

The Ethics of Incidental Findings and Genomic Sequencing Research

Benjamin E. Berkman, JD, MPH

NIH Department of Bioethics
and
NHGRI Bioethics Core

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

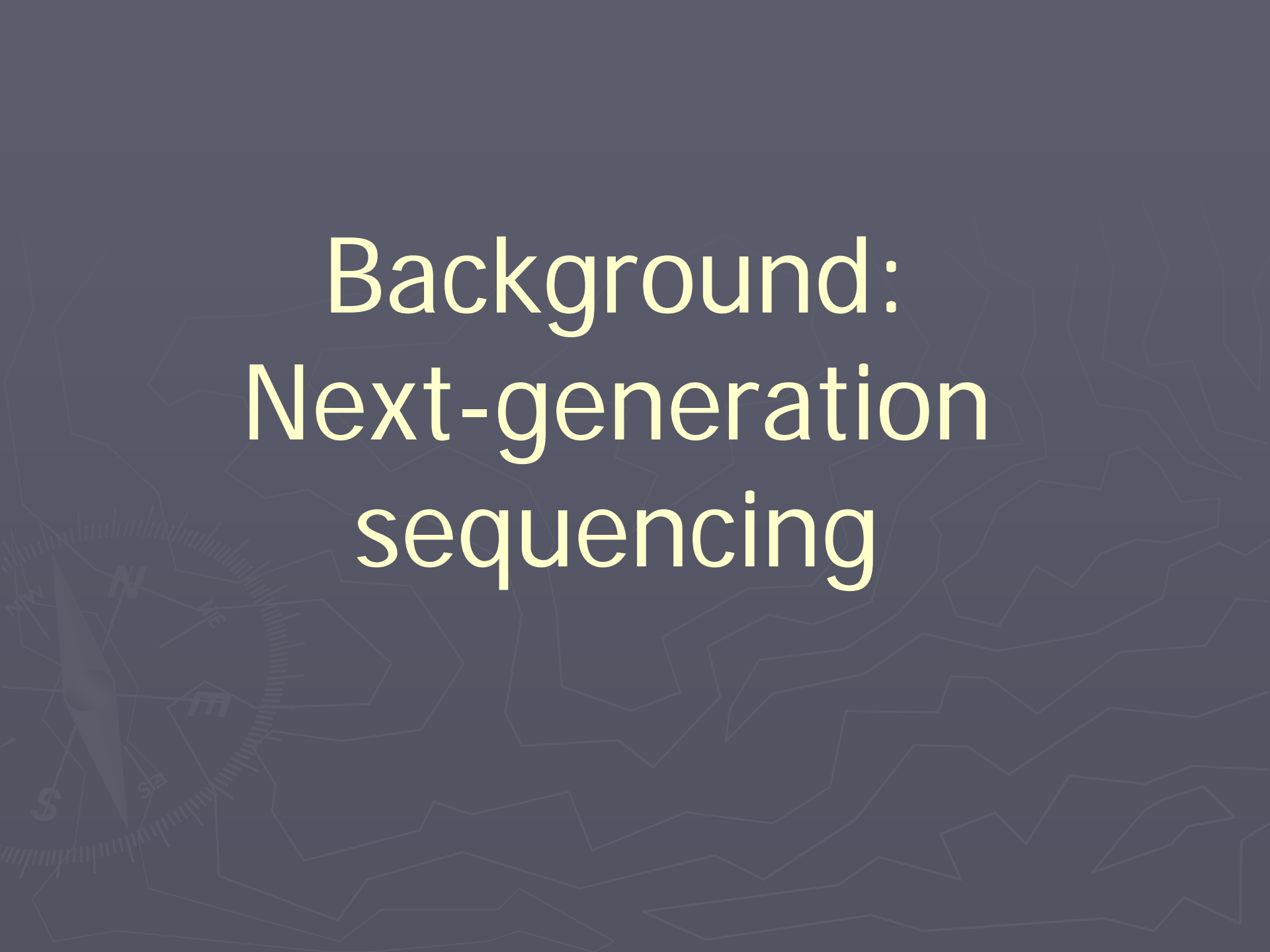
- ▶ The research team planned to de-identify the samples obtained.
- ▶ The relevant consent language read:
 - “Your name and anything else that could identify you will be removed and kept in a separate file. There will be a master list that links the code number to your name. This list will be stored 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?

