

“Neglected Ethical Issues in Biobanking” Presented by R. Jean Cadigan & Gail E. Henderson

April 28, 2020

Online Questions from Registrants

On April 28, 2020, Drs. Jean Cadigan and Gail Henderson conducted an ENRICH Forum webinar titled “Neglected Ethical Issues in Biobanking.” This presentation focused on findings from their research regarding concerns about biobank sustainability and the underutilization of sample collections. A multitude of questions arose from this presentation which could not all be addressed during the allotted time. In furtherance of our educational mission, we are posting responses to the questions that were not answered during the recorded presentation.

1. *“What is the role of advocacy groups in promoting research with biobanked samples and data?”*

Advocacy groups have taken increasingly prominent roles in the development of research biobanks. For example, the [NCI Cancer Moonshot Biobank](#) has convened an External Scientific Panel to help guide patient engagement efforts, which includes several patient advocates. The panel provides input to many aspects of the Moonshot Biobank including the protocol and consent documents, and website development.

The role of advocacy groups has been particularly important for rare disease conditions, exemplified by the [Genetic Alliance. A 2006 Genetics in Medicine article by J.D. Cody](#) about families playing a role in advocacy for their affected children is a personal account and has some good references. In addition, biobank collections for cancer, infectious diseases and other conditions have been motivated by advocacy groups. Over the past two decades, there has been considerable evolution of patient-initiated biobank collections, exemplified by the [Metastatic Breast Cancer Project](#). This collection is run by [Corrie Painter](#) and housed at the Broad Institute in Massachusetts. Several articles have been written on the topic of advocacy groups and biobanks or genomic research, including [Koay et al. \(2013\)](#) and [Shaibi et al. \(2016\)](#). For a sense of how the issue of patients and patient advocacy groups promoting research use of their own data is evolving, please see the 2019 NCI Cancer Moonshot [Symposium on Personal Control of Genomic Data for Research](#). Topics discussed include how individuals can access and control their own data, how data is made available for researchers, and platforms that have arisen to facilitate research interactions. Speakers included patients and representatives from patient advocacy groups (including Corrie Painter, above).

2. *“What are the main reasons for low requests for samples/data, as you noted to be the case in about 50% of the projects in the US Biobank Study?”*

We were surprised with our finding, which was from our 2012 data. We are not sure of the answer to this question, and there are probably a variety of reasons relevant to different kinds of biobanks. We simply identified it as an important, neglected ethical issue for biobanks which we wrote about in our 2014 *Genetics in Medicine* commentary, [“Underutilization of specimens in biobanks: an ethical as well as a practical concern?”](#) It is clear that the funding, scientific questions, and other factors related to a biobank being established are not necessarily related to requests for specimen use. Using interview data from our [networked biobanking study](#) (Kyle Brothers and Aaron Goldenberg, MPs), we are currently examining this issue further. Preliminary analyses suggest that low requests for samples/data relate to issues such as lack of marketing, emphasis on collection rather than distribution of samples/data, lack of planning, and type of collection.

3. *“What about the ‘bookend’ issue of returning results when science is still evolving?”*

This is an important question, and it has often been raised in the context of returning genetic results produced by next-generation sequencing. Several articles produced by the University of North Carolina-Chapel Hill’s [NCGENES Study](#) (part of the NHGRI-, NCI-, and NIHMD-funded [Clinical Sequencing Exploratory Research \[CSER\] consortium](#)) document the uncertainty in both negative and positive genetic diagnoses, and that study participants expected that sequencing results would be examined again in light of an evolving literature. See, for example, two articles by Debra Skinner and colleagues: [“The nuanced negative: Meanings of a negative diagnostic result in clinical exome sequencing.”](#) *Sociology of Health and Illness*, 2016; and [“Possibly positive or certainly uncertain?: Participants’ responses to uncertain diagnostic results from exome sequencing.”](#) *Genetics in Medicine*, 2017.

Whether a biobank has a duty to return results to participants is hotly debated with no clear answer. The issue becomes more muddled when considering what kind of results a biobank might return (e.g., medically actionable, secondary, incidental, and/or uncertain findings). NCI convened an early [workshop](#) on this issue, in 2010. NCI also funded a grant on [returning genomic results to family members](#), an issue that arises when a cancer biobank participant has died. [A summary of the symposium](#) was published in Fall 2015.

The American Society of Investigative Pathology published a [position paper](#) in May 2020 containing several recommendations for researchers using human biospecimens regarding their return of donor research results, including the need to develop an IRB-approved communications plan, and to discuss the return of results as part of the informed consent process.

