty to disclose significant incidental findings, might there be an obligation for researchers to actively look for these findings?
  - Gliwa C, Berkman BE. Do researchers have an obligation to actively look for genetic incidental findings? *American Journal of Bioethics* 13(2): 32-42 (2013).
- Standard view: “researchers generally have no obligation to act as clinicians and affirmatively search for IFs,” (Wolf et al. 2008)

Questions

- Assuming that there is some obligation to return incidental findings that one stumbles upon, do investigators have a duty to look for incidental findings?
  - Probably not right now, or in the distant future, but perhaps in the near future.
- What if a list of “reportable” variants existed
  - A committee-compiled and regularly-updated list of variants that meet a certain threshold of validity, severity, and actionability
    - e.g., ACMG 56

Lurking disagreements and controversial issues

- What is the principle on which an obligation to disclose rests?
- Why can’t we agree on a set of common definitions?
- How much does the research context matter?
- When is reconsent required?
- Do researchers have a duty to look for incidental findings?
- **When is it appropriate to disclose genetic information to relatives of the (deceased) proband?**
- Is the right not to know absolute?

Disclosure to Relatives

The American Journal of Bioethics, 12(10): 1–8, 2012
ISSN: 1526-5161 print / 1536-0075 online
DOI: 10.1080/15265161.2012.699138

Target Article

Genomic Inheritances: Disclosing Individual Research Results From Whole-Exome Sequencing to Deceased Participants' Relatives

Ben Chan, Lawrence University
Flavia M. Facio, National Human Genome Research Institute
Haley Eidem, National Human Genome Research Institute
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Leslie G. Biesecker, National Human Genome Research Institute
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Whole-genome analysis and whole-exome analysis generate many more clinically actionable findings than traditional targeted genetic analysis. These findings may be relevant to research participants themselves as well as for members of their families. Though researchers performing genomic analyses are likely to find medically significant genetic variations for nearly every research participant, what they will find for any given participant is unpredictable. The ubiquity and diversity of these findings complicate questions about disclosing individual genetic test results. We outline an approach for disclosing a select range of genetic results to the relatives of research participants who have died, developed in response to relatives' requests during a pilot study of large-scale medical genetic sequencing. We also argue that studies that disclose individual research results to participants should, at a minimum, passively disclose individual results to deceased participants' relatives.

Keywords: genomics, medical genetics, research, genetic, personal genetic information, bioethical issues, ethics, research

Disclosure to Relatives

- Should genetic research results of potential clinical benefit be disclosed to a deceased participant's relatives?
- If so, under what circumstances and through what mechanism should they be disclosed?

Lurking disagreements and controversial issues

- What is the principle on which an obligation to disclose rests?
- Why can't we agree on a set of common definitions?
- How much does the research context matter?
- When is reconsent required?
- Do researchers have a duty to look for incidental findings?
- When is it appropriate to disclose genetic information to relatives of the proband?
- **Is the right not to know absolute?**

The Right Not to Know

Baseline Question

- Do research participants have a right not to know their own genetic information? In other words, would it be acceptable for them to choose not to receive any GIFs?

A Case

- P is having her genome sequenced and during the informed consent process opts not to receive any secondary results. During their analysis, her physicians (or the research team) 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.

Questions

- Should the physicians return the results even though P indicated that she didn't want to know secondary findings?
- Would it be appropriate to have a strong default for returning high value information **without asking** about a preference not to know?

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."

Standard View

- If a participant has asserted a desire not to know and such consent is valid, standard ethical analysis suggests that such results must not be returned
  - Autonomy
  - Privacy
- Extensive support in the genetic testing and research ethics literature
  - E.g., BRCA, Huntington's, Alzheimer's
  - Incidental findings guidance documents

ACMG Recommendations

- "Minimum list" of incidental findings to actively seek and report from any clinical sequence (n=56)
- Argued against soliciting patient preferences about receiving incidental findings

Robert C. Green et al., *ACMG Recommendations for Reporting of Incidental Findings in Clinical Exome and Genome Sequencing*, 15 GENETICS MED. 565, 565–66 (2013)

Controversy!


Genetics inMedicine | SPECIAL ARTICLE

Recommendations for returning genomic incidental findings? We need to talk!

