Incidental Findings and Next-Generation Genomic Sequencing

Benjamin E. Berkman, JD, MPH
Office of the Clinical Director, NHGRI
and
Department of Bioethics, Clinical Center
National Institutes of Health

Disclaimer

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

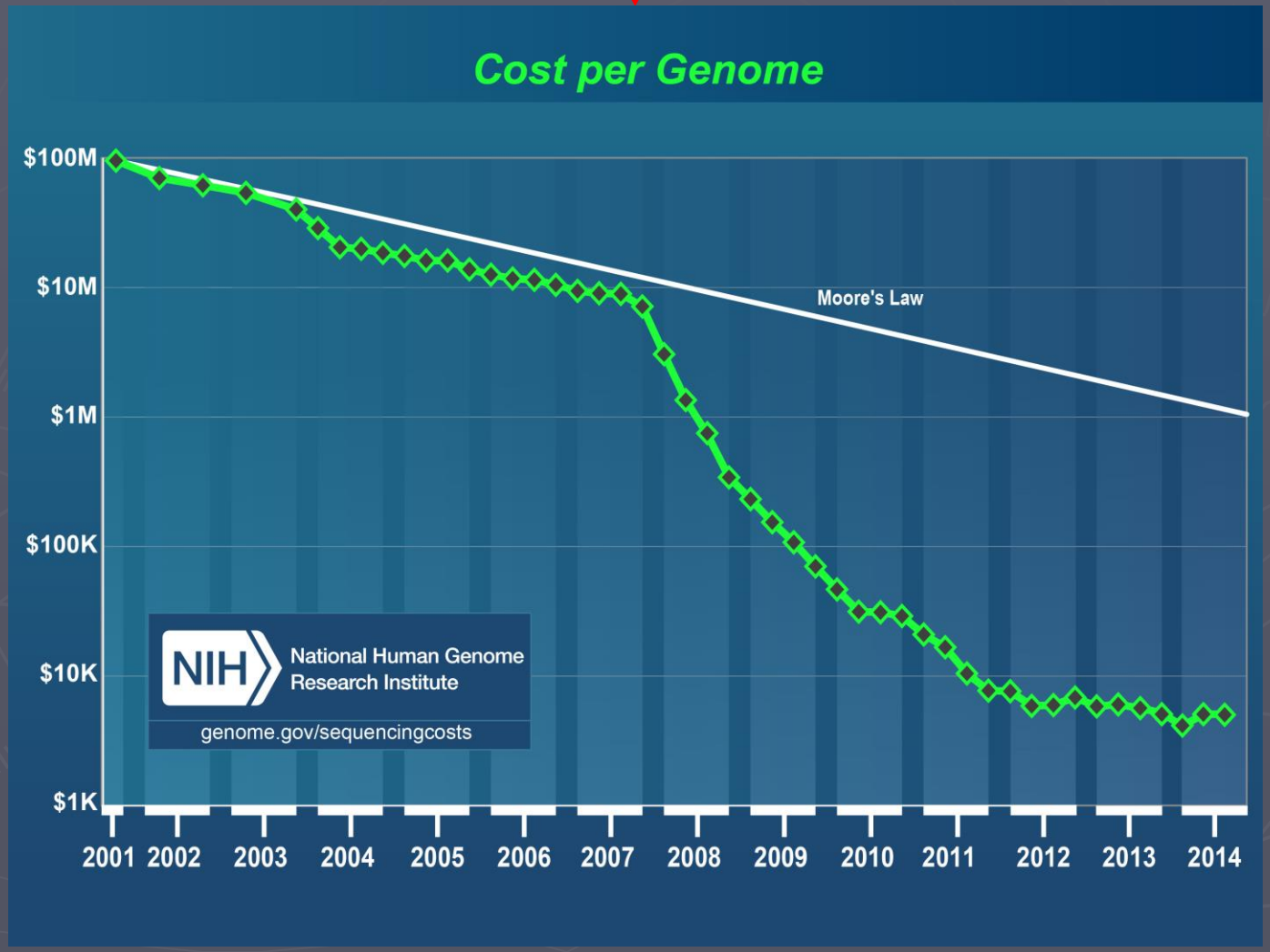
Roadmap

- Next-generation sequencing
- Genetic incidental findings (GIFs)
- Unresolved ethical controversies and questions

