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

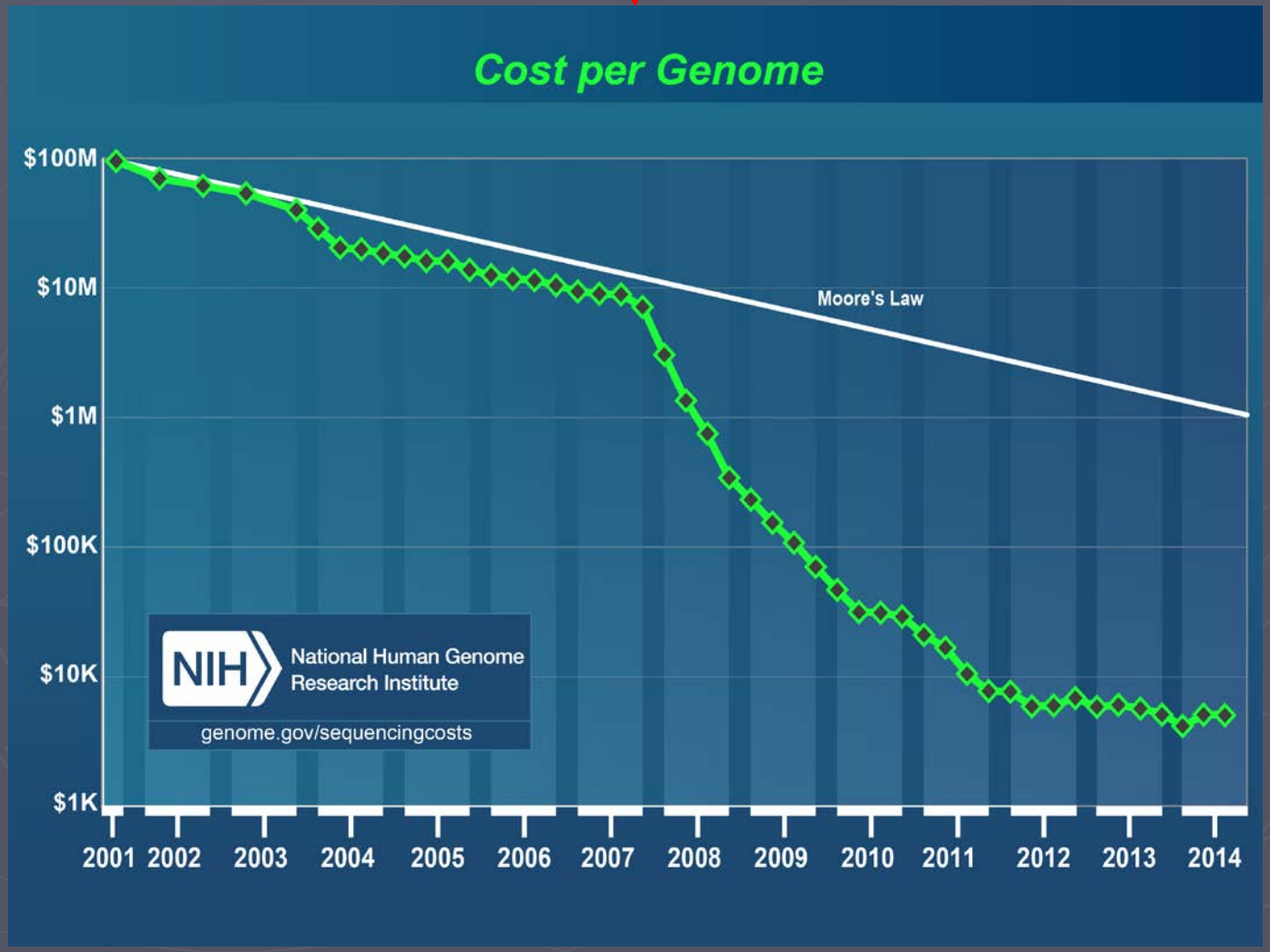
- An incidental result is:
  - "[A] finding concerning an individual research participant *that has potential health or reproductive importance* and is discovered in the course of conducting research *but is beyond the aims of the study*"