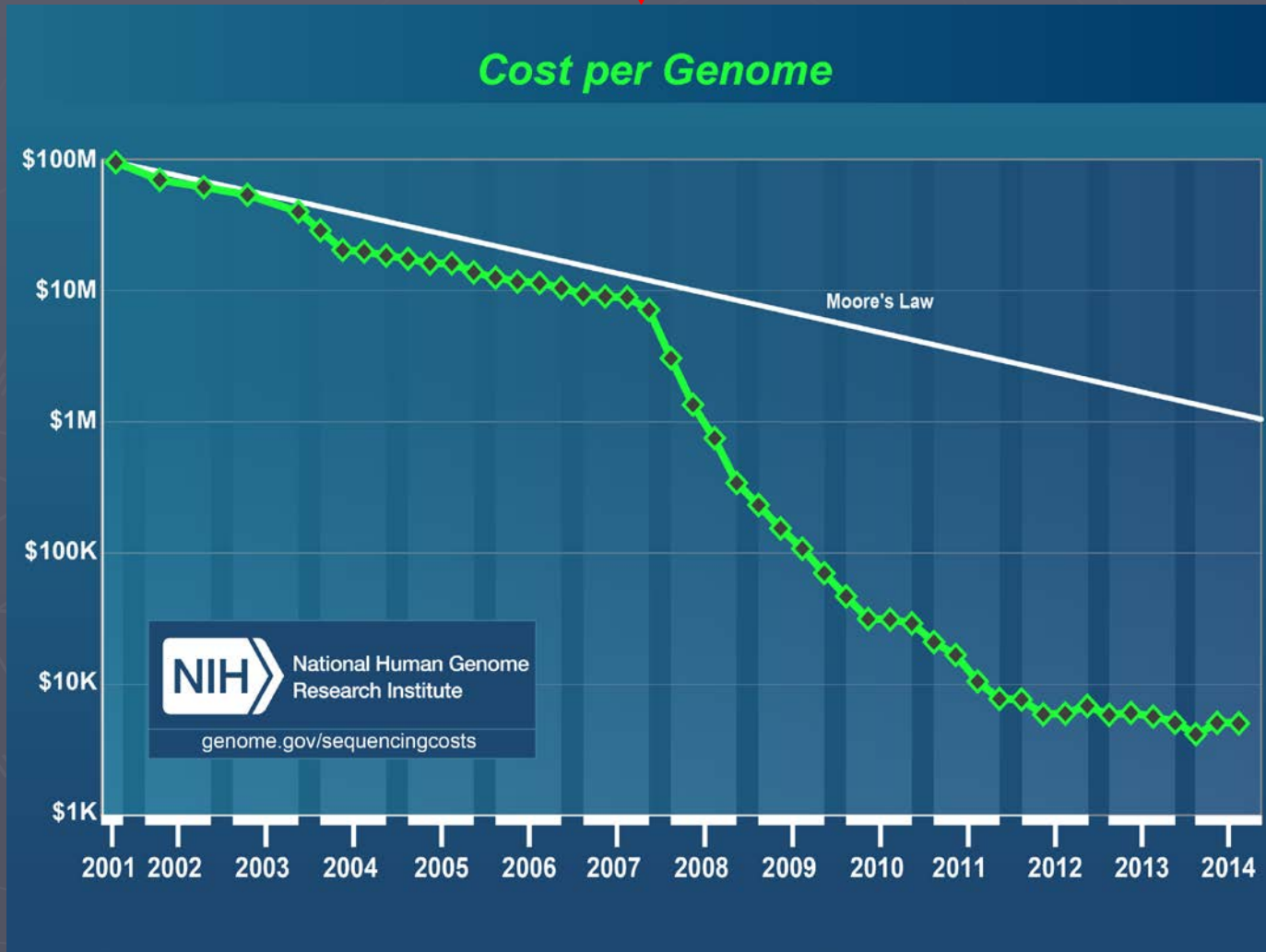


Background: Next-generation sequencing

Advancing Sequencing Capacity



Next-Gen Sequencing



En Route to Routine Whole-Genome Sequencing

Targeted Genetic Research

Whole 'Exome'