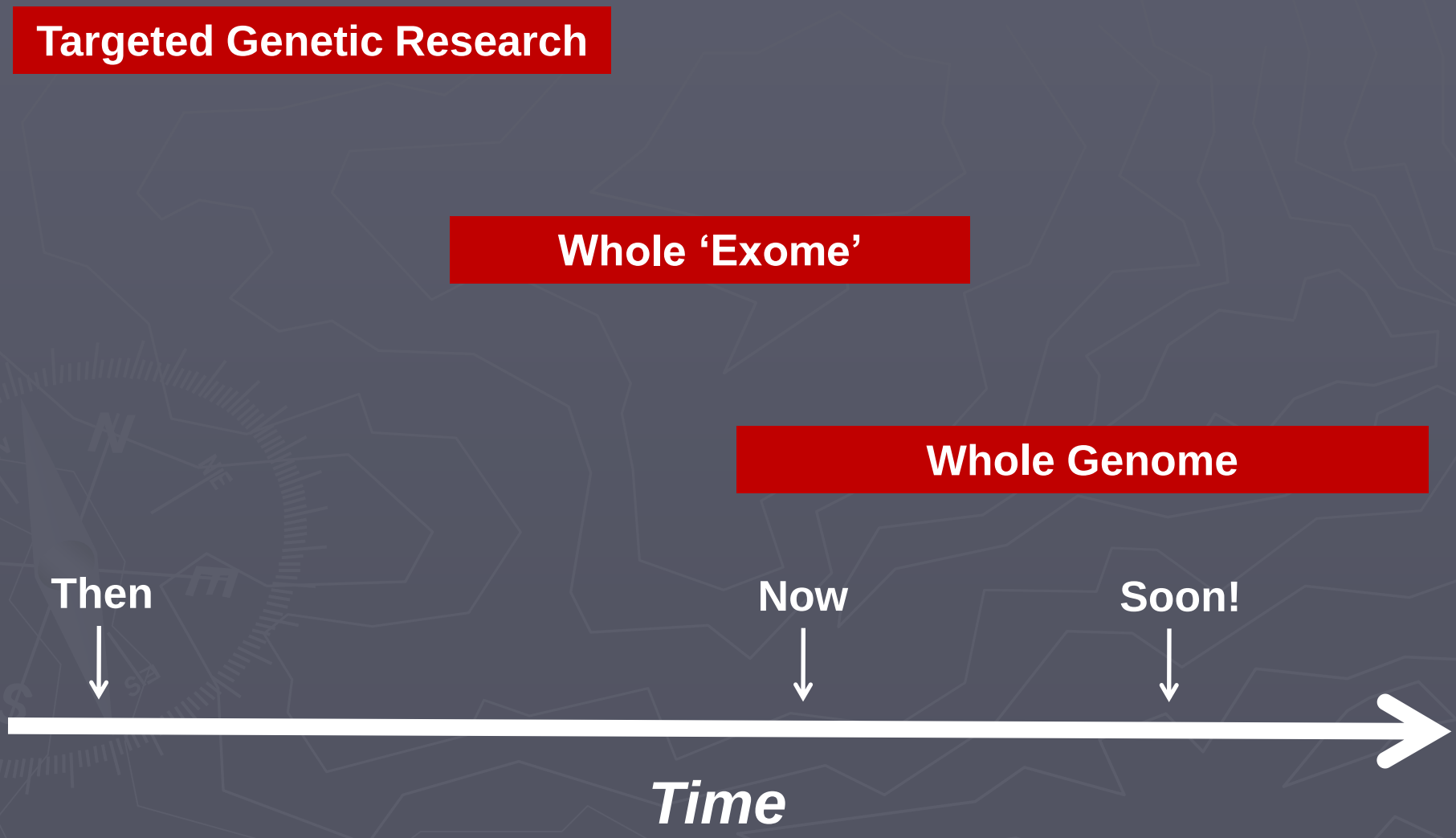
Background: Next-generation sequencing

Advancing Sequencing Capacity

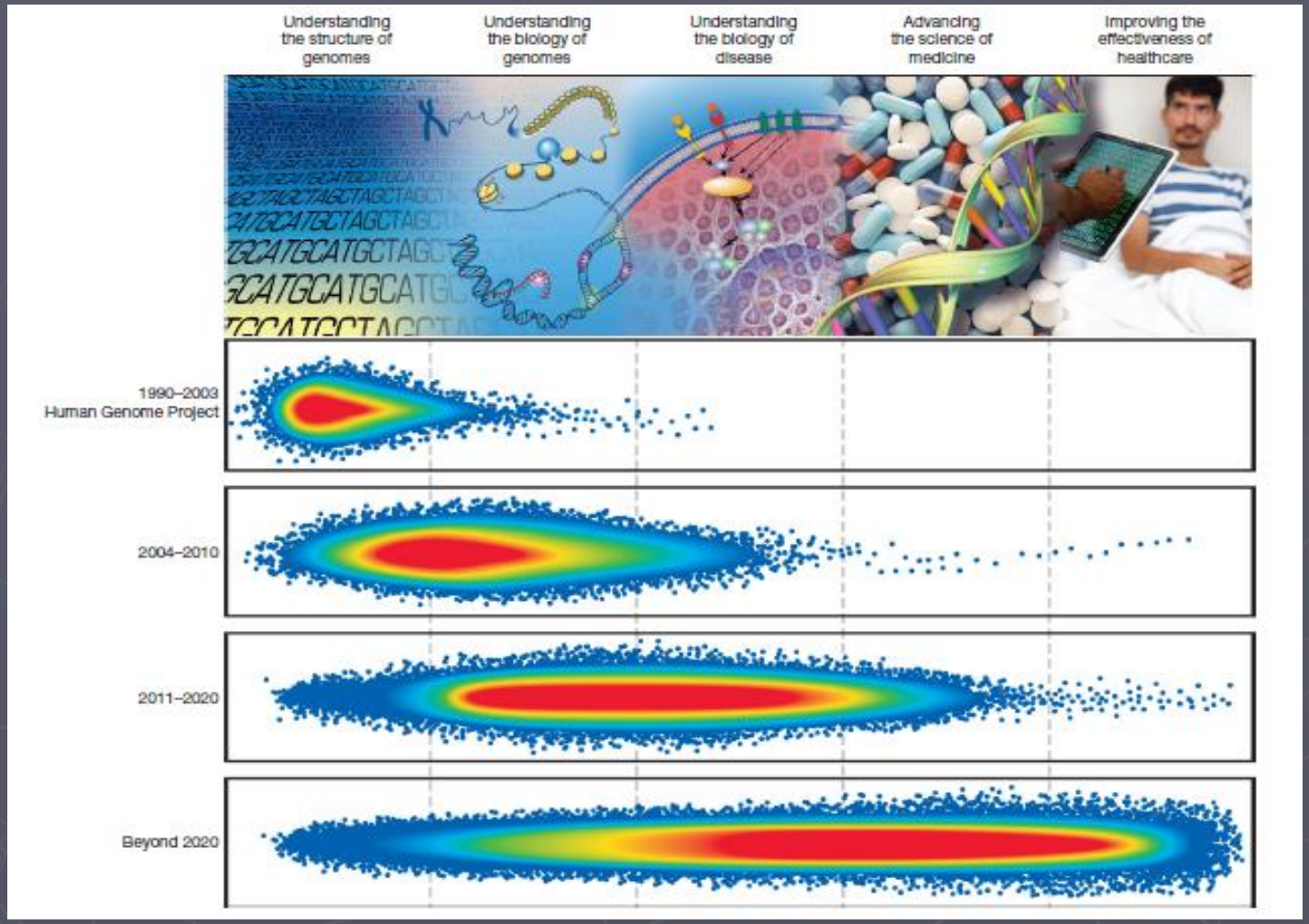
Next-Gen Sequencing



En Route to Routine Whole-Genome Sequencing



The Future of Genomic Medicine



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

Genetic Incidental Findings

Definition

- An incidental result is:
  - A clinically significant finding that arises from a test or procedure, but that is beyond the original purpose for which the test or procedure was conducted

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 genetic incidental findings

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 testing 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 patient or research participant, but rather how many results will be identified in each.

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 purpose of the test.

- Revised assumption #2
  - For diagnostic or research 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

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.