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

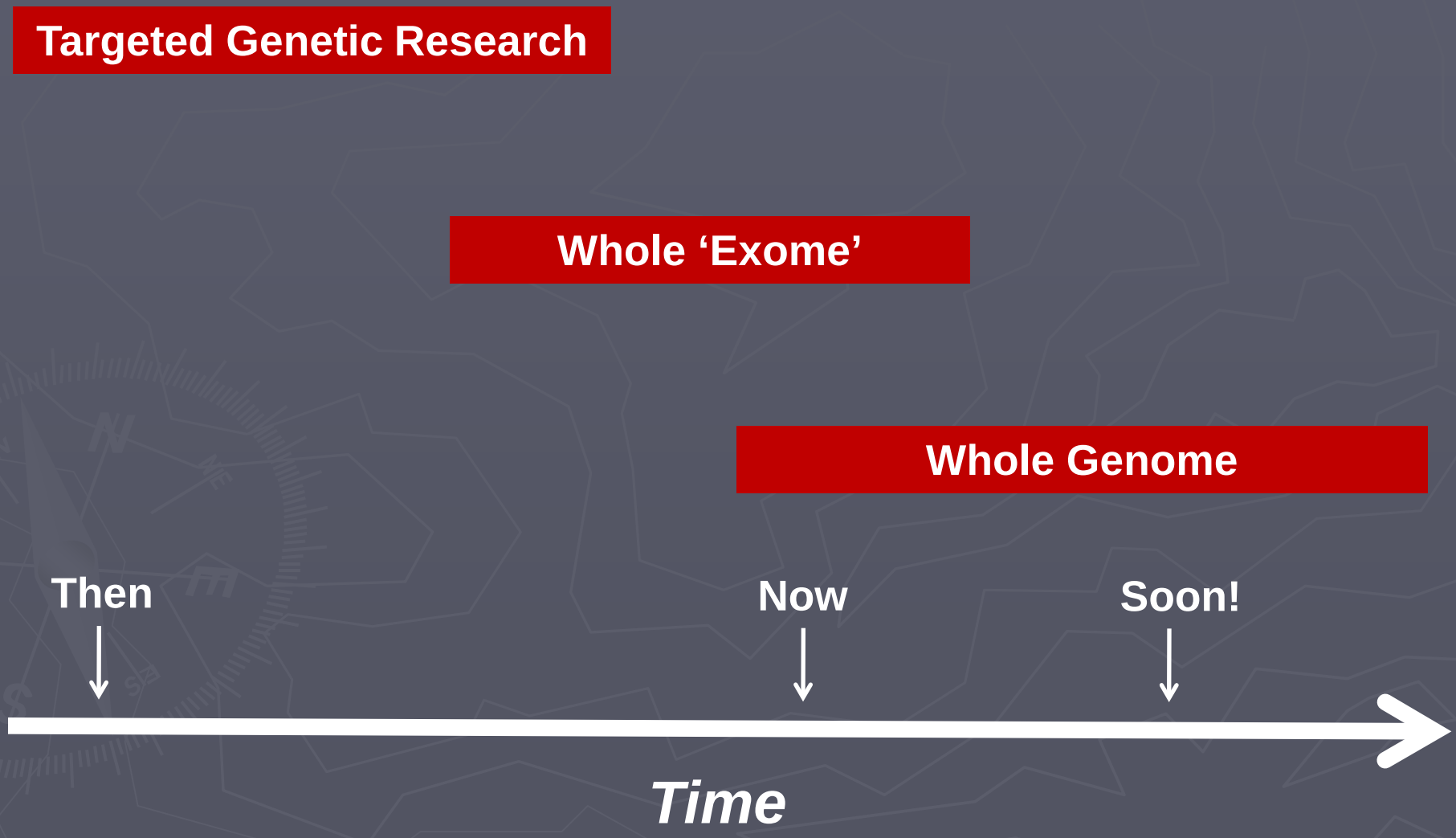
Background: Next-generation sequencing