4. *“With reference to the ethics ‘bookends,’ this model assumes an individual participant. Are there findings on public health impacts or political collectives (e.g., American Indians, Alaskan natives)?*

You make an important observation that our ethical framework – really since the inception of bioethics as a discipline – has focused on the individual participant rather than on community or group risks and harms. The cardinal [Belmont Report](#), for example, highlights the importance of individual autonomy and nowhere does it speak of the importance of community as an ethical value, though there has been some attention in bioethics scholarship to the issue of communities for more than a decade. Regarding American Indian and Alaska Native (AI/AN) communities, [indigenous scholars](#) have called for the need to respect tribal sovereignty and community values when engaging in research with indigenous people, understand their concerns and perspectives, and address research questions relevant to the community. See also, work from the [Center for the Ethics of Indigenous Genomic Research \(CEIGR\)](#), an NHGRI-funded [Center of Excellence in ELSI Research](#). These ethical imperatives have been increasingly recognized at the NIH. See, for example, [Sara Hull's work](#) at the NHGRI, the NIH [Tribal Health Research Office](#), and a 2016 meeting on [Precision Medicine and Cancer in American Indian and Alaska Native Communities](#) held in collaboration with NCI.

5. *“In the survey conducted by Drs. Cadigan and Henderson, was there any marketing plan implemented by any of the biobanks and was there any data collected on that? There was some data collected on business plan. Did their business plan include marketing?”*

We did not collect data on marketing plans. It is, of course, quite possible that biobanks that had a business plan also had a marketing plan.

6. *“What are the ethical issues to consider with long term planning and sustainability for a birth cohort study?”*

Many cohort studies, including birth cohorts, were established before the collection of biological specimens was commonplace; and thus *informed consent* to collection of specimens and data is the first ethical issue to be considered. Cohort members must be contacted and provide consent for collection, storage, and research use of specimens and data. For example, a highly utilized British birth cohort study, the [National Child Development Study](#), followed 17,000 people born during March 3-9, 1958, to the present; it explores social and biological predictors that influence opportunities in life. Likewise, the [National Longitudinal Study of Adolescent to Adult Health](#), which is a nationally representative sample of US adolescents in grades 7-12 during the 1994-95 school year, has carried out five waves of data collection. In the interim, they began collecting specimens from the cohort, with the appropriate consents. The second ethical issue, as you have rightly noted, is *planning for sustainability*, which respects the contributions of these individuals. Cohort studies

are particularly vulnerable to loss of funding because collecting longitudinal data is expensive, although their ability to provide longitudinal results also means that their scientific value increases over time.

7. *“How will trust by participants factor in this biobank focus for sustainability?”*

Trust is extremely important as a reciprocal feature of biobank stewardship. Donors/participants must have trust that the investigators or managers of the biobank will protect their interests; honor their contributions by ensuring that the best use of the specimens and data is made; and be transparent about the processes and procedures. In our 2013 article in *Science Translational Medicine*, [“Stewardship practices of U.S. biobanks.”](#) we proposed that stewardship was essential across the lifespan of the specimen. The article discusses findings from our survey of 456 US biobank managers that addressed whether and how biobanks steward their specimens. The findings reveal that most biobanks do not create ongoing relationships with contributors but do practice stewardship over storing and sharing of specimens. Biobanks now need guidance to fully articulate stewardship practices that ensure respect for contributors while facilitating research.

8. *“Do you predict that biobanks will lack sustainability also due to a lack of inclusion? There seems to be a lack of diversity in biobanks, and generally the same populations tend to be targeted for biospecimen donations. How can this inclusion/diversity be improved?”*

We agree that diversity is very important in collections. Personalized/precision medicine studies, including the use of polygenic risk scores; have highlighted the problems with results not being applicable to minority populations (who are still underrepresented in biobanks). [Recent NIH calls for research on evidence-based genomic medicine](#) require a substantial number of participants to be drawn from minority or underrepresented populations.

In our [networked biobank interview study](#), we found evidence that some biobanks were trying to diversify the populations from whom they collected specimens/data in order to make the collection more scientifically valuable and thus more sustainable. They did this through strategically selecting additional sites for their network based on the demographic populations of the patients seen at those sites (these were predominately sites based at medical centers, so patients were the population recruited). It seemed to be an effective strategy for some networks. We do not know, however, if increasing diversity results in increased utilization.

9. *“Can the speakers elaborate on the need for marketing that was mentioned? I.e does the literature support that? Or was the need seen somewhere specifically? Very interesting and important!”*

The need for marketing was something identified by the people we interviewed for the networked biobank study. Several believed that a marketing plan was needed to ensure utilization of the resources. Regarding the literature, many articles call for the need for marketing in biobanking to increase utilization (sometimes in the context of overall business planning). See, for example, this [empirical study](#) by Marianne Henderson et al. in *Biopreservation and Biobanking*, November, 2018, showing the links between having a business plan and engaging in marketing activities. We do not know if there are studies that examine the direct effectiveness of marketing on utilization.

10. *"Are cell lines commonly included as a type of biobank specimen?"*

In our 2012 survey of biobanks that Dr. Henderson described, we found that 37% had cell lines. In our more recent [study of networked biobanks](#), a much smaller percentage stated that they had cell lines. However, one of our network biobank respondents did identify creating cell lines as a way of enhancing value of the network.