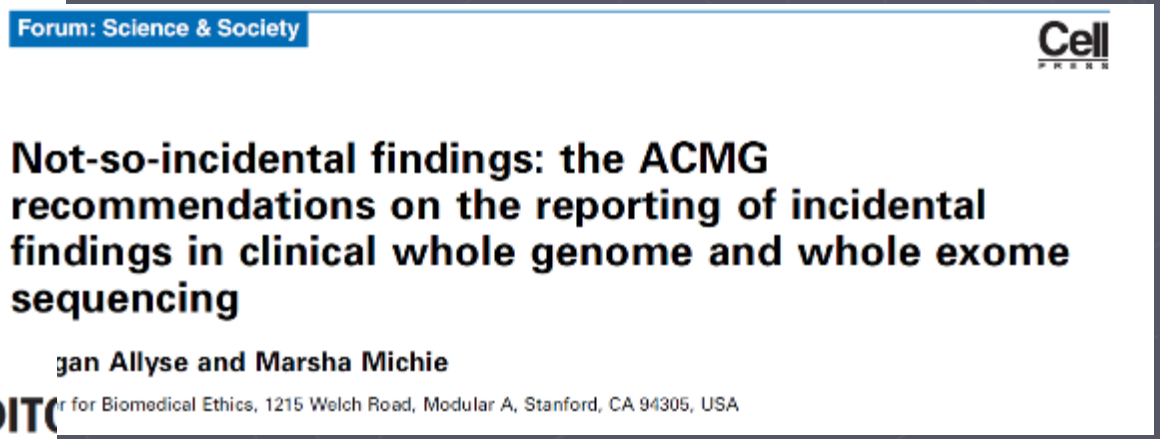
Wylie Burke, MD, PhD[1], Armand H. Matheny Antommaria, MD, PhD[2], Robin Bennett, MS, CGC[3], Jeffrey Botkin, MD, MPH[4], Ellen Wright Clayton, MD, JD[5], Gail E. Henderson, PhD[6], Ingrid A. Holm, MD, MPH[7,8], Gail P. Jarvik, MD, PhD[9], Muin J. Khoury, MD, PhD[10], Bartha Maria Knoppers, JD, PhD[11], Nancy A. Press, PhD[12], Lainie Friedman Ross, MD, PhD[13], Mark A. Rothstein, JD[14], Howard Saal, MD[15], Wendy R. Uhlmann, MS, CGC[16], Benjamin Wilfond, MD[17], Susan M. Wolf, JD[18] and Ron Zimmern, FRCP, FFPHM[19]


POINT-COUNTERPOINT

Patient Autonomy and Incidental Findings in Clinical Genomics

Returning genetic incidental findings without patient consent is misguided.

Susan M. Wolf,[1]* George J. Annas,[2] Sherman Elias[3]

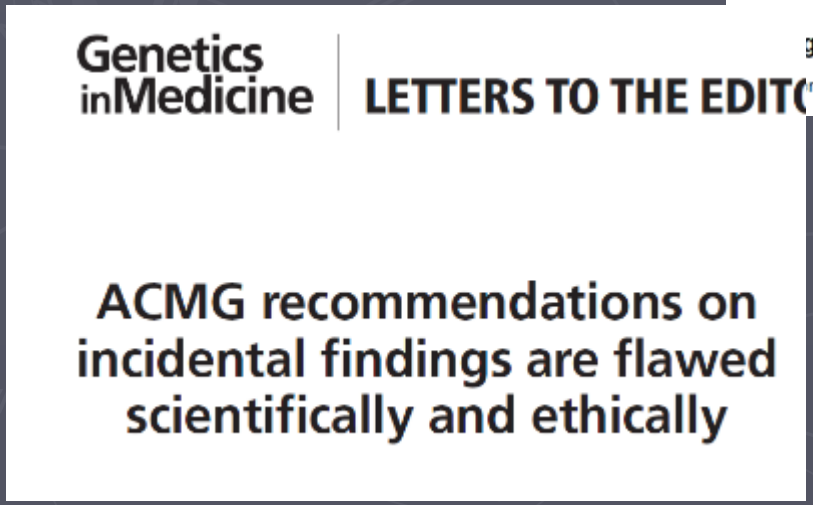

Forum: Science & Society

Cell

Not-so-incidental findings: the ACMG recommendations on the reporting of incidental findings in clinical whole genome and whole exome sequencing

gan Allyse and Marsha Michie

r for Biomedical Ethics, 1215 Welch Road, Modular A, Stanford, CA 94305, USA


Genetics inMedicine | LETTERS TO THE EDITO

ACMG recommendations on incidental findings are flawed scientifically and ethically

How Strong Are People's Views on the RNTK?

- There is a right not to know:
  - 96% (baseline)
  - 63% (specific case)
- There isn't a right not to know
  - 2% (baseline)
  - 26% (specific case)
- Unsure
  - 1% → 11%

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.