Advancing Sequencing Capacity

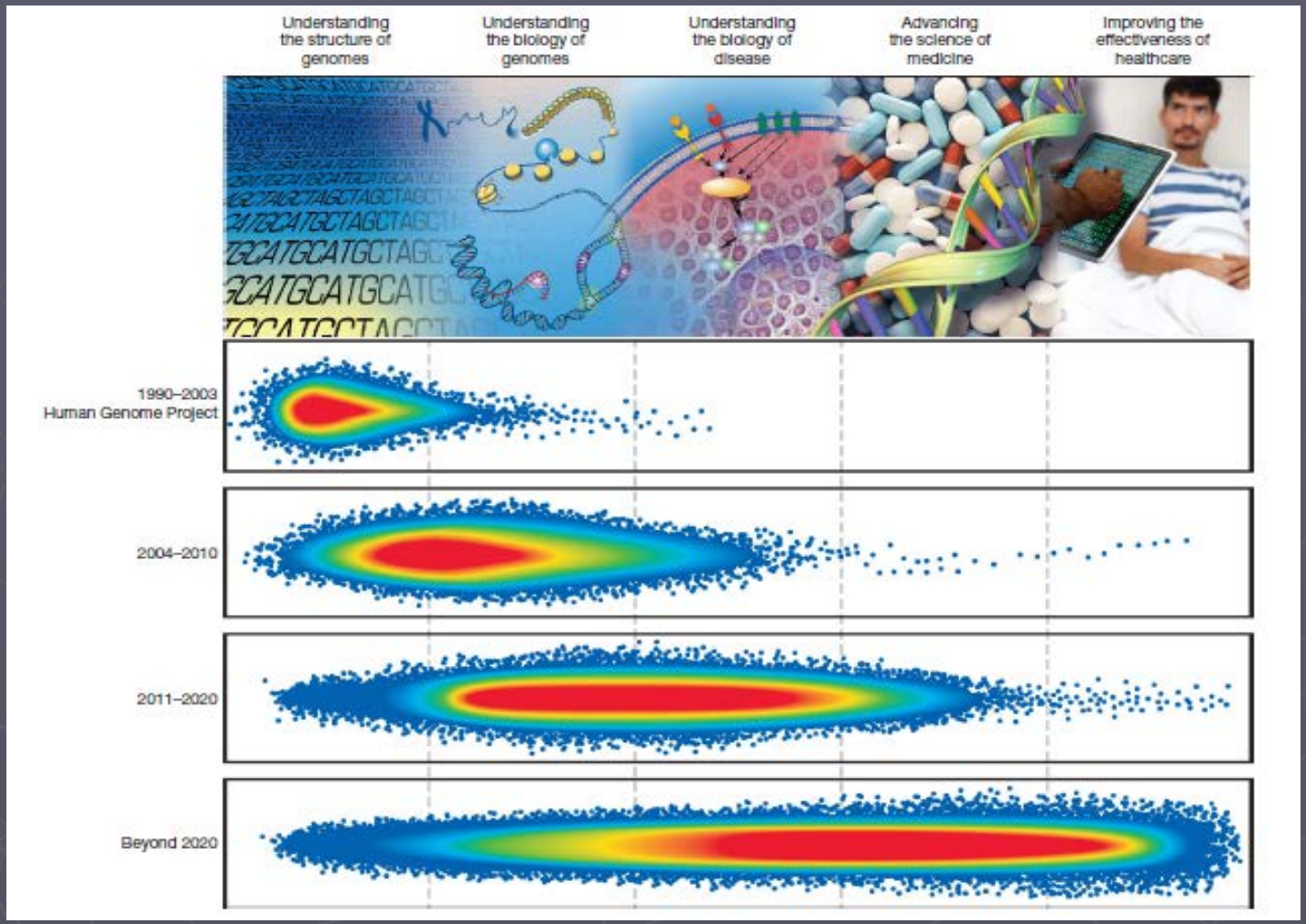
Next-Gen Sequencing



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.

