

The barriers to sample and data sharing between biobanks in Switzerland

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Flora Margaret Antonia Colledge

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Genehmigt von der Medizinische Fakultät**auf Antrag von:**

Referat:

Prof. Dr. Bernice Elger

Co-Referat:

Prof. Dr. Jakob Passweg

Externe Experte:

Prof. Dr. Alberto Bondolfi

Basel, den _____

Dekan

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PART 1: BACKGROUND

1.1 1 INTRODUCTION

A common theme can be identified in the introductory passages of most scholarly articles concerning biobanks. This theme can be perhaps best described as one of recent, yet speedy, development.¹⁻³ This is in large part linked to the concurrent boom in genomic research and medicine, as information about the human genome begins to be used to “uncover the genes that play a significant role in the hereditary contribution to common disease.”⁴ The WHO report on genomics and world health of 2003 already predicted that “unprecedented advances in the science of genomics [...] has important implications for health improvement,”⁵ and this prediction has proven true in the subsequent decade. Genomic studies require large pools of samples as DNA sources;⁶ other forms of medical research too are coming to depend on the convenient, large-scale, international sample provision which biobanks can offer.⁷

Biobanks – a study in diversity

There is no universally employed, or accepted, definition of the term “biobank” (this matter is addressed in detail in Chapter 3.2, below). Recognized as distinct entities for a little over a decade (the term itself dates from this time),³ a biobank is some form of collection of biological material, frequently but not necessarily stored together with data concerning this material.⁸ Although collections of biological material have existed for decades,⁹ kept in the back cupboards of surgeons and pathologists, the recognition that such collections are valuable for research, and can be made available to external groups, marks the transition to “biobanking.” Biobanks can comprise animal, insect and plant samples;¹⁰ in this project, only collections of human material and data are addressed. The kinds of samples stored in a human biobank include blood, saliva, sperm, urine, tumour sections, organ sections, whole organs and skin cells¹¹. Some biobanks may have a variety of such samples for a single individual, collected simultaneously or over a period of time.¹² In the majority of cases, biosamples will be accompanied by patient or donor data, which can range from basic demographic information to specific case history, at varying levels of anonymity.¹³

Numerous types of biobank can be identified, although the distinctions between them are not always clear-cut. Some banks are started prospectively, perhaps with the goal of gathering a set number of samples; they may or may not have a planned research goal for those samples¹⁴. Some banks may come into being retrospectively, as samples which were stored informally in a hospital are categorized and classified.¹⁵ The term can apply equally to collections of human gametes, stored exclusively for future use by the donors, who have paid for the service, as to freezers storing saliva samples from a representative sample of an entire population, purely for research purposes. This variety reflects the many potential applications of banked samples. Different diseases, research goals, and study groups will all envisage different uses for their collections, and the storage is accordingly diverse.¹⁶

When it comes to size, biobanks again vary widely,¹⁷ ranging from small refrigerators containing a few dozen samples collected in the course of routine clinical work, to planned, population-wide resources such as the UK Biobank, which has recruited 500,000 individuals who will provide numerous biosamples over many years.¹⁸ The value of a collection is to some degree a product of its

size, relative to the prevalence of the condition in the population; greater size enables the statistical validation which renders research powerful.¹⁹ Biobanks focusing on rare diseases may have relatively few samples, but are still valuable resources if they are able to amass high quality material from a significant number of affected individuals. While conducting research with human subjects on a large scale is an enormous undertaking, the progress of biobanking has meant that amassing statistically significant numbers of biosamples is now more feasible for researchers²⁰.

Finally, stored samples can be used for research that was unforeseeable even a few years ago, not to mention thirty or forty²¹. Biosamples taken at that time can still be perfectly preserved (though the individuals they were taken from may have no idea that they exist, and may indeed have moved far away from the initial site of collection, or passed away.²²) Likewise, samples may be taken today by researchers without any specific research goal in mind (though this may be limited by local ethics committees, an issue discussed at various points below).²³

Beyond storage units

The potential benefits of biobanks for biomedical research have received much attention in the last decade. In the popular press, Time Magazine, in 2009, named biobanks as an “idea changing the world right now”,²⁴ emphasizing the enormous value of population-wide repositories, and the potential to build gene profiles associated with specific diseases. Biobanks have rapidly and widely become lauded as indispensable tools for biomedical research. Cambon-Thomsen (2004) concisely sums up three explanations for this: “[...] the growth of biomedical research has increased the number of people who might benefit from biobanks; the growing size of the collections increases their scientific value; and the range of applications of databanks has grown, especially in genomics and in population genomics.”²⁵ Biobanks have potential benefits for a large number of individuals because they make possible investigation into the effects of myriad lifestyle and environmental factors on health and disease,^{26,27} factors which to some degree affect us all. Furthermore, as repositories of genetic information, they are also at the forefront of the move towards personalized medicine,²⁸ the tailoring of health treatment based on individual responses to drugs and therapies. Biobanks with a particular research focus (for example, liver tumours) aim to provide new insight and treatment options which could benefit future, if not current, sufferers.²⁹

A secondary aspect of biobank research is its much lower invasiveness vis-à-vis research “subjects”.³⁰ Investigations can be carried out on samples without the need for a human subject to be present over days and weeks, subjected to numerous tests and return visits to a hospital³¹. The taking of the sample itself is also frequently far less unpleasant than protracted interventions; in many cases, a sample can be taken within a few seconds, painlessly, or is obtained during the course of routine diagnostic or therapeutic processes. However, it must also be borne in mind that sample provision is not completely effortless; in many cases (for example in longitudinal studies), donors must continue to give samples at regular intervals, and fill out questionnaires or undergo additional tests.³² The potential benefit for the donor must also not be overemphasized; as Andersson (2010) notes, “...Usefulness for research is in general increasing with increasing storage time, whereas the opposite is true for usefulness for the patient’s own clinical diagnosis...”³³

Additionally, caution must be taken with regards to the claims that biosample research implies fewer risks for sample donors than traditional human subject research does for participants. This is true, in so far as there will be no side-effects, unexpected adverse reactions, or painful symptoms which will affect a sample donor when his or her sample is used.³⁴ There is however a significant risk element in

biosample research posed by the potential to identify sample donors.³⁵ Depending on the degree to which the sample has been anonymised, and the amount of accompanying clinical data, there is a real possibility that a sample could be matched to its donor. This in turn can have several negative consequences for the donor. He or she may be at risk of stigmatization for having a particular health condition, may face difficulties with health insurance companies, and may be in the unpleasant position of knowing less about his or her own health status than a group of unknown researchers.³⁶ Identifying a supposedly anonymous sample donor is a serious violation of that individual's privacy, and there is consequently important emphasis placed on the measures to reduce this risk. This is discussed in detail in Chapter 2.2 below.

While the above goes some way towards demonstrating why biobanks are such potentially powerful research tools, it is crucial to bear in mind that the value of biobanks does not lie with the banks themselves, or with their sample collections.³⁷ The value of a collection is the research it enables.^{38,39} In other words, the only valuable biobank is one which is frequently used. Researchers must therefore be able to identify, contact, and receive samples from biobanks;⁴⁰ the banks themselves must be able to obtain, store, and ship samples. As Kaye (2011) notes, "Research is increasingly of a global nature with data and samples exchanged, accumulated and created through a number of dynamic research networks and collaborations that involve multi-disciplinary teams located in different countries."⁴¹ This transnational aspect of biobanking is what enables large sample sizes, and consequently statistically powerful research. *Providing* good quality samples for research is at least one, if not the most, important feature of biobanks⁴². This fact is the foundation of what follows in this thesis.

Important distinction

Before continuing, it is important to clarify one of the key terms in the title of this thesis, and how it is used, and not used, throughout. The biosample provision process may be referred to as transferring, making accessible, exchanging, or supplying; our initial idea was to employ the term "sharing". Sharing implies a give and take relationship, and this back and forth aspect is generally a feature of the biosample provision system. Biobanks may trade samples back and forth, or send them to researchers on the understanding that they will receive some kind of recognition, or perhaps collaborate in some way in the research. Furthermore, numerous research groups may be able to make use of the same set of samples, so a biobank can be said to "share" the samples amongst them. However, after time spent researching the situation in Switzerland, and discussions with those in the field, there are reasons to argue that sharing may not always be the most appropriate description of what is done with biosamples for research. First, some biobanks have a cost recovery system to offset any financial burden of shipping samples (indeed, some commercial biobanks also sell human tissue at a profit), a process which is far more accurately characterized as "service provision" than sharing; they may also offer advice and diagnostic services in this transaction. In addition, the fact that in Switzerland, samples tend to move between research groups more frequently than from third-party biobanks to researchers, means that the term "sharing" misses the spirit of collaboration and mutually beneficial cooperation which characterizes these exchanges.¹ Overall, it seems that the

¹ It is also important to bear in mind that the expression „data sharing“ is also widely used in the literature on genetic and genomic research, yet has quite a different meaning. Individuals working with the data derived from such research are typically required to make it available so that others may test, or avoid duplicating, their results. This data has been defined as "the full range of research results, techniques, and materials useful in future investigations" (Campbell, 2002). It is not the data often accompanying samples, which I deal with in

multiple kinds of biobank also entail multiple forms of sample provision process. Therefore, no single term is used throughout this thesis; in some cases, sharing may be the best description of the process, while in others, exchange or provision is more accurate.

Untapped potential

The importance of access to biosamples is highlighted in the literature.⁴⁴ As noted in the opening sentence of this thesis, these articles are frequently reactions to the rapid rise in importance of biobanks.

However, coupled with this are numerous calls for more fully exploiting the potential of these banks.^{45,46} As Clark (2010) puts it: “We are currently in an “age of the biobank [...] Despite this, significant challenges remain and jeopardize the ability of research using human biospecimens to make the impact it should.”⁹ Vaught, Kelly, and Hewitt (2009) echo this: “[...] specimens are collected and stored for lengthy periods before being used, delaying their productive use by researchers, and possibly delaying new discoveries and treatments for patients. It is therefore reasonable to hypothesise that these extremely promising research tools are not yet being used to their fullest potential. The question then is, why not?”⁴⁷

Despite, indeed perhaps because of, its rapid evolution, the biobanking world is not yet operating smoothly. Obstacles and inefficiencies exist. Specifically, numerous commentators now pinpoint the problem as a lack of sharing.⁴⁸⁻⁵¹ Among authors who address this issue, there are some particularly elegant summings-up of the problem. In an article synthesizing the European efforts to promote closer biobank collaboration, Ballantyne (2008) explains that “...the mission of pooling resources, sharing samples and exchanging data represents a difficult task...”⁵² Hagen and Duke (2004) reiterate that it is the accessibility of sample collections, not the collections themselves, which must be the focus of improvements: “...in spite of their seemingly overwhelming size, greater networking between these national initiatives could only further benefit our understanding of the most common causes of morbidity and mortality.”⁵³ Enabling sample sharing and exchange is urgently required in order that biobanking can move forward: “Only when we all share our toys, and put as much information and resources into the precompetitive space, will we really make a dent in the challenges. This means we must find ways to build shared infrastructure systems, essentially über-registries and biobanks...” (Horn, 2010)⁹ This is a major roadblock which, in light of the explosive growth of genomic research, affects even established organisations: “[...] even the major academic hospitals are not capable of swiftly setting up the needed large data and sample collections on their own or performing all the necessary research; therefore, the research pipeline needs to be able to take part in multicenter medical research in cooperation with other institutes and industry on a national and, if needed, international level. On a national and international level, research infrastructures would be needed to support such a form of cooperation.” (Riegman, 2011)⁵⁴ The raw material to enable advances in research exists: the challenge now is to connect this material with those who need it. As Horn and Riegman, above, suggest, Dillner and Andersson (2011) also stress the lack of infrastructure that contributes to the problem: “Although it is commonly perceived that lack of sufficiently high numbers of samples is the major bottleneck of the research in molecular

this thesis. The data discussed here is exchanged as a part of the initial research, and not made available so that this research can later be validated. Campbell, E.G. *et al.* Data withholding in academic genetics - Evidence from a national survey. *Jama-Journal of the American Medical Association* **287**, 473-480 (2002).

medicine today, very large amounts of samples do indeed exist and bottlenecks are more related to the fact that the clinical biobanks have not been designed to work as a scientific infrastructure.”⁵⁵

Based on these findings, there are three potential explanations for why commentators feel that biobanks could be more widely, frequently or thoroughly used. First, they may be wrong. However, since the great majority of authors addressing the subject work in, or closely with, biobanks, and their analyses have at least partly contributed to the substantial sums of money devoted to improving the field, this suggestion is unpersuasive. Second, it may be that researchers have no desire to carry out the projects that these banks enable, they may prefer to gather and work with their own sample collections, rather than accessing others. This explanation is unsatisfying too; first, many biobanks are created or managed by individuals who are also actively engaged in research, and second, calls by researchers for better sample accessibility are also documented. Third, it may be that biobanks should indeed be used more, that researchers are indeed eager, but that obstacles are currently preventing this from occurring. It therefore becomes reasonable to consider the hypothesis that obstacles to researchers accessing biosamples may be one of the factors which explains the current under-use of biobanks.

Contents of the thesis

Above, the foundations have been laid which introduce a currently pressing roadblock to the further development of biobanking. The goal of this thesis is to examine the causes of the insufficient sample sharing. In order to do this, several steps must be taken. First, the material in the literature which discusses barriers to sample sharing in biobanking will be presented. One significant difficulty which is currently receiving attention at the highest level of biomedical research regulation will then be addressed in more detail. In 2008, research using biosamples was for the first time specifically addressed by the Declaration of Helsinki. The relevant paragraph, which influenced numerous other national regulatory documents, is a first step towards tackling one obstacle to sample sharing: the appropriate form of consent which must accompany the biosamples. The revision and the difficulties in regulating this field are discussed. Since the completion of the article, the Declaration has once more been revised, and comments on this are included in the summary.

This is followed by the results of a past empirical study with Swiss ethics committee members, who were questioned about their approaches to informed consent for research using samples from biobanks. These findings corroborate the statements of our interviewees on consent (see Chapter 3.5), and suggest that the topic of informed consent is one which requires further attention in order to facilitate biobank sharing.

Following this introduction, we move on to the empirical part of the current study. This comprises the results of the main body of research, and is supplemented by findings from a second empirical investigation. The findings from 36 interviews with biobank stakeholders on the subject of barriers to sharing in biobanking are presented. The results of the literature review are first compared to the variety of barriers cited by interviewees, in order to develop a clearer picture of the current situation in Switzerland, and to explore whether the predominance of certain issues in the literature matches the real-world experiences of a sample group of professionals. With this comparison, a picture of the significant obstacles to biosample sharing evolves

The barriers which were described with unprecedented detail by the interviewees are then examined in greater detail. First, the fact that there is no current globally-accepted definition of the term

biobank is discussed, and this has a number of potentially negative implications for biosamples researchers.

The next focused topic is that of authorship on publications arising from biosample research. As sample exchange typically involves some form of collaboration between independent research groups, assigning appropriate, mutually satisfactory authorship credit becomes a significant concern. This section illustrates how current practices reported by our interviewees may be negatively impacting on sample sharing, as inappropriately assigning authorship damages the very practice that is so important to researchers.

The fairness of current sample sharing practices, and stakeholders' perceptions of what this term means, is discussed in Chapter 3.4. Mutual satisfaction is an essential element in encouraging successful collaboration, and we obtained valuable data about researchers' interests and priorities in a subject sparsely addressed in the literature to date.

The final subject addressed is that of informed consent for biobank research, discussed in the theoretical section. I present the responses of our interviewees regarding this issue, and in particular their views on the role ethics committees play in obtaining consent.

This dissertation concerns the current situation in Switzerland, insofar as all interviews were carried out with individuals who were employed by Swiss institutions at the time of interviewing. While the findings cannot simply be generalized to make claims about the global field of biobanking based upon these results, it is emphasized that a third of our respondents were not themselves Swiss, and that the majority has spent at least some significant period of time working for institutions in other nations. This, combined with the necessarily international aspects of biosample research, allows for cautious optimism that some of the results can be extrapolated the global situation. However, given the discrepancies between the findings from the literature review and those from the interviews, and particular the comments from some interviewees that certain ways of working are "Swiss ways", the generalizability of these results must not be taken for granted; this is addressed in more detail in Chapter 3.1 below. The aim was to develop insight into the current obstacles to sharing biosamples in Switzerland: the nature of our responses leads us to feel confident that our interviewees understood this aim, and provided us with the information to develop our research goals.

Peer-reviewed publications

The following published articles can be found in this thesis:

A Review of the Barriers to Sharing in Biobanking. Colledge, F., Elger, B. Howard, H. Biopreservation and Biobanking. December 2013, 11(6): 339-346. doi:10.1089/bio.2013.0039.

Impossible, Impractical, and Non-Identifiable? New Criteria Regarding Consent for Human Tissue Research in the Declaration of Helsinki. Colledge, F., Elger, B. Biopreservation and Biobanking. June 2013, 11(3): 149-152. doi:10.1089/bio.2013.0006.

What is a biobank? Differing definitions among biobank stakeholders. Shaw, D., Elger, B., Colledge, F. Clin Genet. 2014 Mar;85(3):223-7. doi: 10.1111/cge.12268. Epub 2013 Oct 16.

"Conferring authorship": biobank stakeholders' experiences with publication credit in collaborative research. Colledge, F., Elger, B., Shaw, D. PLoS One. 2013 Sep 30;8(9):e76686. doi: 10.1371/journal.pone.0076686. eCollection 2013.

Sample and data sharing barriers in biobanking: consent, committees, and compromises. Colledge, F., Persson, K., Elger, B., Shaw, D. Ann Diagn Pathol. 2014 Apr;18(2):78-81. doi: 10.1016/j.anndiagpath.2013.12.002. Epub 2013 Dec 20.

References:

1. Hansson, M.G. Ethics and biobanks. *Br J Cancer* **100**, 8-12 (2009).
2. Hewitt, R.E. Biobanking: the foundation of personalized medicine. *Curr Opin Oncol* **23**, 112-9 (2011 B).
3. Elger, B.S. & Caplan, A.L. Consent and anonymization in research involving biobanks - Differing terms and norms present serious barriers to an international framework. *Embo Reports* **7**, 661-666 (2006).
4. Collins, F.S. & McKusick, V.A. Implications of the Human Genome Project for medical science. *JAMA* **285**, 540-4 (2001).
5. WORLD HEALTH ORGANIZATION. Genomics and world health: report of the Advisory Committee on Health Research. *EB* **112/4**(2003).
6. Cambon-Thomsen, A., Ducournau, P., Gourraud, P.A. & Pontille, D. Biobanks for genomics and genomics for biobanks. *Comp Funct Genomics* **4**, 628-34 (2003).
7. Haga, S.B. & Beskow, L.M. Ethical, legal, and social implications of biobanks for genetics research. *Adv Genet* **60**, 505-44 (2008).
8. Tansey, J. & Burgess, M. The foundations, applications and ethical dimensions of biobanks. *Electronic Working Papers Series*. (2004).
9. Betsou, F. *et al.* What Are the Biggest Challenges and Opportunities for Biorepositories in the Next Three to Five Years? *Biopreservation and Biobanking* **8**(2010).
10. Day, J. & Stacey, G. Biobanking. *Mol Biotechnol* **40**, 202-213 (2008).
11. Asslauer, M. & Zatloukal, K. Biobanks: transnational, European and global networks. *Briefings in Functional Genomics & Proteomics* **6**, 193-201 (2007).
12. Knoppers, B. & Hudson, T. The art and science of biobanking. *Human Genetics* **130**, 329-332 (2011).
13. Hirtzlin, I. *et al.* An empirical survey on biobanking of human genetic material and data in six EU countries. *Eur J Hum Genet* **11**, 475-88 (2003).
14. Shickle, D. The consent problem within DNA biobanks. *Stud Hist Philos Biol Biomed Sci* **37**, 503-19 (2006).
15. Andrews, L.B. Harnessing the benefits of biobanks. *Journal of Law Medicine & Ethics* **33**, 22-+ (2005).
16. Gibbons, S.M.C. REGULATING BIOBANKS: A TWELVE-POINT TYPOLOGICAL TOOL. *Medical Law Review* **17**, 313-346 (2009).
17. Shickle, D., Griffin, M. & El-Arifi, K. Inter- and intra-biobank networks: classification of biobanks. *Pathobiology* **77**, 181-90 (2010).
18. <http://www.ukbiobank.ac.uk/about-biobank-uk/>.
19. Schroder, C., Heidtke, K.R., Zacherl, N., Zatloukal, K. & Taupitz, J. Safeguarding donors' personal rights and biobank autonomy in biobank networks: the CRIP privacy regime. *Cell and Tissue Banking* **12**, 233-240 (2011).
20. Yuille, M. *et al.* Laboratory Management of Samples in Biobanks: European Consensus Expert Group Report. *Biopreservation and biobanking* **8**, 65-69 (2010).
21. Hawkins, A.K. & O'Doherty, K. Biobank governance: a lesson in trust. *New Genetics and Society* **29**, 311-327 (2010).

22. Helgesson, G. & Johnsson, L. The Right to Withdraw Consent to Research on Biobank Samples. *Medicine, Health Care and Philosophy* **8**, 315-321 (2005).
23. Petersen, A. 'Biobanks' "engagements": engendering trust or engineering consent?'. *Genomics, Society and Policy* **3**, 31 - 43 (2007).
24. Park, A. 10 Ideas Changing the World Right Now: Biobanks. *Time Magazine* (2009).
25. Cambon-Thomsen, A. The social and ethical issues of post-genomic human biobanks. *Nat Rev Genet* **5**, 866-73 (2004).
26. Lichtenstein, P. *et al.* Environmental and heritable factors in the causation of cancer--analyses of cohorts of twins from Sweden, Denmark, and Finland. *N Engl J Med* **343**, 78-85 (2000).
27. Ioannidis, J.P. & Adami, H.O. Nested randomized trials in large cohorts and biobanks: studying the health effects of lifestyle factors. *Epidemiology* **19**, 75-82 (2008).
28. Roden, D.M. *et al.* Development of a Large-Scale De-Identified DNA Biobank to Enable Personalized Medicine. *Clin Pharmacol Ther* **84**, 362-369 (2008).
29. Petersen, A. Securing our genetic health: engendering trust in UK Biobank. *Sociology of Health & Illness* **27**, 271-292 (2005).
30. Eriksson, S. & Helgesson, G. Potential harms, anonymization, and the right to withdraw consent to biobank research. *Eur J Hum Genet* **13**, 1071-6 (2005).
31. Steinsbekk, K.S., Kare Myskja, B. & Solberg, B. Broad consent versus dynamic consent in biobank research: Is passive participation an ethical problem? *Eur J Hum Genet* (2013).
32. Hogan, J.W., Roy, J. & Korkontzelou, C. Handling drop-out in longitudinal studies. *Stat Med* **23**, 1455-97 (2004).
33. Andersson, K. *et al.* The interface of population-based cancer registries and biobanks in etiological and clinical research--current and future perspectives. *Acta Oncol* **49**, 1227-34 (2010).
34. Ursin, L. Biobank research and the right to privacy. *Theoretical Medicine and Bioethics* **29**, 267-285 (2008).
35. Kaufman, D.J., Murphy-Bollinger, J., Scott, J. & Hudson, K.L. Public Opinion about the Importance of Privacy in Biobank Research. *Am J Hum Genet* **85**, 643-54 (2009).
36. Hoppe, N. Risky business: re-evaluating participants risk in biobanking. in *Human Tissue Research: A European Perspective on the Ethical and Legal Challenges* (eds Lenk, C., Hoppe, N., Beier, K. & Weisemann, C.) (Oxford University Press, Oxford, 2010).
37. Meir, K. *et al.* The Human Face of Biobank Networks for Translational Research. *Biopreservation and Biobanking* **9**, 279-285 (2011).
38. Akst, J. Biobank yields results. in *the-scientist.com*.
39. Rothstein, M.A. Expanding the ethical analysis of biobanks. *Journal of Law Medicine & Ethics* **33**, 89+ (2005).
40. Fernow, J. & Ulleras, E. EU project will increase researcher access to biobanks. in *Centre for Research Ethics and Bioethics, University of Uppsala* (2013).
41. Kaye, J. From single biobanks to international networks: developing e-governance. *Hum Genet* (2011).
42. Betsou, F. *et al.* Towards norms for accreditation of biobanks for human health and medical research: compilation of existing guidelines into an ISO certification/accreditation norm-compatible format. *The Quality Assurance Journal* **11**, 221-294 (2007).
43. Campbell, E.G. *et al.* Data withholding in academic genetics - Evidence from a national survey. *Jama-Journal of the American Medical Association* **287**, 473-480 (2002).
44. Yuille, M. *et al.* Biobanking for Europe. *Brief Bioinform* **9**, 14-24 (2008).
45. Harris, J.R. *et al.* Toward a roadmap in global biobanking for health. *Eur J Hum Genet* **20**, 1105-11 (2012).
46. Hansson, M.G., Dillner, J., Bartram, C.R., Carlson, J.A. & Helgesson, G. Should donors be allowed to give broad consent to future biobank research? *Lancet Oncol* **7**, 266-9 (2006).
47. Vaught, J., Kelly, A. & Hewitt, R. A Review of International Biobanks and Networks: Success Factors and Key Benchmarks. *Biopreservation and Biobanking* **7**, 143-150 (2009).

48. Watson, R.W.G., Kay, E.W. & Smith, D. Integrating biobanks: addressing the practical and ethical issues to deliver a valuable tool for cancer research. *Nat Rev Cancer* **10**, 646-651 (2010).
49. Elger, B.S. & Biller, N. Biobanks and research: scientific promise and regulatory challenge. in *Biobanks and Tissue Research, The Public, the Patient and the Regulation* 37-52 (Springer, Dordrecht, 2011).
50. Vegvari, A., Welinder, C., Lindberg, H., Fehniger, T.E. & Marko-Varga, G. Biobank resources for future patient care: developments, principles and concepts. *J Clin Bioinforma* **1**, 24 (2011).
51. Boggio, A. Transfer of Samples and Sharing of Results: Requirements Imposed on Researchers. in *Ethical Issues in Governing Biobanks: Global Perspectives* (eds Elger, B., Biller, N., Mauron, A. & Capron, A.M.) (Ashgate Publishing Ltd., Aldershot, 2008).
52. Ballantyne, C. Report urges Europe to combine wealth of biobank data. *Nat Med* **14**, 701 (2008).
53. Hagen, H.E. & Carlstedt-Duke, J. Building global networks for human diseases: genes and populations. *Nat Med* **10**, 665-7 (2004).
54. Somiari, S.A., Riegman, P., Morente, M.M., Baust, J.M. & Stacey, G. What are Some Top Accomplishments You Would Like to See in the Field by 2015? *Biopreservation and Biobanking* **9**, 3-4 (2011).
55. Dillner, J. & Andersson, K. Biobanks collected for routine healthcare purposes: build-up and use for epidemiologic research. *Methods Mol Biol* **675**, 113-25 (2011).

1.2 RESEARCH OBJECTIVES

This project was undertaken with the following aims.

- 1) Establish whether there are currently obstacles affecting the sharing and/or exchange of biological samples and/or data amongst biobanks and researchers. Document these obstacles.
- 2) Establish the degree to which obstacles are experienced by biobank stakeholders currently working in Switzerland. Document their experiences.
- 3) Analyze findings, comparing data from the literature and the empirical investigation.
- 4) Identify areas of particular importance in the field, describe them, and suggest possible solutions.

1.3 METHODOLOGY

Our methodology is described in detail in the Methods section of each article presented below. Therefore, it is unnecessary to repeat these details here. The full interview guide used, as well as the timetable which structured the research, can be found in Chapter 4.5, Appendices.

1.4 COLLABORATIVE TEAM

Although this work is the doctoral project of Flora Colledge, several individuals were involved in the development of the articles that appear below, and the design of the research. This was particularly important for two reasons; first, it is the nature of qualitative research that numerous individuals must perform the same data coding process in order to verify the findings; and second, the unexpected depth with which a number of themes were addressed necessitated the contribution of new team member who could properly develop themes for publication.

Bernice Elger, professor and head of the Institute for Biomedical Ethics, developed the initial concept and research question, and elaborated the study hypotheses and methodological approach. Upon completion of the data collection, she performed content analysis on all transcripts and compared these findings with Flora Colledge and Heidi Howard. She contributed to the development of each manuscript based on these codes. Furthermore, she developed the article on the Declaration of Helsinki together with Flora Colledge, and provided the data and input on the article on ethics committees.

Heidi Howard, former senior research at the Institute, worked on the initial research question and hypotheses, and took the lead in formulating the interview guide. She was instrumental in developing, selecting articles, and writing and editing the literature review. She searched for interviewees carried out a number of interviews. She analysed, coded and compared all transcripts with Flora Colledge and Bernice Elger. In the middle of the project, she accepted an offer to work in a different institution, and consequently did not contribute to the manuscripts developed from the empirical data.

David Shaw, a senior researcher at the Institute for Biomedical Ethics, analysed all transcripts and codes specifically addressing the issues of definitions, authorship and consent. He contributed substantially, in one case as first author, to the manuscripts on these topics, and was instrumental in their successful publication.

