Ethics & Regulation of Genomic Research

Cold Spring Harbor Laboratory
Advanced Sequencing Technologies & Bioinformatics Analysis
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Jessica Mozersky, PhD MBE

Assistant Professor of Medicine

Bioethics Research Center

Washington University in St. Louis
School of Medicine

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BIOETHICS RESEARCH CENTER

Outline for today

- What is special about genetic information?
- Common Rule updates as a way to highlight key issues:
  - Informed Consent
  - Future Research / Data Sharing
  - Blurring Research and Clinical Boundaries
  - Return of Research Results
- **Goal:** update on regulations, raise awareness of issues, consider ongoing challenges, and strategies for going forward

Principles of biomedical ethics

- Autonomy
- Beneficence
- Non-maleficence
- Justice

Principles can conflict

- Individual rights and social benefits will often be in tension, i.e.:
  - Individual right to privacy
  - Social benefit of data sharing in terms of knowledge produced
- Necessarily involves risk/benefit tradeoffs or decisions that aim to balance conflicting principles

What is special about genetic information?

- Genetic knowledge is intrinsically different from other kinds of knowledge about individuals → unique duties and obligations
    - Genetic Exceptionalism
- What is special or unique about genetic information?

What is unique about genetic info?

1. **Predictive** (early, late onset, asymptomatic)
   i. Discrimination / Stigma

2. **Implications for biological relatives**

3. **Implications for reproductive decision making**

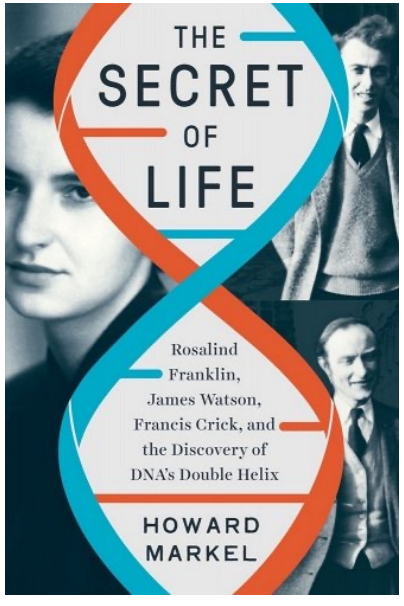
4. **Uncertainty:** may contain information of unknown significance but could change in future when more is known

5. **Personal:** unique identifier (paternity, forensics)

6. May have **cultural significance** for persons or groups/communities

Social Context of Genetics

- Belief that genes “determine our fate”
- Rarely is this the case
- Most disease are complex and multi-factorial in causation



Law enforcement may access commercial data

How Genetic Genealogy Helped Catch The Golden State Killer

JV Chamary Contributor ⓘ
Science
Journalist and science communicator

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We will find you: DNA search used to nab Golden State Killer can home in on about 60% of white Americans

Researchers call for limiting how ancestry databases can be used to protect privacy

11 OCT 2018 • BY JOCELYN KAISER

Genetic Information Non Discrimination Act (GINA)

- Genetic information is subject to special laws

- A federal law that prohibits discrimination based on genetic information in health insurance and employment
  - Prevents denying insurance or employment based on genetic risk

- Does not protect long term care or other types of insurance
  - Risk of Alzheimer Disease

Many forms of human genetic research

- Wide array and diverse forms and types of genetic research across all stages of life

- Implications of information differ depending on context, type of test done, research population …
  - Heritable or not?
  - Have we seen this variant before? Do we know what it means?
  - Actionable or not?
  - CLIA lab?
  - Is participant alive or not?

Challenges to research with genetic data

- Separation (in time and space) between sample collection and actual research
    - Future research, risks and benefits unforeseeable
    - New data likely to arise
    - Results relevant beyond individual (family, deceased donor)

Challenges to research with genetic data

- Samples may have been collected for a different purpose
  - Re-consent?
  - Cost / Burden
  - Incidental findings

Challenges to research with genetic data

- Patient autonomy and right to know
  - Direct to consumer testing
- Blurring boundaries between clinical care and research
  - Default denial of research results in all cases less feasible

What is the Common Rule?

