

Returning Results in Biobank Research: Global Trends and Solutions

Eva De Clercq,¹ Jane Kaye,² Susan M. Wolf,³ Barbara A. Koenig,⁴ and Bernice S. Elger^{1,5}

In many countries around the world, biobanks have become crucial resources for the conduct of biomedical research, facilitating many kinds of research, including international collaborations. The focus of this special issue is on a looming ethical issue that has become a focus of debate—the return of research results and incidental findings to biobank participants. Although the articles in this issue do not provide a final answer to the ethical, legal, and social dilemmas that arise in the context of the return of results, the intent of the collection is to approach this issue from multiple perspectives and within an international context spanning the United Kingdom, continental Europe including Eastern Europe, the United States, and the Middle East.

Keywords: biobank, return of results, guidelines, dilemma, ethics

IN MANY COUNTRIES around the world, biobanks have become crucial resources for the conduct of biomedical research, facilitating many kinds of research, including international collaborations. In 2009, *Time* magazine included biobanks on the list of 10 ideas that would change the world (Kinkorová, 2016), as they have become essential resources for the advancement of medical research and healthcare. As repositories of a wide range of biological material (such as tumor tissue, cells, blood, and DNA) linked to different kinds of clinical and research information, they function as a library of the human organism (Moore and Casper, 2014) and can provide source material for genomic and other research in a wide range of disease areas. The potential of biobanks to assist in disease prevention and treatment explains the increasing importance of biobanks over the past two decades—public and private, small- and large-scale, and national and international (Elger, 2010).

Biobanks have long tested existing regulatory frameworks and guidelines (Kinkorová, 2016). Although regulations have evolved to oversee biobanks (Beier and Schnorrer, 2011), they continue to lag behind technological innovations in biobanking. Biobanks pose a challenge to the traditional legal guidelines for research on human subjects and genetic material as they are designed for the open-ended pursuit of scientific research goals, and aggregate materials from a range of populations (Elger *et al.*, 2008). Moreover, existing regulations are difficult to harmonize and implement across various countries, even though genomic and other research

using biobanks crosses national borders (Elger *et al.*, 2008; Gottweis and Kaye, 2012). Biobank governance needs to consider legal, ethical, and social issues on multiple levels—the population represented in the biobank, the national context, and international concerns (Garrett *et al.*, 2015; Stranger and Kaye, 2009).

Research shows that knowledge of biobanks is limited among the lay public (Gottweis and Kaye, 2012). These findings are concerning, as public awareness is important to improve trust and participation and thus to guarantee the long-term operational and financial sustainability of biobanking (Gottweis and Kaye, 2012). Public fears over privacy protections, vulnerability to discrimination, and loss of control over decision-making may prevent people from participating in biobanks. To encourage greater public trust, research needs to be carried out ethically and transparently (Stranger and Kaye, 2009). Debates to date have focused on a number of issues, including how to design informed consent (specific consent to particular studies, tiered consent to particular types of studies, blanket consent to future research uses, or dynamic consent that allows consent to be obtained online and changed over time) and how to protect the privacy and identity of specimen donors, given the risk of re-identification in genomic research.

The focus of this special issue is on a newer and looming ethical issue that has become a focus of debate—the return of research results and incidental findings to biobank participants (Wolf *et al.*, 2012; Bledsoe *et al.*, 2013; Wolf, 2013).

¹Institute for Biomedical Ethics, University of Basel, Basel, Switzerland.

²Nuffield Department of Population Health, University of Oxford, Oxford, United Kingdom.

³Law School, Medical School, University of Minnesota, Minneapolis, Minnesota.

⁴Institute for Health Aging, University of California, San Francisco, California.

⁵University Center of Legal Medicine of Geneva and Lausanne, University of Geneva, Geneva, Switzerland.

Although the articles in this issue do not provide a final answer to the ethical, legal, and social dilemmas that arise in the context of the return of results, the intent of the collection is to approach this issue from multiple perspectives and within an international context spanning the United Kingdom, continental Europe including Eastern Europe, the United States, and the Middle East.

The articles in this collection explore the ongoing debate on the return of results to biobank donors using national and international variations in terminology. Scholars, but also biobanks and people whose samples are included in biobanks, use a variety of terms to describe those whose samples (and health information) are analyzed and the findings that may be considered for return. For example, in the biobank of Lausanne, Switzerland, consent forms consistently use the term “biobank participants,” whereas according to a qualitative study in the United Kingdom, patients themselves seem to think of themselves as “sample donors” (Locock and Boylan, 2016). Some scholars make a distinction between research results and incidental findings to indicate whether a result was sought in pursuit of explicit research aims or obtained in the course of research but beyond those formal aims. Others point out that in the field of biobanking, the difference between these two concepts can become arbitrary, as typical biobank research is untargeted and future research aims are largely undefined (Elger, 2008, 2010).