Kirsten Persson, a doctoral student at the Institute, analysed all transcripts and specifically addressed the issues of ethics committees and informed consent. She elaborated these codes and compared them with David Shaw, Bernice Elger, and Flora Colledge. She played a key role in developing the article on this issue, as joint first author with Flora Colledge.

Jakob Passweg, senior physician at the Hematology Laboratory at the University Hospital of Basel, contributed to the development of the overall results analysis. His experience in the field enabled key issues to be properly identified and described, and his comments were also essential in formulating a clear research question and ordering of the thesis.

PART 2: THEORETICAL EXAMINATION

2.1 1 A REVIEW OF THE BARRIERS TO SHARING IN BIOBANKING

Flora Colledge, Bernice Elger, Heidi Howard

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Abstract

Although biobanks are gaining importance as tools in the field of biomedical research, enabling investigators to access large numbers of catalogued samples and/or data, most have not reached their full potential. Numerous obstacles may prohibit the efficient sharing of, and access to their sample and data collections. In order to minimize or overcome these obstacles while meeting ethical criteria, the first step is to identify the challenges to sharing between biobanks and between biobanks and researchers, thus enabling targeted solutions to be implemented. To date, no article has specifically addressed the full scope of currently-identified barriers to sample sharing, yet such a list is essential if these matters are to be dealt with swiftly. We have reviewed the literature on biobanks in order to identify the issues mentioned as barriers to sharing samples with or without data. Our literature search identified 15 barriers, including among others, logistical, ethical and legal issues. We provide a description of all barriers, discuss key themes, and conclude that empirical research is required to determine the full extent of the problems addressed in the literature.

Introduction

Biobanks are “organized collections of biological samples and associated data”.¹ Although often used in the context of materials and data from humans, the term is also employed to describe collections of plant and animal matter;² this review addresses only collections of human material. Biobanks vary greatly based on, among other characteristics, the size, degree of accessibility, the reason(s) for the collection (clinical studies, academic research, judiciary or forensic reasons), and the types of institutions in charge of the collection and/or management of the biobank (public or private, for profit or not). The prevalence of biobanks of human material for medical and academic research has been increasing over the last decade, as has the recognition that the large size of collections increases their scientific value.³ The growing importance of biobanks for research, diagnosis and medical advancement has been emphasized by many academic authors.⁴⁻⁷ Furthermore, in 2009, Time Magazine named biobanking as one of the ideas that is “changing the world now”.⁸

The general tone of recent literature is that biobanking for biomedical research is now an established practice, and it should be exploited to its full potential.⁹⁻¹¹ In 2008 the European Science Foundation appealed to the European biobank community to combine the wealth of biobank data and materials: “There is an urgent need for the coordination and harmonization of biobanking and biomolecular resource infrastructure”.¹⁰ As a concrete sign of this desire to unite European efforts in biobanking, the European Union reserved 5 million Euros for the Biobanking and Biomolecular Resources Research Infrastructure (BBMRI) project. Harmonisation of operating practices, networking and

increased funding are among the methods suggested for advancing the field, and are intended to allow biobanks to build up statistically significant sample collections, and bring them into closer contact with the researchers who use them.^{9,10,12-15} While these positive steps forward are crucial, it is also necessary to examine the current specific roadblocks to sample distribution, which must be managed and/or removed before the full research potential of biobanks can be achieved. One of the primary goals of human biobanks is to make resources available to the researchers who need them. Barriers to the accessing or sharing of resources can therefore reduce the usefulness of biobanks, at the regional, national and international levels. To date, no article has specifically addressed the full scope of currently-identified barriers to sample sharing, yet such a list is essential if these matters are to be dealt with efficiently.

We define a barrier to sharing as any factor which constitutes an obstacle in the sharing process, be it logistical, ethical, or theoretical. The term “barrier” is not used here in an absolute pejorative sense, or to suggest that every obstacle to sharing is completely undesirable; we recognize that some processes which can, in some ways, limit sample and data sharing, such as ethical review, are necessary and desirable. We consider sharing as the process of biobanks (or scientists with registries or laboratory collections) supplying samples with or without data to those requesting it. We do not address herein the particular problems of initial sample collection by the biobank, unless these specifically impact on the subsequent sharing of samples with others once the samples and data have already been collected. In order to provide a structured list of the obstacles to sharing samples with or without data, we have conducted a review of the literature. In identifying and discussing these issues, we aim to provide a unique and focussed resource which will allow stakeholders to recognise and understand potential obstacles to sharing, and in doing so allow for a more concrete approach to devising solutions to optimize ethical sharing above and beyond the general calls for harmonization and standardization.

Methods

We conducted a literature search concerning the obstacles to sharing samples with or without data in biobanking. We searched three databases: PubMed, Web of Knowledge and JStor. Key terms used in pairs and sequentially included: (biobank OR biobanks OR biorepository OR data bank) AND (sharing OR barriers OR challenges OR obstacles OR problems OR nomenclature OR terminology OR practical OR ethical OR consent OR governance OR legal OR data collection OR territoriality OR justice OR fair OR fairness). The articles retrieved included all those published until June 26th 2012 (inclusive). The term biobank is relatively recent, appearing in PubMed for the first time in 1996, and used more frequently from 2000 onwards, therefore, no lower date limit was set on the search. After eliminating all double entries, we read and evaluated the abstracts (or introductions, for articles without abstracts) of all remaining articles to assess their relevance to our study and papers were included if they explicitly addressed barriers to sharing samples with or without data in biobanking. Articles addressing only the sharing of data were excluded. We then used a “snowball” approach to obtain additional relevant articles from the reference list of initially selected articles. The full text of articles was then scrutinised to identify the obstacles to sharing samples with or without data in biobanking. Since the goal of this article is to identify in as much detail as possible the barriers to sharing as discussed in the academic literature, we counted only those issues which were addressed in the context of stopping, deterring, complicating or hindering sharing. Themes or areas that were addressed in general as benefiting from improvement in biobanking*, of which the literature has many examples, were not interpreted as being barriers to sharing. Our aim in using this more

restrictive interpretation was to avoid the reification of barriers by confusing a call for optimisation with the existence of an obstacle.

Any issue which was cited specifically in the context of hindering sharing was selected, and the full sentences (or sentences) were then extracted from the articles and placed in a table. The procedure was performed by FC and HCH independently, and results were then compared. Any discrepancy was discussed until both authors agreed on the full list of barriers extracted from the articles. Once each mention of a barrier had been agreed upon, they were further defined and organized into groups based on commonalities. The category labels given to each group of barriers were initially developed by FC based on the list of barriers identified in the articles and not on pre-existing categories. These categories were then discussed for coherence by FC and HCH and the final categories were agreed upon by all authors. These three categories are an attempt to further reveal where some of these barriers may principally originate from but we underline that they are indeed non-exclusive, and do overlap with each other, such that some barriers may have some characteristics from all categories.

Findings

Twenty-seven articles published between 2003 and June 2012 and authored by 23 distinct first authors were retrieved using the search strategy described above. The nature of the articles ranges from empirical studies, to reviews, to commentaries and discussion articles, with the latter two being the most numerous. We report on 15 barriers to sharing samples with or without data found through this search. The identified barriers were organized into three macro-categories (Table 1): internal issues, external issues and ethical issues. These macro-categories are designed to focus the review and group similar topics. They are not mutually exclusive or exhaustive, but are meant as a way to organise this article, and reflect the way in which we have chosen to approach these issues.

Table 1: Definitions and examples of the 15 barriers to sharing in biobanking identified in 27 articles

Barrier Categories	Definition	Barriers	Number of times mentioned*	Examples
Internal issues	Barriers which exist within the workings of the biobank itself, and over which the biobank exerts the most control.	SOPs Availability Awareness Fees Networks Governance	8 3 1 2 4 4	Damage to samples in transit, lack of publication of a biobank's resources leading to low demand for samples.

External issues	Barriers imposed on biobanks by external factors, which the biobank itself has less control over.	Commercialisation Legal issues IP and patents Nomenclature Publication credit	2 10 6 2 2	National laws prohibiting human tissue export.
Ethical issues	Barriers which involve bio-ethical considerations, such as fairness, and patient autonomy.	Consent Territoriality Prioritisation Safe Transfer/ Confidentiality	4 3 1 1	Consent forms which limit the scope of research in order to protect patients, but which prohibit collaboration.

* This refers to the number of times the barrier was mentioned explicitly as a barrier to sharing samples with or without data in the articles studied. We recognize that some of these barriers have been mentioned in articles as a general problem in biobank operations but these were not included here.

Internal issues: standard operating procedures, availability, awareness of existence, fees, networks, governance

Internal issues are those over which the biobank exerts most control, either because it established the systems (which cause problems), and/or because it has the wherewithal to change them. They are issues which arise from the way the bank currently runs, and over which, crucially, professionals involved with that bank exert influence.

As defined by Asslaber and Zatloukal (2007), standard operating procedures (SOPs) “should define the whole process of sample acquisition, sample processing and preservation as well as storage and retrieval”.¹² Given the large range of activities included in this category, it is not surprising that barriers in SOPs are mentioned frequently in the literature, with only legal issues being more frequently cited. The differences in procedures between banks are described as a challenge, and in some cases, the bank’s current practices may be sub-optimal, and therefore a barrier, regardless of the differences with other banks.

Many of the problems with respect to SOPs are related to the quality of the stored samples and this is identified by Myles et al (2011) as the primary challenge in biospecimen exchange.¹⁷ Biobanks may be unable to assure the quality of their samples,^{17,18} or correctly link the patient’s treatment history to a particular sample or, there may be a lack of clinical data.¹⁷ The variety of methods by which biobanks store and process the samples was mentioned, as researchers obtaining samples from numerous sources may have difficulty working uniformly with them.^{13,19-21} Samples are thus not exploited to their fullest potential.¹¹ Along the same line, and specifically with respect to international interoperability Kiehntopf and Krawczak (2011) address in more detail the following

aspects: pre-analytical sample-handling, the standard pre-analytical code, sample quality management, technological issues (with respect to storage, retrieval, sample identification and automated technical processes), sample-related IT and data-management and shipping.²⁰ From an empirical study of European biobanks, Zika et al. (2011) also identified the complications related to shipping with dry ice as being a barrier.²¹ Budimir et al (2011) sum up the issue by stating that biobanks with “different designs and different settings” can hinder sharing, and that international harmonisation is therefore needed.²²

Sample availability, by which we mean the existence of a useable number of samples in a bank, is mentioned on three occasions as a hindrance to sharing. We address it because it is indeed mentioned in the specific context of sharing, despite the contradictory issue that if samples are unavailable in the first place, sharing is a moot point. Availability is brought up as a barrier to biobanks which are engaged in sharing, but could do more if more samples were obtainable. The lack of “local” biobanks which would facilitate sample collection by potentially being easily accessible to both researchers and donors is mentioned, in an interesting contrast to the general recommendations for more centralised banking.²³ An example at the micro-level is the sharing of prostate cancer samples, which is limited by the fact that such samples are in high demand, yet little tissue is, in fact, collected.²⁴ The general scarcity of certain kinds of sample is also mentioned by Myles et al (2011).¹⁷

Related to the topic of availability, but not strictly the same notion, Zika et al (2011) mention the lack of knowledge or awareness of existing sample collections as a barrier to sharing.²¹

The financing of biobank infrastructure and personnel is a big challenge to the existence of biobanks.^{11,25} That being said, the specific issue of cost or fees with respect to sharing samples specifically was not mentioned often. Fees charged by biobanks (cost recovery rather than profit-generating) are mentioned as obstacles on two occasions. Somewhat surprisingly, prohibitive costs shutting out certain users are not brought up, nor are for-profit banks mentioned. Rather, the issue is confusion about costs. Biobank fee structures, which will have been elaborated internally, are said to become confusing as they differ from one another in a networking context.¹⁷ At a more basic level, however, the very practice of assigning a financial value to samples is problematic. To do so responsibly, the variety of man-hours, the potential usefulness of the sample, and the finances of those who might wish to access it must all be considered, yet there are no concrete guidelines to help calculate how these factors can and should be quantified.²⁶

Also an internal issue, to a certain extent, is the matter of networks of biobanks. The lack of efficient networks in biobanking is mentioned three four times as a barrier. Having to elaborate and decide on the details of biobank management, ownership, and confidentiality, issues which are in and of themselves sometimes problems in biobank sharing, limits the effectiveness of creating and or sustaining collaborative networks.^{20,21} Asslaber and Zatloukal (2007) emphasize that the fragmented nature of biobank networks, especially in Europe, is a key factor preventing biobanks from pooling their samples, and hence prohibiting researchers from accessing large sample and data sets.¹² As a potential aid to create functioning biobank networks, the lack of which stands in the way of proliferating “well organised and accessible” collections, Yuille et al. (2008) describe the BBMRI as a network with a “distributed hub structure” that has as an aim to “enable access by researchers to different sample types (with associated data) collected under different study designs”.¹¹

Biobank governance, widely discussed in biobanking literature, is touched on four times specifically in the context of problems in sharing. Governance in biobanking refers to the systems, procedures and documents which regulate the banks' activity, and to the people who oversee this sphere; without innovation in this realm, the flow of research material will be limited.²⁷ Biobanks in certain institutions may sometimes place restrictions on access to their data in order to protect their mandate,¹² an issue which can also be considered in the context of territoriality. On the other end of the scale, attempts by those who govern biobanks to broaden their sharing policies can be met with resistance from researchers, who are either confused by the changes or seek to limit access to their findings samples for the territorial reasons identified below.²⁸ While we have included governance in our list of internal issues, certain aspects of the problem, such as legislative and guideline documents, may be imposed from outside the bank itself. Governance may therefore also be a partly external issue and/or an ethical matter, and as such may share some characteristics with the legal and ethical issues mentioned below. With respect to guidelines, Elger and Caplan summarize the problem regarding international collaboration by saying that many national and biobank-specific "guidelines contain clearly divergent recommendations in important areas, which interfere with international collaboration. Not only do different systems exist for the collection of data, and the processing of samples but also the guidelines reflect fundamentally different ethical frameworks".¹⁶

External issues: commercialisation, legal issues, intellectual property and patents, nomenclature, publication credit

The constraints imposed on biobanks from sources external to biobanks themselves constitute some important barriers to sample and data sharing, and in contrast to internal issues, are less controlled by the biobank operators. Typically the obstacles take the form of requirements, imposed by non-biobank organisations, designed to improve some aspect of biobanking, but which also have an unwanted secondary effect of causing difficulties in sharing.

The potential to commercialise biobank samples represents a further barrier to sharing. While Hewitt et al (2011b) merely mention that this is so, suggesting that the broader issue is the effect of commercialisation on public trust,¹⁸ elsewhere it is noted that the biotechnological policies which influence sharing are dominated by the market interests of industry.²⁹ In other words, biobanks may be prevented from making their samples available, at least to certain groups, or researchers may likewise be prohibited from storing their samples in banks with an open sharing policy, due to the conditions of funding they receive from private biotechnological companies.

Legal issues were the most frequently listed barriers to sharing in biobanking from our pool of articles. Legal issues here refer to national or international laws, and exclude non-legally binding agreements and guidelines created between biobanks and other parties. The latter agreements are not mentioned in the literature as being problematic because of their legal status, and are therefore included in the internal issues section, in sub-categories such as governance. Despite the frequency with which legal barriers are mentioned, there is little variation in the main problems mentioned. Broadly, the divergence of regulations on the uses, storage, transfer and nature of tissues and data is repeatedly mentioned as an obstacle to international collaboration.^{11,12,21,30-33} Laws and guidelines contain "clearly divergent" instructions, which can be either prohibitive or confusing.²⁰ Furthermore, tissue export or import is limited or banned by certain countries.³⁴ Even within the European Union, a disruptive amount of variance exists.^{11,32} Based on their survey of 126 biobanks, Zika and co-authors state that most of the problems in sharing samples were related to legislative barriers.²¹ The

effort and biobank-specific organisation required to understand and comply with these regulations is a secondary barrier.²⁷

Intellectual property (IP) rights and patenting are also primarily legal issues; we feel they merit separate attention here as the barrier they pose is described distinctly from broader legal questions. IP and patents are mentioned six times as challenges in sharing in biobanking. When a patent or claim of intellectual property is anticipated on some work deriving from banked samples, access to those samples may be restricted, at least for a set time period.³⁵ This fact may further erode public trust in biobanking, as the public are not keen to see beneficial research restricted for ostensibly financial reasons.³⁰ Such restrictions, where they exist, may stop the optimum use of such samples by cutting out other research groups, and limits the knowledge-mining uses of the samples or data.^{17,18,1} However, as Cambon-Thomsen et al (2007) point out, confusion about the very nature of IP and patents, even when no restrictions are yet in place, may be a hindrance to some researchers.²⁸

Nomenclature concerns the terms used in the medical or scientific field, and not just those terms which are specific to biobanking. The profusion of terms relating to sample and data types, research methods, and databases is, in part, a natural result of changing language habits over the years, but is of course highlighted when samples taken ten years ago are compared with those obtained more recently. The problem is exacerbated on the international level, where even if all collaborations take place in English, the various translations and culturally different uses of words are still not likely to make for easy collaboration. Nomenclature may, therefore, be an important barrier to international sharing.³³ Pearson (2004) also points out that medical histories which accompany samples are useless if those from different institutions use different words.¹³

Publication credit and proper recognition of time and effort devoted to creating a useful tool (like bioresources) can be a difficult issue in all spheres of academic research, not just biobanking. Shickle et al (2010) point out that access to samples might be conditional on publication credit, and not simply “altruistically” available. This is distinct from researchers not wanting to make samples available at all (addressed below, as territoriality); in this case, the obstacle is meeting conditions, rather than confronting sheer unwillingness to share.³⁶ According to Cambon-Thomsen (2003), biobanks which are not properly credited or recognised for their work in establishing and maintaining their samples will not receive the professional recognition that they need to keep attracting researchers, and will risk becoming storage warehouses with no “clients”,³⁷ or potentially losing funding: hence, their samples will not be shared with a wider pool of researchers.

Ethical issues: consent, territoriality, prioritisation, recognition, safe transfer/confidentiality

Ethical issues appear as a distinct category, although they can in some cases be both internal, that is, under the control of the biobank, and external, as they are to some extent imposed by socio-cultural context and/or national standards. However, in all cases they are examples of decisions which require some degree of moral reasoning to resolve and we therefore judge that they merit separate attention here.

The question of informed consent for biobank research is ubiquitously mentioned in the literature.^{16,38-41} This is not surprising considering the huge role the topic plays in the ethical sphere of biomedical sciences. Indeed, not obtaining the proper consent can prevent samples and associated information from ever being used at all in biobank research.⁴² However, informed consent explicitly mentioned as a hurdle to sample sharing is relatively rare in the articles retrieved through our search.

Consent, when mentioned strictly as an obstacle to sharing, appears in different contexts. Consent forms differ between biobanks, or between the institutes which initially collect the samples and then send them to banks.^{13,20,39} Therefore researchers may be unable to use the samples or data for certain projects. This is linked to the difficulty of obtaining consent for prospective research, as it is difficult to inform donors of as-yet unplanned projects.³⁹ It is stated that the current formulation and interpretation of most biosample consent forms hinders data sharing, as they were not conceived with transnational projects in mind.⁴³ Kiehntopf and Krawczack specify that regarding the interoperability of consent to use samples and data, the prime issues of interest are the right to transfer to third parties and the scope of research allowed.²⁰

The barrier that we have called “territoriality” describes the phenomenon of unwillingness to share data or samples; this can also be described as wanting to keep samples and data exclusively for one’s own research. In the literature, territoriality is generally attributed to individual researchers, rather than to biobank managers or operators.¹⁷ The axiom “publish or perish” appears, in light of the fact that researchers may well be keen to foster an environment of trust and altruism in their field, but are equally aware that the samples, especially rare ones, can be an entry into prestigious research teams.³⁶ More broadly, “elitism and competition”¹⁷ among researchers is a threat to sharing, and access to data is therefore “vulnerable to researchers’ incentives”.²⁹

Prioritisation refers to the weight the biobank assigns to competing research projects (i.e. those which seek to use the same samples simultaneously). It is mentioned only once in the literature. Fortin et al (2011) indicate that banks which seek to prioritise the work of local researchers, even with the laudable goals of supporting their community and keeping donors close to the work, will be hindering others, at the national and international level, from accessing their samples.²⁶ This is not a barrier to all forms of sharing, as the samples are still in use, but rather an obstacle to wider sharing.

Recognition is also cited as a potential hurdle to sharing. This barrier is indirect in a way that most others mentioned here are not; in other words, it does not currently hamper sharing, but the net effect, if left unchecked, would be to damage the biobank, and hence its potential to operate successfully. According to Cambon-Thomsen (2003), biobanks which are not properly credited or recognised for their work in establishing and maintaining their samples will not receive the public recognition that they need to keep attracting researchers, and will risk becoming storage warehouses with no “clients”,⁴³ or potentially losing funding.

The ability to transfer useful data or information relating to samples while maintaining the confidentiality of the donors’ information is held to be a difficulty particularly in international collaboration.³³ Although data is usually transferred with samples, the reverse is not always true and data-sharing has become a topic in and of itself. In this respect, data-sharing may include the sharing of both clinical information as well as results of analysis using samples and clinical data. Since we focus this review on the sharing of samples with or without data, we have not included articles dealing only with data sharing.

Discussion

Based on the articles included in this review, we identified 15 obstacles to sharing samples with or without data in biobanking. This is the first review which specifically identifies and discusses the obstacles to sharing addressed in the academic literature. Our findings show that a broad variety of barriers have been discussed. The majority of issues receive one or two mentions; however, a small

number are cited by numerous authors. Two identified barriers (legal issues and SOPs) are mentioned frequently, and IP and patents also emerged often.

Although the attention which the barriers receive appears to vary significantly, the conclusions to be drawn from this require caution. It cannot be presumed that the frequency directly corresponds to the actual severity or extent of these barriers in practice. Certain frequently-cited factors may seem overemphasised or relatively unproblematic to some readers and stakeholders. For instance, certain banks may experience no problems at all with storing or shipping samples, while others will feel that a shortage of samples is unlikely to hinder sharing.⁹ While we do not suggest that any of the issues mentioned in the literature were invented or were purposefully ignored by the authors, it is important to note the following: i) the large majority of articles retrieved through our search do not aim to address barriers to sharing per se. Many articles simply mention barriers in the introduction and/or discussion and hence do not elaborate on these issues; ii) some aspects may have been repeated due to their perceived importance, whether or not this reflects the current state of affairs in biobanking; iii) less than a third only about a third of the articles under study actually addressed empirical data on barriers to sharing. In the absence of such data, it is impossible to assess how accurately the issues in the literature reflect current experiences. Our findings are a valuable initial approach, but require comparison with further empirical research.

Our results do, however, provide indications of what authors feel are important hurdles to sharing; therefore, we suggest that legal issues, SOPs, and to a lesser extent IP and patent considerations, are particularly problematic issues facing the biobanking world. An interesting aspect of this result is that each of these issues affects biosample sharing in a different way. National laws are an obstacle to sharing because they conflict with one another, but the effects of this are magnified because the laws, as they stand, are non-negotiable, and the very networking solutions designed to overcome this obstacle can be hampered by it.¹² Goebel et al point out that biobanks can circumvent some gaps in the transnational legal setting by drafting their own contracts to regulate cross-border sharing;⁴⁴ however, as some authors emphasise, uniform regulation must be developed, and biobank stakeholders alone cannot achieve this.^{31,45}

SOPs, on the other hand, can, to some degree, be influenced from within the biobanking sphere. Our findings suggest that the problem in this case is not only one of divergence, but also one of quality. As Shaw and Patterson note, the rise in translational and genomic research has meant a greatly increased demand for samples which are not only well preserved, but are accompanied by comprehensive clinical data. This places an extra burden on surgeons and pathologists, who are often not the end-users of those samples, or even directly involved with the biobank itself.⁴⁶ Numerous suggestions for enhancing the sample extraction and preservation process already exist;^{47,48} a number of the articles which identified this barrier did so in the context of discussion on biobank networks.^{11,13} It may be the case that barriers which are in the process of being overcome are more frequently cited, by way of "introduction" to the proposed solutions.

Intellectual property rights and patenting, while cited fairly often as barriers, differ from general legal issues and SOPs in that these are, to a degree, self-imposed desirable limitations to widespread sharing. In this sense, they may be considered less as obstacles than as tools to support innovation, with some restriction on sharing as a secondary side-effect. While they therefore, in some cases, curb sharing, the benefits accruing to researchers and the public may offset this.^{35,49}

In contrast to those barriers which are frequently mentioned, it is interesting to note that ethical issues receive relatively little attention in terms of barriers to sharing; even the issue of informed consent is mentioned infrequently. This is in marked contrast to the plethora of articles on the ethical aspects of biobanking, particularly the ongoing debates on the optimal measures for obtaining consent.⁵⁰⁻⁵² This may mean that ethical issues are fairly unproblematic in terms of sample sharing, but have a greater impact on sample acquisition (or that the focus, anyhow, has been on the latter); and/or that as with IP and patenting, ethical issues are a desirable measure to limit the risks harms (to participant privacy and autonomy) associated with widespread sharing. While both of these explanations may be at play, we feel that, particularly in the case of informed consent, the necessity of some restriction on sharing is well recognized. Consideration regarding the justifiability of the barriers discussed in this review, and the extent to which they should be “kept” in place will also be an important step in optimizing ethical and responsible sample sharing.

Limitations

Our review of the literature has certain limitations. First, it must be emphasised that our decision to exclude papers which imply barriers may mean that certain issues were not addressed, but as mentioned above, our goal was to avoid accidentally, either through our own perception bias or the ambiguity of the writing, including issues which were not in fact intended to be seen as barriers. Second, it must be noted that some of the papers referred to here are out of date by as much as eight or nine years.^{13,33} Hence, while we do not feel there are any completely obsolete issues mentioned here, some problems may be less pressing in light of recent developments in networking or sample processing. Third, the articles captured in our search range from surveys, to reviews, to commentaries. Therefore, as mentioned above, some problems are mentioned in a more hypothetical way than others. While it could be useful to analyse the rates at which problems are mentioned as concretely occurring versus merely being suspected to occur, the lack of empirical studies and relatively small literature pool on this topic means that such an exercise would be unlikely to produce valid results. Finally, our inclusion criteria and our desire to use explicit statements mean that we excluded articles that did not mention sharing in the abstract or introduction, which we understand means that we may have missed articles that discuss this subject later on in the article. Furthermore, our decision to exclude articles that deal solely with data sharing mean that we have not included such important articles as that by Kaye et al (2009) or Knoppers et al (2011).^{53,54} which provide important insight into aspects on data sharing. However, since data sharing, especially within the realm of genomics has created an entire field of study of its own, we feel it would be best to address this issue separately.

Conclusion

Biobanks are important tools for researchers and clinicians. Regardless of their size and scope, they exist to enable some extent of access to biological samples and/or data. Facilitating this access is an essential step to maximise the research potential of biobanks; to date, no single article has sought to unify the numerous obstacles to sharing mentioned in the literature. As a first step towards tackling these obstacles, we have compiled and discussed the above list of barriers to sharing samples with or without data, as a basic overview of some of the challenges biobanks and their stakeholders face. What is required now is empirical research to determine whether biobank operators and stakeholders are in fact experiencing the issues identified, and whether other obstacles exist that have not been mentioned in the literature. Biobanks have not yet fulfilled their potential, and

overcoming obstacles to their efficient operation is essential.^{55,56} The consolidation of this list of issues is the first step needed to studying existing problems, and ultimately to find solutions.

References

1. Cambon-Thomsen, A. The social and ethical issues of post-genomic human biobanks. *Nat Rev Genet* 5, 866-73 (2004).
2. Day, J.G. & Stacey, G.N. Biobanking. *Mol Biotechnol* 40, 202-13 (2008).
3. Gatter, K. Biobanks as a Tissue and Information Semi-Commons: Balancing Interests for Personalized Medicine, Tissue Donors and the Public Health. (2012).
4. Finkelstein, S.N., Sinsky, A.J. & Cooper, S.N. Biobanks: Will They Help Promote the Genomics Revolution? *Pharmaceutical Discovery* Nov/Dec 2004(2004).
5. Tansey, J. & Burgess, M. The foundations, applications and ethical dimensions of biobanks. *Electronic Working Papers Series*. (2004).
6. Oosterhuis, J.W., Coebergh, J.W. & van Veen, E.B. Tumour banks: well-guarded treasures in the interest of patients. *Nature Reviews Cancer* 3, 73-77 (2003).
7. Riegman, P.H., Morente, M.M., Betsou, F., de Blasio, P. & Geary, P. Biobanking for better healthcare. *Mol Oncol* 2, 213-22 (2008).
8. Park, A. 10 Ideas Changing the World Right Now: Biobanks. *Time Magazine* (2009).
9. Betsou, F. et al. What Are the Biggest Challenges and Opportunities for Biorepositories in the Next Three to Five Years? *Biopreservation and Biobanking* 8(2010).
10. Ballantyne, C. Report urges Europe to combine wealth of biobank data. *Nat Med* 14, 701 (2008).
11. Yuille, M. et al. Biobanking for Europe. *Brief Bioinform* 9, 14-24 (2008).
12. Asslauer, M. & Zatloukal, K. Biobanks: transnational, European and global networks. *Briefings in Functional Genomics & Proteomics* 6, 193-201 (2007).
13. Pearson, H. Summit calls for clear view of deposits in all biobanks. *Nature* 432, 426 (2004).
14. Caulfield, T. et al. Research ethics recommendations for whole-genome research: consensus statement. *PLoS Biol* 6, e73 (2008).
15. Hagen, H.E. & Carlstedt-Duke, J. Building global networks for human diseases: genes and populations. *Nat Med* 10, 665-7 (2004).
16. Elger, B.S. & Caplan, A.L. Consent and anonymization in research involving biobanks - Differing terms and norms present serious barriers to an international framework. *Embo Reports* 7, 661-666 (2006).
17. Myles, R. et al. Stakeholder research on biospecimen needs and reactions to the development of a national cancer human biobank by the national cancer institute. *Journal of the National Cancer Institute. Monographs* 2011, 16-23 (2011).