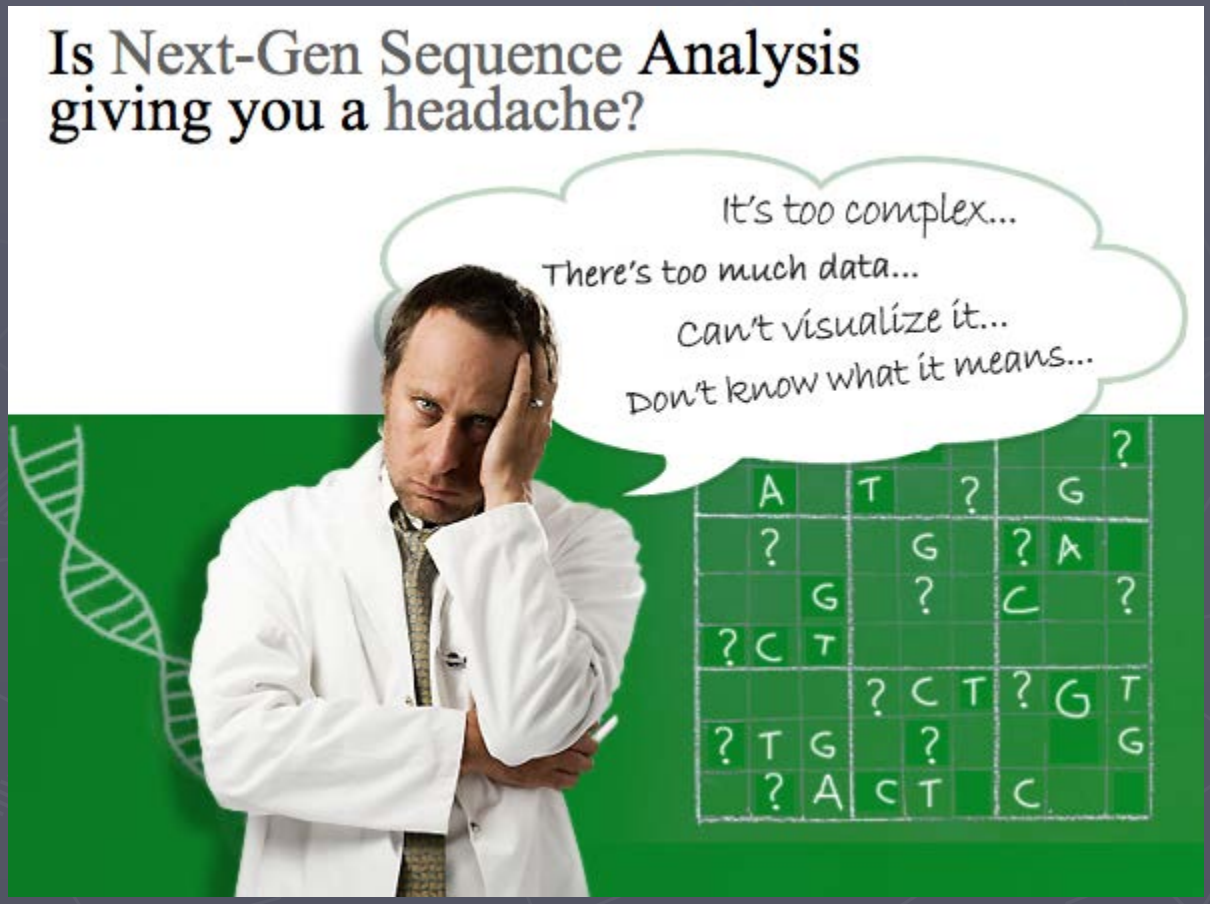
- Revised assumption #2
  - For experimental approaches based on WES/WGS, this distinction between incidental and non-incidental findings will become less meaningful.