Whole Genome

Then



Now



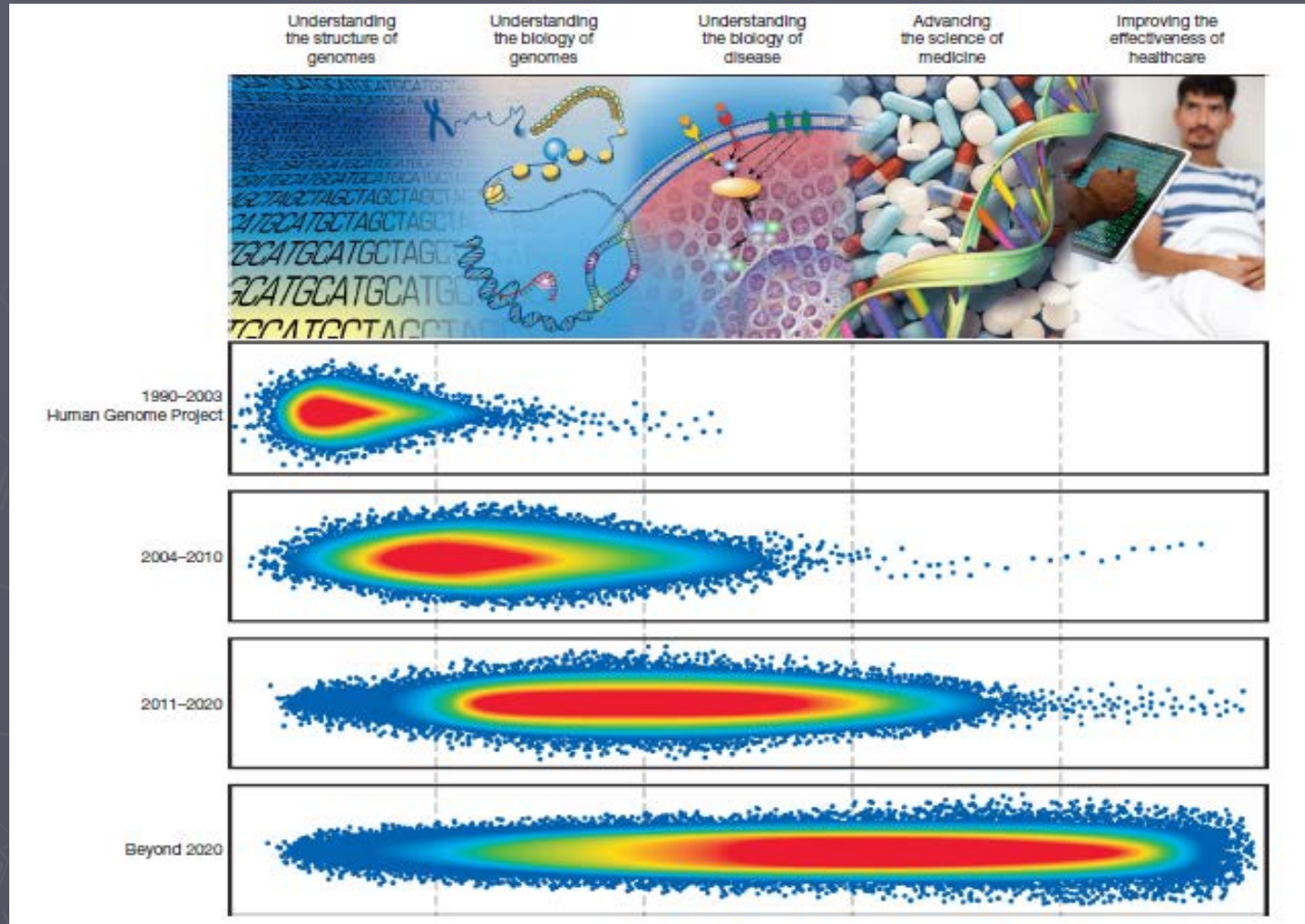
Soon!



Time



The Future of Genomic Medicine



Green, et. al., Nature, 2011,
“The Future is Bright”.

Incidental Findings in Genetic Research

The background of the slide is a dark blue-grey color. On the left side, there is a faint, light-colored graphic of a compass rose with a needle pointing towards the top-left. To the right of the compass, there are faint, light-colored lines representing a topographic map or contour lines.

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.)