Need For a Comprehensive Analysis

- The focus on an autonomy-based RNTK has had the unfortunate effect of short-circuiting discussion of the topic
  - Focus on the harms associated with not honoring individual preferences
- Need a comprehensive analysis of the harms **and** benefits of honoring **or** ignoring the RNTK.
- Which mistake do you want to make:
  - unwanted disclosure
  - or lost opportunity for medical intervention

Three Questions

- 1. How many people don’t want to know profoundly important genetic information about themselves?
- 2. If people are given genetic risk information that they didn’t want to know, what is the magnitude of their actual harm?
- 3. How many people undergoing genomic sequencing would erroneously or accidentally not receive potentially lifesaving information if we actively solicit patient preferences about knowing or not knowing?

Who Doesn't Want to Know?

- Overwhelming majority of people would want to be given genetic risk information that will have a direct impact on their health
  - 96% (Kaufman et al.)
  - 98% (Middleton et al.)
- Tiny group that might not want this information
  - Individuals for whom clinical action might not be indicated
    - Patients with a terminal illness
    - The elderly
    - People with a religious objection to receiving medical treatment
  - Bracket these cases rather than have them drive policy

Psychological Harms

- Affective forecasting literature
- Minimal psychological impact of negative genetic information in a range of contexts

Psychological Harms

- Society is “systematically overestimate[ing] the durability and intensity of the affective impact of events on well-being…resulting in a culture of risk-aversion in which patients may be opting out of potentially beneficial diagnostic and treatment regimes.” (Peters et al., 2014)

Discrimination

- Evidence suggests that:
  - Fear of discrimination is high
  - But actual cases are very hard to find
- Health insurance and employment
  - GINA enforcement
- More examples of discrimination in other insurance contexts (e.g., life, LTC)

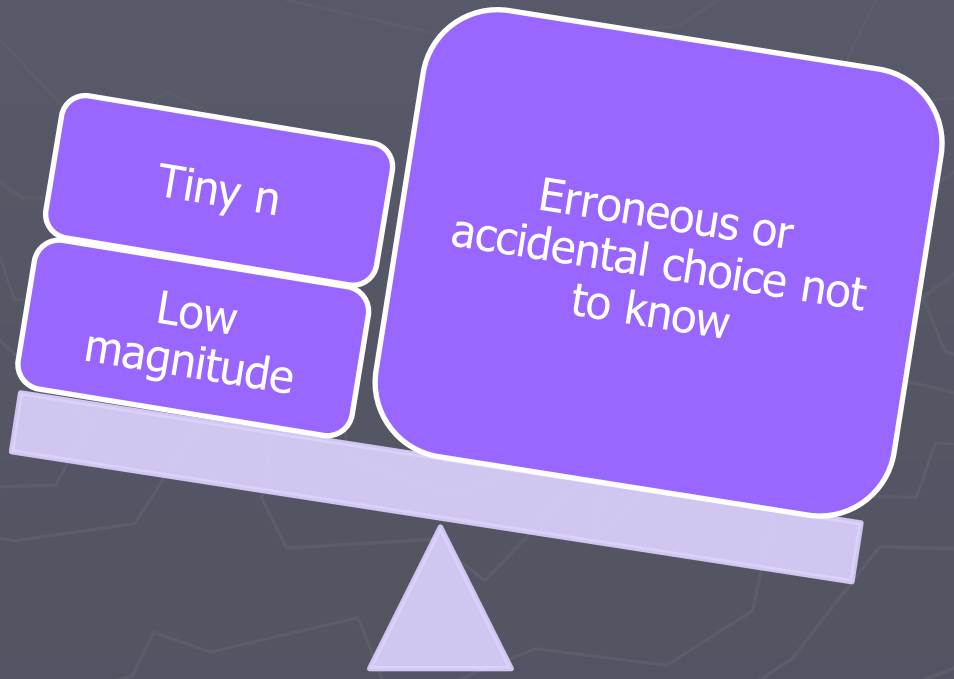
Challenges of Ascertaining Preferences

- Engagement with and understanding of consent forms
- Particular concern about the complexity of genomic information
- Difficulty in describing a wide range of types of genetic information
- Capturing uncertainty and shifting preferences over time

Weighing the Evidence

Harm of imposing information

Cost of a strong RNTK



Conclusions

- Prevailing autonomy-based view: strong RNTK
  - [Philosophically shaky]
  - [Legal RNTK questionable]
  - Support for the RNTK is soft
  - Strong RNTK would do more harm than good
  - [Other considerations (moral distress and genetic exceptionalism) weigh in favor of a more limited view]

Conclusions

- For high impact genetic information, there should be no active solicitation of patient preferences
  - Except when clinical action would not be indicated
- In the rare case that someone independently requests to not learn about this information
  - In-depth counseling...but ultimately the decision should be honored if not knowing remains their clearly stated preference.

Berkman BE. Refuting the Right Not to Know. *Journal of Healthcare Law and Policy* 19(1): 1-75 (2016).

Thank You

Questions?

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