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.

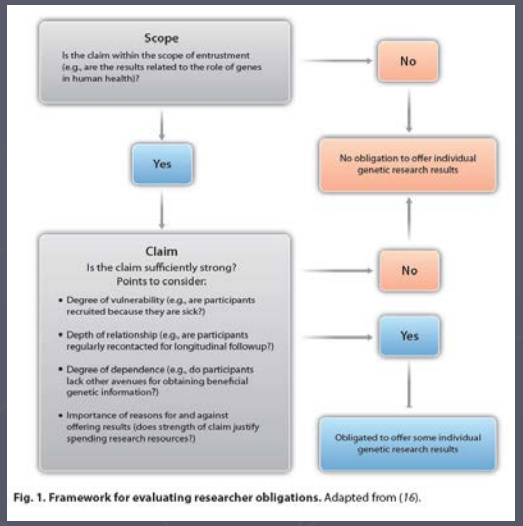
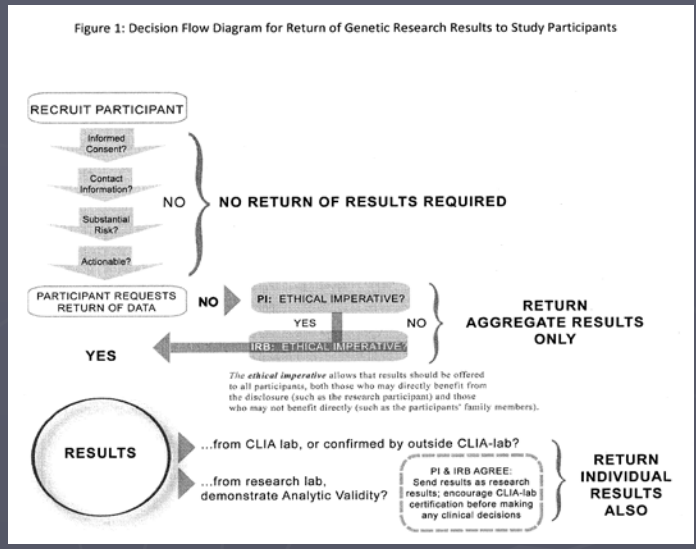
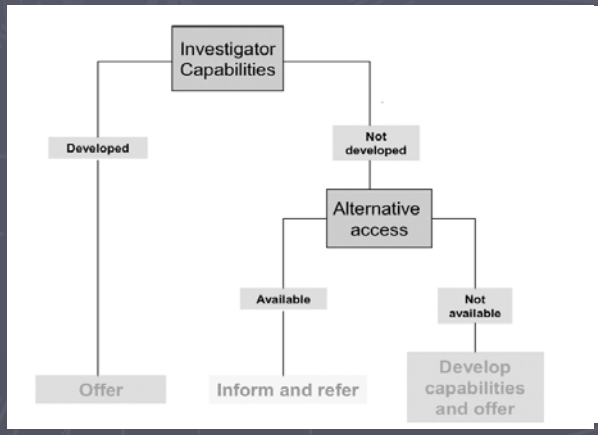
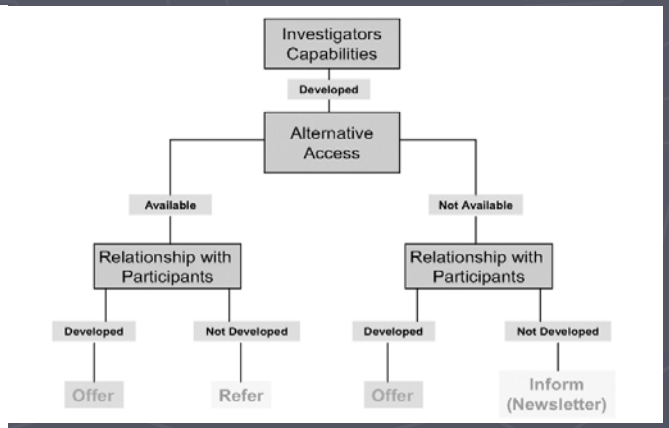


Fig. 1. Framework for evaluating researcher obligations. Adapted from (16).







