RESEARCH ETHICS

Research Practice and Participant Preferences: The Growing Gulf

Reframing research practice to align with participant interests is important for ensuring long-term success of genomic investigation.

S. B. Trinidad,[1]* S. M. Fullerton,[1] E. J. Ludman,[2] G. P. Jarvik,[3] E. B. Larson,[2] W. Burke[1]

"The irony is, if you had asked me, I probably would have consented" (*1*). So said Andrea Beleno, a plaintiff suing the Texas Department of State Health Services over its role in the use of newborn screening blood samples in research. Carletta Tilousi, a plaintiff in the Havasupai tribe's lawsuit against the Arizona Board of Regents, expressed similar sentiments: "I'm not against scientific research. I just want it to be done right. They used our blood for all these studies, people got degrees and grants, and they never asked our permission" (*2*).

A spate of recent events—e.g., other conflicts over newborn blood samples (*3*–*5*), the return of biospecimens to the Yanomamö people (*6*), and the best-selling account of the origins of the HeLa human cell line widely used in research (*7*)—has raised questions about trustworthiness of the research process at a time when new approaches to genomic research place a premium on study participation. Although many related issues deserve attention—e.g., ethical use of "leftover" clinical samples, public attitudes about data sharing, and appropriate consent for general-purpose repositories—we focus on repurposing of existing research data and samples.

Harms to Dignity

Many potential harms that might arise from participation in genomic research and how likely they are to occur are not well known. This should not imply, however, that harms to dignity have not occurred. Claims of harm include breaches of autonomy and privacy, stigmatization or other negative social consequences, and uninvited challenges against deeply held beliefs [e.g., (*8*–*11*)]. Financial settlements, restrictions on research, and destruction of samples have been used to make amends, but they cannot undo injury to individuals and their communities. Such "solutions" may delay scientific advances that could improve human health.

These issues are especially fraught for genomic research, where new, high-throughput approaches require massive data inputs. To achieve needed sample sizes and increase efficiency, genome scientists have begun to pool biospecimens and data from prior studies. However, neither the Common Rule (*12*), a U.S. federal policy regarding human subjects protection, nor the U.S. Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule (*13*), which protects the privacy of individually identifiable health information, applies to such materials. And under conditions defined by the U.S. Office for Human Research Protections (*14*), studies using only coded samples and data (*15*) are not classified as human subjects research. Current U.S. federal policies promote "secondary use" of federally funded data, mandating sharing within the research community and strongly encouraging deposition of data in public repositories such as the NIH database of Genotypes and Phenotypes (dbGaP) (*16*, *17*).

"… consider how the consent process could foster respectful engagement, rather than merely mitigate risk."

Many disease-specific and general-purpose repositories have attracted large numbers of participants, obtaining informed "blanket" consent at the outset for a broad range of potential purposes, and some studies document participant support for reuse of research samples for new purposes (*18*–*21*). For example, over 90% of respondents in a national U.S. survey would be willing to have their samples and health data placed in a biobank for research. However, views on consent were mixed: 48% preferred one-time, "blanket" consent, whereas 42% wanted the opportunity to reconsent for each use of their data (*22*). In one study, 15% of participants did not understand that signing the consent form would allow their excess clinical samples to be used in research (*18*). Studies also suggest that individuals may be less willing to share data for "government-funded" or pharmaceutical company research (*23*, *24*). Disagreement about optimal policy continues: Some argue that stronger regulatory oversight is needed (*25*); others contend that opt-out models, in which consent is presumed unless explicitly denied, in conjunction with robust de-identification, provide sufficient protection (*26*).

Participants Value Being Asked

Recent studies at Group Health, a nonprofit health-care system based in Seattle, provide new data about participant views. As one of five sites participating in the electronic Medical Records and Genomics (eMERGE) Network, Group Health planned to use data from an existing cohort, the Adult Changes in Thought (ACT) Study (*27*), to investigate the accuracy of phenotypes derived from electronic medical records. ACT participants—unlike those enrolled in general-purpose biobanks established at other eMERGE sites—had volunteered for a particular study. Although the original ACT consent covered data sharing among colleagues of the study investigators, it did not address wider sharing. For this reason, and because dbGaP was new and its possible risks largely undefined, the institutional review board (IRB) determined that reconsent was needed for Group Health to use ACT data for the eMERGE project.