In the last three years, debate has been heated over how much control to give individuals over analysis and return of results, as not all participants may wish to be informed of their results. In 2013 the American College of Medical Genetics and Genomics (ACMG) released a practice statement that provoked debate by urging analysis of 56 (since ACMG 2016, 59) extra genes whenever clinical sequencing was undertaken, with no opportunity for patients to decline the extra analysis while still receiving the clinically indicated sequencing (Green et al. 2013). ACMG has subsequently altered its guidance on clinical sequencing to permit patients to opt out of the extra analysis (ACMG 2015). In their perspective article, Elger and De Clercq apply the ACMG 2013 guidelines to research, by arguing in favor of adopting in the research and biobanking context a return-of-results policy that limits participants’ ability to refuse clinically relevant results. The authors claim that it is impossible to grant participants the right to know and the right not to know simultaneously. They state that biobanks should allow donors to participate only if they are aware of and agree to this return policy. In their view, this is the only honest way to regulate the return of results to participants and to maintain trust in biobanks.

In the second paper, Judit Sándor examines the relevant international and national – in particular, Hungarian – legal frameworks and the obstacles to returning results to donors in biobanks or genetic databases. She argues that early legislative attempts followed the model of biomedical research and had a strong focus on data protection and anonymization. As a result, donors’ future therapeutic interests were not taken into account. She states that with the emergence of a concept of biological citizenship, more and more individuals insist on their rights and needs, even though regulatory models have not changed to support this. Sándor argues that a participatory model of biobank governance would offer more benefits to biobank participants who want to have access to research results.

In line with Sándor, Cadigan and colleagues state that biobanks in the United States have been guided mainly by the research imperative, with little attention to donors’ interests in research results. Like Elger and De Clercq, they argue that failure to address the issue of return of results could compromise donors’ trust and thus lead to the operational unsustainability of biobanking. They note that although many international guidelines for best practices in biobanking advocate for disclosure of results, those guidelines do not provide actual criteria to determine when, how, and what kind of results should be returned. The authors consider biobanks to be forward thinking—and thus professional and accountable—if they have a concrete return-of-results policy (independently of whether the policy supports return of results or not). In their survey, less than two-thirds (62%) of 327 U.S. biobanks that had access to donors’ identifying information reported having such a policy. The majority of these biobanks (57%) reported policy stating that results would never be returned, 38% of biobanks reported policy stating that results would be returned under certain conditions, and 5% had policy stating that results would always be returned.

The development of policies on return of results is an even more contentious issue in the case of pediatric biobanks. Involving children in biobank research is necessary not only because of the many diseases that affect children, but also because many adult conditions have their antecedents in childhood. In her article, Ingrid Holm addresses the challenges that arise when trying to balance the decisional prerogative of parents and the autonomy and best interests of children in the context of return of results in U.S. biobanks. She proposes a dynamic model that takes into account the developing autonomy of the child and the decision-making authority of parents.

For policies to be effective, they also need to address the concerns and the preferences of the stakeholders involved. The following three articles in this issue explore stakeholders’ attitudes toward return of results.

The qualitative study by Barazzetti and colleagues explores the views of physicians (general practitioners and specialists) and citizens on broad consent and the return of clinically relevant research results in Switzerland. They show that citizens are ambivalent. On one hand, there is a perceived responsibility to know research results, as they may also affect family members. On the other hand, individuals have a long-recognized right not to know. It can be difficult to understand probabilistic information about statistical risk and thus grasp the predictive power of genetic results. The authors suggest that return policies should address the importance of training physicians in “practical genetics,” so that they can provide support for individuals’ management of genomic information.

Alahmad and Dierckx conducted a survey on a sample population of medical researchers, physicians, and lay people to explore their opinions on the return of results obtained from medical research at the national biobank in Saudi Arabia. Most participants agreed that donors have the right to receive and biobanks have the duty to provide clinically relevant research results. Compared with lay people, physicians and researchers were more likely to reject the need to provide clinically actionable results. Likewise, physicians, followed by researchers, were more likely than lay people to reject giving biobank participants the right to decline unwarranted information.

Siminoff and colleagues take up the issue of return of results in the context of families' decision to donate tissue of a deceased relative to a biobanking project in the United States. The authors highlight that very few genomic research projects have considered returning results to family members of deceased donors. They argue that return of results could constitute an important incentive for participation, in addition to altruistic motives. They emphasize that the return of results requires law and policy to inform donors about possible risks and potential for psychological distress. Their data demonstrate that rather than inhibiting donations, conversations about risks lead to a greater comfort with tissue donation for genetic research. They predict that biobanks will increasingly return all actionable results.

The next two articles in the special issue warn of practical, technical, and interpretative barriers to return of results. Holm, Yu, and Joffe argue that a fruitful discussion on returning results to research participants requires a thorough understanding of how these results are generated and interpreted. They provide a brief overview of this intricate process—covering DNA-targeting methods, sequencing, mapping, variant calling, annotation, and interpretation—and show that there is considerable room for error in each of these phases. They argue that the risk of identifying and thus returning false-positive, uncertain, or overstated research results cannot be ruled out. Furthermore, the need to confirm these findings has important cost implications. The authors make a case for limiting return to results that are highly likely to be pathogenic.