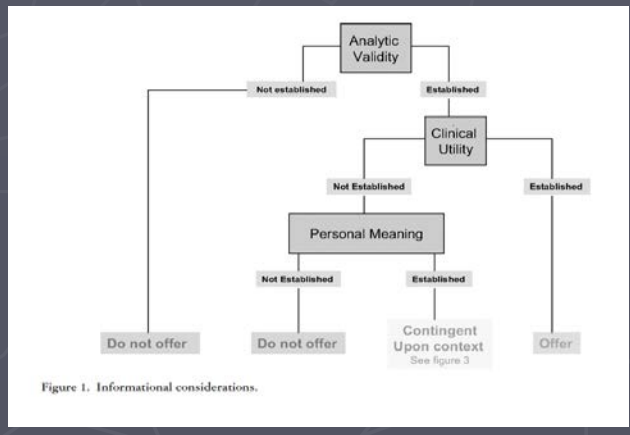


Figure 1. Informational considerations.

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 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?
- Do researchers have a duty to look for incidental findings?
- When is it appropriate to disclose genetic information to relatives of the proband?
- How strong is the right not to know?

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

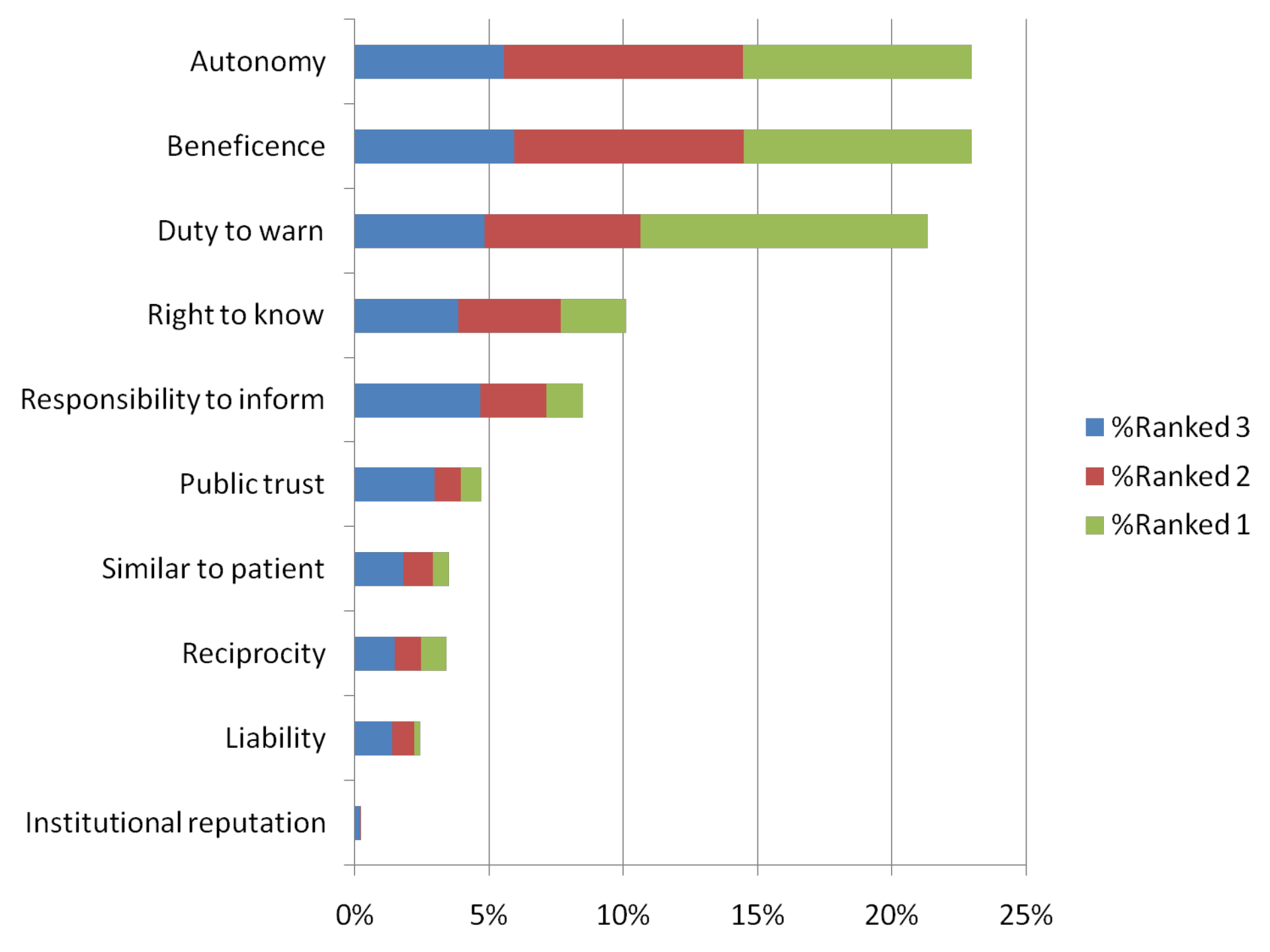
Initial Views on Whether There is an Obligation to Disclose GIFs