18. Hewitt, R.E. Biobanking: the foundation of personalized medicine. *Curr Opin Oncol* 23, 112-9 (2011 B).
19. Lopez-Guerrero, J.A. et al. TuBaFrost 4: access rules and incentives for a European tumour bank. *Eur J Cancer* 42, 2924-9 (2006).
20. Kiehintopf, M. & Krawczak, M. Biobanking and international interoperability: samples. *Hum Genet* (2011).
21. Zika, E. et al. A European survey on biobanks: trends and issues. *Public Health Genomics* 14, 96-103 (2011).
22. Budimir, D. et al. Ethical aspects of human biobanks: a systematic review. *Croat Med J* 52, 262-79 (2011).
23. Watson, P.H. et al. Evolutionary concepts in biobanking - the BC BioLibrary. *J Transl Med* 7, 95 (2009).
24. Eiseman, E., Bloom, G., Brower, J., Clancy, N. & Olmstead, S. Case Studies of Existing Human Tissue Repositories: "Best Practices" for a Biospecimen Resource for the Genomic and Proteomic Era. *RAND Science and Technology* (2003).
25. Harris, J.R. et al. Toward a roadmap in global biobanking for health. *Eur J Hum Genet* 20, 1105-11 (2012).
26. Fortin, S., Pathmasiri, S., Grintuch, R. & Deschenes, M. 'Access arrangements' for biobanks: a fine line between facilitating and hindering collaboration. *Public Health Genomics* 14, 104-14 (2011).
27. Kaye, J. From single biobanks to international networks: developing e-governance. *Hum Genet* (2011).
28. Cambon-Thomsen, A., Rial-Sebbag, E. & Knoppers, B.M. Trends in ethical and legal frameworks for the use of human biobanks. *Eur Respir J* 30, 373-82 (2007).
29. Taylor, P.L. Research sharing, ethics and public benefit. *Nat Biotechnol* 25, 398-401 (2007).
30. Joly, Y. & Knoppers, B.M. Pharmacogenomic data sample collection and storage: ethical issues and policy approaches. *Pharmacogenomics* 7, 219-226 (2006).
31. Kaye, J. Do we need a uniform regulatory system for biobanks across Europe? *European Journal of Human Genetics* 14, 245-248 (2006).
32. van Veen, E.B. et al. TuBaFrost 3: regulatory and ethical issues on the exchange of residual tissue for research across Europe. *Eur J Cancer* 42, 2914-23 (2006).
33. Boggio, A., Biller-Andorno, N., Elger, B., Mauron, A. & Capron, A.M. Comparing guidelines on biobanks: emerging consensus and unresolved controversies. (2005).
34. Hewitt, R. & Hainaut, P. Biobanking in a fast moving world: an international perspective. *J Natl Cancer Inst Monogr* 2011, 50-1 (2011 A).

35. Chokshi, D.A., Parker, M. & Kwiatkowski, D.P. Data sharing and intellectual property in a genomic epidemiology network: policies for large-scale research collaboration. *Bulletin of the World Health Organization* 84, 382-387 (2006).
36. Shickle, D., Griffin, M. & El-Arifi, K. Inter- and intra-biobank networks: classification of biobanks. *Pathobiology* 77, 181-90 (2010).
37. Cambon-Thomsen, A. Assessing the impact of biobanks. *Nat Genet* 34, 25-6 (2003).
38. Gibbons, S.M.C. REGULATING BIOBANKS: A TWELVE-POINT TYPOLOGICAL TOOL. *Medical Law Review* 17, 313-346 (2009).
39. Salvaterra, E. et al. Banking together - A unified model of informed consent for biobanking. *Embo Reports* 9, 307-313 (2008).
40. Stjernschantz Forsberg, J., Hansson, M.G. & Eriksson, S. Biobank research: who benefits from individual consent? *BMJ* 343, d5647 (2011).
41. Steinbekk, K.S. Biobank - When is Re-consent Necessary? *Public Health Ethics* 4, 236 - 250 (2011).
42. Forsberg, J.S., Hansson, M.G. & Eriksson, S. The risks and benefits of re-consent. *Science* 332, 306; author reply 306 (2011).
43. Budin-Ljosne, I., Tasse, A.M., Knoppers, B.M. & Harris, J.R. Bridging consent: from toll bridges to lift bridges? *BMC Med Genomics* 4, 69 (2011).
44. Goebel, J.W. et al. Legal and ethical consequences of international biobanking from a national perspective: the German BMB-EUcoop project. *European Journal of Human Genetics* 18, 522-525 (2010).
45. Morente, M.M. & Alonso, S. Current challenges of human tumour banking. *Hematol Oncol* 23, 54-6 (2005).
46. Shaw, P.M. & Patterson, S.D. The value of banked samples for oncology drug discovery and development. *J Natl Cancer Inst Monogr* 2011, 46-9 (2011).
47. Andersson, K. et al. The interface of population-based cancer registries and biobanks in etiological and clinical research--current and future perspectives. *Acta Oncol* 49, 1227-34 (2010).
48. Otto, M. et al. Roadmap and standard operating procedures for biobanking and discovery of neurochemical markers in ALS. *Amyotroph Lateral Scler* 13, 1-10 (2012).
49. Simon, B.M. How to get a fair share: IP policies for publicly supported biobanks. *Stanford Journal of Law, Science & Policy* 1(2009).
50. Hansson, M.G., Dillner, J., Bartram, C.R., Carlson, J.A. & Helgesson, G. Should donors be allowed to give broad consent to future biobank research? *Lancet Oncol* 7, 266-9 (2006).
51. Tomlinson, T. Respecting donors to biobank research. *Hastings Cent Rep* 43, 41-7 (2013).

52. Steinsbekk, K.S., Kare Myskja, B. & Solberg, B. Broad consent versus dynamic consent in biobank research: Is passive participation an ethical problem? *Eur J Hum Genet* (2013).
53. Kaye, J., Heeney, C., Hawkins, N., de Vries, J. & Boddington, P. Data sharing in genomics--reshaping scientific practice. *Nat Rev Genet* 10, 331-5 (2009).
54. Knoppers, B.M. et al. Towards a data sharing Code of Conduct for international genomic research. *Genome Med* 3, 46 (2011).
55. Baust, J.G. A Crisis in Biobanking. *Cell Preservation Technology* 3(2005).
56. Scott, C.T., Caulfield, T., Borgelt, E. & Illes, J. Personal medicine-the new banking crisis. *Nature Biotechnology* 30, 141-147 (2012).

2.2 IMPOSSIBLE, IMPRACTICAL, AND NON-IDENTIFIABLE? NEW CRITERIA REGARDING CONSENT FOR HUMAN TISSUE RESEARCH IN THE DECLARATION OF HELSINKI

Flora Colledge, Bernice Elger

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Abstract

The 2008 revision of the Declaration of Helsinki includes a new paragraph dealing specifically with the standards of informed consent required for research involving identifiable human tissue samples and/or data. In cases where obtaining consent would be impossible or unduly burdensome, researchers may now proceed without it, following approval of the project by an ethics committee. This is a significant development in the Declaration, yet so far it has received little attention. We examine the implications of paragraph 25, and assess its role in the debates on proper sample handling. In particular, we question whether the use of the term “identifiable” weakens the paragraph, as its meaning depends on national context. Relying on this term to designate samples which could be traced to the donor, and therefore carries risk for that donor, is impossible if its meaning is not universally accepted. The Declaration of Helsinki is now entering a new revision phase. In order to protect sample donors, paragraph 25 should be enhanced, and the remit of the Declaration strengthened, by a more precise description of which samples and data count as identifiable.

Introduction

The Declaration of Helsinki, developed in 1964 by the World Medical Association (WMA), is the core set of ethical principles governing biomedical research. It provides concise guidance to medical practitioners and researchers on all aspects of research involving humans, identifiable human biological material and/or data. At the heart of the document is the requirement to inform potential subjects about proposed research, and obtain their consent before it is carried out. This reflects the roots of the Declaration in the ten principles of the Nuremberg Code, a reaction to the horrific human experiments carried out during the Second World War.^{1,2} Since its creation the document has been revised six times: the WMA states explicitly that the current version is the only valid and applicable one. Furthermore, in the 2000 revision, the document declared its own primacy over other national and international guidelines and laws, stating that these must not directly contradict the Declaration’s broad provisions.³ While the Declaration of Helsinki is not legally binding, its Article 14 states that researchers should make clear in their study protocols how they adhere to its principles. The document is also a cornerstone of ethical guidance for physicians globally, which many national medical associations and ethics committees turn to when developing their own guidelines and laws.^{4,5}

A defining feature of the Declaration is its brevity.⁶ Designed to be readable within fifteen minutes, each paragraph is as concise as possible, with no word used unnecessarily. It is therefore especially noteworthy that in the revision of 2008, an entire new paragraph was dedicated to the issue of obtaining consent for research involving human samples and data. However, despite the Declaration's central role in the field of bioethics, this revision has received comparatively little mention in the literature. Fewer than 25 articles discuss the 2008 changes in detail, and of these, few go further than mentioning that a new paragraph is in place, while none offer any detailed analysis of the change itself, or the reasons for it. Indeed, in his account of the revision process leading to the 2008 version, Kuroyanagi only mentions that the new paragraph "ratifies our reality", as human tissue research is becoming increasingly common.⁷ This is particularly striking as the changes regarding placebo-controlled trials, implemented in the 2000 revision, have received extensive attention and commentary.^{8,9}

It is essential not only to draw attention to the significance of paragraph 25, but also to foster dialogue on the reasons for its creation, and on potential revisions to its wording. We aim to fill the gap in the literature regarding revisions to the Declaration. Our paper situates the paragraph in the debates surrounding human sample use, and explores the wording and its implications for sample research. We conclude that improvements could be made to the paragraph in order to strengthen its protection of human research subjects, and to solidify the Declaration's role as the international standard in bioethics.

A new paragraph

All previous versions of the Declaration included human samples and data in the general provisions governing research on human beings. This is made explicit in paragraph 1:

"The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data."

Up until 2000, all human subject research had to satisfy the requirement of paragraph 22, that "the subject should be informed..." and that "the physician should then obtain the subject's freely-given informed consent". In the 2008 version, although all relevant principles still apply to research involving human data and tissue, projects which use only these have been accorded their own paragraph. The new paragraph 25 states that:

"For medical research using identifiable human material or data, physicians must normally seek consent for the collection, analysis, storage and/or reuse. There may be situations where consent would be impossible or impractical to obtain for such research or would pose a threat to the validity of the research. In such situations the research may be done only after consideration and approval of a research ethics committee."

As noted above, research which makes use exclusively of human tissue and data is rapidly proliferating, and recognition that this research requires different regulation is necessary and timely.¹⁰ The paragraph is a reflection of, and reaction to, current debates in the literature on how to handle tissue samples.¹¹⁻¹⁵ It covers the issues of informed vs. broad consent, the waiving of the need for any form of consent, and the identifiability of samples. These topics are new to the Declaration, but also fairly new in the field of biomedical ethics. Below, we address each issue in turn, explaining

the discussions which surround them, the Declaration's approach, and the implications of its current wording.

The role of "consent"

Paragraph 25 represents a small revolution in the spirit of the Declaration. Previously, its key feature was the absolute need for informed consent from competent adults.¹⁶ Now this requirement can, in some cases, be waived. Waivers of consent are not unheard of in human sample research. The American Society of Human Genetics (ASHG) guidelines of 1996 state that the requirement for informed consent may be waived in certain (unspecified) circumstances,¹⁷ as do the US National Bioethics Advisory Commission guidelines on human subject research.¹⁸ Introducing waivers of consent in the Declaration of Helsinki, however, is a significant step motivated by the rapid expansion of biobanking, and the resulting increased focus on the use of human tissue. A large body of literature exists concerning the difficulties in obtaining informed consent for samples taken years ago, or for routine diagnostic purposes, and the limitations that traditional consent requirements place on researchers.¹⁹⁻²² In addition, the paradox of obtaining informed consent for as yet unplanned research has also motivated suggestions that a move towards less strict consent forms may be necessary for tissue samples.²³ Including the potential for waivers in the Declaration is a response to the need for new ways of dealing with tissue samples.

It is crucial to note that the wording of paragraph 25 calls for "consent", as opposed to "informed consent". This leaves open the possibility of obtaining broad consent at the time of tissue collection, whereby donors agree to any type of research being performed on their samples in the future. Broad consent has been praised for facilitating future sample research while still honoring patient autonomy, and criticized for paying only lip service to the consent process, as no real information is provided to donors.²⁴ Interestingly, the ASHG guidelines explicitly reject "blanket consent" as a viable option, implying that a waiver is preferable to this type of consent. That the Declaration allows for the possibility of seeking broad consent, as well as for waivers, is a strong endorsement of these approaches.

Justifying waivers

The wording of the Declaration concerning the conditions under which waivers are justified is the key element in paragraph 25 and requires careful analysis. The question remains as to how much openness of interpretation is explicitly part of the wording and how narrow definitions should be in order to prohibit certain types of misinterpretation of the paragraph. Three terms are used to provide conditions for a waiver of consent. These are "impossible", "impractical", and "threat to validity". Interpreting and applying these conditions involves a risk-benefit analysis on the part of ethics committees.

In a foreseeable "worst-case scenario", a committee may determine that seeking consent for the use of a sample is indeed impractical (perhaps due to high financial cost, or based on previous attempts at contacting donors), and approve the study, while fully competent donors continues with their life, unaware that their samples are being used in research that he may be fully opposed to. Errors by the committee in assessing risk, or widely differing national standards, are also potential undesirable outcomes. This is particularly true if "impracticality" is assessed as a balancing of inconvenience or costs to the researcher and perceived risks of the study. For example, potentially time-consuming or expensive attempts to re-contact previous donors for new consent will seem more impractical, given

presumed low risks of harm to these donors. By contrast, equally effort-intensive measures would be deemed obligatory in more traditional human subject research. In spite of this, we agree that the balancing of risks and benefits should lie in the hands of research ethics committees (RECs), as this permits adaptation to different cultural and domestic contexts. Discretion concerning the lengths which researchers must go to before the need for consent is waived is an appropriate part of these committees' work,²⁵ and is already standard practice in applying the United States' Common Rule, and the HIPAA Privacy Rule.²⁶

However, the scope of the Declaration itself is not a matter of context-specific application. It is intended to govern all human subject research, and therefore employs a number of terms which are not left for RECs to interpret, but which specify the aims of particular principles. In paragraph 25, this term is "identifiable". Although it is used to describe the type of samples which require REC approval, the term's use in different countries means that currently, the Declaration is not universally applicable, a problem we discuss in the following section.

Identifiability

Paragraphs 1 and 25 state that only "identifiable human material and data" are covered by the principles. This excludes anonymous and irreversibly anonymised samples, where any link to the donor has been lost or destroyed. Identifiability of samples is of key concern, as it is the principal risk factor in human material research, much as physical harms are the main risks in traditional human subject research.²⁷ If a donor's sample can be identified, this can have serious consequences: stigmatization of individuals or groups, problems obtaining health insurance, and the loss of the "right not to know" are all potential outcomes of a sample being linked to the donor.²⁸ It is therefore important that in cases where the donor could be identified, every care is taken to ensure that this does not occur. This becomes increasingly important as large-scale, multi-center projects proliferate, samples are transferred away from the sites of the initial collection, and donors are more difficult to contact regarding the use of their tissue.²³

The most serious concern with the current wording of paragraph 25 is its reliance on the term "identifiable" to describe which samples must be accompanied by traditional consent, and/or ethics committee approval. Identifiability is ambiguous not because the term is inherently vague, but because it is used differently in different countries. Formerly in the United States and in Europe, samples were said to be "identifiable" if they were anonymized, coded, but could be potentially be traced back to the donor. However, in 2004 the United States' Office for Human Research Protections (OHRP) amended their guidelines to include a new definition of the term. Samples which are coded and anonymized are no longer held to be "identifiable" providing there is some impediment, either legal or imposed by an ethics committee, to the researchers accessing the codes which would lead to identification of the donor. Samples are defined as unidentifiable because of a procedural barrier, not the absence of a link to identifying data.²⁹ The use of these samples is therefore not considered human subject research, and so falls outside the remit of the US Common Rule, its federal policy governing such research (which as noted above, also permits waivers of consent in some cases). In practice, much of the sample research in the United States does not make use of tissue categorized as "identifiable" according to the 2004 OHRP statement, and consequently does not fall under the jurisdiction of the Declaration of Helsinki, despite the fact that identical studies, if carried out in Europe, would do so. This approach has been criticized for providing insufficient protection to donors, as, particularly in the case of whole genome research, DNA samples

can be identified despite the lack of accompanying clinical data³⁰ (so long as the individual's unique sequence subset or single nucleotide polymorphism data are known.)^{31,32} Communities, such as social or ethnic groups, are also at risk of stigmatization if identified; indeed, paragraph 17 of the Declaration specifically calls for the protection of community groups in research.³³

It is unclear in what sense "identifiable" is used in the Declaration of Helsinki. While it may have been in the minds of the drafters of paragraph 25 to allow some flexibility in the interpretation of "impractical" circumstances, the term "identifiable" must be precise and specific, in order that researchers and RECs are certain about what sort of material the Declaration refers to.

The Declaration is, among other things, a force for harmonization: its principles are intended to be universally acceptable, and numerous previous revisions have been undertaken to minimize confusion about its applicability. Having asserted its own primacy, the Declaration must continue to live up to its role as core text on research ethics and set high standards for researchers and review boards where this is needed. While an organization may choose to ignore its guidance, as the USA's Food and Drug Administration has recently done,^{7,34} it should not be easy for researchers to dodge requirements for ethical conduct by redefining the limits they are bound by.

The importance of identifiability in this paragraph should not be underestimated: this term is crucial in providing protection for the donors of the tissue. For this reason, a precise definition of "identifiable" is an essential and valuable addition to paragraph 25.

Conclusions

The Declaration of Helsinki remains the most cited document on international guidance in research ethics. Its two main aims are the protection of research participants and harmonization of research ethics worldwide. These two goals can only be fulfilled if a balance is struck between allowing RECs to incorporate some variations based on local context and culture in applying the Declaration,³⁵ yet not detracting from the universal nature of the underlying principles that are crucial to the protection of research participants, and are not open to negotiation.. The field of human sample research exemplifies both values: donors must be protected from possible misuse of their samples and data, while simultaneously international collaboration must be facilitated to enable efficient research. Sample research is both growing and evolving rapidly, and at present highly prescriptive regulations are not appropriate measures. Paragraph 25 is a well-judged approach to the issue, requiring ethical oversight in sample research, while allowing local committees some flexibility in their decisions. However, the variations in the meanings attributed to the term "identifiable" results in this paragraph lacking a clear meaning that can be universally applied.

In our view, paragraph 25 should be enhanced, and the remit of the Declaration strengthened, by a more precise description of which samples and data count as identifiable. This change would have the dual effect of reinforcing more clearly the protection of research subjects and supporting the harmonization of international nomenclature and research ethics guidance. Human tissue and data research is becoming increasingly transnational, and the Declaration of Helsinki must respond to this fact.

References:

1. Puri KS, Suresh KR, Gogtay NJ, Thatte UM. Declaration of Helsinki, 2008: implications for stakeholders in research. *Journal of postgraduate medicine*. 2009; 55(2): 131-4.

2. Declaration of Helsinki--nothing to declare? *Lancet*. 1999; 353(9161): 1285.
3. Rid A, Schmidt H. The 2008 Declaration of Helsinki — First among Equals in Research Ethics? *The Journal of Law, Medicine & Ethics*. 2010; 38(1): 143-8.
4. Eckenwiler LA, Ells C, Feinholz D, Schonfeld T. Hopes for Helsinki: reconsidering "vulnerability". *J Med Ethics*. 2008; 34(10): 765-6.
5. Goodyear MD, Krleza-Jeric K, Lemmens T. The Declaration of Helsinki. *BMJ*. 2007; 335(7621): 624-5.
6. Carlson RV, Boyd KM, Webb DJ. The revision of the Declaration of Helsinki: past, present and future. *British journal of clinical pharmacology*. 2004; 57(6): 695-713.
7. Kuroyanagi T. On the 2008 Revisions to the WMA Declaration of Helsinki. *Japan Medical Association Journal*. 2009; 52 (5): 293 -318.
8. Forster HP, Emanuel E, Grady C. The 2000 revision of the Declaration of Helsinki: a step forward or more confusion? *Lancet*. 2001; 358(9291): 1449-53.
9. Vastag B. Helsinki discord? A controversial declaration. *JAMA : the journal of the American Medical Association*. 2000; 284(23): 2983-5.
10. Riis P. Perspectives on the Fifth Revision of the Declaration of Helsinki. *JAMA : the journal of the American Medical Association*. 2000; 284(23): 3045-6.
11. Mueller MR, Instone S. Beyond the informed consent procedure: continuing consent in human research. *Ciencia & saude coletiva*. 2008; 13(2): 381-9.
12. Steinbekk KS. Biobank - When is Re-consent Necessary? *Public Health Ethics*. 2011; 4((3)): 236 - 50.
13. Ludman EJ, Fullerton SM, Spangler L, Trinidad SB, Fujii MM, Jarvik GP, et al. Glad you asked: participants' opinions of re-consent for dbGap data submission. *Journal of empirical research on human research ethics : JERHRE*. 2010; 5(3): 9-16.
14. Forsberg JS, Hansson MG, Eriksson S. The risks and benefits of re-consent. *Science*. 2011; 332(6027): 306; author reply
15. Trinidad SB, Fullerton SM, Ludman EJ, Jarvik GP, Larson EB, Burke W. The Risks and Benefits of Re-Consent Response. *Science*. 2011; 332(6027): 306-.
16. Resnik DB. Re-consenting human subjects: ethical, legal and practical issues. *Journal of Medical Ethics*. 2009; 35(11): 656-7.
17. American Society of Human Genetics. Statement on Informed Consent for Genetic Research. *Am J Hum Genet*. 1996; 59: 471-4.
18. National Bioethics Advisory Commission. Ethical and Policy Issues in Research Involving Human Participants. Bethesda, Maryland; 2001.
19. Gaskell G, Gottweis H. Biobanks need publicity. *Nature*. 2011; 471(7337): 159-60.

20. Hoeyer K. Donors perceptions of consent to and feedback from biobank research: time to acknowledge diversity? *Public Health Genomics*. 2010; 13(6): 345-52.
21. Salvaterra E, Lecchi L, Giovanelli S, Butti B, Bardella MT, Bertazzi PA, et al. Banking together - A unified model of informed consent for biobanking. *Embo Reports*. 2008; 9(4): 307-13.
22. Lunshof JE, Chadwick R, Vorhaus DB, Church GM. Science and society - From genetic privacy to open consent. *Nature Reviews Genetics*. 2008; 9(5): 406-11.
23. Cambon-Thomsen A. The social and ethical issues of post-genomic human biobanks. *Nat Rev Genet*. 2004; 5(11): 866-73.
24. Hansson MG. The need to downregulate: a minimal ethical framework for biobank research. *Methods Mol Biol*. 2011; 675: 39-59.
25. Dal-Re R, Avendano C, Gil-Aguado A, Gracia D, Caplan AL. When should re-consent of subjects participating in a clinical trial be requested? A case-oriented algorithm to assist in the decision-making process. *Clinical pharmacology and therapeutics*. 2008; 83(5): 788-93.
26. Clayton EW. Informed consent and biobanks. *J Law Med Ethics*. 2005; 33(1): 15-21.
27. Malin B, Loukides G, Benitez K, Clayton EW. Identifiability in biobanks: models, measures, and mitigation strategies. *Hum Genet*. 2011; 130(3): 383-92.
28. Lowrance WW, Collins FS. Ethics. Identifiability in genomic research. *Science*. 2007; 317(5838): 600-2.
29. Elger BS, Caplan AL. Consent and anonymization in research involving biobanks - Differing terms and norms present serious barriers to an international framework. *Embo Reports*. 2006; 7(7): 661-6.
30. McGuire AL. Identifiability of DNA data: the need for consistent federal policy. *Am J Bioeth*. 2008; 8(10): 75-6.
31. Rodriguez LL, Brooks LD, Greenberg JH, Green ED. Research ethics. The complexities of genomic identifiability. *Science*. 2013; 339(6117): 275-6.
32. Lin Z, Owen AB, Altman RB. Genetics. Genomic research and human subject privacy. *Science*. 2004; 305(5681): 183.
33. de Vries J, Jallow M, Williams TN, Kwiatkowski D, Parker M, Fitzpatrick R. Investigating the potential for ethnic group harm in collaborative genomics research in Africa: is ethnic stigmatisation likely? *Social science & medicine (1982)*. 2012; 75(8): 1400-7.
34. Wolinsky H. The battle of Helsinki: two troublesome paragraphs in the Declaration of Helsinki are causing a furore over medical research ethics. *EMBO Rep*. 2006; 7(7): 670-2.
35. Singer PA, Benatar SR. Beyond Helsinki: a vision for global health ethics. *BMJ*. 2001; 322(7289): 747-8.

2.3 CONSENT REQUIREMENTS FOR RESEARCH WITH HUMAN TISSUE: SWISS ETHICS COMMITTEE MEMBERS DISAGREE

Flora Colledge, Sophie de Massoungnes, Bernice Elger

Abstract

Questions: In Switzerland, research with identifiable human tissue samples, and/or its accompanying data, must be approved by a research ethics committee (REC) before it can be allowed to take place. However, as the demand for such tissue has rapidly increased in recent years, and biobanks have been created to meet these needs, committees have had to deal with a growing number of such demands. Detailed instructions for evaluating every kind of tissue request are scarce. Committees charged with evaluating research protocols therefore sometimes face uncertainty in their decision-making.

Methods: We examine how a pool of Swiss REC members deal with a number of cases involving human tissue, in order to determine the standards they adhere to, and their understanding and implementation of existing laws and guidelines.

Results: There is considerable divergence in the approaches and decisions of Swiss REC members regarding human tissue sample requests, particularly concerning the issue of informed consent. Despite recent trends towards less strict consent requirements for biosample research, many of our respondents continue to employ demanding standards for researchers. Furthermore, the disagreement between different committees, and in some cases, members of the same committee, may have a negative impact upon the assessment of research protocols.

Conclusions: Our data suggests that there is uncertainty and disagreement on some matters, which should be addressed as far as possible in order to ensure efficient and harmonious review of research protocols.

Introduction:

Research involving human tissue, with or without accompanying clinical data, is currently regulated in Switzerland by a number of sources. The most specific is the new Law on Research on Human Subjects (Humanforschungsgesetz), which addresses tissue samples in Articles 32 to 35¹, but is not yet in force. The Swiss Academy of Medical Sciences (SAMS) has developed a full set of guidelines outlining best practices for biobanks, and these also offer some guidance on work with tissue samples². Elsewhere, the Federal Law on Pharmaceuticals and Medical Products³, and the various cantonal laws, also apply to some aspects of such research.

While the SAMS and existing European guidelines^{2,4,5} and domestic law provide some important information for researchers, and the ethics committee members who must regulate this research, the rapidly evolving nature of the field, coupled with the increase in demand for tissue samples, means that there are still unclear issues arising⁶. How exactly should the degree of anonymisation of the samples affect the ethical review process⁷? What sort of consent form must be obtained for human tissue samples⁸⁻¹³? Should results be returned to donors, particularly if a potentially

dangerous diagnosis is uncovered¹⁴? These matters are still widely debated in the literature, yet they are crucial for research ethics committees (RECs) in their assessment of research protocols.

Studies assessing the decision criteria of RECs are scarce¹⁵ and do not specifically address research involving biological samples. Our study is an initial assessment of the approaches of Swiss REC members to research protocols involving informed consent to human tissue sample use. We aim to discover how the committees and their members respond to such requests, whether responses differ between committees and their members, and some of the reasons for their approval or rejection of various parts of the study protocol. By understanding the ways in which decisions are made, and what areas produce uncertainty, it is possible to uncover issues which may require more discussion and clarification for REC members and researchers. The aim of our study was not to obtain statistically representative results, but to explore broadly which issues are the most controversial and why. We therefore adopted a qualitative approach, asking participants to provide comments, in order to understand the reasoning behind the decisions of the committee members. The study is also a didactic means to encourage further discussion of the addressed issues, and the results were presented at the SAKK State of the Art Symposium in November 2011.