- Set of federal human subject regulations regarding conduct and oversight of human research
- Effective Jan 21 2019
- Applies to all federally funded activities

- The Common Rule updates reflect changes in the types and scope of information that is being produced
  - Data sharing and future research dramatically changed over time
    - Informed consent needs to reflect these changes
  - Genetics is explicitly highlighted
  - Move toward sharing **research results**

Updates to Informed Consent Process

1. **Statement of future research and storage plans for biospecimens required**

   - May be used for future research or shared with other researchers without re-consent after identifiers have been removed

   OR

   - Information that biospecimens will not be used for future research even if identifiers removed

Updates to Informed Consent Process

2. For research involving biospecimens, whether the research

will (if known) or might include **whole genome sequencing** (i.e., sequencing of a human germline or somatic specimen with the intent to generate the genome or exome sequence of that specimen).

Stored specimens and data are valuable to advance research

- **We don’t want to hinder advances in knowledge**
- Consent for secondary / future research is a main challenge (Common Rule reflects this)
- Ethically, goal is to find a balance between enabling research (social benefits) and respecting individual autonomy

Broad Consent

"Process in which participants agree prospectively to have their samples, genomic data, and other health information retained for use in any future research *deemed appropriate by a biobank and/or relevant oversight bodies*." (Garrison et al. 2016)

Consent Options

Approaches to Consent for future research with biospecimens

	TYPE OF CONSENT	DESCRIPTION
Less burden, less control	No consent	Do not obtain donor consent
	Blanket	Consent to future research with no limitations
	Broad*	Consent to future research with specified limitations
	Checklist	Donors choose which types of future studies allowed
More burden, more control	Study specific	Consent for each specific future study

*Framework proposed here couples initial broad consent with oversight and the possibility of ongoing communicati

Grady et al. AJOB 2015 (15):9 "Broad consent for research with biological samples: workshop conclusions"

Audience Question

I would give broad consent for my DNA sequence to be used for future research with:

1. No one
2. University scientists and researchers at my institution
3. University scientists and researchers at my institution and non-profit institutions
4. University scientists and researchers at my institution, non-profit, and for profit institutions

I want some level of control over the **types of future** research conducted with my genetic data?

Yes or no? Why or why not?

JAMA Network Open

Original Investigation | Health Informatics

Patient Perspectives About Decisions to Share Medical Data and Biospecimens for Research

Jihoon Kim, MS; Hyeoneui Kim, RN, PhD; Elizabeth Bell, MPH; Tyler Bath, BS; Paulina Paul, MS; Anh Pham, BS; Xiaoqian Jiang, PhD; Kai Zheng, PhD; Lucila Ohno-Machado, MD, PhD

Genetic Data Sharing:

- No one: **9.1%**
- University scientists and researchers at my institution only: **31.3%**
- University scientists and researchers at my institution and outside non-profit institutions: **19.4%**
- University scientists and researchers at my institution, outside non-profit institutions, and for profit institutions: **39.2%**

N=1246 patients at 2 AMCs

What do the Data say?