The ethnographic study by Lazáro-Muñoz and colleagues examines the deliberations of a committee of researchers in the United States deciding which medically actionable results to return based on recommended selection criteria (severity of disease outcome, likelihood of severe outcome, effectiveness of intervention, acceptability of the intervention, and the knowledge base supporting the first four criteria). The authors show how applying each of these criteria involves a subjective judgment. They argue that decision-makers should be aware of this inevitable subjectivity and acknowledge it in a transparent way to maximize the social and medical utility of research results.

The ethical issues related to biobanking and the return of results are influenced by public opinion on recent developments in human genetics and genetic testing. Therefore, the special issue concludes with a survey study by Chokoshvili and colleagues on the attitudes of the general public in Belgium towards genetic testing. The authors conclude that adequate guidelines are needed to address the concerns of healthcare users and to ensure an ethically sound and socially acceptable implementation of new genetic tests. These guidelines may inform the development of policies for the return of results in biobanking.

The debate over return of results is an important one for biobanks. The articles included in this collection show that although a number of difficult dilemmas persist, the discussion is evolving. New trends point toward a growing consensus among ethics scholars, biobanks, and researchers. There is increasing agreement about the ethical obligation to consider returning clinically important research results. This is evidenced by the growing number of biobanks that offer these kinds of results. At the same time, there is an increased awareness of the need for clear policies and international

harmonization of the criteria used to determine which results to return, as well as how and when.

A major goal of this special issue is to provide insights into the progress of these debates and increase understanding through the publication of an international collection of articles on return of results from biobanks. A second goal is to use this special issue to stimulate a dialogue among all of the stakeholders (including biobankers, researchers, research participants, and specimen donors, as well as policy makers) on the issues and the progress to date in the return-of-results discussion. International work on return of results in the context of biobank research reveals feasible and ethically acceptable solutions for biobanks, allowing them to adopt return-of-results policies that will be supported by specimen donors and the public.

Acknowledgments

This work was supported by grant number R01 CA154517 from the National Cancer Institute (NCI) and National Human Genome Research Institute (NHGRI) at the National Institutes of Health (NIH), along with funding from the Brocher Foundation, the Wellcome Trust, and the Swiss Academy of Medical Sciences. The views expressed are those of the authors and not necessarily the views of the funders.

Author Disclosure Statement

No competing financial interests exist.

References

- ACMG Board of Directors (2015) ACMG policy statement: updated recommendations regarding analysis and reporting of secondary findings in clinical genome-scale sequencing. *Genet Med* 17:68–69.
- ACMG Board of Directors (2016). Recommendations for reporting of secondary findings in clinical exome and genome sequencing, 2016 update (ACMG SF v2.0): a policy statement of the American College of Medical Genetics and Genomics. *Genet Med* [Epub ahead of print] DOI:10.1038/gim.2016.190.
- Beier K, Schnorrer S (2011) Ethical and legal aspects of human tissue and biobank research in Europe: Report on the Tiss.EU project and its results. Scripted. *J Law Technol Soc* 8:99–105.
- Bledsoe MJ, Clayton EW, McGuire AL, *et al.* (2013) Return of research results from genomic biobanks: Cost matters. *Genet Med* 15:157–159.
- Elger BS (2010) *Ethical Issues of Human Genetic Databases: A Challenge to Classical Health Research Ethics*. Routledge, New York.
- Elger BS, Biller-Andorno N, Capron AM (eds) (2008) *Ethical Issues in Governing Biobanks: Global Perspectives*. Routledge, New York.
- Garrett SB, Koenig BA, Brown A, *et al.* (2015) EngageUC: developing an efficient and ethical approach to biobanking research at the University of California. *Clin Transl Sci* 8:362–366.
- Gottweis H, Kaye J (2012) *Biobanks for Europe: A Challenge for Governance*. European Commission, Directorate-General for Research and Innovation; Luxembourg: Publications Office of the European Union.
- Green RC, *et al.* (2013) ACMG recommendations for reporting of incidental findings in clinical exome and genome sequencing. *Genet Med* 15:565–574.

- Kinkorová J (2016) Biobanks in the era of personalized medicine: Objectives, challenges, and innovation. *EPMA J* 7:4.
- Locock L, Boylan AR (2016) Biosamples as gifts? How participants in biobanking projects talk about donation. *Health Expect* 19:805–816.
- Moore LJ, Casper MJ (2014) *The Body: Social and Cultural Dissections*. Routledge, London, New York.
- Stranger M, Kaye J (2009) *Principles and Practices in Biobank Governance*. Routledge, New York.
- Wolf SM, Crock BN, Van Ness B, *et al.* (2012) Managing incidental findings and research results in genomic research involving biobanks and archived data sets. *Genet Med* 14: 361–384.
- Wolf SM (2013) Return of results in genomic biobank research: Ethics matters. *Genet Med* 15:157–159.

Address correspondence to:
Eva De Clercq, PhD
Institute for Biomedical Ethics
University of Basel
Bernoullistrasse 28
Basel CH-4056
Switzerland

E-mail: eva.declercq@unibas.ch