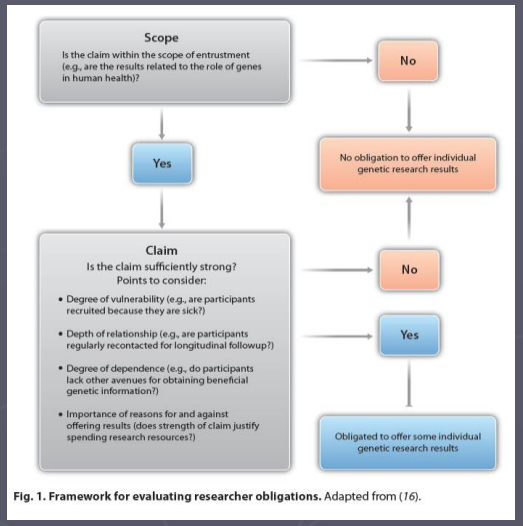
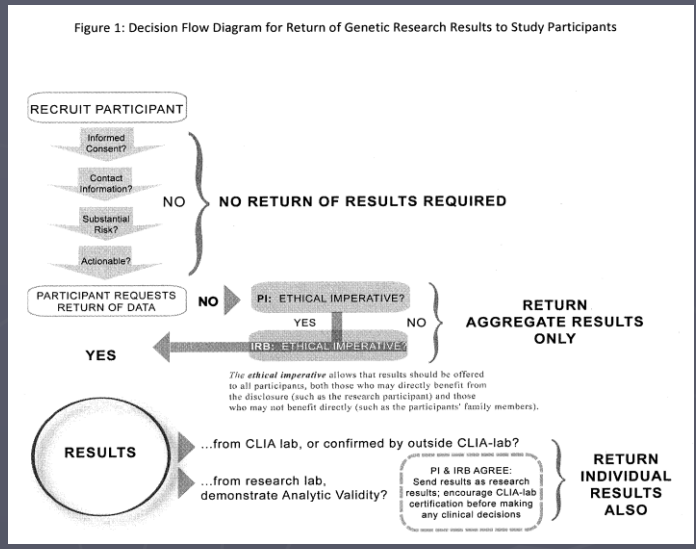
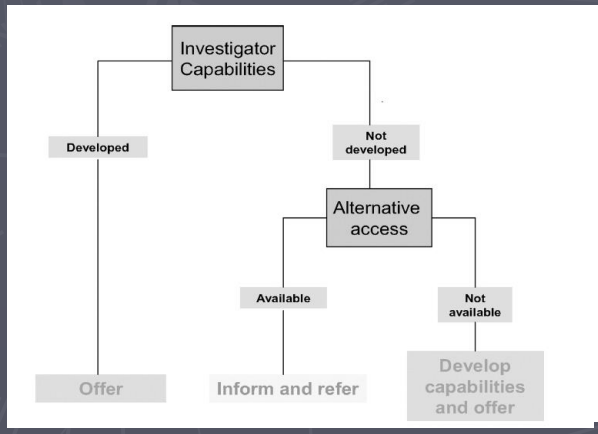
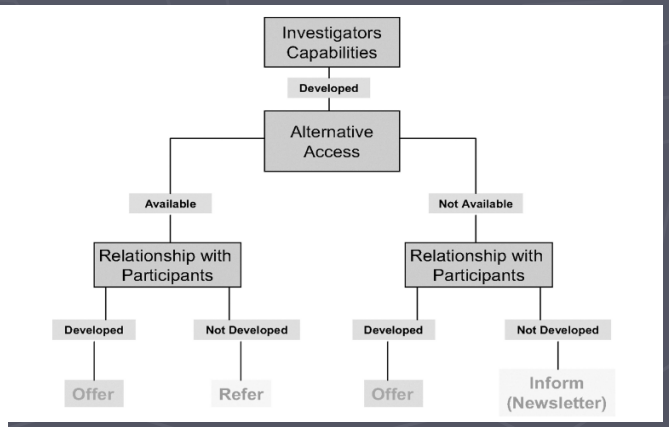


Fig. 1. Framework for evaluating researcher obligations. Adapted from (*16*).