Official journal of the American College of Medical Genetics and Genomics

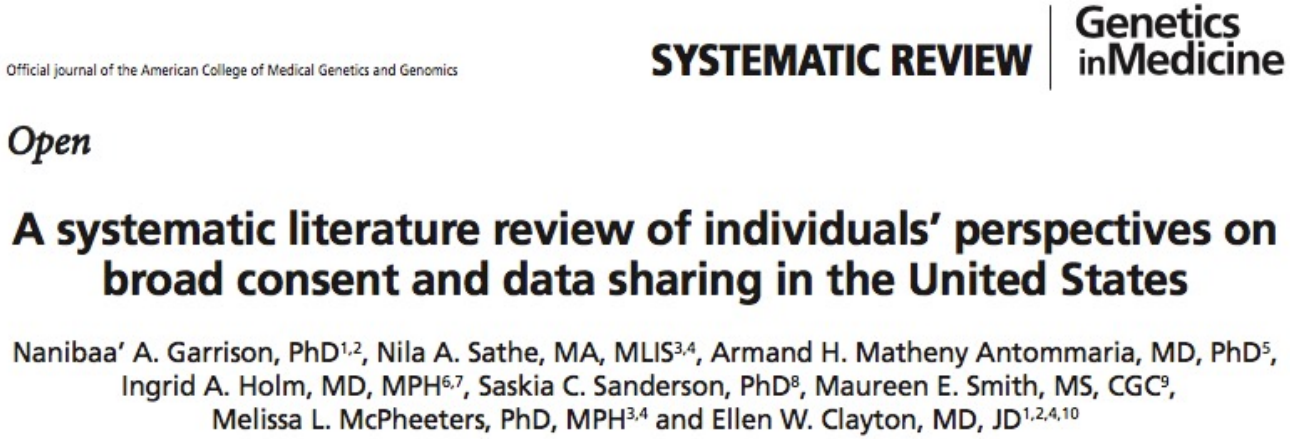
SYSTEMATIC REVIEW | Genetics inMedicine

Open

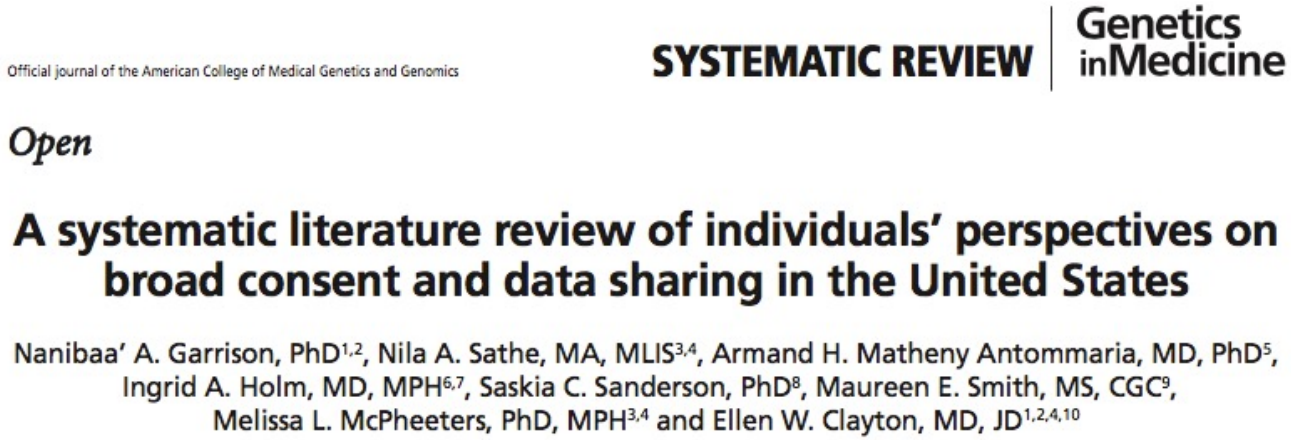
A systematic literature review of individuals' perspectives on broad consent and data sharing in the United States

Nanibaa' A. Garrison, PhD[1,2], Nila A. Sathe, MA, MLIS[3,4], Armand H. Matheny Antommaria, MD, PhD[5], Ingrid A. Holm, MD, MPH[6,7], Saskia C. Sanderson, PhD[8], Maureen E. Smith, MS, CGC[9], Melissa L. McPheeters, PhD, MPH[3,4] and Ellen W. Clayton, MD, JD[1,2,4,10]

- **Broad consent generally** preferred over tiered or study specific (especially if only option) so long as:
  - De-identified, communicate logistics, address privacy
  - Opt-in vs. opt-out – more diversity in preferences