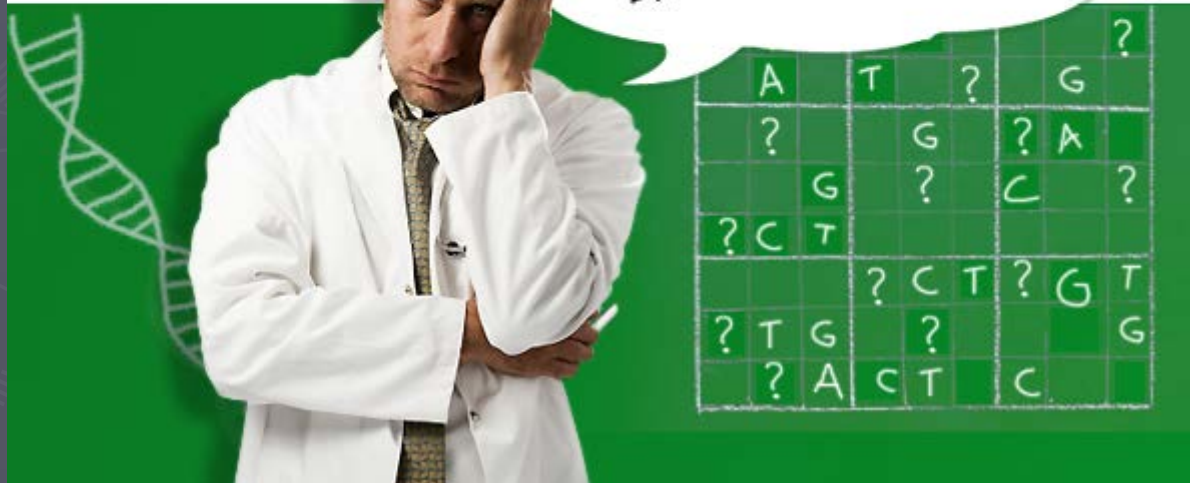
▶ Revised assumption #3

- 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

Is Next-Gen Sequence Analysis giving you a headache?

It's too complex...
There's too much data...
Can't visualize it...
Don't know what it means...



The background is a dark blue-grey color with a faint, light-colored graphic. On the left side, there is a compass rose with a needle pointing towards the top-left. To the right of the compass, there is a faint outline of a map or a geographical area. The overall aesthetic is clean and professional.

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 re-consent required?
- ▶ 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 disclose 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 disclose 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 disclose 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

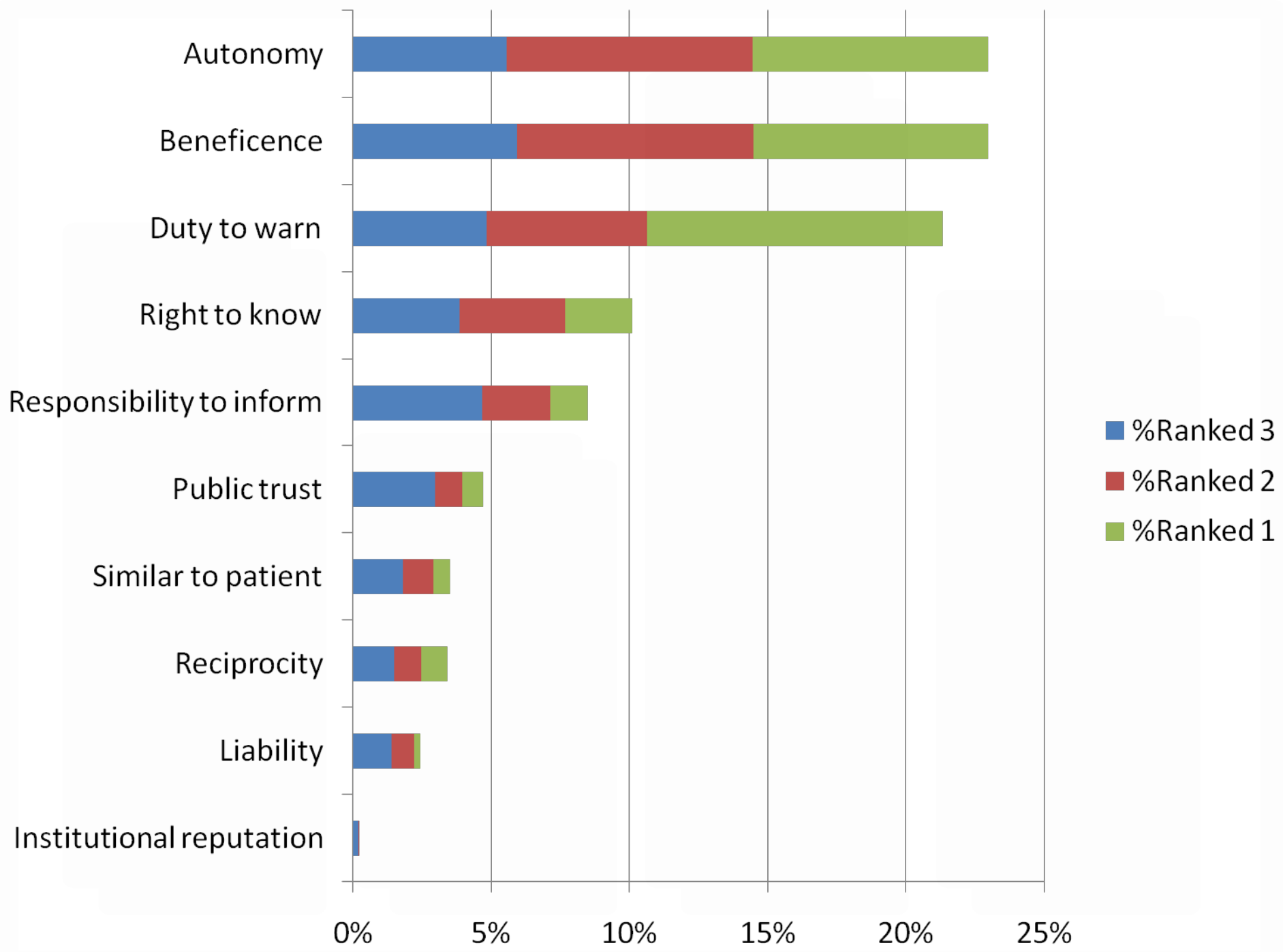
Do you believe that researchers have an obligation to disclose genetic incidental findings to participants?