Methods:

After discussions with a number of Swiss ethical and legal experts and researchers involved in biobanking, a questionnaire was created based upon three case study examples, with several questions following. Responses were given using a Likert scale (certainly agree, probably agree etc. to certainly disagree)¹⁶, and we asked participants to provide comments after each question explaining the reasons for their responses. The case studies were designed to prompt responses on the committees' approach to proposed research using human data and tissue.

Questionnaires were sent to the presidents of all working RECs in the French speaking parts of Switzerland. While the cantons of Valais and Vaud have one cantonal commission with or without subjections, Geneva was at the time of the study composed of 4 research ethics (sub)committees supervised by one central commission at the University Hospitals of Geneva, and we included all 4 subcommittees. At the time of the study, the joint commission of the cantons Neuchatel, Fribourg and Jura was under reconstruction and not available and was therefore not included. Committee presidents were informed about the study in writing, and at a meeting of the Arbeitsgemeinschaft der Ethikkommissionen (AGEK), the Swiss umbrella organization of all RECs. One phone call and one follow up email were used as reminders. Ethical approval for this study was not required due to the nature of the research (non-invasive with a non-vulnerable population.)

Three case study questions were used to introduce the issues to participants. The first concerns (1) a request for tissue sample without accompanying data. The second (2) concerns a request for tissue with accompanying data. The third (3) deals with the drafting of a biobank's consent form. Completed questionnaires were analysed by all authors. Responses were grouped according to Likert scale levels, and comments were analysed and categorized by theme.

Results:

Overall, we received a total of 31 completed questionnaires: 22 members of committees from Geneva, 6 from Vaud, and 2 from Valais responded. One commission president opted to discuss the questionnaire during a committee meeting and to provide one single response for the entire REC,

while in the other committees, participants answered the questionnaire individually and anonymously.

We include some totals representing the results of the Likert scale questions not to make representative quantitative conclusions, but in order to indicate which issues were particularly controversial among respondents. In what follows, we present these results in particular to discuss the corresponding commentaries that elucidate reasons explaining the controversies.

Box 1: request for tissue sample without accompanying data.

Case 1

A researcher working in the gynecological department of a university hospital is undertaking a study on the efficacy of chemotherapy on breast cancer. He/she has noticed that in some cases chemotherapy is very successful, while in other cases it seems to have no effect on the tumor, and maybe be nothing but dangerous for the patient due to its side effects.

He/she wishes to carry out a comparative study between cases responding well to treatment and cases showing no response, in order to potentially identify markers for tumor response to chemotherapy.

He/she contacts the head of the pathology institute explains the project, and asks for 50 samples of anonymised mammary carcinoma, 25 of which responded successfully to treatment, 25 of which did not. To ensure that the samples are comparable, he/she asks the pathologist to provide tissue At the same TNM stage. For this study, the researcher does not require the patients' medical records or information.

Case 1: Must a request for tissue for research purposes without accompanying data be approved by the entire REC? (see appendix: case 1)

The great majority of respondents replied that, according to the recommendations followed by their committee, such a request would need to be approved by the committee as a whole, not fast-tracked (i.e. decided by the president only). Respondents mentioned that the president alone was not the appropriate judge of such requests, and that the study protocol still had to be carefully verified.

Would you approve the project if the sample were irreversibly anonymised?

A total of 21 out of 31 participants responded in favor of this proposition, with only four strongly opposing it. Respondents were also asked whether the patient's consent would be required in such a case. Twelve respondents stated that consent would be necessary, 16 that it would not be necessary, while the rest were undecided. Of those who felt that consent was not necessary, the decisive factor was the lack of risk to the patient: "No risk of misuse"; "No benefit or risk to donor"; "Unnecessary and costly administrative procedure". Those who said that consent ought to be obtained felt that "regardless of study type, the patient must be informed", and that "a biopsy is the patient's property".

Would you approve the project if the samples were reversibly anonymised (i.e. identifiable via a code)?

Elaborating on the previous question, participants were asked whether the degree of anonymisation was the decisive factor in their approval of a project. In this case, 22 out of 31 respondents wrote they would still approve the project, although notably, more chose the “probably” option than in the previous question.

Box 2: request for tissue with accompanying data.

Case 2

A colleague of the previous researcher is also interested in factors related to breast cancer. He/she hypothesizes that certain tumours discovered during mammograms are stable, and, if left untreated, they would only rarely evolve into invasive carcinomas. In line with current treatment protocols, all suspected tumors are biopsied, and he/she would like to carry out a study on the possible difference between tumors in terms of malignancy.

He/she contacts the pathologist, tells him about the project, and asks for 100 samples of breast tumor, diagnosed in the last 5 years. He/she also asks for access to the medical records in order to obtain information about the samples, such as the size of the tumor five years ago, the development of the case (recurrence, new tumor, death), the patient’s age, if signs for other cancers are present, and family history.

The researcher also thinks that if he/she discovers predictors for malignancy, indicating, for example, risks of recurrence, it would be best to inform the patient. With this in mind, he/she asks the pathologist for reversible anonymised samples only, in order that the patient could be identified by the pathologist if necessary.

Case 2: Must a request for tissue for research purposes with accompanying data be approved by the entire REC?

Once again, there was virtual unanimity on the fact that such samples, regardless of the degree of anonymisation, must be approved for use by the entire committee.

Is the consent of the donor necessary for such a tissue request?

A total of 18 respondents stated that consent was required if the tissue was irreversibly anonymised, and 11 felt that it was, at least probably, not necessary. For the use of identifiable samples, 27 said consent would be required, with only two stating that it might not be necessary. When asked to explain their views on both cases, most held that consent was an automatic requirement for sample use. One participant stated: “Quality and results depend on the cooperation of the donor, which is only possible if he has consented”, while another wrote “If the samples are not irreversibly anonymised, the patient must be asked if he wishes to receive results, and potentially, bad news.” However, another respondent felt that “There are situations in which it is preferable that the patient not be contacted.”

Should the discovery of a potentially bad health outcome be shared with the donor?

A total of 23 respondents thought that at least probably, such a discovery should be shared with the donor. Four disagreed, and four were unsure. Many of those who felt that the information should be shared commented on the fact that this must be made clear, and established, at the time of obtaining consent. Those who felt that perhaps the patient should not be contacted cited the possible unreliability of the study, and indeed the patient’s desire. The respondent had apparently

assumed that the patient was aware of this possibility, and therefore agreed, in principle, that results should generally be returned.

Box 3: drafting of a biobank's consent form

Case 3

A surgeon, who is also the head of a laboratory, intends to undertake a project on colorectal cancer, and its development, including initial stages, genetic risk factors, metastatisation, etc. For the project, he/she would like to develop a broad consent form for all patient hospitalized for surgery, in order to build a biobank in collaboration with the pathology institute. He seeks permission from the local ethics committee.

Currently, the surgeon wants to use samples and clinical data for a project on the APC gene, linked to colorectal cancer, and in future, he/she would like to use these samples for unspecified projects. In order to minimize the burden on patients, he/she would like to present them with the following consent form:

“ I consent to my sample(s) and clinical and personal data being stored, so that they may be used for (please tick all that apply):

Any medical research.

Medical research into colorectal cancer.

Research on the APC gene.”

Case 3: Do RECs find a multiple choice consent form acceptable?

A total of 12 out of 31 respondents reported that they were probably or certainly opposed to a multiple choice consent form (see appendix: case 3, highlighted in the box), while 15 would at least probably accept it. An examination of the data reveals that in two separate cases, members of the same REC held diametrically opposing views.

Should the choice permitting the samples to be used in any future medical research appear on the form (broad consent)?

Respondents who opposed this formulation of a broad consent felt that the patient would not be sufficiently informed to make a proper decision. Interestingly, they indicated that a broad consent was practically impossible, not simply undesirable. Among the comments on this proposal were: “Too vague”, “Insufficient information for the patient”, “Prior consent would be required”, and “The protocol must describe the specific goals of the research”. One respondent cited the SAMS guidelines on biobanking stating that Article 4.3 of the guidelines does not permit broad consent (however the respondent apparently had a different understanding of the guidelines, as in fact, the article does allow for a “general” form of consent encompassing unspecified future uses).

Of those in favor of broad consent, only one respondent gave a reason: “Patients in a hospital must expect their samples to be used in future research unless they sign a form refusing this.” On this point, in three separate cases members of the same committee gave diverging responses.

Should the choice permitting the samples to be used for research on colorectal cancer appear on the form?

Respondents in favor of this proposition approved of the fact that it limited the scope of the research to a specific domain, and that it was explicit enough to ensure that the donor would know what he

was agreeing to. One respondent explained “It seems sensible to me that if one goes to the trouble of creating a biobank, one ought to be able to use the samples for any aspect of colorectal cancer research, with the proper REC approval.”

Those who opposed this choice stated, once more, that it was too broad. One respondent felt that it would be sufficient to indicate that the intended research was in the field of genetics. Others felt that this option was still too vague to enable the donor to be properly informed in his consent, though this option seemed to be generally more acceptable than the previous one..

Should the choice permitting the samples to be used for research on the APC gene appear on the form?

Certain respondents again felt that this choice was “vague”, with one stating that “One must always specify the exact details of the research project,” and another stating that even research on a specific gene might have many aspects which the donor would not be aware of.

Others felt that this provision was unduly limiting, as “it would require the researcher to re-contact his patients if he wished to perform further research” and “it’s restrictive: one could discover useful things on colon cancer.” One committee showed that two members held opposing views on this topic.

Discussion

Discussions about criteria for ethics approval of research involving tissue samples have been a feature of literature in a theoretical form for some time. The uniqueness of our study is that we have used real world detailed case examples and solicited the opinions of REC members about whether and under which conditions the projects should be approved. This debate can only be meaningfully advanced if the discussion takes into account real-world situations, and with the stakeholders directly involved in the decision making.

For these reasons, a particularly important finding of our study is that there is considerable divergence in the approaches and decisions of Swiss REC members regarding human tissue sample requests. In some cases, only a few members of certain committees express different viewpoints, or raise questions concerning the examples used. However, on a number of issues, there are significant differences in approach. Some differences may be due to cantonal or institutional regulations, and are a normal part of the operations of the committees. More importantly, our results also demonstrate that members of the same cantonal committee hold opposite views. Divergence might be caused by a lack of knowledge, understanding, or clarity of laws and guidelines and would point to a need for more specific training and clarification from the inter-cantonal REC association (AGEK, Swiss ethics). These being the areas which can and must be improved on in order to allow optimal REC functioning, it is essential to understand their extent. Our findings are an initial indication of areas which require some harmonization efforts.

The most notable finding of our study is that all three case examples, the greatest areas of disagreement concerned informed consent. Below, we discuss the points which produced significant differences, and suggest ways in which this could be minimized.

Questions related to case 1 revealed that a high level of disagreement existed between committee members on whether research involving irreversibly anonymised samples, with no accompanying

clinical data, would require the informed consent of the donor. The SAMS guidelines² state, in section 4.3 that no express consent is required for such research. Irreversibly anonymised samples are widely held to pose virtually no risk to donors when used in research, and it is frequently argued that this lessens the need to obtain fully informed consent^{17,18}. Hence, requests for consent by RECs risk slowing the progress of research^{12,19}.

While at the time of the survey and at present the law on human subject research is not in effect, it is important to note that the parliament approved the final text of the law in September 2011. It stipulates that the law is not applicable for research involving anonymised human biological material (Art 2, alinea 2). It is also worth noting that the World Medical Association (WMA) “has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data”²⁰; only identifiable material is mentioned. The SAMS guidelines emphasise, however, that inappropriate irreversible anonymisation should be avoided: “Both in the interests of the patients and in the interests of research, samples and data should not be irreversibly anonymised, as far as this is possible. For the patient, irreversible anonymisation means that generally he can no longer be informed of relevant results; for research, it means that the samples and the data lose in informative value”²(p.6).

Regarding case 2, the most noteworthy result is that almost two-thirds of respondents are convinced that consent is necessary for samples accompanied by clinical data, regardless of whether or not they were irreversibly anonymised. As above, the SAMS guidelines and the Declaration of Helsinki do not make such a requirement.

When comparing case 1 to case 2 it seems that the existence of accompanying clinical data is a motivating factor in the need for obtaining consent. Whether committee members feel that this increases the risk (which will depend on the richness of the data and the procedure of anonymisation), or that it increases the chance that useful results are found (a realistic possibility, given the views on return of results) is not clear, but responses suggest that members are adhering to guidelines rather than reacting to the sensitivity of the case. This suggests that a number of respondents overestimate the need for consent.

Case 3 gives some of the most detailed explanation of respondents’ decision making, and provides insight into Swiss committees members’ approaches to the divisive field of consent in biobanking. Informed consent procedures typically receive a great deal of focus in ethics review²¹. In Switzerland, informed consent is protected, though not explicitly, by Article 10 of the Swiss constitution²² and Article 28 of the Civil Code²³. As well as being a crucial aspect of every international declaration on health care ethics since the Nuremberg Code, it is defended by Article 1 of the SAMS manual on research on human subjects²⁴. Switzerland therefore operates under a legal and ethical framework which recognizes the primacy of informed consent in medical research.

Of the individual consent options (which could, but must not necessarily, form part of a multiple choice form), a majority of respondents opposed the notion of a broad consent. An even greater majority, however, were in favor of the two more specific options for consent. The more restrictive option (APC gene research) was no more favored than the slightly broader one (colorectal cancer research). Interestingly, respondents who would accept a multiple choice form would in most cases also accept a more broad consent. These options represent a somewhat enlarged approach to consent in comparison to the traditional human subject requirements, so the correlative acceptance of both ideas is perhaps to be expected.

Our results show that only about half of the respondents approve of these more open approaches to consent, demonstrating that this remains controversial among the participating REC members. According to the final version of the coming federal law on human subject research, biological material may be reused in coded or non-coded form if the sample source has consented after having received sufficient information (“nach hinreichender Aufklärung”). The exact definition of how general or detailed the information may be in order to be considered sufficient will remain at the discretion of individual RECs.

Our results indicate that at present REC members prefer to err on the side of restriction as many respondents have chosen to adhere to the traditional form of consent used in clinical trials. However, there seems to be growing agreement that the specifics of the study protocol can affect the level of consent and the details of information deemed necessary. Clearly, the interpretation of the SAMS guidelines should be clarified in further training for REC members. Indeed, the guidelines do not prohibit broad consent, as one respondent claimed, but might require more specific consent, if the primary investigator is aware of his planned research and reuse of the samples before he takes the samples. Here again, if the sample is part of a tissue extraction undertaken for treatment purposes, the need for specific consent may not arise (for a full discussion of the intricacies and different scenarios which can occur, see Junod and Elger, (2010)¹).

Finally, it should be noted that in case 3, on a number of occasions, members of a single ethics committee give different responses as to how their committee operates. This represents a noteworthy lack of agreement about the very policies and practices of the committee. If not all members of one committee agree about how protocol review should be handled, transparent criteria need to be used to resolve the inconsistencies. Our study highlights the need for committees to work closely, and together with committees from other cantons, in order to ensure a well-argued and transparent level of ethical review.

Limitations:

Our study has several limitations. We have included only RECs from one language region in Switzerland. Due to the higher number of REC members in the subcommittees in Geneva, the opinions of REC members in this canton are overrepresented. On the other hand, this represents to some extent the charge of protocols: RECs in cantons with university hospitals treat a much higher number of protocols than RECs in cantons without a university hospital. Furthermore, our aim has not been to present a quantitative overview about opinions in Switzerland but to explore agreement and disagreement as well as the reasons for it among REC members of the same committees and across some other cantons. The research design, including the qualitative analysis of the comments, has enabled us to show significant controversy. Another limitation is the hypothetical nature of the cases. We did not evaluate how RECs would react to real protocols and answers could be influenced by social desirability. However, we ensured strict anonymity of the answers, and given their sometimes controversial tone, we have no indication for a one-sided social desirability bias.

Conclusion:

Disagreement between REC members and different RECs¹⁵ occurs for three main reasons. Different committees may assess risks and benefits using particular paradigms, or may assign different worth to certain values, for example patient autonomy versus public good²¹. This is an integral part of the ethical review process itself, allowing for consideration of local norms and standards, and detailed

analysis of the need for research in that particular time and place. However, as addressed above, disagreement can also be caused by a lack of knowledge or a variable interpretation of relevant laws and guidelines (or indeed, the details of the protocol), or by an absence of such documents. In all of these cases, decisions are influenced by inappropriate external factors, hence differences of this kind should be minimized as far as possible. However, it is important to bear in mind that guidelines and laws as well as their interpretation may change over time, and are also sometimes left deliberately vague. Legislators may have purposely left certain parts of the law open to interpretation to allow for a degree of variation and adaptation to local culture or circumstances. The lack of specificity may, however, have the secondary effect of leaving committee members with insufficient guidance¹⁵.

Our results indicate that there are some differences in the decisions made by Swiss ethics committees which cannot be explained simply by regional differences. Particularly important are the approaches to requiring informed consent for unidentifiable samples, and the various views on the level of consent necessary when tissue samples are obtained. We have suggested that this may be a result of the fact that traditional paradigms of informed consent are giving way to more relaxed recommendations in the case of tissue samples, and that certain ethics committees have yet to “catch up” with these changes.

It is essential that ethics committees in Switzerland are fully aware of the laws which will affect their assessment of study protocols, and that all members of the committee are kept up to date with new developments. A Switzerland-wide training and information programme for committee members would be one way of working towards this²⁵. Consultation with committees on the optimum way to transmit such information would also be a useful step. It has also been suggested that ethics committees could create sub-groups with specialisms in certain types of study¹⁵.

As samples of human biological material become increasingly widely used in research, the traditionally strict requirements for informed consent are becoming more flexible, reflecting the potential benefits of such research, and the minimization of physical risk to human donors. Switzerland’s new law on human subject research and recent changes to the Helsinki Declaration²⁶ reflects this trend. At present, there is a division in Swiss ethics committees on a number of issues concerning the use of human biosamples. While this division perhaps is to be expected at a time when regulations are changing, differing standards within RECs and between cantons are undesirable. They may be confusing to researchers, hamper prospective studies, and even contravene accepted guidelines. In addition, certain cantons may develop a reputation as being “easy to please”, while others will be avoided for their strict regulations, with potentially disruptive effects in scientific research in Switzerland. Our results show that discrepancies do exist across all participants, i.e. between cantons as well as within committees. Education and further training of researchers and committee members on ethical and legal issues surrounding research involving biobanks would be helpful to clarify uncertainties and to support timely and harmonized research review.

References:

1. Bundesgesetz über die Forschung am Menschen (Humanforschungsgesetz, HFG). 2011.

2. SAMS, Swiss Academy of Medical Sciences. Directive on Biobanks, Obtainment, preservation and utilisation of human biological material: <http://www.samw.ch/de/Ethik/Richtlinien/Aktuell-gueltige-Richtlinien.html> (accessed March 23, 2010)2006, Basel: SAMS.
3. Federal Law on Pharmaceuticals and Medical Products (Law on Medical Products, LPT). 2000.
4. COE Council of Europe. Rec(2006)4 of the Committee of Ministers to member states on research on biological materials of human origin: <https://wcd.coe.int/ViewDoc.jsp?id=977859> (accessed July 30, 2009). 2006.
5. OECD, Guidelines on Human Biobanks and Genetic Research Databases: http://www.oecd.org/document/12/0,3343,en_2649_34537_40302092_1_1_1_1,00&&en-USS_01DBC.html (accessed July 30, 2010)2009, Paris: OECD.
6. Beier, The Ethical and Legal Regulation of Human Tissue and Biobank Research in Europe: Proceedings of the Tiss.EU Project, K. Beier, et al., Editors. 2011.
7. Eriksson, S. and G. Helgesson, Potential harms, anonymization, and the right to withdraw consent to biobank research. *Eur J Hum Genet*, 2005. 13(9): p. 1071-6.
8. Salvaterra, E., et al., Banking together - A unified model of informed consent for biobanking. *Embo Reports*, 2008. 9(4): p. 307-313.
9. Mueller, M.R. and S. Instone, Beyond the informed consent procedure: continuing consent in human research. *Cien Saude Colet*, 2008. 13(2): p. 381-9.
10. Dal-Re, R., et al., When should re-consent of subjects participating in a clinical trial be requested? A case-oriented algorithm to assist in the decision-making process. *Clin Pharmacol Ther*, 2008. 83(5): p. 788-93.
11. Stjernschantz Forsberg, J., M.G. Hansson, and S. Eriksson, Biobank research: who benefits from individual consent? *BMJ*, 2011. 343: p. d5647.
12. Elger, B.S. and A.L. Caplan, Consent and anonymization in research involving biobanks - Differing terms and norms present serious barriers to an international framework. *Embo Reports*, 2006. 7(7): p. 661-666.
13. Ludman, E.J., et al., Glad you asked: participants' opinions of re-consent for dbGap data submission. *J Empir Res Hum Res Ethics*, 2010. 5(3): p. 9-16.
14. Rothstein, M.A., Expanding the ethical analysis of biobanks. *Journal of Law Medicine & Ethics*, 2005. 33(1): p. 89-+.
15. de Champlain, J. and J. Patenaude, Review of a mock research protocol in functional neuroimaging by Canadian research ethics boards. *J Med Ethics*, 2006. 32(9): p. 530-4.
16. Norman, G., Likert scales, levels of measurement and the "laws" of statistics. *Adv Health Sci Educ Theory Pract*, 2010. 15(5): p. 625-32.
17. Brothers, K.B., Biobanking in pediatrics: the human nonsubjects approach. *Personalized Medicine*, 2011. 8(1): p. 71-79.

18. Malin, B., et al., Identifiability in biobanks: models, measures, and mitigation strategies. *Hum Genet*, 2011. 130(3): p. 383-92.
19. Helgesson, G., In Defense of Broad Consent. *Cambridge Quarterly of Healthcare Ethics*, 2012. 21(1): p. 40-50.
20. WMA World Medical Association. Declaration of Helsinki, 59th WMA General Assembly, Seoul, October 2008. <http://www.wma.net/e/policy/b3.htm> (accessed August 3, 2009). 2008.
21. Martin-Arribas, M.C., I. Rodriguez-Lozano, and J. Arias-Diaz, Ethical review of research protocols: experience of a research ethics committee. *Rev Esp Cardiol (Engl)*, 2012. 65(6): p. 525-9.
22. Article 10, Federal Constitution of the Swiss Confederation of 18 April 1999.
23. Article 28, Swiss Civil Code of 10 December 1907.
24. Swiss Academy of Medical Sciences. *Research with Human Subjects. A manual for general practice*. 2009.
25. Singer, P.A. and S.R. Benatar, Beyond Helsinki: a vision for global health ethics. *BMJ*, 2001. 322(7289): p. 747-8.
26. Colledge, F. and B.S. Elger, Impossible, impractical, and non-identifiable? New criteria regarding consent for human tissue research in the Declaration of Helsinki. . Accepted in March 2013 by *Biopreservation and Biobanking*, 2013.

PART 3: RESULTS OF THE EMPIRICAL RESEARCH

3.1 OBSTACLES TO WIDENING BIOSAMPLE RESEARCH

Flora Colledge, Jakob Passweg, Bernice Elger

Potential barriers to biosample and data sharing risk slowing the development of this field.¹⁻³ Many authors call for increased expansion and collaboration in biobanking and point towards difficulties in the sharing process.^{4,5} A systematic literature review identified numerous obstacles, including in particular the lack of homogeneity in standard operating procedures (SOPs), legal issues, and intellectual property and patent rights.⁶ The review is the first to address the explicitly documented obstacles in the exchange or availability of biosamples and data. However, a number of issues which might typically be seen as central themes in the biobanking process were found to be mentioned only rarely in the literature as explicit barriers. This is somewhat surprising, given the wealth of articles calling for increased sharing and methods to achieve this.

It is therefore essential to gather empirical data on barriers in the biobanking world. This will provide confirmation regarding which of the obstacles identified in the literature exist in practice, their severity and extent, but will further enable the discovery of barriers mentioned sparsely, or not at all. It is possible that issues which receive great attention in the literature do not, or no longer, pose significant difficulties to those working in the field; equally, important issues may well be overlooked. This may be due to a disparity between those who work in biobanking, and those who write about it. It is also possible that some of the identified yet rarely mentioned barriers remain underreported in relation to their extent because they represent socially undesirable points of view, which could damage a researcher's career, should they be attributed to a particular individual. Feelings of "territoriality", a lack of desire to make samples available to others, may not be readily admitted to, and this applies also to reluctance in joining collaborative groups, networks, or working parties. Finally, it must be considered that biobank stakeholders may "not know what they don't know"; in other words, they may feel that their efforts to share samples and collaborate are sufficient, but they lack awareness about relevant networks, collaborative partners and advanced sharing techniques. In order to fully assess these possibilities, targeted empirical research is necessary.

A qualitative study was therefore carried out, in order to validate, contradict and/or supplement the findings from the review, and extend the literature dealing specifically with obstacles to biosamples and data sharing. Data was obtained through interviews with biobank stakeholders currently working in Switzerland. The reasons for employing this method were a) to obtain information on a wide range of themes, some of which might be unanticipated b) an interview setting would allow for a full exploration of the experiences of the interviewee, c) guaranteed anonymity would enable stakeholders to discuss issues which they might refrain from publicly airing, and d) personal meetings

would open the door to meeting other individuals involved in the industry through word-of-mouth recommendations.

Methods

Participants

Participants in this study were biobank stakeholders currently working in Switzerland. In order to obtain a wide pool of experiences, a broad approach was taken to the term “stakeholder”. As many individuals as possible working in connection with a biobank, cohort study, in pathology, oncology or cardiology, or involved in the drafting of Swiss laws and guidelines concerning human biosamples were identified. Identification was made through internet searches and personal contacts. A “snowball effect” was anticipated, whereby interviewees would provide the names of other possible interviewees. The aim was to interview 40 stakeholders. Due to the hypothesized snowball effect, the interview process began before all stakeholders had been identified.

Interview process

Once potential interviewees had been identified, they were sent an email describing the project and inviting them to take part. Attached was a list of sample interview questions. Timing was described and anonymity was assured. If no response was obtained, a follow up email was sent two weeks later. If the second email received no response, candidates were telephoned to request participation. In case of a refusal of a stakeholder we searched for a person closely resembling the category of the previously approached person in terms of function, professional background and type of biobank network.

If participants agreed to the interview, a date and time was set. Participants were offered the option of an interview face-to-face or over the telephone. Participants were also given some discretion over the timing of the interview. Interviews were carried out in English, except in two cases in which participants felt not sufficiently at ease to communicate in English. Hence, one interview was carried out in German and one in French. Participants were assured that the interview material would remain confidential. Interviews were recorded using the open source software Audacity.

The interview process was semi-structured, based on an interview guide developed by the study team. The guide was developed based on information derived from the literature (both the above-mentioned review and general biobanking literature) and the resulting hypotheses concerning the barriers to biobanking.

Results

Among the approached 70 stakeholders 36 individuals working in connection with biobanks in Switzerland agreed to participate (17 in person interviews and 19 phone interviews). Among the non-participants, 25 individuals never answered e-mails or phone calls. The remaining 9 responded but declined, stating in all cases either that they had no time, or that based upon our description of the study, they could not be helpful in answering our questions. In practice, no significant snowball effect occurred, and only one contact with a subsequent interviewee was made based on the information provided during an interview.

Analysis

Each interview was transcribed based on the recording, and anonymised by substituting code numbers for identifiers such as names and places of work. The transcribed interviews were read in full by each member of the research team involved in the development of the manuscripts. Flora Colledge, Heidi Howard and Bernice Elger then carried out a thematic analysis on the documents to identify and group key words, concepts, phrases and attitudes. The main themes were identified and selected for further analysis by Flora Colledge, and these findings were then compared to the themes identified by Heidi Howard and Bernice Elger, to ensure that no issues were overlooked. For each interview, a list of emerging themes was noted. The themes from every interview were then pooled, and the transcripts were read again to identify sub-themes. Subsequently, David Shaw and Kirsten Persson read every transcript to identify all mention of the themes we have addressed previously.^{7,8} Jakob Passweg helped to develop the main themes addressed in the Discussion.

While the foundations laid by the literature review served in developing the interview guide, the coding of the interview transcripts was not focused on the barriers identified in the review. Rather, every mention of any kind of obstacle to biosample sharing, explicit or not, was coded. It was borne in mind that some of the issues identified in the review might appear, but also that new themes would emerge, due to the specific conditions experienced by the interviewees, and due to the dearth of empirical research on barriers included in the review.

Below are the main findings concerning barriers which arise from the qualitative empirical data. These results will be discussed in comparison to the literature review, highlighting new themes or a shift of focus and perceived severity of barriers identified in the interviews.)