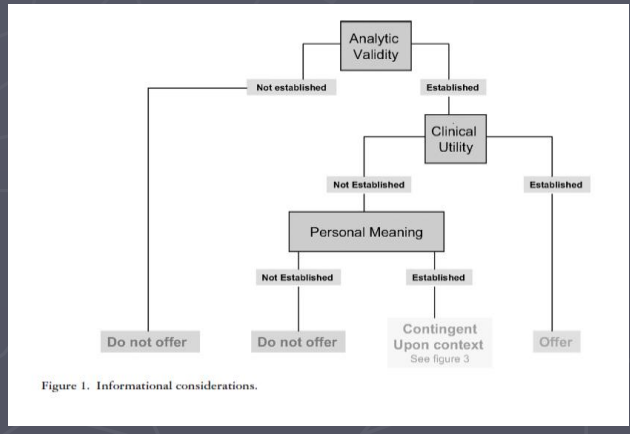


Figure 1. Informational considerations.

Unresolved Ethical Controversies and Questions

Lurking disagreements and controversial issues

- **What is the principle on which an obligation to disclose rests?**
- Is there a duty to look for incidental (i.e. secondary) findings?
- When is it appropriate to disclose genetic information to relatives of the proband?
- Under what circumstances should doctors and researchers be held liable for failing to disclose an incidental finding?
- How strong is the so-called “right not to know”?

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%

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?
- **Is there a duty to look for incidental (i.e. secondary) 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

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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 patient's relatives?
- If so, under what circumstances and through what mechanism should they be disclosed?
- What subset of the results should be disclosed?
- How much weight should privacy and logistical concerns be given?

Lurking disagreements and controversial issues

- What is the principle on which an obligation to disclose rests?
- Is there a duty to look for incidental (i.e. secondary) findings?
- When is it appropriate to disclose genetic information to relatives of the proband?
- **Under what circumstances should doctors and researchers be held liable for failing to disclose an incidental finding?**
- How strong is the so-called “right not to know”?

State of the debate

- Emerging majority view that there is some obligation to return some findings in some contexts
- Varying and/or context specific justifications in support of obligating disclosure
- Attempts to articulate clear practice standards have been met with significant resistance (e.g., ACMG Recommendations)