In parallel with the reconsent effort, focus groups about large-scale genomic research engaged ACT participants and other Group Health patients (*24*). ACT participants expressed trust in Group Health and the ACT investigators; described altruistic motivations; and voiced few concerns about privacy, confidentiality, or discrimination. It is thus unsurprising that the vast majority (86%) of ACT participants agreed to have their study data deposited in dbGaP.

However, willingness to reconsent did not equate to a lack of interest in how, or by whom, participants' information may be used (*28*). Focus group participants expected researchers to act as responsible stewards of volunteers' contributions and wanted researchers to be forthright about study procedures and any potential risks (*24*). In a survey of 365 ACT participant reconsenters, 90% reported that it was important that Group Health asked

[1]Department of Bioethics and Humanities, University of Washington, Seattle, WA 98185, USA. [2]Group Health Research Institute, Seattle, WA 98101, USA. [3]Department of Medicine, Division of Medical Genetics, University of Washington, Seattle, WA 98195, USA.

*Author for correspondence. E-mail: sbtrini@uw.edu

Published by AAAS

their permission for data sharing. Opt-out consent would have been unacceptable to 40% of respondents, and 67% said that notification of dbGaP submission after the fact would have been unacceptable. Seventy percent said it would have been unacceptable if their data were shared with neither notification nor permission.

Investing in Trust Relationships

For ACT participants, the reconsent process documented researchers' respect. Being given a choice about uses of their data that were not contemplated at the time of original consent was important, not because they found particular kinds of studies objectionable, but because the request represented a tangible demonstration of the researchers' trustworthiness and regard. It should be noted that, demographically, ACT participants represent the type of people most willing to take part in research: older, mostly white, and relatively well educated. If the majority of this population favors reconsent for wide data sharing, others may be more likely to want an opportunity to weigh in.

A broad consent form (e.g., for samples to be used in "future studies of diseases associated with aging") may provide legal cover to the researcher who wishes to parlay single-study collections into a future biobank; but such protections may not promote trust between researchers and participants. Researchers and IRBs should consider how the consent process could foster respectful engagement, rather than merely mitigate risk.

For studies in which reconsent is feasible—e.g., when participant contact is ongoing or fairly recent, and most participants are still living—efforts to reengage can be a worthwhile investment. Yet careful thought must be given to when reconsent is merited and how to avoid inadvertently harassing participants. Considerations include the practicability of the reconsent process and the degree to which new uses of data represent a substantive departure from the original study in terms of both scope and risk.

Recommendations

Current practices presuming that study participants do not wish to hear from researchers, or that participants find general, one-time consent acceptable, may be contrary to participant preferences. Establishment of repositories using de-identified, clinically collected samples—often authorized through a generic statement in the consent-to-treat form—may threaten trust in the research enterprise, potentially derailing research efforts if they receive public attention.

We propose a shift from paternalistic protections to respectful engagement with individuals and groups whose conceptions of risk, benefit, and harm deserve consideration. Such an approach would treat participants as true stakeholders in research, who willingly take on risk because they see potential benefits to society as outweighing potential harms. Researchers and IRBs need to invite perspectives of participants and communities, and funders need to make resources available to establish and maintain relationships and stewardship-based governance approaches (*29*, *30*).

Researchers, IRBs, and funders must reconsider approaches to consent and notification for data-sharing resources. Chief among needed innovations are (i) methods to ensure that participants are informed about the use of their data in research, including potential inclusion in data repositories, and to grant the opportunity to decline participation in wide sharing; (ii) mechanisms to provide access to current information about how samples are being used, on either an individual or study-wide basis; (iii) transparent, accountable oversight processes that include community representation; and (iv) opportunities for participants to provide input concerning stewardship of their data, e.g., dialogue between researchers and participants (*31*), ongoing community consultation (*32*), or deliberative processes (*33*).

In some cases (e.g., if the majority of participants have died, or the original study was many years ago and participants cannot be located) such measures may prove infeasible, and a different obligation arises. At a minimum, researchers should provide clear descriptions and justifications of research procedures, in public venues readily available to individuals who may have been study participants or their families (e.g., in health system newsletters and local media). Public comment should be invited. To the extent that researchers, funders, and IRBs can engage the public in discussions about responsible, realistic study procedures, they create the opportunity for shared understanding and mutual support. They should seek new methods to foster public education and encourage dialogue about the value of data-sharing and options available to stay informed about research.

As one commentator recently wrote, "[w]e are only one scandal away from legislation that will regulate or even prohibit the use of de-identified data for research purposes." (*34*) The positive message is that many participants view themselves as having an ongoing stake in research to which they have donated samples and data. They want to be asked (or at least kept informed) about changes in research. Reframing research practice to align with this interest is an important step toward ensuring long-term success of genomic investigation.