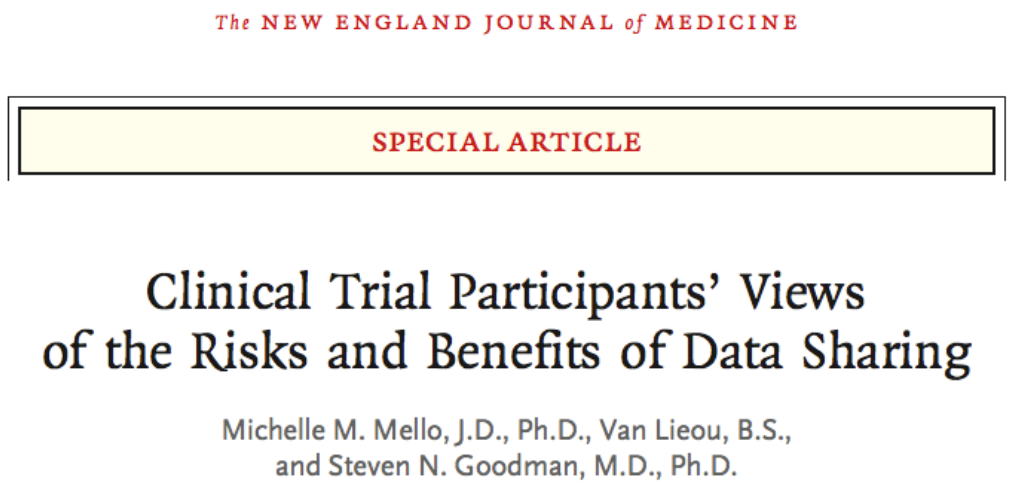


- High willingness for **data sharing** overall
- Support lower if commercial access, and among individuals with P&C concerns
- Where available, data suggests lower support among under-represented minorities



- 93% clinical trials participants willing to share data (including genomic data) with university

- 82% willing to share with for profit companies



N=771 clinical trial participants at 3 AMCs

New NIH Data Sharing Policy

Final NIH Policy for Data Management and Sharing

Notice Number:

NOT-OD-21-013

Key Dates

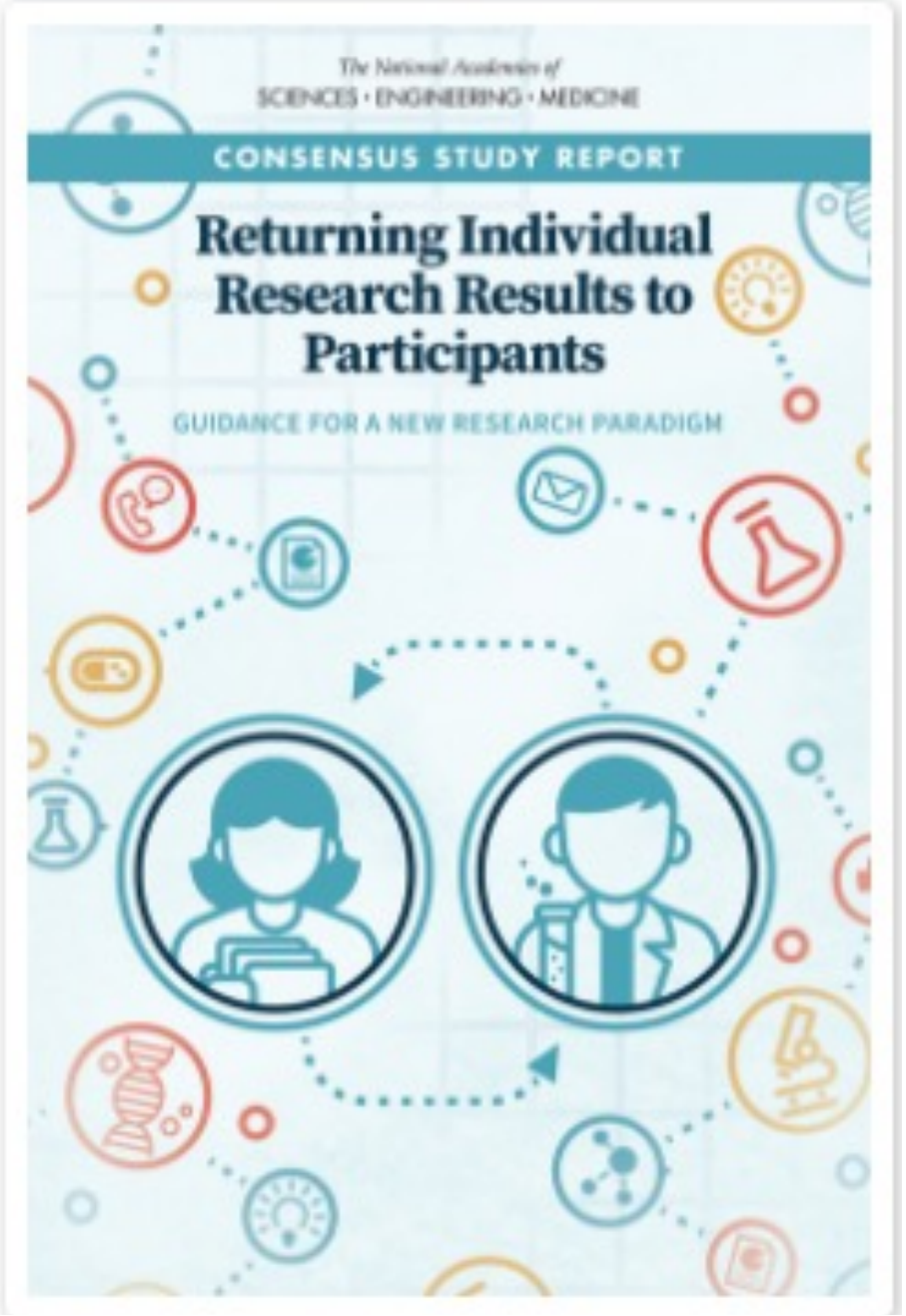
Release Date:	October 29, 2020
Effective Date:	January 25, 2023