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%

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?
- Do researchers have a duty to look for incidental findings?
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- How strong is the right not to know?

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
- "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?**
- Do researchers have a duty to look for incidental findings?
- When is it appropriate to disclose genetic information to relatives of the proband?
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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

Lurking disagreements and controversial issues

- What is the principle on which an obligation to disclose rests?
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- **Do researchers have a duty to look for incidental findings?**
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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?
- Do researchers have a duty to look for incidental findings?
- **When is it appropriate to disclose genetic information to relatives of the (deceased) proband?**
- How strong is the right not to know?

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
Sara Chandros Hull, National Human Genome Research Institute
Leslie G. Biesecker, National Human Genome Research Institute
Benjamin E. Berkman, National Human Genome Research Institute

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?
- What subset of the results should be disclosed?

Lurking disagreements and controversial issues

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- **How strong is the right not to know?**

The Right Not to Know

Baseline Question

- Do research participants have an absolute 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.

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 Ethical Review

- 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

Results (n=796)

- Baseline RNTK
  - Definitely yes: 79%
  - Probably yes: 17%
  - Probably no: 2%
  - Definitely no: 0%
  - Unsure: 1%
- Specific case
  - Definitely yes: 8%
  - Probably yes: 18%
  - Probably no: 28%
  - Definitely no: 35%
  - Unsure: 11%

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

Questions

- Are traditional conceptions about the “right not to know” appropriate in a genomic research context?
- How should a subject’s desire not to know genetic information be solicited?
- Are there any (limited) circumstances where it might be ethically appropriate to override an individual’s expressed wish not to know genetic information about themselves?
  - See e.g., ACMG guidelines
  - Berkman BE, Refuting the Right Not to Know, *Journal of Health Care Law and Policy* (in press).

Questions

- Would it be appropriate to have a strong default for returning high value information **without asking** about a preference not to know?

Tradeoffs

- 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

Tradeoffs

- Three questions
  - How many people genuinely don't want to know genetic information about themselves that could have a profound impact on morbidity or mortality?
  - If people were given genetic risk information that they would have preferred not to know, what is the magnitude of the harm they actually experience?
  - 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?

Thank You

Questions?

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