Logistics – fragmented views

Standard operating procedures were cited as problematic by a great majority of our respondents. Shipping was variously described as costly, time-consuming, liable to be delayed at border customs controls (in particular, two participants stated that the Italian border control could take several days to clear), and impossible or difficult due to legal restrictions in other nations (China, Russia and the United States were cited as examples). One respondent explained that incorrect boxes of samples occasionally were sent to the laboratory. Regarding the quality of samples themselves, there was no consensus among participants. While some felt that the biosamples they received were of poor quality, due to improper preservation methods or the sample itself being different to what was described (i.e. healthy tissue rather than tumour tissue), these comments were in almost all cases followed by a caveat that the issue is only a minor one. Two individuals also addressed the difficulty of finding, and maintaining, suitable storage facilities (sufficient space for freezers, backup generators in case of power cuts). However, more than half of respondents stated that sample quality was not a problem.

The nomenclature used to describe samples and diagnoses was cited as a hindrance to efficient sample use post-sharing by two respondents, who mentioned that temporal or regional variances could make the subsequent identification of samples challenging.

Six respondents addressed some aspect of the financial side of the biobanking process. A small number stated the obtaining funding to set up a biobank (as part of a larger, cohort study) was extremely difficult, with one respondent emphasizing the fact that biobanks themselves do not always have a foreseeable, concrete research output:

“I mean, the health insurances don’t pay you for biobanking. And then the hospitals don’t pay you for biobanking, so this is always done on, on third parties’ money. And that’s a limiting factor.” (I5)

Obtaining and powering freezers, equipment for taking and preserving samples, and paying the salaries of lab technicians were given as examples of costs which are difficult to cover. However, the majority of respondents did not experience this particular financial issue, and those who did were not working in a hospital or laboratory, but rather for an independent study as part of an academic institution. Regarding compensation, eight respondents stated that they had a cost-recovery system in place for shipping samples, with eight stating that they did not. Three respondents were involved in the pharmaceutical industry, while the rest stated that there was no profit-generating aspect of their biobank. One participant stressed that the difficulty of valuing a biosample, and all the work that had gone into obtaining it, would itself be a barrier to commercializing the sample. Only one respondent stated that they would consider making their samples available, for a fee, to the pharmaceutical industry; numerous other respondents rejected this idea, although two had received grants from the industry. Financial issues were therefore only identified as being problematic or burdensome by a small number of respondents.

Resources – lack of awareness leads to underuse

Sample availability was identified by six respondents as being an obstacle to establishing a large sample collection, with one suggesting that the lack of large medical centers in Switzerland was a contributing factor (see below for more on the issues attributed to Switzerland.) By contrast, five respondents held that sample availability was never a problem, and that indeed there would always be more samples than research projects. As one put it:

“[...] one realizes very quickly that the numbers of biosamples is rarely the limiting factor and it’s mostly the number of high impact proposals that are submitted that may be limited[...].” (I15)

The awareness of the existence of a sample collection was a theme addressed by approximately half of participants, although it must be noted that these comments are indirect. On the one hand, eight individuals stated that their biobank or sample collection was a relatively new establishment, and hence they had rarely or never been contacted by others interested in obtaining samples. On the other hand, a number of participants said they were keen to engage in sample sharing and collaborative research, but were not aware of any establishments with the type of samples they required. Three also commented that a Swiss or international networking facility would be welcome, but that no such thing existed, despite the fact that such organizations are, in fact, operational (see sections on networks and Biobank Suisse, below.) This issue is also particularly striking in light of participants’ comments about personal contacts in the industry (see below).

When asked about their experiences with biobank networks, several participants expressed either skepticism or ignorance. Five reported that they were a member of some form of network designed to put them in contact with other researchers in their field; only one individual reported membership in a “biobanking network” (in this case, the International Society for Biological and Environmental Repositories). Seven stated that they were not a member of any network, with four noting that they only sought collaboration with individuals with whom they had a specific interest in working. Two also expressed skepticism that biobank-specific networks would be successful in uniting researchers in the long term. One respondent specifically stated:

"[...] it might be wrong, but in the past I've seen many large scale things pass by... and then... for me it's important that we do not plan over five years something and then it goes down in the sixth year, but that we are also active and can function. And then I do not see really their long term resources to do such a really large... large scale project." (I5)

However, three individuals reported that they were not aware of any networks, but would potentially be interested in such a system of meeting other potential research collaborators. One spoke of the need for a central banking facility connected to this network, and deplored the fact that "[...] there is nothing like this in Switzerland." (I4) A lack of awareness of networks, not just biobanks, therefore also appears to be at play.

Networking – signs of reluctance

During the course of the interviews, ten respondents mentioned Biobank Suisse when asked about their networking activities. Biobank Suisse operates as a "broker" organization, aimed at linking researchers with samples via a members-only database, whilst also holding annual meetings to address key issues in the field. Three interviewees reported positive experiences with the organization, stating that they had found the meetings and IT support helpful. Seven, however, expressed concerns, stating variously that they had never been contacted despite their involvement in the network; that the database required data which they were unable to provide for confidentiality reasons; or that such a network was an unappealing medium of contact for those working with biosamples. This last issue was addressed particularly well by one respondent, who went on to elaborate on the role of personal contacts in the biobanking field (see next section):

"I am pathologist, and I know how these...how function, how works the research. In pathology. So it's very difficult to give our sample to someone that we don't know. So many of our research activity with other centers, it function for personal, personal connection [...] So if someone, if I receive a mail, please, there is this study, working on colon cancer or breast cancer, and they need such kind of cancer, we are very reluctant to give our samples so. Why? It's much easier if someone say, Hi, I am working on this topic, what do you think, do you have some cases like these, we would like, very happy, we are very happy to embark in such collaboration with you... it's completely different, you see what I mean?" (I29)

Professional contacts play a central role

The role of personal contacts, connections, and at times, friendships, emerged as an extremely significant yet unprecedented theme in the course of this study. When asked how they identified individuals to engage in sample transfer with, twelve stakeholders said that they collaborated with researchers they already knew. Reasons given for this were that researchers' fields were small enough that everyone who could realistically be interested in collaboration was already known to them (through contact during training, and later at conferences and so on.) Seven respondents stated that they would only share samples within a collaboration where the other party was already known to them, and four reported that they would only collaborate in this way if they needed the samples for their own research goals. Personal contact was also cited as a basis for trust, essential in collaboration, and as a motivator for sharing samples. A number of the respondents who stated that personal contacts formed the majority of their collaborations echoed the words of I29, above, reporting that this is "how things are done" in the field, and is therefore the standard route for sharing biosamples.

The other side of the professional contacts coin is the potential difficulties which can arise through a two-party approach. The issue of territoriality was addressed by seven participants. They stated that certain individuals were indeed reluctant to share their samples due to concerns about being “scooped” by other researchers, fear of losing control over the samples, or a desire to garner prestige for oneself or one’s institution. One respondent noted that no research group or biobank would be willing to be the first to make all its samples and/or data available, out of fear that others would not follow suit. However, one respondent stated that territoriality is only an issue in more “common” areas of research: in the cases of specific, population-based studies, the likelihood that any other group would seek to carry out similar research is very low.

Twelve respondents reported that they had a website concerning their biosample collection, while five stated that they did not. Among those who did, the frequency of updates, and general importance of the website, varied significantly. Three individuals mentioned that their website was intended to advertise the fact that their samples were available, and one reported that they had already received requests based on this information. However, the majority rarely updated the information, and did not advertise the extent or type of their sample collection. Two respondents also added that they rarely looked at the websites of other prospective collaboration partners.

Regulatory issues – low concern levels

Legal issues were cited by six stakeholders as posing difficulties to the sharing of samples. While only a small number of participants cited laws in other countries as limiting sharing (addressed in SOPS, above), several made comments concerning the laws in Switzerland; two in fact stated that it was illegal to ship biosamples outside of Switzerland.

Ten individuals reported that they did not currently use a material transfer agreement in their biosample exchanges with others. Nine stated that they did. Those who did not use one reported that trust was sufficient guarantee for them, and that they saw no need to overly formalize the process; this was frequently attributed to the fact that the collaborators were already known to the respondents through prior personal contacts (as described above.)

Intellectual property rights and patenting were addressed only once in our interviews. The respondent in question stated that these considerations would certainly limit the sharing between researchers of genomic data; biosamples themselves were therefore never linked to the question of IP or patents.

Further widely discussed matters – consent and publication credit

The issue of publication credit, or authorship, was addressed in detail by our respondents. The findings regarding the impact of this issue on biobanking are addressed in a separate paper.⁹

Consent was addressed by approximately two-thirds of our respondents, with many addressing the topic thoroughly and identifying unexpected themes which impact upon biobanking in Switzerland. The findings on consent are also addressed elsewhere.⁸

The Swiss perspective

Finally, twelve individuals mentioned issues specifically pertaining to Switzerland as being barriers to wider sample sharing. Three stated that the federal nature of the country, with its 26 cantons,

complicated collaborations as there was a sense of separation between researchers. Three stated that the mentality, or culture, of biosample sharing is not yet well established. Two mentioned that biobanks in this country were being underused due to lack of recognition of their importance. Two individuals also emphasized that the small size of the country makes sharing difficult, as there are not a great variety of individuals working in specific fields. Finally, as already noted above, the lack of a central storage facility, and the lack of large-scale medical centres for recruiting, were also brought up.

Discussion

This data reveals a number of discrepancies with the findings of the literature review on the same topic. Barriers cited frequently in the literature were mentioned less often, or regarded as less severe, by our interviewees. By contrast, certain issues cited rarely in the literature addressing barriers explicitly (although in some cases apparent elsewhere in the literature as implicit barriers) were frequently addressed, or considered significant. Most notably, there was significant divergence amongst the interviewees themselves with respect to the perception and evaluation of various barriers. This is particularly important to note, as it may provide evidence of efficient troubleshooting methods employed in some biobanks which could be more widely adopted. Divergence may also be due to the differing interests of biobanks stakeholders, as discussed below.

The most striking finding of our interviews is the juxtaposition of respondents' views concerning the obtaining of samples. A third of our interviewees reported sharing samples with individuals they had previous professional relationships with as their primary method of sample exchange. Furthermore, a surprising third reported that this was the only way they would consider undertaking sample sharing, with four of these interviewees stating that they would only do so in cases where it was absolutely necessary to further their research. This was also a key reason cited by those who were skeptical of Biobank Suisse and other networks. Seven interviewees reported that territoriality on the part of other researchers had limited their access to samples, which supports the self-reported reluctance of some researchers to make samples freely available. It must also be remembered that two interviewees, as reported in our paper on definitions,⁷ were reluctant to have their samples collections caught up in the regulatory difficulties caused by owning an "official" biobank, a phenomenon recorded in other interviews with biosample researchers.¹⁰ Such reluctance is also likely to extend to time-consuming cooperation with efforts to document available Swiss biosamples, which may be resisted unless clear benefits for the researcher are apparent.

However, highlighting the divergence in interviewees' attitudes, many respondents regretted the lack of networking opportunities and contacts from other researchers, or felt willing to share but reported that there were no such opportunities in Switzerland. It appears that there is a division in biobanking between those eager to widen their collaborative pool (but who are unaware even of existing opportunities, a distinct problem in itself) and those who are satisfied with a more limited route involving personal contacts. Crucially, we do not appear to have two groups content with the status quo, but at least one group which feels that obstacles to sharing do exist, and potentially, some members in the second group whose reliance on personal contacts has meant that they may overlook broader possibilities for sample acquisition.

An initial approach to this finding must take into account the local context. Twelve respondents mentioned that certain issues, which they identified as being specific to Switzerland, were barriers to biosample sharing. Their comments, above, are plausible explanations for some of the discrepancies

in stakeholders' perceptions of the sharing situation. It presents a fragmented picture of the current situation in Switzerland, with some stakeholders keen to move towards a situation where central biobanks act as sample "dealers", while others prefer to work with colleagues on prospectively collected samples for particular studies. Again, this is a situation which is to be expected, given the differing nature of researchers' goals. The aim here is not to criticize those who are less eager to make human biosamples available to all-comers, but rather to examine how a strong research environment for both groups of stakeholder can be developed. These results give reason to believe that, for some stakeholders, there are both barriers and a lack of information in biosample sharing.

However, caution must be taken in overemphasizing the Swiss situation, as many of the comments made by the interviewees apply in the international context. Europe is composed of small countries which are likely to experience the same difficulties in obtaining large numbers of samples at the national level. The great majority of the interviewees worked in other countries, or are not Swiss nationals, and drew on these experiences in responding to the questions. Switzerland is also undergoing the same development of new regulations and guidelines that are taking place in other countries.

The above findings exemplify the kind of socially undesirable attitudes which anonymous interviewing brings to the fore. In addition, they demonstrate significant differences in approach on the part of various biobank stakeholders.

Other differences with the results of the review are revealed. It is extremely important to note the controversy of sample availability. This issue was mentioned only three times in the literature reviewed, and by a sizable minority of respondents to the interview, as being a barrier to sharing. However, a similar sizable minority of respondents stated with confidence that availability is never an issue with human biosamples, and that methods of putting existing samples to good use are what is lacking, not samples themselves. This is a view echoed elsewhere in the literature,³ with several large-scale banks reporting low rates of sample use,⁴ and is a significant discrepancy to consider. First, it is reasonable to assume that two very different types of sample, or groups of sample type, are being discussed. Depending on the format of the research, the rarity of the disease in question, the biomarkers of concern, and so on, it is true that there are likely to be many very useful samples being overlooked for some research purposes, while other studies must gather new material for their specific goals.

The heterogeneity of the biobanking world has emerged as a key theme of the literature in general,¹¹⁻¹³ so such contrasting views are to be expected. What must be borne in mind, though, is that in light of the subsequent interviewees' comments about lack of knowledge of other biobanks and networks, and the tendency to share samples with researchers already familiar to them, it may to some degree be true that useful samples are going to waste because lack of awareness, not availability, is the issue. If this is the case, it is a disappointing waste of material which has been collected, in many cases, from a public who wishes to see their material further research. It is in any case also a waste of resources to recollect a great number of samples which are lying in wait in a freezer elsewhere. The consequences of this potential problem (for the results unfortunately cannot shed light onto whether, or to what extent, useful samples go unused) will be addressed in greater detail below, in relation to further findings from the interviews.

Given the size of Switzerland and other European countries, it is unreasonable to assume that individual research centres (whether in universities or otherwise) can amass the same number of

samples as comparable organizations in North America, despite the economic and logistical advantages.¹⁴ It must also be noted that creating a national registry of samples would involve huge investment, both of time and money, on the part of both the organizers and every research group involved.¹⁵ The Swiss National Science foundation has recently undertaken this task, reserving 204 million CHF for the linking of biobanks and the furthering of translational medicine.¹⁶ Meanwhile, the Swiss Academy of Medical Science is seeking to incentivize collaborative projects.¹⁷ The efforts made by Biobank Suisse show that appropriate formats exist, but they may still be missing opportunities to link researchers across different disciplines, essential for translational research. At present Biobank Suisse lists only three partner institutions on its website, yet has a sophisticated database with detailed information about available samples (approximately 60 000 from some 23 000) patients. Biobank Suisse also provides multi-level support for researchers, including the promotion of the biobanking software CAISIS, and an informed consent template suitable for Switzerland. While some of our interviewees reported dissatisfaction with this system, and refrained from getting involved, the complaints of other participants about the lack of networking suggest that Biobank Suisse has not yet managed to fill the gap in Switzerland. Given what is available, and the report from our interviewees on what is still lacking to optimize biosample sharing, consideration can be given to the opportunities for moving forward.

The suggestion that the needs of stakeholders, rather than the basics of biobanking, must now be the focus, is supported in an article by Simeon-Dubach and Watson, who suggest that the current generation of biobanks must enhance their value with regard to the requirements of stakeholders, and ensure their own sustainability.⁴ They suggest that greater focus on quality, stock management and accreditation are all important for the biobank, while researchers can play their part by reporting their research findings each time they use specimens from a particular bank. In this way, a system of mutual benefit, trust, and also professionalism is developed.

Limitations

Our study has certain limitations. First, in an interview setting, it is always possible that the interviewee will avoid certain responses that might be deemed professionally undesirable, in order to avoid creating an unfavorable impression among peers. However, the reporting of a number of contentious issues in our results leads us to believe that this was not a universal limitation. Second, our field of experts was recruited in Switzerland; thus, the results are necessarily reflective of current practices in this country, which limits their generalizability to some degree. We emphasize again that the great majority of participants had spent considerable time working overseas, were not Swiss national, and/or are engaged in work with colleagues in other countries.

Conclusion

While these are certainly important steps for biobanks and researchers to consider, the fact remains that when biobanks are spread between universities, hospitals, and individual laboratories, their visibility is necessarily limited, and entirely dependent on the efforts of the staff, whose time may already be overfilled. Increased participation in established biobanking networks such as the International Society for Biological and Environmental Repositories (ISBER), its European chapter the European, Middle-Eastern and African Society for Biopreservation and Biobanking (ESBB), and the research infrastructure, the Biobanking and Biomolecular Resources Research Infrastructure (BBMRI) is a logical and necessary first step.

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References:

1. Betsou, F. *et al.* What Are the Biggest Challenges and Opportunities for Biorepositories in the Next Three to Five Years? *Biopreservation and Biobanking* **8**(2010).
2. Vaught, J., Kelly, A. & Hewitt, R. A Review of International Biobanks and Networks: Success Factors and Key Benchmarks. *Biopreservation and Biobanking* **7**, 143-150 (2009).
3. Harris, J.R. *et al.* Toward a roadmap in global biobanking for health. *Eur J Hum Genet* **20**, 1105-11 (2012).
4. Dillner, J. & Andersson, K. Biobanks collected for routine healthcare purposes: build-up and use for epidemiologic research. *Methods Mol Biol* **675**, 113-25 (2011).
5. Hagen, H.E. & Carlstedt-Duke, J. Building global networks for human diseases: genes and populations. *Nat Med* **10**, 665-7 (2004).
6. Colledge, F., Elger, B. & Howard, H.C. A Review of the Barriers to Sharing in Biobanking *Biopreservation and Biobanking* **11**, 339-346 (2013).
7. Shaw, D.M., Elger, B.S. & Colledge, F. What is a biobank? Differing definitions among biobank stakeholders. *Clin Genet* **85**, 223-7 (2014).
8. Colledge, F., Persson, K., Elger, B. & Shaw, D. Sample and data sharing barriers in biobanking: consent, committees, and compromises. *Ann Diagn Pathol* **18**, 78-81 (2014).
9. Colledge, F.M., Elger, B.S. & Shaw, D.M. "Conferring authorship": biobank stakeholders' experiences with publication credit in collaborative research. *PLoS One* **8**, e76686 (2013).
10. Rothmayr, C. Biobanks: Governance in Comparative Perspective – Edited by Herbert Gottweis and Alan Petersen. *Governance* **22**, 759-761 (2009).
11. Gibbons, S.M.C. REGULATING BIOBANKS: A TWELVE-POINT TYPOLOGICAL TOOL. *Medical Law Review* **17**, 313-346 (2009).
12. Asslaber, M. & Zatloukal, K. Biobanks: transnational, European and global networks. *Briefings in Functional Genomics & Proteomics* **6**, 193-201 (2007).
13. Kiehntopf, M. & Krawczak, M. Biobanking and international interoperability: samples. *Hum Genet* (2011).
14. Rogers, J., Carolin, T., Vaught, J. & Compton, C. Biobankonomics: A Taxonomy for Evaluating the Economic Benefits of Standardized Centralized Human Biobanking for Translational Research. *JNCI Monographs* **2011**, 32-38 (2011).
15. Vaught, J., Rogers, J., Carolin, T. & Compton, C. Biobankonomics: Developing a Sustainable Business Model Approach for the Formation of a Human Tissue Biobank. *JNCI Monographs* **2011**, 24-31 (2011).
16. Mehrjahresprogramm 2012 – 2016. Planungseingabe zuhanden der Bundesbehörden. (ed. Nationalfonds, S.) (Stämpfli Publikationen AG, Bern, 2010).
17. Meier-Abt, P. Die Schweiz braucht mehr Biobank. *Digma* **13**(2013).

3.2 WHAT IS A BIOBANK? DIFFERING DEFINITIONS AMONG BIOBANK STAKEHOLDERS

David Shaw, Bernice Elger, Flora Colledge

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Abstract

Aim: While there is widespread agreement on the broad aspects of what constitutes a biobank, there is much disagreement regarding the precise definition. This research aimed to describe and analyse the definitions of the term biobank offered by various stakeholders in biobanking.

Methods: Interviews were conducted with 36 biobanking stakeholders with international experience currently working in Switzerland.

Results: The results show that, in addition to the core concepts of biological samples and linked data, the planned use of samples (including sharing) is held to be a key criterion. It also emerges that some researchers avoid the term in order to circumvent certain regulatory guidelines, including informed consent requirements.

Conclusion: Developments in the field of biobanking will be complicated if researchers are unaware, or deny that their collection is a biobank. A clear definition of the term is therefore an important step towards fostering collaboration amongst researchers, enabling them to more easily identify potential sources of samples.

Introduction

Human biobanks for medical research are an increasingly important scientific resource. These repositories of biosamples and data provide researchers with the opportunity to access large pools of material, and gain insight into disease development. They are therefore widely regarded as instrumental in enabling the development of new therapies, preventive strategies and diagnostic techniques. Biobanks are now highly regulated in most countries, and many official national and international guidelines offer definitions of biobanks. These definitions differ in their details, but the majority state that biobanks are repositories of biological samples with accompanying linked data. For instance, the Organisation for Economic Co-operation and Development (OECD) defines biobanks as “structured resources that can be used for the purpose of genetic research and which include: (a) human biological materials and/or information generated from the analysis of the same; and (b) extensive associated information.”¹ The UK Biobank Ethics and Governance Council has stated that “the most robust contemporary definition of ‘biobanks’ is ‘rich collections of data plus biospecimens, specifically developed as resources for research’”.² As in both these definitions, the term “biobank” is normally used for repositories that are intended for use in research, rather than for diagnostic purposes. Using different terminology for different types of repository allows different regulatory regimes and consent procedures to be applied.

However, the extent to which biobank stakeholders are aware of and agree or disagree with official definitions is unclear. Given the many differences in biobank type, size, and research focus, and the lack of an accepted formal definition, it is unsurprising that numerous definitions also appear in the

literature.^{3,4} While in some cases the differences are minor, in others they are fairly significant. For example, Vaught, Kelly, and Hewitt state that “Biobanking involves the collection... of biological samples and their associated clinical data and information”⁵ while Kaye claims that “it is unclear whether a biobank consists of just DNA samples or whether it includes personal information or data as well”.⁶ In contrast, Cambon-Thomsen states that “the collected samples do not need to be physical... [and can] contain only the data plus information on the sample origin and its geographical provenance.”⁷ The same author stated in an earlier publication that “The concept of biobank includes the biological samples themselves”, indicating how even individual definitions can themselves change over time.⁸

Definitions are an important issue because the laws and regulations designed to govern biobanks are unlikely to be effective if biobankers themselves are unaware that their collections of samples are biobanks, or if they are reluctant to define them as such due to the regulatory requirements which can ensue. Furthermore, uniting researchers in collaborative networks will also be difficult if awareness about the existence, extent, and value of sample collections remains limited. In order to investigate this issue, and other potential barriers to biobanking, qualitative interviews were conducted with 36 stakeholders with international experience currently working in Switzerland.

Methods

Interviews

In order to explore their definitions of a biobank, we conducted interviews with key stakeholders involved in biobanking. Based on a review of existing debate reported in the literature we developed a guide for conducting semi-structured interviews. We used purposive sampling, with the goal of identifying key stakeholders in biobanking in Switzerland through publications, biobank and academic networks, as well as personal contacts and a snowball approach. Among the stakeholders identified were biobank managers, pathologists, researchers, clinicians, lawyers and ethicists. Questions about definitions were included within a broader interview guide and were preceded by more general questions about biobanking activities. Our specific aim with regard to the issue of the definition of a biobank was to allow stakeholders to freely express their own definitions in response to the question “what is your definition of a biobank?”, and explore their criteria with follow-up questions. Interviews were carried out in person or over the phone based on the preference of interviewees and travel convenience, and were transcribed verbatim; they were conducted in English in order to ensure comparability. Two exceptions were made for interviewees who were not sufficiently fluent in English, with one interview carried out in French and one in German. Confidentiality was fully guaranteed and transcriptions were anonymized in order to prevent identification through names or recognizable situations. The study protocol was submitted to the local cantonal research ethics committee (EKBB) and we received a positive response after an expedited process (minimal risk study not involving patients).

Response

A total of 36 individuals working in connection with biobanks in Switzerland agreed to participate. Among the non-participants, 25 individuals never answered e-mails or phone calls. The remaining 9 responded but declined, stating in all cases either that they had no time, or that based upon our description of the study, they would not be helpful in answering our questions. In cases where stakeholders refused to participate we identified a person closely resembling the category of the

previously approached person in terms of function, professional background and type of biobank network.

Analysis

The transcribed interviews were read in full by four members of the research team (including all the authors). Data were analyzed following classical qualitative methods.⁹ Transcripts were coded to identify key themes, concepts, phrases and attitudes. The authors compared codes and agreed upon the organization of sub-codes.

Results

Biological material / data

The majority of participants share the opinion that a biobank must contain both biological samples and data; see Box 1 for some typical responses. Several participants said that biobanks must be “systematic” or “structured”, where structured means “a reproducible way and a transparent way of how the things got in there.”(I27). Some interviewees made a distinction between a “repository” or “collection”, which do not (need to) have data, and a biobank, which does:

“A repository is... the difference between a repository and a biobank is, a repository is a collection of biopsecimens. Maybe also some data. A biobank... by definition have to have both: biospecimens and data. Otherwise it’s not a biobank.” (I11)

In contrast, a minority of participants stated that a biobank need not contain data: “It’s an organization to store... biological samples for later usage.” (I19) In terms of the biological material itself, a minority of participants mentioned that the biological material need not be human: “...it’s... I would say it’s extremely broad... it’s any biological material being animal, plant...that is.... You know located somewhere.”(I16) A few participants claimed that the samples must be of several different types of (human) tissue:

“I would maybe restrict it to... to biological material... tissue and, and fluid.... And I don’t know if I would go so far to say that every DNA or RNA or protein piece is a biobank.” (I25)

Box 1: Biobank stakeholder’s views on the general definition of “biobank”

I4: “A biobank, well it’s a systematic collection of biological samples...”

I27: “Any structured sample collection of biological material.”

I28: “That is biological material... that is annotated...so a certain amount of clinical data that is linked to biological material.”

I36: “...it’s a physical... physical collection of... biological samples, so samples of... of organismic origin...together with... meta, or information about these samples.”

I9: “I think a biobank is any part of the body, either liquid or consistent, I think, and it’s frozen down and kept together with clinical data, obviously you need data about the person and, and so on, yeah.”

I13: “A biobank, this is, this is for me a place where you collect and store biospecimens from patients, together with clinical information that you can use at some point for starting some, some new projects. Yeah, that would be the definition of a biobank.”

Size

Most participants did not mention size as being part of the definition of a biobank, but a minority did think that size was relevant. Several participants stated explicitly that size could determine whether a group of samples constituted a collection or a biobank: "...it's not a biobank to have ten samples in a freezer and Excel sheet. That's a collection." (I31).

Another participant said that whether a collection of samples was a biobank depended on how rare the disease in question was:

"It very much depends on... I mean if you have a rare disease, even a few samples are quite valuable. If it's a more common disease you may need several samples because, depending on... I mean, depending on the scientific question, you may not answer a question with ten patients. In Hepatitis C for examples, it would be very difficult, unless you are looking at a very rare phenotype." (I17)

Use of samples

A substantial minority of participants mentioned the intended use of samples as being a component of the definition of a biobank. Among those who did mention the purpose for which samples would be used, all mentioned research (see Box 2 for examples). One participant expressed an objection to biobanks with no specific purpose:

"I resent the idea of biobank without questions... I think that biobanks should be focused on questions. On scientific and clinical questions." (I32)

The same participant stated that s/he had to "...fight with my hospital which is creating a biobank which I think is useless..."(I32). Finally, the importance of diagnostic biobanks and of potential rediagnosis was also mentioned by several subjects.

Box 2: Biobank stakeholders' views on the use of biobank samples

I28: "And, let's hope it's used for research, or for... clinical work."

I24: "...a biobank ... is used to do research that has nothing to with the direct treatment of the patient anymore."

I12: "...to provide researchers or clinicians with, with tissue, and data."

I13: "...A biobank, this is, this is for me a place where you collect and store biospecimens...that you can use at some point for starting some, some new projects."

I36: "I just want to make this possible, research on biological samples, and this is how I would do it. That's more the... like the banker, not... the banker he doesn't have, he doesn't own the money, he basically offers services, if people have money, he can handle that... and... make more out of it."