11. *"Biobank = only human specimens?"*

Thank you for this important, clarifying question. Biobanks are certainly not limited to human specimens. However, for our studies we restricted eligibility to only those biobanks that contained human specimens.

12. *"Should an IRB require that pharmaceutical sponsors who request additional optional samples from subjects on their therapeutic trials provide a detailed description of a created biobank and its SOPS, funding and sustainability in the protocol?"*

While there aren't express regulatory requirements that research participants be informed about biobank funding and sustainability, the answer from an ethical standpoint is, ideally, yes. Providing this level of detail to subjects contributes to transparency of practices and helps to promote trust. Collecting and storing additional samples from subjects in a therapeutic trial is a common practice in many types of studies. If this is required by pharmaceutical sponsors, it raises the question of why and for what purpose, and especially whether profit-generating products will be created that should be documented for trial participants.

Moreover, in the US, the [Federal regulations protecting human research subjects](#) require, when appropriate, that biobanking informed consent forms include: "A statement that the subject's biospecimens (even if identifiers are removed) may be used for commercial profit and whether the subject will or will not share in this commercial profit" [45 CFR 46.116 (c)(7)]. Ownership of specimens has been addressed by a series of legal cases, and this is sometimes mentioned in consent forms. Consent should be requested before any additional research samples are

obtained, informing participants of the purpose of collection, risks and benefits, and other required components of consent. Most nontherapeutic research procedures are not expected to offer direct benefit to volunteers, but rather risks are justified by expectation of knowledge gained. A number of concerns have been raised about these procedures. Kimmelman and colleagues published a [commentary](#) with recommendations for how investigators, sponsors, and ethics committees might improve evaluation and implementation of studies involving invasive nontherapeutic procedures. Attention has focused on oncology research, but nontherapeutic procedures take place in many studies. Finally, the request to do optional procedures in a research study may not discourage enrollment, yet it may be a significant and perhaps under-recognized burden for participants. One outstanding ethical concern is whether there are pressures for trial participants to volunteer even if a procedure is labeled “optional.”

13. *“Did you look at consents for networked biobanks?”*

No, we did not look at the consent forms used by networked biobanks.

14. *“Can government funded or academic biobanks send samples to companies? If so, what considerations should be covered?”*

As part of their services, biobanks may send (or sell) specimens to companies that will carry out research objectives. Whether or not government or academic funding was key to creating the biobank, there should be documented plans for how specimens can be used in the future and for what purposes. Some biobanks may treat sending or selling to another entity as a transaction; others may require companies to keep them informed about the results of the specimen use and/or return leftovers. This is part of general stewardship over the life course of the specimen, as we described in our article [“Stewardship practices of U.S. biobanks,”](#) *Science Translational Medicine*, 2013.

15. *“Given the current COVID-19 outbreak, what could be the specific ethical issues facing biobank research? How can the associated risks be mitigated?”*

COVID-19 poses many ethical challenges for biobanks at the interface of medical ethics and public health surveillance. For example, [as reported in the New England Journal of Medicine](#), samples collected in the Seattle Flu study - a community-wide pandemic surveillance platform - were re-purposed when coronavirus surfaced in order to test for Covid-19 infection. as reported in the *New York Times* around the start of the pandemic in the United States, there are differing ethical perspectives about whether biological samples collected for influenza research could, without further IRB review, be interrogated for the presence of COVID-19 virus. The ethical issues associated with re-purposing biobank collections during a pandemic will be explored at an [NCI ENRICH Forum](#) presentation on July 21, 2020, 1-2pm Eastern time. Details can be found on the [NCI ENRICH Forum website](#).

16. *"Please clarify more about stakeholders who seek to use biobank specimens. It sounds like the focus was always after the biobank was built, but there was no mention about understanding the need before building the bank."*

Some biobanks/networks may be more conducive to early planning for how the resources will be used, such as those devoted to particular medical conditions, and especially, rare diseases. In our interview study with networked biobanks, several respondents talked about the importance of understanding the needs of researchers/science to inform what specimens and data would be collected. They framed these discussions in terms of the need to plan ahead to ensure utilization, sustainability, and value.

17. *"I'm curious about how these principles apply to repositories of physiologic sensor data. Is there a bright line with a wet biological sample?"*

We're not familiar with how physiological sensor data are typically stored within repositories or accessed for research. It may be that repositories for physiologic sensor data face the same issues as biobanks regarding funding to continue their operations, utilization of the data by other researchers, and planning for sustainability. Generally, physiological sensor data obtained in the context of research would be subject to the same research policies and regulations as other research data, including data derived from biological samples. So, there is not necessarily a "bright line" between biological samples and other research data like physiologic sensor data. That said, there is a long history and context for how biologic samples have been collected from donors, banked by institutions, and used for all manner of research in the US. This has informed how the ethical thinking developed around the use of biologic samples and the creation of biobanks, which does not easily apply to sensor data. Looking forward, it may be that physiological sensor data may raise its own sensitivities, for example if obtained using devices with geolocation or other markers for identifiability.