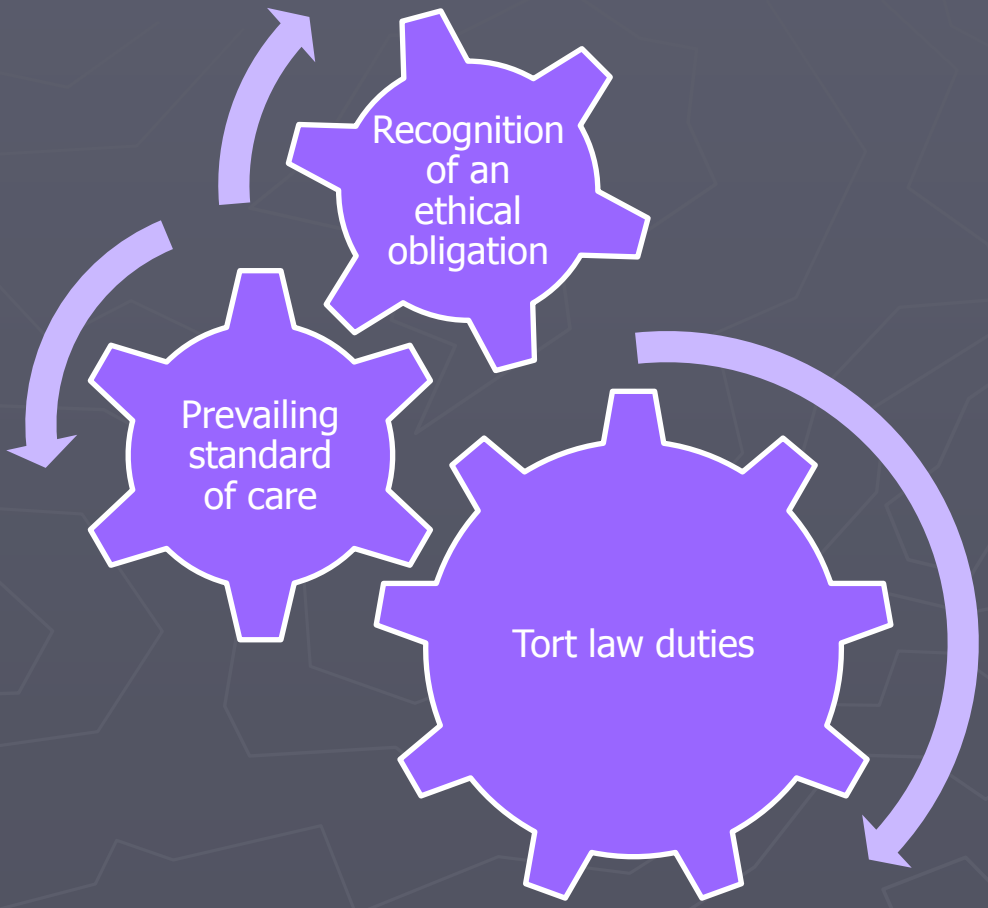
State of researcher practice

- Without clear guidance researcher practice varies widely
  - Remain silent
  - Return nothing
  - Return only in some circumstances
  - Exercise clinical judgment
  - Solicit participant preferences
- Often appeal to terms like
  - Clinical significance
  - Actionability

The Problem

- There is a gap between:
  - The emerging view that researchers have an ethical obligation to return at least some IFs,
  - the reality that some, but not all, researchers choose to return IFs
- There has been much concern about the potential for legal liability arising from inconsistent approaches to returning IFs

Ethics Driving Liability?



Questions

- Is there a legal obligation for researchers to return incidental findings?
- What is the appropriate legal standard to which we should hold researchers?
  - No vague criteria (clinically significant, actionable, etc.)
  - Three acceptable options
    - Return nothing
    - Return everything
    - Return findings consistent with a compendium
- Guidance to judges
  - Interpreting unclear consent language
  - Ascertaining when is reasonable reliance warranted

Lurking disagreements and controversial issues

- What is the principle on which an obligation to disclose rests?
- Is there a duty to look for incidental (i.e. secondary) findings?
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- **How strong is the so-called "right not to know"?**

The Right Not to Know

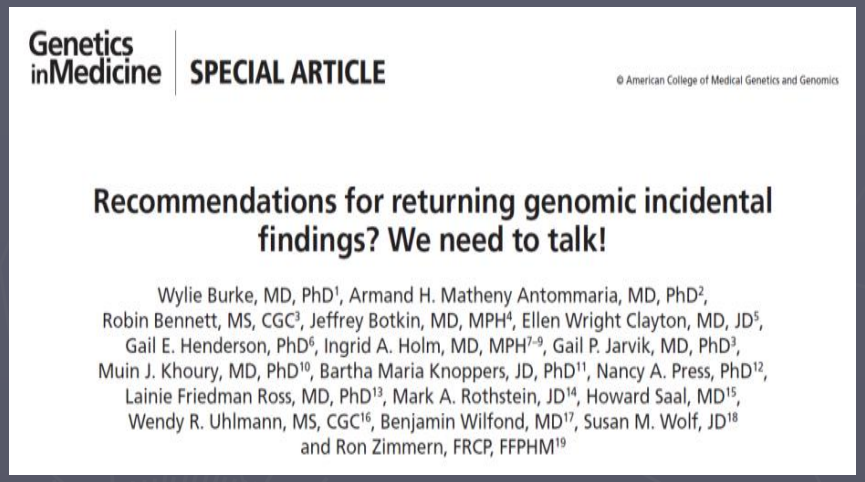
One Area of Apparent Consensus?

- 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."

American College of Medical Genetics and Genomics (ACMG) Recommendations

- "Minimum list" of incidental findings to report from any clinical sequence (n=56)
- Variants on the list should be actively sought by the laboratory
  - "Opportunistic Screening"
- Argue against soliciting patient preferences about receiving incidental findings
  - Clinicians have a fiduciary duty to warn patients about high risk variants where an intervention is available