Sharing

Some interviewees mentioned sharing as a key component of a biobank: "I think a biobank should be something that is used by different researchers, and collaborators also, it's not something you are only doing for yourself." (I30). Another participant thought that sharing was relevant to determining whether his/her collection actually was a biobank:

"So, if you, that's the question, if your definition of a biobank is any storage of samples, then yes, we have a biobank, if biobank means it's so to say like external... we have samples for anybody... Then no, we have no biobank." (I26)

Avoidance of the term “biobank”

Several participants said that some biobank stakeholders (on some occasions including themselves) choose not to call their sample collections “biobanks” in order to avoid regulation “because of the legal aspects” (I22):

“if I would call it biobank, I would get into a lot of troubles....because all these crazy regulations concerning with biobanking...The problem with biobanking is...these people who have brought up this, this topic, had thought, thought of, had invented... a whole, very long list of regulations, how you have to deal with biobank specimens, how the patient has to get involved yeah, and this for us, only meant increase of bureaucracy, complicated, complicated the whole thing... for example exchange of archival material, even anonymous, between departments, which was... which was a custom, which was a regular habit, yeah, is now very difficult because what is missing for our archive material is the... a written consent of the patient.” (I22)

The same participant went on to explain why these regulations meant that very valuable samples might go unused:

“...but we have all these, we have all these wonderful specimens with very rare tumours, and so, and these data, these, these... data security issues... now almost prohibits that we reuse these, these specimens, yeah? We always have to say that we use them for quality control. That’s allowed, yeah?...but that’s... that becomes legally difficult.” (I22)

Another participant also mentioned avoiding the biobank ‘tag’ because of the issue of consent:

“people will start thinking about whether they want to be biobank or not...because biobanking then is... you know, it's, to be a biobank, considerable effort.... I mean if you call it a biobank you would have to have informed consent forms.” (I27)

Discussion

Biological material and data

The views of most participants were in line with the official definition of the Swiss Academy of Medical Sciences (SAMS, see below), although only one participant mentioned this particular definition specifically. As such, biological material and data were seen as the baseline criteria for a biobank. Interestingly, however, several interviewees suggested that some collections that contained both material and data might nonetheless not be a biobank, with one suggesting that a collection could have some linked data without being a biobank, and two suggesting that even large DNA/RNA collections might not be a biobank. This is a departure from the majority of the commonly-used definitions of the term; it is possible that such comments arose due to the regulation issues associated with biobanks (see below). In contrast, some interviewees stated that even collections without data were technically biobanks; this view seemed to be more common among pathologists, even if they admitted they would hesitate to call them biobanks in practice. This may be because some pathologists’ collections are composed only of samples, with the data being stored elsewhere; it could be argued that such a collection only becomes a biobank when hospital data are linked to the samples.

Size

Most participants agreed that size was not an important part of the definition of a biobank, but a few claimed that a relatively small number of samples and linked data is simply a collection. This is in accordance with the UK Biobank Ethics and Governance Council criterion of a “rich collection”, but it is unclear why a “poor” collection with linked data should not also be regarded as a biobank and subject to regulation. Furthermore, as another interviewee pointed out, the value of a sample is linked to the rarity of a disease, meaning that size alone does not determine the richness of a sample.

Use of samples

Almost all participants who mentioned the intended use of samples stated that research is the main purpose of biobanks, which is in line with the UK and OECD definitions. Interestingly, one participant claimed that biobanks focused on a central question are more valuable than those used for general purposes, but unfortunately did not provide any clear reasons for this belief.

Sharing

Although sharing is not mentioned in most official definitions of biobanks, it is encouraging that several participants saw sharing samples with external institutions as a key aspect of a biobank, as this practice is widely promoted as a means of facilitating research.¹⁰⁻¹²

Avoidance of the term “biobank”

Perhaps the most interesting finding is that several participants admitted that they would not describe their collections as “biobanks” despite the fact that they did meet a number of the commonly held criteria. One noted that calling his collection a biobank would lead to him getting into trouble. To this interviewee, the perceived overregulation of biobanks means that adopting the term to describe sample collections brings with it a number of undesirable consequences. While choosing to avoid the term “biobank” is not in itself problematic, carrying out research upon samples without ethics committee approval could be regarded as research misconduct. This participant and another admitted describing research as quality control in order to circumvent biobanking regulation. This is a common problem in research review generally: researchers wish to avoid the perceived complications of obtaining approval from an ethics committee, so instead attempt to label their study as audit or evaluation.^{13,14} While this might be understandable from a pragmatic perspective, conducting research without the necessary approval contravenes the basic principles of the Declaration of Helsinki, and is against the law in many jurisdictions (as one participant seemed to realize).¹⁵ The attitude of the interviewees in question appeared to be that this is just how things get done in their line of work; the lack of a standard definition allows such practices to continue, as the choice of what to call one’s sample collection is, to some degree, decided on a case-by-case basis. (This attitude of “this is how things are done” parallels the attitudes of some biobankers to authorship and fairness in sharing). While a globally accepted definition of the term “biobank” cannot in itself encourage individuals to call their collections biobanks, it may facilitate holding medical practitioners accountable for the use they make of certain samples. We discuss this point further below.

Several participants also mentioned the burden of obtaining informed consent from patients. Of course, some sample collections are genuinely not biobanks and it would not be helpful or necessary to require informed consent for use of such samples. One participant expressed his frustration that

regulations make it difficult to use valuable samples that were obtained without consent. A new law governing human subjects research in Switzerland comes into force on the 1st of January 2014 and will allow the use of historic samples without patients' consent, which could address researchers' concerns to some extent.¹⁶ However, this option does require approval from an ethics committee, which means that there might still be some motivation to claim that research is "quality control".

The importance of a clear definition

Our results make it clear that there is widespread disagreement about the definition of a biobank. This may have important implications for sharing and cooperation between biobanks and regulation of the use of biological samples. First, if a researcher thinks that his collection is not a biobank, he is unlikely to respond to any local, national or international communications concerning biobanks or biobank networks. Such researchers are therefore less likely to share samples with other biobanks or ask for samples to be shared with them. Second, if a researcher does not think he has a biobank, he will not think that any relevant biobank standards or regulation apply to him (see previous section). This means that the use of samples might not be regulated properly. While poor sample quality and inadequate regulation are also important barriers to sharing, ignorance or denial that a collection is a biobank can act as a barrier to sharing even if quality and governance are of a high standard.

What, then, is the best definition of a biobank? Remarkably, no previous paper has focused on the issue of exactly what a biobank is. As mentioned above, a wide range of definitions are provided by official bodies and in the literature. The results from our study confirm that samples and data are seen as the basic requirements for a biobank, with use of samples also identified as an important aspect. Our interviewees generally felt that the size of the collection was unimportant, which reflects the majority of national laws and guidelines.¹⁹ If we are to arrive at an ideal definition, it will be necessary to decide whether size and/or use are essential components of a biobank.

The SAMS provides the following definition:

Biobanks are systematic collections of samples of human body substances (e.g. organs, tissue, blood, cells etc.) and DNA as carrier of genetic information. Data that contain information on the donor (demographic data, type of disease etc., but also genetic data) are stored, either together with the samples or separately.²⁰

In fact, we would argue that this definition is actually superior in one respect that offered by the OECD, because it does not dictate that the information associated with biobanks must be "extensive". A biobank can be a very valuable resource without having particularly detailed associated data or (as one participant mentioned) thousands of samples, and imposing such conditions would allow very many collections to remain outwith biobank regulation despite their importance for medicine. However, while it avoids this problem, the SAMS definition has the contrasting disadvantage of casting the net too widely: it would include any collection of routinely collected biological specimens with linked data, even if such a collection was never intended to be used for research.

As such, we would suggest that the best definition of a biobank would be one that does not refer to the size of sample collections or the richness of data, but does state that the purpose of the biobank

is research. Adding the research criterion to the definition has the dual benefits of reflecting current biobank practices, and regulating what needs to be regulated without accidentally catching collections that would not require for their intended purpose. This ensures that any samples that are to be used for research will be regulated, but those used for quality control, diagnostics or forensics (none of which require consent) will not. This would also avoid the problem of researchers having to deal with regulation when they have no intention of using historical samples. Therefore, we tentatively suggest a definition such as the following: “A biobank is any collection of human biological samples and linked data that is to be used for research.”

A clear and widely accepted definition of biobanks would remove the ambiguity currently surrounding some collections, making it easier for researchers to determine whether any given collection is in fact a biobank. However, in addition to publicizing the SAMS or an alternative consensus definition, it may be necessary for individual institutions to conduct internal audits of collections to check that no biobanks are being overlooked; some institutions have established committees for this latter purpose. Such audits could also help increase the number of biobank samples available for sharing.

Conclusion

The results of this study reveal that there is substantial disagreement among biobankers about exactly what a biobank is. There is a general consensus regarding the key criteria of biological samples, data, and their use for research, but quite divergent views on the importance of size, sharing, and diversity of samples. Defining biobanks is an important part of regulating biomedical research, but the possibility that such definitions might be unwelcome for a variety of reasons has not previously been explored. Clear definitions of biobanks and education of biobank stakeholders may be necessary to facilitate future biobank development and sharing. Tighter regulation of non-biobank collections and sanctions for those who attempt to ignore guidelines may be necessary to prevent researchers exploiting this loophole.

References:

1. OECD Guidelines on Human Biobanks and Genetic Research Databases. (2009).
2. UK Biobank Ethics and Governance Council. (2007).
3. Shickle, D., Griffin, M. & El-Arifi, K. Inter- and intra-biobank networks: classification of biobanks. *Pathobiology* **77**, 181-90 (2010).
4. Gibbons, S.M.C. REGULATING BIOBANKS: A TWELVE-POINT TYPOLOGICAL TOOL. *Medical Law Review* **17**, 313-346 (2009).
5. Vaught, J., Kelly, A. & Hewitt, R. A Review of International Biobanks and Networks: Success Factors and Key Benchmarks. *Biopreservation and Biobanking* **7**, 143-150 (2009).
6. Kaye, J. Do we need a uniform regulatory system for biobanks across Europe? *European Journal of Human Genetics* **14**, 245-248 (2006).
7. Cambon-Thomsen, A. The social and ethical issues of post-genomic human biobanks. *Nat Rev Genet* **5**, 866-73 (2004).
8. Cambon-Thomsen, A., Ducournau, P., Gourraud, P.A. & Pontille, D. Biobanks for genomics and genomics for biobanks. *Comp Funct Genomics* **4**, 628-34 (2003).
9. Mayring, P. *Qualitative Content Analysis*. *Forum Qualitative Sozialforschung / Forum: Qualitative Social Research [On-line Journal]*, 1(2). Available at: <http://qualitative-research.net/fqs/fqs-e/2-00inhalt-e.htm> [Date of access: 07.01.2013], (2000).

10. Salvaterra, E. *et al.* Banking together - A unified model of informed consent for biobanking. *Embo Reports* **9**, 307-313 (2008).
11. Kiehntopf, M. & Krawczak, M. Biobanking and international interoperability: samples. *Hum Genet* (2011).
12. Riegman, P.H., de Jong, B.W. & Llombart-Bosch, A. The Organization of European Cancer Institute Pathobiology Working Group and its support of European biobanking infrastructures for translational cancer research. *Cancer Epidemiol Biomarkers Prev* **19**, 923-6 (2010).
13. Warlow, C. Clinical research under the cosh again. *BMJ* **329**, 241-242 (2004).
14. Wade, D.T. Ethics, audit, and research: all shades of grey. *BMJ* **330**, 468-471 (2005).
15. The Declaration of Helsinki. (1964).
16. Bundesgesetz über die Forschung am Menschen (Humanforschungsgesetz, HFG). (2011).
17. Icelandic Act on Biobanks No. 110/2000.
18. Swedish Act on Biobanks (2002:297).
19. Council, G.N.E. Biobanks for Research: Opinion. (2004).
20. Biobanks: Obtainment, preservation and utilisation of human biological material. (ed. Sciences, S.A.o.M.) (Basel, 2006).
21. <http://www.gla.ac.uk/schools/dental/studentstaff/researchgovernancesub-group/>.

3.3 “CONFERRING AUTHORSHIP”: BIOBANK STAKEHOLDERS’ EXPERIENCES WITH PUBLICATION CREDIT IN COLLABORATIVE RESEARCH

Flora Colledge, Bernice Elger, David Shaw

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Abstract

Background: Multi-collaborator research is increasingly becoming the norm in the field of biomedicine. With this trend comes the imperative to award recognition to all those who contribute to a study; however, there is a gap in the current “gold standard” in authorship guidelines with regards to the efforts of those who provide high quality biosamples and data, yet do not play a role in the intellectual development of the final publication.

Methods and findings: We carried out interviews with 36 individuals working in, or with links to, biobanks in Switzerland, in order to understand how they interpret, apply and value authorship criteria in studies involving biosamples. The majority of respondents feel that authorship is an important motivating factor in working and publishing collaboratively. However, our findings suggest that in some cases, authorship guidelines are being ignored in favor of departmental standards which recognize “scientific work” as meriting authorship.

Conclusions: Our results support the current calls in the literature for an alternative method of crediting biomaterial contributions, in order to ensure appropriate authorship inclusion and promote collaborative research involving biobanks.

Introduction

In recent years, there has been a steady increase in clinical research involving large numbers of collaborators, often spanning multiple departments and research centers, sometimes between several countries. This is partly due to the growing importance of translational research, whole genome studies, and biobanks.¹ It is now possible, and even necessary, for researchers to pool resources from around the globe, either by sharing clinical or genetic data, or by sending physical samples to one another.² Consequently, many individuals are involved in some phase of these studies, and their contribution must be acknowledged in the final stage of the research process: publication.³

Being credited as an author on scientific articles is an essential part of a researcher’s career.⁴ In some countries it is also a yardstick by which academic departments are assessed and awarded funding.⁵ Coupled with the above-mentioned “team sport” nature of current research, it is not surprising that the increase in multi-collaborator studies has been matched by an increase in authors on published articles.⁶ Author lists of several dozen names are now commonplace; some papers have hundreds.^{7,8} In light of this, even those accustomed to the norms of scientific research have raised eyebrows about how so many contributors can be said to have had a hand in authoring a single work.⁹

The criteria for authorship developed by the International Committee of Medical Journal Editors (ICMJE) have stood for almost thirty years, with periodic revisions, and are adhered to by the majority of biomedical journals (some of which also have their own detailed standards.)¹⁰ They state that authors must make a “substantial contribution” to the conception, analysis or obtainment of the material, the drafting or revision of the manuscript, *and* approval of the final version. The goal is to ensure that any individual listed as an author can defend the work.¹¹ However, bending and breaking of these rules is widely reported;^{12,13} it is frequently taken as given that certain authors on a paper may have made only a few comments, or scanned a draft. Jostling for a place (and particularly a prestigious place) on the author list can lead to bickering and, in some cases, significant career setbacks, especially for those in dependent positions who lack negotiation authority.

Projects involving biosamples from multiple sources add another complication: how to credit people who have provided essential materials, but have not necessarily contributed significantly to the analysis or reporting that followed.¹⁴ In such cases, the research could not have taken place without the contribution of these individuals, who nonetheless do not meet the full ICMJE criteria. To credit such contributors as authors would therefore violate the current guidelines if they are interpreted in the stricter sense. This potentially creates a problem for the development of biobanking, in that those who manage and provide samples might feel they are not receiving sufficient recognition for their work if the authorship criteria are respected.¹⁵ This issue has been neglected in the biobanking literature, and our results reveal some important findings on this topic.

Methods

Ethics statement

The study protocol was submitted to the local cantonal research ethics committee (Ethik Kommission Beider Basel) and we received a positive answer after an expedited process (minimal risk study not involving patients). The ethics committee did not require written consent to be obtained for the competent, non-vulnerable individuals who took part in this non-clinical study. Verbal consent was therefore obtained and recorded at the beginning of each interview.

Study protocol

Semi-structured interviews were carried out with individuals working in, or with close links to, biobanks based in Switzerland. Using purposive sampling, we aimed to identify appropriate individuals through author lists on publications, biobank and academic networks, professional contacts, and a snowball approach. Biobank managers, pathologists, researchers, clinicians, lawyers and ethicists were all identified and approached, first by initial and follow-up email, and in the case of non-response, by telephone. Depending on the convenience of the interviewee, interviews were then arranged either in person or by telephone. The interviewer followed a semi-structured interview guide (see details on development below), and interviewees were informed that they should feel free to introduce issues not addressed by the interviewer. Confidentiality was granted; subsequent transcriptions were fully anonymised in order to prevent identification through names or recognizable situations.

The interview guide was developed in tandem with a literature review on current roadblocks to wide biosample sharing. Issues identified in the literature informed the key question areas, following a brief section to obtain demographic data. Questions regarding authorship were posed in the context

of a broader interview guide which addressed other biobanking activities. Questions covered the motivating effect of authorship, interviewees' perceptions and experiences with current authorship arrangements, and possible problems with the status quo.

Following each interview, verbatim transcriptions were made. Upon completion of the interview process, these were analyzed by four members of the research team, including all authors. Content analysis and coding, following classical qualitative methodology,¹⁶ was carried out independently in order to develop themes and sub-themes. These were then compared amongst four team members, including all authors. The authors then agreed upon the themes for this article. The qualitative methodology we employ is based on the model outlined by Mayring in "Qualitative Content Analysis", employing first inductive development, then deductive development, of themes. Due to the relatively small sample size and nature of our interview guide, we did not develop a model to categorize our findings beyond the general subject groupings we present in the text. Instead, we opted to present broad themes using quotations extensively, in order to give a descriptive overview of our findings, rather than seeking to quantify particular response categories.

Results

70 stakeholders were approached; 36 of these agreed to be interviewed for our study (17 face-to-face, and 19 by telephone). Amongst those who did not participate, 25 could not be contacted by either phone or email; the remaining nine replied with a refusal, stating either that they did not have time to participate, or that they felt that they could not be helpful in answering our questions, based upon an introductory description of the study. In each instance of non-participation, we sought to identify stakeholder with similar professional qualities and biobank affiliation. Participants include seven biobank managers, three lawyers or ethicists working in the field of biobanking, two administrators, and numerous clinicians from various disciplines. A small number work for private organizations, with the majority employed by an academic institution. Our group contains Swiss, British, Swedish, Italian and German nationals. The majority of interviewees have also worked and/or trained abroad for several years.

In all but two cases, interviews were carried out in English in order to ensure comparability. Exceptions were made for individuals who felt more comfortable expressing themselves in their mother tongue. Consequently, one interview was carried out in German and one in French. Interviews lasted between 30 minutes and one hour.

Authorship as motivating factor

The great majority of those interviewed agreed that authorship on a publication was indeed a motivating factor in collaborative research and sample sharing, although none stated that it was the chief factor. A number of different reasons as to why authorship credit is such a strong motivator were cited. Prestige in publishing in a well-known journal was often mentioned, with some respondents noting that this was important for institutions as well as individual careers: "...there's another opportunity to put your laboratory in a bigger paper that will make *Nature* again, then you share the samples." (I35). Another noted that the influence of funding bodies was a factor: "...it's very important for you to have, let's say, a first authorship in a very good journal, because that will help you to get money for research in the next round of grant applications..."

While “publish or perish” is the oft-cited mantra of university departments, our respondents also emphasized that non-academic institutions have an interest in publication credit: “...for example, we are not a university institute, but it’s nice for us to be part of a publication which is visible...” (I22); “...for some, let’s, say gastroenterologists in private practice, that’s quite an achievement, they see publication with their name on it even indirectly, and they can, show it in their private practice...” (I15).

Two respondents also stated that authorship acts as an alternative motivator to financial compensation for sample use: as one put it, “Authorship is a kind of payment.” (I6)

However, a sizeable group stated that authorship was not a motivating factor, or at least not the most important one, in encouraging sample exchange. The small number who suggested that authorship did not motivate collaboration at all stressed that this would be an inappropriate focus for biobank stakeholders and researchers. This sentiment was echoed among the slightly larger group who felt authorship was simply not the main motivation: “ I think it’s not always possible, it’s not always applicable, but I think the motivation should... it’s like with money. And I think one should not work for the payment, just having that as prior aim, but this is something you need to go further.” (I6) Respondents felt that answering research questions was the key motivating factor: “It’s not that we just do it for publications, I mean we do it because we want to answer the scientific questions.” (I7)

Although respondents did not discuss it in terms of a motivational aspect, the visibility which authorship brings to the researcher’s biobank was noted several times. When asked about how they identified potential collaborators, respondents pointed towards publications: “ ...it wasn’t looking for biobanks, and then, but it was more that they publish in an area so you got aware of them.” (I14)

Criteria for authorship

When questioned about the criteria which must be met to become an author on a paper, our interviewees identified a variety of considerations. A large number felt that authorship was a form of recognizing contribution: “...people ... wanted to be recognized for the work they are doing...And recognition in university, is authorship.”(I18)

Interviewees who held this view of authorship generally stated that involvement in the research process was the necessary element: “If they do some scientific [work] then it’s no question to be a co-author.”(I11)

Several participants described criteria for authorship using numbers and percentages of samples (or patients) contributed relative to the study size: “... if you share ten samples in a biobank that has 500, then they do some research, and they publish something, is it fair that you ask co authorship, or then you... the only thing was you took ten samples?” (I33) In most cases, they stated that while this method was often employed in some way, it was not clearly established in all cases prior to collaboration, and sometimes led to confusion : “Now this is not always easy, because some senders they give me fifteen patients, others they give me one patient, and then each one of them wants to be recognized, because, someone gave me one patient, four clinicians were involved in that or whatever, and the sender that gave me fifteen patients gives me only two clinicians, so how do I keep... a sense of justice?” (I32) A small number do, however, have a standard policy based on

numbers contributed; for example: “And the few, you know, there's a limited amount of authors that can be listed, so we will also pick those who have the highest amount of samples contributing.”(I28)

While discussion of the criteria for authorship was somewhat vague, some interviewees had strong sentiments about what were *not* sufficient criteria. In direct contrast to the comments above, several stated that guidelines on authorship do not recognize mere sample contribution as grounds for inclusion: “The criteria to be on a paper, are pretty clearly defined, I think you have to, just to send samples or to be, or recruit patients, that’s not enough.” (I24) There was a marked distinction between respondents who agreed with this standard: “...what is the scientific work to go to the cellar and open a freezer and take out some samples?” (I11); “...publication for me means also exchange of effort between the researcher.” (I6) and those who appeared to recognize the standard, but knowingly ignore it: “...but that's just the way it works, the way it works is that if you want their samples you have... or their patients, you have to.. do yourself the work, and be accommodating. You can, maybe you can call this very unfair, but that's the way the world is.”(I27); “... I cannot contribute, because I need the data to...say something. And then I said it’s nice... if you want to keep me as a co-author it’s ok, but.. and then we come back to the criteria for the co-author, you should be involved and you should know what they [other authors] say [in the paper].”(I33)

Difficulties

Biobank stakeholders we spoke to reported experiencing certain problems directly related to authorship arrangements. In view of the comments above, it is interesting to note that a few interviewees disagreed strongly with the suggestion that providing samples should not lead to authorship. Broadly, the notion that contributing samples is “mere” administrative work was contradicted: “Absolutely no. Absolutely no. This is... so... underestimated, our effort. So you need a lot, a lot of time, manpower also.” (I29); “... and we always fight to being credited when biological samples are used, so that... some of the researchers who join later, the project, who are just not aware what it had cost to, to get all these samples organized, they think it’s just available to be used...”(I14)

Beyond the issue of whether or not collaborators deserve authorship for a given contribution, several respondents stated that arguments over inclusion and position do occur, sometimes with serious consequences: “I’ve seen so many friendships destroyed because of authorships, and I don’t want to be part of that.” (I32)

The most frequently mentioned grievance in such disagreements was the use of rank, or hierarchy, to determine authorship, rather than man hours: “... big boss in one lab that I know well signed the paper, the guy who had the initiative and the idea, and the postdoc who did the work was in the acknowledgments. Big boss wants his name on it... if he’s a schmuck he’s a schmuck.” (I32)

Even amongst respondents who had not experienced any difficulties, personal relationships, in particular the influence of the lead investigator, were noted as being instrumental in establishing authorship: “I think it’s fair in this department, I think it’s a culture that the boss creates, whether it is fair or not.” (I9)

Interestingly, one respondent brought up the possibility of refusing an offer of authorship due to disagreement with the use of their samples: “... even if this person would pay me a lot, I, I would not

agree. If this center would say, “You are going to be on the publication” and I cannot trust what they’re doing... it did even happen during the years that I refused to have my name.” (16)

Numerous authors on science papers

Finally, several of our interviews brought up the topic of the ever-increasing number of authors on scientific papers. Those who had been working in the field for a long time noted that this phenomenon is relatively new: “I was struck by the fact that [a few decades ago] maybe on 5% of scientific papers has co-authors...” (134). Another described the discussions about assigning credit in such cases as “...like a souk... I’m not going to fight with 179 other co-authors...” (132) Despite the potential for conflict in such a situation: “...you put together your samples, and you do a genetic study, then you identify something, a publication comes out, and it is clear that not everybody can be a first author or last author.”(130) All those who discussed the issue were ambivalent about the development: “...if you have a publication, and, and you’re the author number thirty-two, of fifty-five, what is the value of that? You can publish in *Nature*, it’s still nothing.” (111) It was also suggested that this ambivalence might be a reflection of individual career status, rather than the lack of value in being one amongst many authors:“... these researchers, they are very advanced... they don’t care that much if they are 1 in 300 authors because they have the name already.” (135)

Discussion

To our knowledge, this is the first qualitative study which has sought to describe and analyze the experiences and perceptions of biobank stakeholders regarding the attribution of authorship in research using human tissue and/or data. As tools for biomedical research, biobanks are also by default tools for publishing findings, and authorship is a crucial aspect of professional life for the majority of individuals working in connection with biobanks. In multi-center, population-wide or transnational studies, the number of individuals with a stake in having their name on a paper may be very high. In view of the difficulties associated with publication credit, our results provide valuable insight into how affected individuals perceive, and deal with, current practices.

Our interviewees were nearly unanimous in agreeing with the proposition that authorship is a motivation to make samples available to other researchers, or collaborate with individuals external to their own department in some way. However, a significant number stated that it was not their main motivation, and several respondents made comments to the effect that chasing authorship could in some cases be a distraction from research itself. Given that this latter attitude may be a more socially desirable one, it is interesting to note how many respondents were ready to admit that authorship was in fact a strong motivator.

Several interviewees also expressed ambivalence about being included on a long list of authors, and stated that this provided few of the above-mentioned career benefits. Indeed, senior authorship seemed to be the most important motivating factor for researchers working at universities, although others found authorship credit as such motivating. Our interviewees also addressed other issues which are prevalent in the literature, such as disputes regarding position and the influence of hierarchy, which are generally accepted as unfortunate but predictable in the course of academic research publication.^{17,18}

Our most interesting finding is the respondents’ views regarding criteria which do, or do not, qualify an individual to appear on the list of authors. As noted above, the ICMJE has three conditions which

must be fulfilled by all authors. It is therefore striking that not only were these conditions, and the document itself, never explicitly referred to; in a number of cases, interviewees adhere to systems which differ significantly. In particular, several interviewees stated that contributing samples (usually above a certain number), or providing some kind of “scientific” input, would be grounds for inclusion as an author (indeed, this is a requirement in some material transfer agreements, such as that of the Chernobyl biobank¹⁹). In some instances, the policy of basing authorship on sample contribution was described, and then questioned or objected to, by the same individual. This indicates a certain acceptance of such conditions as being just “the way it works”, an attitude which supports the literature suggesting that disregard for, and unawareness of, the ICMJE criteria is widespread.^{3,5,20,21}

Our findings indicate that there seems to be a more or less variable culture of attributing authorship that goes beyond the present ICMJE criteria. It is important to stress that what respondents in our study describe is not classical “guest” or “gift” authorship, as the biosample contributions were time-consuming and included significant scientific and organizational work. Clarification of rules and transparency of the types of contributions is of utmost importance, as significant diversion from the guidelines has potentially serious consequences²²; furthermore, systematic disregard for guidelines will devalue them.²³ Several interviewees in our study described policies which seem to contravene a strict interpretation of established guidelines in the sense of both over-inclusion and under-inclusion of authors. Misattribution of authorship is at best “research misbehavior”,²⁴ at worst research misconduct, and can lead to negative consequences for those involved.²⁵ Not being credited as an author may hinder an individual’s chances of promotion or obtaining future research grants (this may also be the case if a researcher’s name is pushed further down the list solely due to lack of seniority).²⁶ Furthermore, inclusion as an author on a paper which is later revealed to have flawed or questionable findings may be just as detrimental as being omitted from the list of an important publication.²⁷ Our interviewees indicate that both excessive and insufficient crediting currently occurs, in accordance with the findings of Glänzel and Schubert, who note that certain studies show a tendency to under-acknowledge in-house collaborators, while collaborations with other departments are more thoroughly credited.^{28,29} Nevertheless, the tacit acceptance of disregard for these criteria remains a troubling aspect of work with human biological samples.

Implications

Although not all participants felt that material contribution merits authorship, and some directly contradicted this notion, the decisive element in the disagreement appears to be the amount of effort required to make samples available, rather than correspondence with the ICMJE’s three criteria. This suggests that authorship is currently viewed as the only valuable method of rewarding and recognizing significant professional effort, despite the fact that not all collaborators may be involved in “authoring” the final work. Respondents also emphasized that publication credit is not only important for its traditional influence on individual careers, but is also a form of promotion for the biobank itself. In the absence of standardized methods of biobank accreditation and indexing, the presence of a member of staff on the author list increases the chances of the biobank being contacted by external parties.