Updates to Informed Consent Process

3. Whether clinically relevant research results, including **individual research results**, will be disclosed to subjects, and if so, under what conditions;

Did you say individual research results?!?

The Tide is Changing.



Return of Research Results

- Promote the ethical values of research
- Recognize contribution of participants
- Respect participant autonomy
  - People want to know
- Evidence of harms is lacking
- Increase trust
- Demonstrate reciprocity for research contributions
- Improve recruitment and retention

Research ≠ Clinical Care

- Historically, research results **not** returned to participants

- Considered outside scope of research

    - Generalizable knowledge vs personal benefits
    - Consents forms may explicitly state this
    - Relationship, or not, between researcher and participant varies widely

Research ≠ Clinical Care

- Clinical criteria regarding return of genetic results:

    1. Clinical Validity (accuracy, reliability, quality control, false positives)
        1. CLIA
    2. Clinical significance (impact on health)
    3. Clinical utility (are the results actionable)

- **Sets a relatively high bar for disclosure**
    - *APOE* status not “actionable” therefore not clinically recommended

Why does this matter?

- It is often cheaper, simpler, faster to conduct a whole exome or genome sequence in research settings
    - Impacts our obligations to participants if we generate additional information even if due to advances in technology/techniques

Secondary genetic findings

- Clinically important findings discovered during genetic research but unrelated to primary purpose of sequencing / research

Genetics inMedicine

www.nature.com/gim

ACMG STATEMENT

ACMG SF v3.0 list for reporting of secondary findings in clinical exome and genome sequencing: a policy statement of the American College of Medical Genetics and Genomics (ACMG)

David T. Miller[1,20], Kristy Lee[2,20], Wendy K. Chung[3], Adam S. Gordon[4], Gail E. Herman[5], Teri E. Klein[6], Douglas R. Stewart[7], Laura M. Amendola[8], Kathy Adelman[9], Sherri J. Bale[10], Michael H. Gollob[11], Steven M. Harrison[12], Ray E. Hershberger[13], Kent McKelvey[14], C. Sue Richards[15], Christopher N. Vlangos[16], Michael S. Watson[17], Christa Lese Martin[18] and ACMG Secondary Findings Working Group[19]*

Genetics in Medicine (2021) 23:1381–1390; https://doi.org/10.1038/s41436-021-01172-3

ACMG 73 Secondary findings

- “a minimum list” of “medically actionable” genes that are unrelated to the test indication but should be evaluated as part of ES/GS

- ACMG 73 provide a guide for research settings, but don’t account for personal utility

Personal Utility

- Personal utility: the extent to which a test has the potential to effect change on a (non—medical) personal level

PAPER

Personal utility in genomic testing: is there such a thing?

Eline M Bunnik,[1] A Cecile J W Janssens,[2,3] Maartje H N Schermer[1]

Takeaways

- Genetic information is considered fundamentally different to other types of information
  - Regulations reflect this

- Consider from the outset what findings likely to arise, process for returning or not, including informed consent and future research uses
  - Broad consent for future research
  - Return of results plan

Takeaways

- Consent forms should be as honest and transparent as possible given what we know
- Don’t make unreasonable promises
  - We can’t guarantee data will never be breached, re-identified
- But we can do our best to protect data and inform individuals about the risks and protections in place
- Work with your IRB

Takeaways

- Move towards returning research results
  - Grant applications may require plans
  - Boundaries between clinical care and research continue to blur

- Translational Science and Precision Medicine will mean increasing *amounts* of data are produced and *types* of results that will need to be returned
  - Personal utility may play a bigger role

Thank you

jmozersky@wustl.edu