Strong Disagreement



Genetics inMedicine | SPECIAL ARTICLE

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

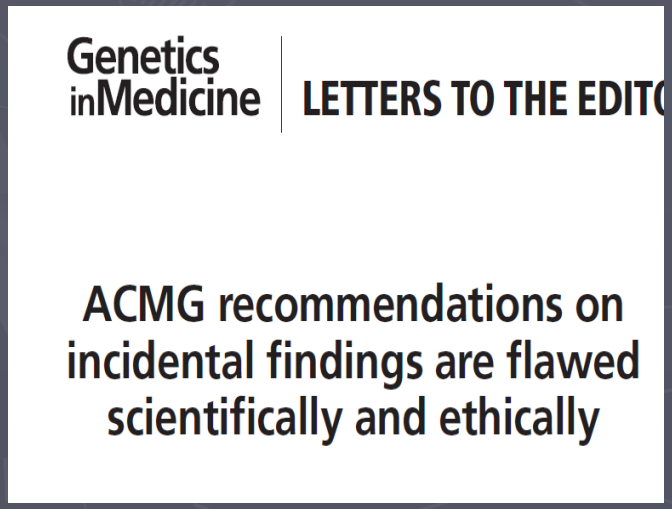
Wylie Burke, MD, PhD[1], Armand H. Matheny Antommaria, MD, PhD[2], Robin Bennett, MS, CGC[3], Jeffrey Botkin, MD, MPH[4], Ellen Wright Clayton, MD, JD[5], Gail E. Henderson, PhD[6], Ingrid A. Holm, MD, MPH[7–9], Gail P. Jarvik, MD, PhD[3], Muin J. Khoury, MD, PhD[10], Bartha Maria Knoppers, JD, PhD[11], 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

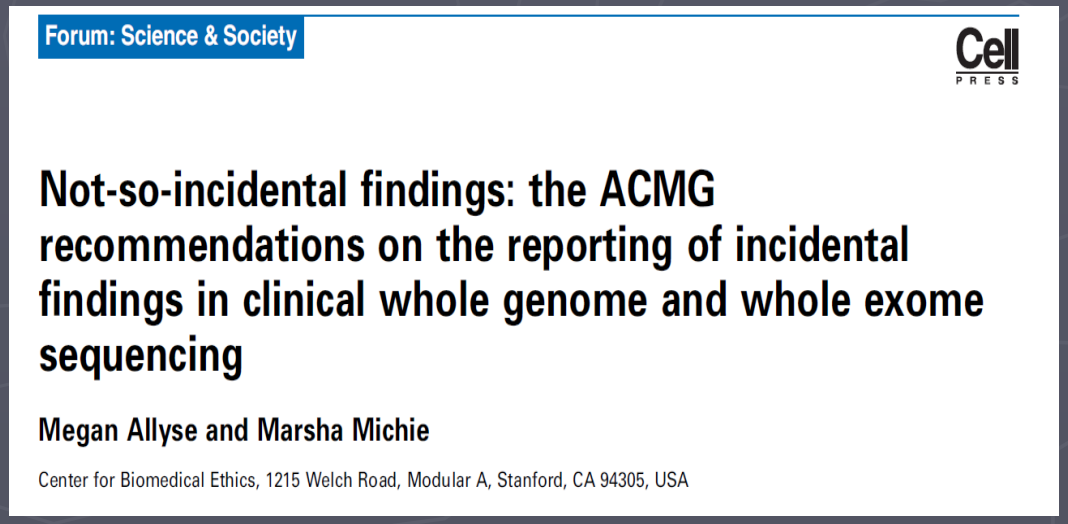
Returning genetic incidental findings without patient consent is misguided.

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



Genetics inMedicine | LETTERS TO THE EDITO

ACMG recommendations on incidental findings are flawed scientifically and ethically



Forum: Science & Society

Cell PRESS

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

Megan Allyse and Marsha Michie

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

ACMG Walk Back

- Overwhelming disagreement from membership
  - Direct feedback, forums, survey
- "consensus among ACMG members that patients should have an opportunity to opt out"
- Updated recommendations to emphasize that: "an 'opt out' option be offered to patients who are considered candidates for clinical genome-scale sequencing."

Baseline Question

- Do people 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 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

- Are traditional conceptions about the "right not to know" ("RNTK") appropriate in a genomic era?
- 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?
- How, if at all, should the RNTK be reflected in informed consent and return of results policies

Thank You

Questions

- Contact:
  - berkmanbe@mail.nih.gov
- Some further reading

- Berkman BE, Hull SC, Eckstein L. The Unintended Implication of Blurring the Line between Research and Clinical Care in a Genomic Age. *Personalized Medicine*, 11(3): 285-295 (2014)
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- 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).