References and Notes

1. A. Harmon, *New York Times*, 25 April 2010, p. WK1.
2. A. Harmon, *New York Times*, 22 April 2010, p. A1.
3. Order Granting Motion to Dismiss, *Bearder* v. *Minnesota*, No. 27-CV-09-5615 (D. Minn. 2009).
4. Storing B. C. babies' blood violates privacy: Group, *CBC News*, 12 May 2010; www.cbc.ca/canada/british-columbia/story/2010/05/12/bc-infant-blood-samples-privacy-violations.html.
5. C. Driver, *MailOnline*, 24 May 2010; www.dailymail.co.uk/news/article-1280891/NHS-creates-secret-database-babies-blood-samples-parental-consent.html.
6. J. Couzin-Frankel, *Science* **328**, 1218 (2010).
7. R. Skloot, *The Immortal Life of Henrietta Lacks* (Random House, New York, 2010).
8. E. Ramshaw, *Texas Tribune*, 22 February 2010; www.texastribune.org/stories/2010/feb/22/dna-deception/.
9. R. Capriccioso, *Indian Country Today*, 21 April 2010; www.indiancountrytoday.com/archive/91728874.html.
10. J. Couzin-Frankel, *Science* **328**, 558 (2010).
11. M. M. Mello, L. E. Wolf, *N. Engl. J. Med.* **363**, 204 (2010).
12. Protection of human subjects, 45 Code of Federal Regulations (C.F.R.) 46 (2005).
13. Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule, 45 C.F.R. Parts 160 and 164 (2002).
14. Office for Human Research Protections, U.S. Department of Health and Human Services (HHS), Guidance on research involving coded private information or biological specimens (HHS, Washington, DC, 2008).
15. A coded sample is considered indirectly identifiable, so long as the key that links samples with identifiers is maintained. Under HIPAA, data deemed by a qualified expert as unlikely to be re-identified are considered de-identified, as are those that do not contain any of 18 designated identifiers.
16. National Institutes of Health (NIH), Final NIH statement on sharing research data (NOT-OD-03-032, HHS, Washington, DC, 2003).
17. NIH, Policy for sharing of data obtained in NIH supported or conducted genome-wide association studies (GWAS) (NOT-OD-07-088, HHS, Washington, DC, 2007).
18. R. D. Pentz, L. Billot, D. Wendler, *Am. J. Med. Genet. A.* **140A**, 733 (2006).
19. L. Johnsson *et al.*, *Eur. J. Med. Genet.* **18**, 1261 (2010).
20. C. A. McCarty *et al.*, *Am. J. Med. Genet. A.* **146A**, 3026 (2008).
21. J. M. Pulley *et al.*, *Cell Tissue Bank.* **9**, 55 (2008).
22. D. Kaufman *et al.*, *Genet. Med.* **10**, 831 (2008).
23. A. A. Lemke, W. A. Wolf, J. Hebert-Beirne, M. E. Smith, *Public Health Genomics* **13**, 368 (2010).
24. S. B. Trinidad *et al.*, *Genet. Med.* **12**, 486 (2010).
25. M. A. Rothstein, *Am. J. Bioeth.* **10**, 3 (2010).
26. K. B. Brothers, E. W. Clayton, *Am. J. Bioeth.* **10**, 15 (2010).
27. W. A. Kukull *et al.*, *Arch. Neurol.* **59**, 1737 (2002).
28. E. J. Ludman *et al.*, *J. Empir. Res. Hum. Res. Ethics* **5**, 9 (2010).
29. M. Yarborough, K. Fryer-Edwards, G. Geller, R. R. Sharp, *Acad. Med.* **84**, 472 (2009).
30. S. M. Fullerton *et al.*, *Sci. Transl. Med.* **2**, cm3 (2010).
31. I. S. Kohane *et al.*, *Science* **316**, 836 (2007).
32. B. B. Boyer *et al.*, *Int. J. Circumpolar Health* **64**, 281 (2005).
33. D. M. Secko, N. Preto, S. Niemeyer, M. M. Burgess, *Soc. Sci. Med.* **68**, 781 (2009).
34. R. Gellman, *Am. J. Bioeth.* **10**, 28 (2010).

35. This work was supported by the eMERGE Network (National Human Genome Research Institute and National Institute of General Medical Sciences, NIH, grant no. U01-HG-004610) and the Washington State Life Sciences Discovery Fund (grant no. 265508).

10.1126/science.1199000