There is no provision in the ICMJE guidelines which reflects the reality of the evolution of research that necessarily implicates multiple centers and collaborators. Some universities, journals and organizations provide their own guidelines which are more adapted to crediting material contributions: the Swiss Academy of Medical Science, whose directives apply to all our respondents

currently, directs authors to their various university guidelines, and provides a list of authorship criteria similar to that of the ICMJE, but requiring that only one condition, rather than all, be satisfied.³⁰ The University of Basel states that authors should “have made a substantial personal contribution to the planning, execution, evaluation, or supervision of a given research publication [...]”, a standard which encompasses the work involved in providing biosamples, with or without accompanying data.³¹ However, the very fact that institutional guidelines differ from the international standard is troubling, as it is likely to confuse researchers, particularly those involved in inter-departmental research. This issue is not confined to Switzerland; the multiplicity of subtly different guidelines from organizations around the globe does little to improve an already complicated matter.

Although some biobanks have a policy of only requiring a mention in the acknowledgement section,³² it is possible that researchers involved in work with tissue samples feel obliged to designate important collaborators as authors in the absence of a universally recognized system for rewarding scientific and material contributions. To achieve this, they may take a broad view of the ICMJE guidelines, accepting that small changes to the draft, and a final reading of the article, satisfy a relaxed interpretation of the requirements. It seems that an addendum to the guidelines which takes into account the possibility of “scientific work” as fulfilling the criteria of study design and creative contribution is now imperative. While some flexibility in guidelines to allow for individual discretion is advisable, a clearer definition of what constitutes “scientific work” is required to avoid continued misappropriation of author credit, and to enable biobank stakeholders and researchers be acknowledged in a meaningful way.

Several alternatives currently exist, or have been proposed, which recognize contributions outside of the traditional authorship framework : these include acknowledgement sections, contributorship statements such as those pioneered by the British Medical Journal,³³ the Biological Resource Impact Factor¹⁵ and the ORCID (<http://www.orcid.org/>) initiative to permit recognition of both bioresources and stakeholders. The latter two are particularly promising prospects for biobank stakeholders, as they are specifically tailored to the challenge of acknowledging sample contribution (important for individuals), yet also to providing visibility and endorsement for sample collections (important for the biobank as a research entity). Suggested methods include assigning biobank unique identifying numbers which can then be used to credit banks that provide resources which lead to publication, and standardized, universally employed recognition of biobank employees in the methods section of articles. Universal adoption of such a system will be a key step in both resolving authorship issues and promoting biobanks as indispensable research resources. It may also be illuminating to look to other disciplines for inspiration. Dozens of particle physics papers, for example have over three thousand authors.³⁴ One collaborative team, in 1998, pioneered a novel set of standards for authorship on all publications issuing from the group, requiring all authors to have worked at the lab for a year, although independent of the direct input of that individual on any particular project. The existence of a “highly bureaucratic internal structure, small size, people doing tasks and thinking together in the same site”³⁵ means that such authorship criteria, while not traditional, are an adaptive means of coping with evolving research norms.

Limitations

Our study has some limitations. First, authorship is a very sensitive issue and in spite of anonymity interviewees might not have felt secure enough to speak openly. In addition we expect a bias

towards social desirability. It is therefore a strong finding that some interviewees admitted openly to be motivated very much by publications. We believe that it is not a significant limitation that interviewees were recruited in Switzerland because there is no reason that their opinions would vary significantly from researchers of other Western countries. Most of the interviewees have international experience and work in international collaborations. None of them reported a different “Swiss way”, but referred to an international authorship culture they encountered as part of their multiple collaborations.

Conclusion

Authorship continues to be a benchmark by which researcher’s careers are measured, yet the guidelines for its attribution are frequently disregarded, in some cases due to ignorance of their very existence. As multiple-author papers proliferate, so too do the problems associated with them. Biobanks are a chief source of the collaborations which produce such papers. Our interviews with biobank stakeholders in Switzerland reveal that authorship is considered a motivating factor for collaborative research, but that there are numerous instances of inappropriate credit and dispute. A main factor in this may be the lack of a suitable alternative method of recognizing the essential contributions of those who provide well-annotated, high-quality bio-specimens, but may not contribute to the intellectual development of resulting articles. In order to maintain the integrity of the authorship system, and encourage the evolution of biobanking, a suitable system of crediting authors must be agreed upon by researchers and journals.

References:

1. Riegman, P.H., Morente, M.M., Betsou, F., de Blasio, P. & Geary, P. Biobanking for better healthcare. *Mol Oncol* **2**, 213-22 (2008).
2. Shickle, D., Griffin, M. & El-Arifi, K. Inter- and intra-biobank networks: classification of biobanks. *Pathobiology* **77**, 181-90 (2010).
3. Wager, E. Bye bye by-line, hello contributors. *Journal of the Royal Society of Medicine* **99**, 542-543 (2006).
4. Wilcox, L.J. Authorship: The coin of the realm, the source of complaints. *JAMA* **280**, 216-217 (1998).
5. Bhopal, R. *et al.* The vexed question of authorship: views of researchers in a British medical faculty. *BMJ* **314**, 1009 (1997).
6. Leopold, S.S. Editorial: Research is a team sport: updated authorship guidelines for CORR. *Clin Orthop Relat Res* **471**, 701-2 (2013).
7. Lander, E. Initial sequencing and analysis of the human genome. *Nature* **409**, 860-921 (2001).
8. Okazaki, Y. Analysis of the mouse transcriptome based on functional annotation of 60,770 full-length cDNAs. *Nature* **420**, 563-573 (2002).
9. King, J.T.J. How Many Neurosurgeons Does It Take to Write a Research Article? Authorship Proliferation in Neurosurgical Research. *Neurosurgery* **47**, 435-440 (2000).
10. Editors, I.C.o.M.J. Uniform requirements for manuscripts submitted to biomedical journals: ethical considerations in the conduct and reporting of research: authorship and contributorship. (2009).
11. Jones, A. Can authorship policies help prevent scientific misconduct? What role for scientific societies? *Science and Engineering Ethics* **9**, 243-256 (2003).
12. Bennett, D.M. & Taylor, D.M. Unethical practices in authorship of scientific papers. *Emergency Medicine* **15**, 263-270 (2003).

13. Wislar, J.S., Flanagin, A., Fontanarosa, P.B. & DeAngelis, C.D. Honorary and ghost authorship in high impact biomedical journals: a cross sectional survey. *BMJ* **343**, d6128 (2011).
14. Mabile, L. *et al.* Quantifying the use of bioresources for promoting their sharing in scientific research. *Gigascience* **2**, 7 (2013).
15. Cambon-Thomsen, A., Thorisson, G.A. & Mabile, L. The role of a bioresource research impact factor as an incentive to share human bioresources. *Nat Genet* **43**, 503-504 (2011).
16. Mayring, P. *Qualitative Content Analysis. Forum Qualitative Sozialforschung / Forum: Qualitative Social Research [On-line Journal]*, 1(2). Available at: <http://qualitative-research.net/fqs/fqs-e/2-00inhalt-e.htm> [Date of access: 07.01.2013], (2000).
17. Erlen, J.A., Siminoff, L.A., Sereika, S.M. & Sutton, L.B. Multiple authorship: Issues and recommendations. *Journal of Professional Nursing* **13**, 262-270 (1997).
18. Riesenber, D. & Lundberg, G.D. The order of authorship: Who's on first? *JAMA* **264**, 1857-1857 (1990).
19. Thomas, G.A. *et al.* Integrating Research on Thyroid Cancer after Chernobyl — The Chernobyl Tissue Bank. *Clinical Oncology* **23**, 276-281 (2011).
20. Barrett, K.A., Funk, C.L. & Macrina, F.L. Awareness of Publication Guidelines and the Responsible Conduct of Research. *Accountability in Research* **12**, 193-206 (2005).
21. Pignatelli, B., Maisonneuve, H. & Chapuis, F. Authorship ignorance: views of researchers in French clinical settings. *J Med Ethics* **31**, 578-81 (2005).
22. Smith, J. & Godlee, F. Investigating allegations of scientific misconduct. *BMJ* **331**, 245-246 (2005).
23. Bhandari, M., Einhorn, T.A., Swiontkowski, M.F. & Heckman, J.D. Who Did What? (Mis)Perceptions About Authors' Contributions to Scientific Articles Based on Order of Authorship. *The Journal of Bone & Joint Surgery* **85**, 1605-1609 (2003).
24. Marris, E. & Check, E. Disgraced cloner's ally is cleared of misconduct. *Nature* **439**, 768-769 (2006).
25. Geggie, D. A survey of newly appointed consultants' attitudes towards research fraud. *Journal of Medical Ethics* **27**, 344-346 (2001).
26. Strange, K. Authorship: why not just toss a coin? *American Journal of Physiology - Cell Physiology* **295**, C567-C575 (2008).
27. Smith, R. Authorship: time for a paradigm shift? *BMJ* **314**, 992 (1997).
28. Glänzel, W. & Schubert, A. Analysing Scientific Networks Through Co-Authorship. in *Handbook of Quantitative Science and Technology Research* (eds. Moed, H., Glänzel, W. & Schmoch, U.) 257-276 (Springer Netherlands, 2005).
29. Laudel, G. Collaboration, creativity and rewards: why and how scientists collaborate. *International Journal of Technology Management* **22**, 762-781 (2001).
30. Scientific Integrity Committee of the Swiss Academies of Arts and Sciences. Authorship in scientific publications: Analysis and recommendations. (Bern, 2013).
31. University of Basel Vice-Rectorate for Research. Code of Academic Integrity and Good Practice in the Conduct of Research. (2011).
32. Vaught, J., Kelly, A. & Hewitt, R. A Review of International Biobanks and Networks: Success Factors and Key Benchmarks. *Biopreservation and Biobanking* **7**, 143-150 (2009).
33. Smith, R. Authorship is dying: long live contributorship. *BMJ* **315**, 696 (1997).
34. Adams, J. Collaborations: The rise of research networks. *Nature* **490**, 335-336 (2012).
35. Jacob, M.-A. But What Does Authorship Mean, Indeed? *The American Journal of Bioethics* **11**, 28-30 (2011).

3.4 4 GETTING A FAIR SHARE: ATTITUDES AND PERCEPTIONS OF BIOBANK STAKEHOLDERS CONCERNING THE FAIRNESS OF SAMPLE SHARING

Flora Colledge, Bernice Elger

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Introduction

Biobanks are a key tool to advance research about the genetic and environmental factors that affect various diseases. In order to enable meaningful results, biobanks need to obtain large amounts of samples. Researchers and clinicians are requested to collaborate and to pool efforts to share available samples.¹ This practice of 'sharing' takes many forms. Biological samples and data may change hands between researchers, pathologists, public or private biobanks, or clinicians, in transactions which can resemble exchange, sale, gifts, or pooling of resources.² This variety is a reflection of the many different branches of biological research in which biobanks play a role, and of the different professionals who find themselves connected in some way to a collection of samples and data. Therefore, all forms of biobanks create new challenges as they involve the collaboration and communication of individuals from a number of backgrounds.³ These collaborations typically involve some 'give and take' from all individuals involved, and are generally undertaken with the goal of achieving some professional recognition for the work that takes place: hence, an important aspect of these collaborations is their fairness. The UNESCO International Declaration on Human Genetic Data 2003 states that countries should 'ensure fair access' in the cross-border transfer of samples and data.⁴ Indeed, a number of biobanks note on their websites that fairness is an integral value of their operations.⁵⁻⁷

In a pluralistic world in which there are different ideas about what is fair, it is nonetheless evident that a lack of perceived fairness can interfere significantly with efficient biobank research. Unwillingness to share certain samples, competing interests of various groups, and lack of recognition for sample provision are just some current examples of this.⁸⁻¹¹ In the absence of any hierarchical or financial dependency, perceived fairness and the feeling of 'getting a fair share out of it' will be a crucial factor in motivating stakeholders to participate in joint biobanking efforts.¹² The importance of fair access has been emphasized in the literature.^{13,14} However, no research has addressed the elements which researchers themselves feel are important for fairness in sample distribution. Even general investigations into how fairness considerations affect collaboration in scientific practice are lacking.

Fairness as a property of human interactions has been characterized in several slightly divergent ways. It has been described as the impartial application of rules, the appropriate doing of what ought to be done, or 'self-centred inequity aversion'.¹⁵⁻¹⁷ It can be attributed (at least) to both processes and outcomes.^{18,19} However, what all theories agree upon is that fairness is an attribute of personal relationships in which things stand to be lost and gained, and that, when fairness is perceived as prevailing, it is a positive, motivating feature of a situation. In other words, promoting fairness is

likely to increase an individual's desire to be involved in collaboration. This is particularly true in the field of biobanking, which not only involves personal interaction with the chance of benefit, but is also a continuously evolving practice. Furthermore, few laws or guidelines address the details of the sharing process, focusing instead on acceptable sample use and consent practices. Exchange is therefore controlled at the biobank/researcher level, so individually perceived values such as fairness are even more important in ensuring motivation to collaborate.

Methods

In order to explore stakeholders' perceptions about fairness and their understanding of whether and how it contributes to biobanking, we conducted interviews with key stakeholders involved in biobanking. Based on a review of existing debate reported in the literature we developed a guide to carry out semi-structured interviews. Our aim was to explore a) what fairness means for those involved in biobanking (and by extension, collaborative scientific research) and b) how biobank-based transactions could be made as fair as possible from the perspective and experience of the interviewees. We used purposive sampling, the goal being to identify key stakeholders in biobanking in Switzerland through publications, biobank and academic networks, as well as personal contacts, and a snowball approach. Among these stakeholders we included biobank managers, pathologists, researchers, clinicians, lawyers and ethicists. Questions about fairness were included within a broader interview guide and were preceded by more general questions about biobanking activities. Interviews were carried out in person or over the phone based on the preference of interviewees and travel convenience and were transcribed verbatim. Interviews were carried out in English in order to ensure comparability. Two exceptions were made for interviewees unable to speak English, with one interview carried out in French and one in German. Confidentiality was fully respected and transcripts were anonymised in order to prevent identification through names or recognizable situations. The study protocol was submitted to the Ethikkommission Beider Basel (local cantonal research ethics committee) and we received a positive response after an expedited process (minimal risk study not involving patients). Data were analysed using classical qualitative methods; categories were identified independently following analysis by the two authors, then compared, and the resulting themes developed.²⁰ In this paper we report results relating to codes and sub-codes concerning fairness within biobanking activities.

Results

Among the 70 stakeholders who were approached, 36 individuals working in connection with biobanks in Switzerland agreed to participate (17 in person interviews and 19 phone interviews). Seven are biobank managers, three work on the legal and ethical aspects of biobanking, two work in administrative roles, and the rest are clinicians in various disciplines. While the majority of interviewees work in universities, a few work for private organisations. Five nationalities are represented, and the majority of interviewees had worked and trained abroad for several years. Among the non-participants, 25 never answered e-mails or phone calls. The remaining nine responded but declined, stating in all cases either that they had no time, or that based upon our description of the study, they could not be helpful in answering our questions. In case of a refusal of a stakeholder we searched for a person closely resembling the description of the previously approached person in terms of function, professional background and type of biobank network.

Defining fairness

The term fairness was never mentioned spontaneously by any of the respondents in the sections of the interview concerning the practice of biobanking, including informed consent and sharing of

Notions of what fairness involves	Interviewee comments
A matter of personal relationships	I1: 'Well what is fair? I told you, in my view it's based on personal connections mainly, and is personal connections fair, no, but... if there's nothing else, it's fair.' I17: 'Well, as long as we deal with fair people, yes, I think so, I hope so.'
A baseline assumption	I27: 'Well I mean, usually when people exchange things, you don't have to look and ask whether it's fair, you have to look, whether it's unfair. Find the unfairness.'
Varies case-by-case	I33: 'I think fairness is a very important point [...] It's relative on the project... Depending on, on what your contribution was to the whole project.'
Implies some restrictions	I25: 'So yes I think it's fair if you... do not have to share the tissue with everybody, because it also grants for some restriction of use.'
Depends on mutual agreement	I4: 'Well...we... we try to make it fair. By putting it written and sending the document back and forth, so that people's parties can make their points and a solution can be found.'

samples. The term was introduced for the first time by the interviewer as part of the final section of the interview guide. First, it is interesting to note that a sizable minority of participants (about one third) responded to this first question about fairness with their own question: some variation on 'What do you mean, fair?' The majority then went on to answer the question by providing some description of fair situations or conditions, without giving a clear definition of fairness itself (see Table 1).

Table 1: Interviewees' initial reactions to the issue of fairness

A slight majority of respondents stated that they would class the current system of sharing - either in their biobank, or, if they were not directly linked to a bank, of biobanks they knew about in Switzerland - as fair. However, a number interviewees said outright that they did not feel the system was fair (see Table 2).

Table 2: Reasons for which interviewees felt fairness was lacking/sub-optimal

Reason for perception of unfairness	Interviewee comments
Unverified publication data	I31: '... it actually is not fair to have publications in Nature where we have no idea whether the sample really had the illness they say... this is not fair, this is... quality of science, or actually input is not controlled at all.'
Lack of rules governing sample use	I24: '[...] there is no set of rules what to do with the sample, I think, that's often very unclear, and that leads to a lot of misunderstandings and aggression and frustration on each end.' I16: 'More fair... maybe it should be clearer to everyone, you know, what are... the rules, what are the guidelines... [we have] struggles and problems, because no one is really sure about what are the guidelines.'
Financial cost associated with sample access	I1: '...in the commercial bank it's not fair because if you don't have enough money, you can't have samples... I believe once the money's involved, it will not be fair... However, from the industry point of view, they would say 'We have the money, and you don't want to give us

	<p>[samples], this is not fair.” But... I consider I would rather keep this for...for the people who need it for themselves.’</p> <p>I26: ‘And that’s a big problem because even if... there’s money for this type of research... the clinicians try to get this money for themselves [...] So... in this way... if a lab is involved that’s usually doing routine work, in most cases this is not informed that this sample is for research tasks.’</p>
Lack of recognition for input	<p>I3: ‘The collaboration is, you give and we take.’</p> <p>I14: ‘Yeah, I think the work and the effort, and the type of infrastructure, is underestimated, I really think that this is underestimated....on an academic type of question, the science is probably under represented, but it’s a supportive function... From the practical, as well as all... the organizational things, or logistic part, I think that is a little bit underestimated.’</p>

Several respondents stated that while they felt that some aspects of the sharing process were less than fair, this compromise had to be made for the sake of continuing with work. Interestingly, these respondents all summed up their position with a similar phrase: ‘I don’t know what... I don’t know what fair is, I think nothing is fair in this world... well it’s not fair, but I think we have to find a way that somehow both of us, both of the parties, can live with it.’ (I17); ‘...since I retired my name is on... from day one, my name practically disappeared from the papers... Which, personally, I don’t think it’s fair. But it’s the way it is. So you have to live with that.’ (I3); ‘How shall I put it... I think the answer I can give is, I can live with it.’ (I15)

Fair conditions

In general, interviewees had far more to say about the fairness of the conditions of their work, and ways in which it could be promoted or increased, than about the definition of fairness itself. Discussion of fair conditions led to two main thematically different responses. While a number of interviewees discussed fairness to external parties (see Table 4), an even larger proportion of respondents (see Table 3) referred primarily to fairness for themselves or fair exchange between biobankers, researchers and other collaborators.

Table 3: Existing or desirable elements contributing to fair sample sharing

Actual/desirable conditions	Interviewee comments
Transparency	<p>I9: ‘[...] in general we, we have a protocol, we wrote the grant, what we want to do, and then there is a PI of this sub-project, and he’s gonna do the study, and the others are part of it. I think that’s fair enough.’</p> <p>I8: ‘[...] the problem, the main problem, from my view, is there should be transparency from the very beginning. At the start of a project it must be clear.’</p> <p>I34: ‘What makes exchange fair... it’s the goal you decide on for the exchange, that is... what the person who makes the request wants to do with the samples, and, let’s say, exactly, a goal, clear and simple, well thought-out.’</p> <p>I24 : ‘Transparent... it doesn’t have to be rules it just should be more transparent , what’s happening.’</p>
Credit for contribution	<p>I9: ‘[...]]it also depends on the institution, in general I had the golden rule that the fellow who does most of the work is the first author, and if I run</p>

	<p>the project I'm the last author[...] Fairness is that those who contributed the most are the most visible, you know.'</p> <p>I35: 'I think it is that each party gets appropriate credit. That it's related to the amount of work, the amount of intellectual contribution, and the financial contribution to the project.'</p> <p>I17: 'I mean I think it's very important... to recognize everybody's input.'</p> <p>I3: '[...] when you have done a lot of work in putting a lot of work and effort into something, then you should have a certain right to it. And within [our study] there is a huge team and everyone has contributed, so they all have a certain right, to me, and that's fairness for me.'</p>
Rules, laws and guidelines	<p>I12: 'Yes I think it's fair. Provided you follow all the rules, which have to be, which have to be followed or done... we have one paragraph saying, ok, if another biobank is following the same rules we have here, then we are allowed to share samples, or give samples to them.'</p> <p>I35: '[...] specific guidelines or specific texts that deal with sharing... that has been debated and scrutinized, worked out by different individuals and different organizations, perhaps that might help.'</p> <p>I17: '[...] it is fair because it's made between peers who must set the rules before any kind of collaborations, and as long these rules are respected...'</p> <p>I13: '... more fair in the future... I don't know... maybe these people from Biobank Suisse they, they should also propose some typical contract for sharing in a fair way information or material from the biobank structure to different users.'</p> <p>I14: '[...] do the best to have it standardized... be part of a network that has certain standards, and not try to have your own solution somewhere, what works for you but cannot be linked... even try to be part of developing a larger system, that makes it fair, and then I think that there are understandable... rules who and how the samples are distributed, and how you could access them... Yeah, I think fair would be really that, that's part of something bigger.'</p>
Mutual benefit	<p>I16: 'I would say, I mean no one is losing anything. [...] I mean if something happens and one of them is profiting... maybe both are profiting.'</p> <p>I13: 'Fair for, for the patient who give the material, for the partners with whom we are working... I think it should be anyway a win-win situation.'</p> <p>I36: 'In general... when it [sharing] happens then it is exactly because everybody sees their mutual interest.'</p> <p>I4: '[...] go from the point of view that the other person is also trying to act in the best of his interests. In the sense of... they don't want to harm you, they want to... have benefit for themselves, so it's just that both parties will try to have the most of the benefit for themselves, and they have to agree on that.'</p>
External control	<p>I14: '[...]but this is done in a, in an understandable, rational, whatever type of way, like with the ethics committee, and the type of questions that there are worked out. Also independently.'</p> <p>I28: 'Well, it's very [fair], because of the committee that reviews them, they are not [cohort] members.'</p>

The quotations shown in Table 3 represent the best examples of respondents' views on key issues; generally, these themes emerged repeatedly throughout the interviews, and stakeholders held similar positions. However, in a few cases, there was divergence. In contrast to the general calls for clear rules and guidelines, one respondent stated:

'[...] I don't like leveling, leveling from the bottom...So I don't want to do that, if I clarify things too much, then I think it may backfire and do more damage than not clarifying it.'(I32)

Similarly, another was cautious about uniform documents:

'I think an important one is that... individual projects are discussed, and also participation, be decided on an individual project basis. So you're not really generally forced to, to participate in anything, that's already important.'(I5)

Table 4: Fairness considerations regarding the public

Considerations	Interviewee comments
Scientific responsibility	<p>I21: 'Well, it [fairness] would be the respect of what was, you know, the ethical considerations, and, that it's good science being done.'</p> <p>I14: 'I hope. I mean, it [fair sharing] certainly would be one of the priorities, actually, because I really believe in the, in the thing, the research has a responsibility to society, and that would be one way.'</p>
Use of public funds	<p>I31: 'I think many studies are designed not on the question, what is an important answer, and then, OK, what tissues do I need to answer this question, but many studies are... because this is a nightmare to get all the tissues, it's done the other way, what tissues do I have, what questions can I ask to my tissues, so this is the way it goes... and this not fair actually, this is not fair for the community who pays, for any, every, everything.'</p> <p>I2: 'I mean I sincerely hope that a proposal that was not fair would not be approved. I mean... we can take the fairness issue with this question to another level, the funding for this project is coming from taxpayer's money... money that's come from taxpayers has a huge castle, and empire, of incredible responsibilities, that scientists had better appreciate, somebody's worked their butt off to make this money...and this is tremendous privilege to be a scientist, that society's giving you this, so you know, the fairness... of sticking to what you said you'd do.'</p>

Discussion

We know of no other study to date which has closely examined stakeholder attitudes to the fairness of scientific collaboration and material sharing between biobanks. As research becomes increasingly transnational and transdisciplinary, and the number of researchers involved in each project grows, this issue becomes ever more pressing. The topic of fairness is a delicate one, and is also difficult to quantify and regulate; nevertheless, as we note above, it is a crucial aspect of ensuring participation in collaborative research, and avoiding obstacles in material exchange. The field of biobanking, which depends upon such exchange, is therefore an ideal focus to understand what fairness entails for researchers themselves.

The most striking result of our study is the strong variance between interviewees' perceptions of whether the current system is fair. There is clear divergence in respondents' experiences, which is consistent with the fact that there is currently a lack of uniform guidelines governing sharing. It is also interesting that three interviewees used the same phrase, 'I can live with it', to characterize their attitude. Given the abstract and potentially sensitive nature of our questions, this response may suggest a fairly negative perception of current conditions, while simultaneously implying that it is not

worth considering further. It is possible that other respondents also discussed conditions that they have learned to 'live with', but which might not be optimally fair when taken out of the daily professional context. The fact that most participants believe that they can live with the current system suggests that any unfairness is at least not intolerably unfair.

Our findings show that biobank stakeholders do not mention the term fairness spontaneously, but do say that fairness is an important aspect of the sample sharing process when questioned directly. Respondents were initially uncertain about the term 'fairness', and were vague about its definition. It is interesting to note that the UNESCO Declaration, and the biobanks which prominently advertise 'fair' sample access on their websites, also do not offer a definition of the term. Nearly all of our interviewees did however have strong notions about what fairness requires in practice. They also answered questions about fair conditions without hesitation, despite the term fairness itself leading to counter-questions. This supports the notion that 'getting a fair share' is important to stakeholders, and they have considered these matters before, even if they have not been called upon to discuss them as such. However, it is also possible that, when confronted with an unexpected line of questioning, respondents adopted the newly-introduced term 'fair' to describe processes that they might previously have described as 'good', 'bad', 'inefficient', etc.

In general, there was a good deal of agreement between respondents on key aspects of fairness. Issues such as transparency, rules, and responsibility to the public were brought up frequently, without prompting, and opposition to these attitudes arose in only a few cases. The need for more, or more visible, guidelines and rules was particularly prevalent. Participants made little comment as to the content of such rules, however; it is unclear whether the mere existence of rules was thought to be sufficient. While visible regulations may help with the transparency of sample exchange, it is arguable that rules in themselves may also be perceived as unfair by some parties. Indeed, their rigidity may produce instances of unfairness in processes which were previously adaptable on a case-specific basis; accordingly, we recommend that written agreements may be a good solution (see below). The desirable criteria for fairness also match a number of points on the 'fair access' scheme employed by the UK DNA bank network. However, our respondents did not bring up the issues of limiting access for non-collaborators, or long-term support and tracking of sample use.¹³

Interviewees also addressed the topics of publication credit, or authorship, and fairness vis-à-vis patients in their responses. These topics were described with unprecedented detail and revealed several interesting and unique perspectives from biobank stakeholders. A detailed analysis of respondents' responses related to authorship, and concerns for patients/donors, is presented elsewhere.

Our results reveal two contrasting aspects of why fairness is a motivating factor, which reflect the theoretical accounts. On the one hand, participants mentioned the systems that can or do promote fairness (Table 3), while on the other, the motivation came from external sources (Table 4). The latter set of reasons suggests an outcome-based approach; the former approach is more process-oriented. Simmons (2003) notes that a distinction can also be drawn between procedures (which establish collaborations) and processes (the progress of said collaboration).¹⁹ This is reflected in stakeholders' concern with establishing collaborative agreements that are universally acceptable upfront, but can also be referred to as insurance that all parties fulfill their obligations.

Interestingly, the process-oriented responses tend to result in fairness for researchers and biobankers, while the outcome-oriented responses resulted in fairness for those not involved in the

sharing process itself. This may be due to the fact that, as mentioned above, sample exchange is still a relatively unregulated field: stakeholders themselves are therefore instrumental in establishing the sharing process, and hence have well-developed notions of fairness which encompass their own needs and interests. Fairness therefore becomes a matter of reciprocity. There is then a second, outward-looking meaning of fairness, which is more a matter of public trust and keeping one's word as a professional. However, this second type of fairness also has a significant influence on motivation. A number of respondents stated that duties to others were an incentive to actively share samples. This is consistent with the partly outward-looking nature of biobank-based research, given its patient-oriented aspects.²¹

Implications

Two respondents mentioned that biobanking is a field in which exchange amongst individuals is indispensable: '[...]sharing is the only reason that you need a biobank, otherwise we don't need biobanks, collections are fine, without sharing, so... for the biobank sharing should be, is their motivation to exist.' (I31); 'Because this is the reason of the biobank. It's not a bank. It's not a money bank, you put your money, you are the only one to take, you know from your account, no, it's for [...] improving translational research.' (I1) Promoting widespread and effective sharing is the priority of a number of governments, research networks, and biobanks themselves. While these bodies may develop infrastructures and guidelines on sample storage and use, researchers' motivation to participate in wide sample sharing is essential to moving the field forward. Given that some participants mentioned that sharing only with known contacts was unfair, better communication between biobanks may also be important to make the system fairer.