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%



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 \neq 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 re consent required?
- ▶ 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?

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

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.

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.

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.

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 59 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.

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 re consent required?**
- ▶ 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?

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

- ▶ Is there something ethically relevant about sequencing such that new consent is desirable?
- ▶ How explicit does consent language need to be in order to authorize sequencing?
- ▶ 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 re-consent required?
- ▶ **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?

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?
- ▶ 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 59

Duty to look?

- ▶ In certain situations, investigators could have an obligation to look for incidental findings in genomic research.
- ▶ An obligation exists when these criteria are met:
 - The analysis is relatively simple and does not strain resources.
 - The genetic information is high quality and likely to yield beneficial information.
 - The researchers are in a unique position to help their participants.

A few years ago...

- ▶ Benefit: Low ↓
 - *Majority* of genetic information is of uneven quality and utility.
- ▶ Need: High ↑
 - Researchers in a unique position to help.
- ▶ Difficulty/burden: Very hard ↓
 - Looking is time consuming.
 - Expertise is limited.
- ▶ **No obligation to look**

Today

- ▶ But technological advances and a definitive list of disclosable variants have shifted the balance
 - Easier to search = lower burden on the researcher
 - Expanding list of high value variants signals that benefit to participants is increasing
- ▶ So perhaps there is a baseline obligation to look, but only for the variants on the list.
 - Assuming centralized resource?

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 re-consent 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?**
- ▶ 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?

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 re consent required?
- ▶ 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?**

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.

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

© American College of Medical Genetics and Genomics

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

Wylie Burke, MD, PhD¹, Armand H. Matheny Antommaria, MD, PhD², Robin Bennett, MS, CGC³, Jeffrey Botkin, MD, MPH⁴, Ellen Wright Clayton, MD, JD⁵, Gail E. Henderson, PhD⁶, Ingrid A. Holm, MD, MPH⁷⁻⁹, Gail R. Jarvik, MD, PhD³, Muin J. Khoury, MD, PhD¹⁰, Bartha Maria Knoppers, JD, PhD¹¹, Nancy A. Press, PhD¹², Lainie Friedman Ross, MD, PhD¹³, Mark A. Rothstein, JD¹⁴, Howard Saal, MD¹⁵, Wendy R. Uhlmann, MS, CGC¹⁶, Benjamin Wilfond, MD¹⁷, Susan M. Wolf, JD¹⁸ and Ron Zimmern, FRCP, FFPHM¹⁹

POINT-COUNTERPOINT

Patient Autonomy and Incidental Findings in Clinical Genomics

Susan M. Wolf,^{1*} George J. Annas,² Sherman Elias³

Returning genetic incidental findings without patient consent is misguided.

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

gan Allyse and Marsha Michie

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

Genetics
inMedicine

LETTERS TO THE EDITOR

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%

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

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?

Thank You



The background is a dark blue-grey color with a subtle pattern of light grey topographic contour lines. On the left side, there is a faint, semi-transparent illustration of a compass rose with a needle pointing towards the top-left. The compass has markings for North (N), South (S), East (E), and West (W), along with intermediate directions like NE, SE, SW, and NW.

Questions?

berkmanbe@mail.nih.gov