The answers given by our respondents show a number of clear fairness criteria that motivate their actions involving biosamples. Developing and promoting these criteria is therefore likely to have a positive impact on the extent of sample sharing. For the most part, the conditions that were important to our interviewees could be enhanced by elaborating written agreements at key stages of the exchange process. This is in line with the findings of Vaught, Kelly and Hewitt, who note that successful biobanks tend to have well-established access policies and published governance standards.²² This may also serve to motivate large-scale exchanges, by acting as a safeguard for researchers who may have had little previous personal contact, and thus not built up the trust which facilitates smaller collaborations. Access policies can satisfy the outward-looking fairness requirements of meeting public expectations for research carried out with their money or tissue samples.²³ 'Fair access', in contrast to less-regulated 'open access' schemes, can provide the restrictions necessary to protect donor privacy and intellectual property.²⁴ These concerns for donors and the public are also essential to recruiting participants and maintaining trust in the biobanking process.²⁵

In addition to access agreements, according recognition for a biobank's compliance with existing guidelines could allow prospective collaborators to see the standards followed by that bank; this could perhaps be incorporated into a system such as that proposed by Anne Cambon-Thomsen, the Bioresource Research Impact Factor.²⁶

Limitations

We have chosen to focus on biobank activities in one country, which could limit the generalizability of our results. However, most of our respondents have an international medical background and

have spent some time working abroad, mostly in adjacent European countries, the UK and the US. Many of them referred not only to practice that they encounter in Switzerland but explicitly mentioned experiences from their work abroad. In addition, a significant number of interviewees referred to international collaborations, i.e. multi-country projects that received international funding. Therefore, we conclude that most parts of our results are generalizable and refer to practice that is found nationally and internationally.

The fact that almost half of the approached interviewees did not answer our request or declined participation could mean that our sample is biased. As we made sure to replace each non-participant with a person from a similar 'category' of participants, we do not think that a bias exists towards particular groups or towards particular views held by the interviewees that agreed to participate. However, it is possible that those who agreed to participate were generally more motivated to conduct further biobank research.

Conclusion

Our findings show that considerations of fairness are important to biobank stakeholders, as sample and data sharing is a major aspect of their work. While most of our interviewees felt that current sharing practices were quite fair, some areas that require improvement were identified, and some instances of outright unfairness were also noted. Perceptions of what constitutes fairness were well-rounded and broad-ranging, taking into account both the inner circles of scientific research, and the general considerations of public and professional responsibility. These clear accounts of fairness mean that improving the status quo should be straightforward. Fairness is a significant factor in motivating researchers to widen the scope of their sample exchange. Since fairness is not something that is regulated per se, encouraging conditions which foster transparency, mutual benefit and professional accountability is a necessary step for biobank stakeholders.

References:

1. Ballantyne, C. Report urges Europe to combine wealth of biobank data. *Nat Med* **14**, 701 (2008).
2. Milanovic, F., Pontille, D. & Cambon-Thomsen, A. Biobanking and Data Sharing: A Plurality of Exchange Regimes. *Genomics, Society and Policy* **23**, 17-30 (2007).
3. Cambon-Thomsen, A. The social and ethical issues of post-genomic human biobanks. *Nat Rev Genet* **5**, 866-73 (2004).
4. UNESCO. International Declaration on Human Genetic Data, Article 18. (2003).
5. Biobank, O.R. About ORB. Available at: <http://wyvern.ndcls.ox.ac.uk/orb/> [Accessed 16th May 2013]. (2013).
6. Trust, B.I. Mission Statement. Available at: <http://biobankireland.com/what-we-do> [Accessed 16th May 2013]. (2013).
7. Institute, C.F.R. Biobank committee members. Available at: <http://www.cfri.ca/biobank/committee> [Accessed 16th May 2013]. (2012).
8. Yuille, M. *et al.* Biobanking for Europe. *Brief Bioinform* **9**, 14-24 (2008).
9. Cambon-Thomsen, A. Assessing the impact of biobanks. *Nat Genet* **34**, 25-6 (2003).
10. Myles, R. *et al.* Stakeholder research on biospecimen needs and reactions to the development of a national cancer human biobank by the national cancer institute. *Journal of the National Cancer Institute. Monographs* **2011**, 16-23 (2011).
11. Taylor, P.L. Research sharing, ethics and public benefit. *Nat Biotechnol* **25**, 398-401 (2007).
12. Yassin, R. *et al.* Custodianship as an ethical framework for biospecimen-based research. *Cancer Epidemiol Biomarkers Prev* **19**, 1012-5 (2010).

13. Yuille, M. *et al.* The UK DNA banking network: a "fair access" biobank. *Cell Tissue Bank* **11**, 241-51 (2010).
14. Hewitt, R. & Hainaut, P. Biobanking in a fast moving world: an international perspective. *J Natl Cancer Inst Monogr* **2011**, 50-1 (2011 A).
15. Fehr, E. & Schmidt, K.M. A Theory of Fairness, Competition, and Cooperation. *The Quarterly Journal of Economics* **114**, 817-868 (1999).
16. Cullity, G. Public goods and fairness. *Australasian Journal of Philosophy* **86**, 1 – 21 (2008).
17. Hooker, B. Fairness. *Ethical Theory and Moral Practice* **8**, 329-352 (2005).
18. van den Bos, K., Allan Lind, E., Vermunt, R. & Wilke, H.A.M. How Do I Judge My Outcome When I Do Not Know the Outcome of Others? The Psychology of the Fair Process Effect. *Journal of Personality and Social Psychology* **72**, 1034-1046 (1997).
19. Simmons, J. Rules of engagement. *Public Management Review* **5**, 585-595 (2003).
20. Mayring, P. *Qualitative Content Analysis. Forum Qualitative Sozialforschung / Forum: Qualitative Social Research [On-line Journal]*, 1(2). Available at: <http://qualitative-research.net/fqs/fqs-e/2-00inhalt-e.htm> [Date of access: 07.01.2013], (2000).
21. *Integrity in Scientific Research: Creating an Environment That Promotes Responsible Conduct*, (The National Academies Press, 2002).
22. Vaught, J., Kelly, A. & Hewitt, R. A Review of International Biobanks and Networks: Success Factors and Key Benchmarks. *Biopreservation and Biobanking* **7**, 143-150 (2009).
23. Simon, B.M. How to get a fair share: IP policies for publicly supported biobanks. *Stanford Journal of Law, Science & Policy* **1**(2009).
24. Gitter, D.M. The Challenges of Achieving Open-Source Sharing of Biobank Data. *Biotechnology Law Report* **29**, 623-635 (2010).
25. Hobbs, A., Starkbaum, J., Gottweis, U., Wichmann, H.E. & Gottweis, H. The privacy-reciprocity connection in biobanking: comparing German with UK strategies. *Public Health Genomics* **15**, 272-84 (2012).
26. Cambon-Thomsen, A., Thorisson, G.A. & Mabile, L. The role of a bioresource research impact factor as an incentive to share human bioresources. *Nat Genet* **43**, 503-504 (2011).

3.5 SAMPLE & DATA SHARING BARRIERS IN BIOBANKING: CONSENT, COMMITTEES AND COMPROMISES

Flora Colledge*, Kirsten Persson*, Bernice Elger, David Shaw

*both authors contributed equally to the development of this article and therefore share joint first authorship

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Abstract

The ability to exchange samples and data is crucial for the rapid growth of biobanking. However, sharing is based on the assumption that the donor has given consent to a given use of her or his sample. Biobanking stakeholders therefore must choose one of three options: obtain general consent enabling multiple future uses before taking a sample from the donor; try to obtain consent again before sharing a previously obtained sample; or look for a legally endorsed way to share a sample without the donor's consent. In this study, we present the results of 36 semi-structured qualitative interviews with Swiss biobanking stakeholders regarding these options and the role of ethics committees in the process of authorizing sharing.

Our results show that despite a lack of legal or guideline-based barriers to general consent, some stakeholders and ethics committees have reservations about this method of consent. In most cases, however, a general consent form is already in use. Many interviewees describe processes involving the ethics committees as time-consuming and cumbersome and their requirements as too demanding for donors/patients. Greater awareness of donors' opinions and preferences and the content of guidelines and recommendations could therefore be helpful for a better justified perspective of biobanking stakeholders and ethical committee members, equally. Finally, it may be necessary to differentiate between procedures governing future samples, where general consent is clearly desirable, and the use of old yet still relevant samples, where the option of using them without consent can be highly beneficial for research.

Introduction

The rapid evolution of the field of biobanking has presented clinicians and researchers with a number of challenges which require different approaches to those faced in research involving human subjects. The potentially huge benefits of accessing samples from large pools, spanning decades, are accompanied by certain difficulties. Stored biosamples must be cleared for use in research projects in line with departmental, national and international laws and guidelines. The focus of the most stringent of these requirements is the form of consent which must be obtained before the samples can be made use of.

Due to the relatively recent developments, and wide-ranging applications, of biosample research, regulatory documents have emerged at staggered intervals, as international organisations, governments and institutions seeks acceptable solutions to regulating such research.¹ Not surprisingly, the documents produced by these various bodies sometimes contain significantly divergent recommendations on informed consent (IC).² While some organisations may require a specific consent to be obtained from the sample donor which covers only one research project, others allow for a general consent to any future use of the sample for research purposes.³ Within the last few years, attention has been turned to harmonising the laws regarding the consent

requirements for biosamples, in part a reflection of the wide debate in the literature on this topic. Although a number of authors stress the potential risks to donors of giving general consent, and suggest that consent to an unknown project is not consent at all,^{4,5} the majority of papers now call for the widespread implementation of a general consent, in order that valuable biosamples can be fully exploited.⁶⁻⁸ Since a core aspect of the worth of biosample collections is their longevity, it is argued, it makes little sense to effectively impose an expiry date on their use by ruling out the unforeseen research of future years. By the same token, existing sample archives which may lack general consent from all donors have also become a focus for medical organisations and governments.

Two options exist for rendering archived material eligible for research: consent can be sought retrospectively (in cases where a limited consent has already been obtained, this is known as “reconsenting”),⁹ or the requirement to obtain consent can be waived.¹⁰ Seeking consent or reconsent is the responsibility of the researchers, and can, particularly in cases where old or poorly catalogued samples are involved, be a time-consuming and complex process. Waivers of consent have therefore become increasingly common; in the absence of laws governing the issue, international and national medical organisations have included this option in their guidelines.

The Declaration of Helsinki (2008) states:

“[f]or medical research using identifiable human material or data, physicians must normally seek consent for the collection, analysis, storage and/or reuse. There may be situations where consent would be impossible or impractical to obtain for such research or would pose a threat to the validity of the research. In such situations the research may be done only after consideration and approval of a research ethics committee” (§ 25.).

Similarly, the recommendation given by the Council of Europe (Steering Committee on Bioethics (CDBI)) states:

1.i. If the proposed use of identifiable biological materials in a research project is not within the scope of prior consent, if any, given by the person concerned, reasonable efforts should be made to contact the person in order to obtain consent to the proposed use.

ii. If contacting the person concerned is not possible with reasonable efforts, these biological materials should only be used in the research project subject to independent evaluation...”

Finally, though it does not address waivers, the Swiss Academy for Medical Sciences (Schweizerische Akademie der Medizinischen Wissenschaften, SAMW) recommends general consent in their guidelines on biobanking: “Consent can generally also cover the further use of the samples and data for future research projects (general consent). Restriction of their use to one specific field of research is possible.”²

The confirmation that all these conditions are fulfilled is the responsibility of the local ethics committee. Thus, researchers must ensure that they have satisfied the committee on all points regarding consent (or the lack of it) before their research can proceed. However, as noted above, the guidelines upon which these committees must base their assessments are evolving and occasionally contradictory; they are also a significant departure from the traditional specific consent requirements for research on human subjects. The extent to which ethics committees influence informed consent requirements has so far been only sparsely addressed in the literature, yet it is during committee meetings that the debate concerning consent has a tangible impact upon research. We asked a group of biobank stakeholders working in Switzerland to discuss their experiences with consent for biosamples, and the ethics approval process. In doing so, we aimed to identify any difficulties in the process which might negatively affect research.

² http://www.samw.ch/dms/de/Ethik/RL/AG/Biobanken_D_06.pdf

Methods

We conducted 36 semi-structured interviews with key stakeholders in Swiss biobanks (researchers, clinicians, pathologists, lawyers, ethicists and biobank managers). For a more detailed description of the methods see Shaw, Elger and Colledge (forthcoming).¹¹

Results

Most of the interviewees identified informed consent as an important part of their work: a great majority of persons mentioned the topic, although they were not explicitly asked about it in many cases. This awareness reflects the enormous number of publications and the broad academic debate about informed consent in the medical field.

One focus of the presented findings here will be on difficulties regarding samples that had been stored without explicit consent and interaction with ethics committees, which have amongst other things the power to approve the use of samples without (re-)consent.

Types of consent

Biobanking stakeholders provided several justifications for the type of consent used in their institutes. A majority prefer a general consent as it means flexibility for future projects:

"I13: [...] our informed consent, [...] they are very general, [...] and based on this we can use these samples for whatever projects [...]"

"I24: [...] they gave consent to use it for other projects, except for any germ line analysis. And I could use it for other, I could give it on, and it had to be anonymised [...]"

"I31: [...] the broad consent is actually a good way Switzerland is going, I would say. [...]"

Another participant emphasises the advantage of having an optional general consent on top of the project-specific IC for a clinical study. That way, it is up to the patient to whether to agree to a specific or a general consent:

"I28: [...] we ask that they provide the material for just the basic pathology department assessment review that's part of the clinical trial, but that we then have, like an additional question that they can mark yes to, or no, whether they would agree for this to be held back, banked for yet unknown translational research or so."

The specific IC, in contrast to general consent, is described as an important limitation to data sharing by two interviewees:

"I21: [...] it's more tricky thing, because we are bound by ICHGCP, and [...] be quite clear what the samples could be used for and where they would go etc., so unless you thought about it in advance, it's difficult to share samples"

"I31: I think this is important basis for having decent sharing where we work now, is informed consent. [...] project specific informed consent, then we don't need to talk about biobanks if we have this, because then we do [...] our little own projects, and that's it [...]"

However, if the patients cannot precisely be informed about the future use of the sample they donate, there might be reasons for them not to sign a consent form. More explicitly, interviewee 21 earlier explained:

"[...] if you want to have high collection rates in a clinical trial, you have to have narrow consents. [...] if you want to go broad, [...] you reduce the number of patients who would sign up for that"

The ethics committee

Ethics committees appear to play a crucial role in imposing limitations on biobanking and sample sharing. A particular reluctance is described by some persons when it comes to the approval of general consent:

"I3: Yes, it was a broad consent, and [...] it was long discussions about this, also how[...] valid is it for[...] the genetic analysis, but the ethical committees decided we don't have to go back to it [...]"

The IC requirements imposed by ethics committees present a challenge as described by this interviewee:

"I12: [...] we have to... send out forms, four five six pages long, just to get a consent of the patient. So why not say, dear patient, we have here a biobank, and [...]we also collect a piece of a diseased tissue from you, and need this for research purposes. Period. So this would be the easiest way, but this is not allowed, so we have to[...] ask them for which kind of research projects we want to perform. We can't answer this, because no one knows in five years which methods are around"

In the next sentence, the same individual emphasizes related difficulties for patients:

"[...] there are many many different thing which have to be read by the patient and answered[...] and many patients [...] don't read it so clearly, because they do not understand it, or they won't understand it, or maybe they are faced with [...] More problematic things. And this is I think the[...] most problematic thing we have here. "

These two statements clearly demonstrate the key problems this interviewee sees in the current IC procedures: over-demanding requirements imposed by ethical committees, the impossibility of explaining the future use of a sample when designing general consent forms, and the potential inability of the patient to be thorough and thoughtful in their decision, which is partially due to the overwhelming bureaucracy of the forms.

The powers granted to the ethics committees by the Declaration of Helsinki can enable a study or biobank to use huge numbers of samples without consent. Their expectations are described as unrealistic and demanding in a way that hinders research, especially when particularly regarding the obligation to re-consent:

"I27: the task was then to get the informed consent from that patients, so they sent letters to all the patients, the problem is that a patient who [...] has been hospitalized [...] a year ago[...], you send them a letter [...], he will either not understand the letter, not respond to the letter, or he might be already dead, and, his spouse is angry at the hospital [...] in the end you get a response by [...] ten percent [...]Of the probands. [...] and then it gets reviewed by the ethics committee, and they say it's very poor quality because only ten percent responded."

A suggested reason for ethics committees' hesitant reaction is that *"[...]they think they need to protect the donors from this and that [...]"*[I21].

A contrasting view is presented by one interviewee, who believes that ethics committee approval wrongly makes people believe that everything is in accordance with patients' wishes:

"I2: if people really gave consent[...] then I think that is a huge barrier.[...] . It's breaking trust, [...]there's no utilitarian arguments that can justify breaking trust with someone who's entered into a consent believing that. [...] I'm not happy that people think you can justify this if an ethics committee says "OK", for me this is a very dangerous direction[...]"

Samples without consent

The handling of samples without consent is one of the most crucial issues described by the biobanking stakeholders within these interviews. One group of participants gave examples of successful (but challenging) re-consenting procedures that were used before the new law was passed:

"I28: Yes, we have material in our older trials, [...] fifteen years ago [...], it wasn't yet so standardised [...] we've actually had to go back and re-consent for a trial where we had eight thousand patients, and it crossed really all the continents, so it was highly intense work that took a lot longer than anticipated. [...] it's not so easy to go back to patients who've been on the trial for eight years or so [...] But in fact we generally received a very good positive response."

I24: "[...] usually if you go back and you have anonymised data, you can do it, but it's work. It's work."

As the guidelines allow the use of samples without consent only when it is impossible to obtain a re-consent, these individuals present cases in which the corresponding paragraphs are not applicable.

Many persons mentioning the samples without consent, however, characterise the process of obtaining re-consents as almost impossible:

"I12: [...] many of the cases of course from the old [...] samples, we don't have any consent. [...] And most of the people [...] already died. And it's very hard to ask for a consent to go to the relatives [...]. So it's, it's problematic. And that's why we explain the ethic committee this this ethic problems. And it depends on the ethic committee, they say ok, no or yes."

"I21: it's a theoretical possibility, [...] I don't think we've done that here, re-consented patients, we might have gone back to ethics committee. [...] But not all the way."

"I18: [...] If you connect every donor twenty years ago ... "Hello, we have... do you remember you had this operation in 1999 and we have still a little bit material of your stomach, and now we want to do research with it, do you agree or not?" [...] they won't do it."

Discussion

In general, two aspects of our findings are particularly notable:

- 1) Although general consent is not only tolerated but explicitly recommended by the Swiss Academy of Medical Sciences, researchers perceive difficulties in using general consent mechanisms for their research. An important factor seems to be ethics committees' reluctance concerning the approval of general consent forms.
- 2) Instead of obtaining general consent, many researchers reported experiences with using large numbers of samples without explicit consent and the procedure of re-consenting - despite the associated difficulties.

Different types

Overall, the issue of informed consent has been widely discussed in the literature, which could be one of the reasons that many interviewees mentioned it without being asked.¹²⁻¹⁶ At the same time, it may also be one of the major issues in their everyday work, so that it came to their minds immediately when talking about dealing with their samples.

The stakeholders' predominant opinion – a preference for general consent due to several difficulties with more restricted versions – is supported by theoretical claims in the literature:

According to Widdows and Cordell¹³ there are several reasons why a narrow informed consent as defined by the Nuremberg Code³ is inappropriate for biobanking. This is in line with the responses of those interviewees, who explained that they preferred general consent to specific consent: They explicitly mentioned the difficulty in providing information about – unknown – prospective research

³ <http://history.nih.gov/research/downloads/nuremberg.pdf>

and to address the donors several times, especially when they work with large sample sizes or over a longer time span.

Considering these reasons, the question is what obstacles obstruct the use of general consent within research institutions. One suggestion mentioned by a minority of stakeholders was the unwillingness of patients to give general consent. Caulfield et al¹⁷ have argued that one-time consent violates the individual's autonomy, and even a carefully developed and long discussed general consent is useless if people are not willing to sign it. However, Elger and Caplan² mention broad acceptance of general consent among donors, and a review by Wendler¹⁸ comes to the same conclusions. These findings support some interviewees' assumptions about patients' potential willingness to cooperate, even when they cannot be informed about details of future projects.

If general consent forms were adopted as a standard, the necessity for reconsenting procedures would become redundant in most cases, and the potential conflicts between researchers and ethics committees regarding the applicability of national and international guidelines could be avoided.

The ethics committee

Although empirical studies suggest many ethics committees have not yet done so,¹⁹ some recent findings suggest that there are several reasons for them to agree to general consent. It is not self-evident that specific consent protects patients' rights while general consent does not. If people are motivated to think altruistically when a general consent form is presented to them,¹⁴ there are even ethical reasons to prefer general consent. In many cases, such as genetic research, a person can have a good reason not to sign a general consent form. However, a partially restricted consent that excludes certain research areas can still be an alternative to the burdensome reconsenting that has to be obtained for every new project.² The inability to provide detailed information about future projects, especially when it comes to data and sample sharing, is characteristic of biobanking¹³ and must be considered when approving the type of consent for a biobank. Furthermore, as interviewee 2 points out, ethics committees cannot make moral decisions for patients and researchers. It is important not to give the impression that having an approved (general) consent form means that it is a moral imperative to sign it. To make an autonomous decision and give informed consent, patients must have a real choice.²⁰ The expectation that researchers will reconsult patients is highly demanding, and international guidelines as well as similar provisions in Art. 34 of the Swiss Human Research Act⁴ that will come into force in 2014 or 2015 facilitate research by defining circumstances in which it is allowed to proceed without consent.

Samples without consent

Reconsenting is commonly considered "logistically impracticable, prohibitively expensive and, in the case of long term projects where the donors have died, impossible".¹⁷ This position is supported by several of our interviewees' statements. In particular, in those cases when patients have died and relatives are asked to agree on behalf of them, the question is whether this process is in some cases more "harmful" to the relatives than the use of the sample without reconsult would have been to the person that passed away – although proceeding without the relatives' consent could be against their will in certain cases, too.

Although some stakeholders state that the reconsulting process is possible, the majority of them describe it as cumbersome and time-consuming. According to the Declaration of Helsinki the ethics committee has to decide whether the conditions for a use without consent are met. Thus, there is a shift for the researchers from simply obeying the law to negotiating with an ethics committee. On the one hand, if the committee is permissive this can result in a successful use of huge numbers of samples from pathologies that were taken long times ago. On the other hand, It can be argued that a better (international) communication structure between biobanks could improve sample access in certain cases even without using samples without consent. However, there is a possibility that, given

⁴ <http://www.bag.admin.ch/themen/medizin/00701/00702/07558/>

the option of using samples without consent, researchers might make less effort to obtain general consent in the first place, and consider the procedure of a retrospective permission via an ethics committee as simpler. What was meant to be an exception could therefore become the standard, excluding donors from the process in an unethical misuse of the consent procedures.

Conclusion

The findings of this study give an overview of biobanking stakeholders' opinions about challenges they face concerning informed consent and the ethics committees. First, it can be stated that despite a lack of legal or guideline-based barriers to general consent, both stakeholders (although only a minority) and ethics committees have reservations about this method of consent. The aspects involving ethics committees suggest that further research is needed regarding their role in biobanking research in general and in dealing with consent for previously obtained samples in particular. Second, it can be concluded that greater awareness of donors' opinions and preferences and the content of guidelines and recommendations could be helpful for a better justified perspective of biobanking stakeholders and ethical committee members, equally. And third, it may be necessary to differentiate between future procedures – where general consent is clearly desirable – and the use of old yet still relevant samples – where the option of using them without consent can be highly beneficial for research.

References:

1. Cambon-Thomsen, A., Rial-Sebbag, E. & Knoppers, B.M. Trends in ethical and legal frameworks for the use of human biobanks. *Eur Respir J* **30**, 373-82 (2007).
2. Elger, B.S. & Caplan, A.L. Consent and anonymization in research involving biobanks - Differing terms and norms present serious barriers to an international framework. *Embo Reports* **7**, 661-666 (2006).
3. Law, I. Respect for autonomy: its demands and limits in biobanking. *Health Care Anal* **19**, 259-68 (2011).
4. Karlsen, J.R., Solbakk, J.H. & Holm, S. Ethical endgames: broad consent for narrow interests; open consent for closed minds. *Camb Q Healthc Ethics* **20**, 572-83 (2011).
5. Caulfield, T. & Kayet, J. Broad Consent in Biobanking: Reflections on Seemingly Insurmountable Dilemmas. *Medical Law International* **10**, 85-100 (2009).
6. Hansson, M.G., Dillner, J., Bartram, C.R., Carlson, J.A. & Helgesson, G. Should donors be allowed to give broad consent to future biobank research? *Lancet Oncol* **7**, 266-9 (2006).
7. Helgesson, G. In Defense of Broad Consent. *Cambridge Quarterly of Healthcare Ethics* **21**, 40-50 (2012).
8. Sheehan, M. Can Broad Consent be Informed Consent? *Public Health Ethics* **4**, 226-235 (2011).
9. Ludman, E.J. *et al.* Glad you asked: Participants' Opinions of Re-Consent for dbGaP Data Submission. *J Empir Res Hum Res Ethics* **5**, 9-16 (2010).
10. Clayton, E.W. Informed consent and biobanks. *J Law Med Ethics* **33**, 15-21 (2005).
11. Shaw, D.M., Elger, B.S. & Colledge, F. What is a biobank? Differing definitions among biobank stakeholders. *Clin Genet* **85**, 223-7 (2014).
12. Whitley, E.A., Kanellopoulou, N. & Kaye, J. Consent and research governance in biobanks: evidence from focus groups with medical researchers. *Public Health Genomics* **15**, 232-42 (2012).
13. Widdows, H. & Cordell, S. The ethics of biobanking: key issues and controversies. *Health Care Anal* **19**, 207-19 (2011).
14. Pullman, D. *et al.* Personal privacy, public benefits, and biobanks: A conjoint analysis of policy priorities and public perceptions. *Genet Med* (2011).
15. Forsberg, J.S., Hansson, M.G. & Eriksson, S. Biobank research: who benefits from individual consent? *BMJ* **343**(2011).

16. Salvaterra, E. *et al.* Banking together - A unified model of informed consent for biobanking. *Embo Reports* **9**, 307-313 (2008).
17. Caulfield, T., Brown, R. & Meslin Eric, M. Challenging a Well Established Consent Norm?: One Time Consent for Biobank Research. in *Journal of International Biotechnology Law* Vol. 4 69 (2007).
18. Wendler, D. One-time general consent for research on biological samples. *BMJ* **332**, 544-547 (2006).
19. Porteri, C., Togni, E. & Pasqualetti, P. The policies of ethics committees in the management of biobanks used for research: an Italian survey. *Eur J Hum Genet* **22**, 260-5 (2014).
20. Whitney, S.N., McGuire, A.L. & McCullough, L.B. A typology of shared decision making, informed consent, and simple consent. *Ann Intern Med* **140**, 54-9 (2004).

PART 4: DISCUSSION

4.1 1 MAJOR FINDINGS

The results of this study provide unique insight into a field which has huge implications for biomedical research in Switzerland, yet until now has never been explored. Biobanks are indispensable tools for research, and permit projects on a scale far beyond what many research groups are able to achieve through solo sample collection. Although Switzerland has a strong biomedical research tradition, and multiple research centres, no examination has been made into the best methods to optimize these resources. Our study is the first to approach biobank stakeholders themselves in order to address the issues brought up by sample sharing. Without the views of individuals involved in the field, any attempt to change the biosample practices of a country risks missing the needs, desires and interests of those who will use any developing infrastructure. This is particularly important at a time of change in the biobanking field, which was the case as we carried out our study; national guidelines, the law, and existing biobanking infrastructure all made significant changes around this time. This study provides a comprehensive chronicle of the spectrum of issues which currently affect biobanks and their stakeholders in Switzerland.

Given the exploratory nature of our research, and the desire for a narrative structure for our results, semi-structured interviews producing qualitative was the optimal approach. This technique ensured that as many relevant issues as possible would be identified and addressed, and absolute necessity given the lack of existing research in this area, and the consequent potential for missing important issues if quantitative measures were employed. It must also be borne in mind that this is, in some aspects, a delicate matter; questions were asked which had the potential to produce “socially unacceptable” answers, or at least answers which might make the interviewee appear as an unsympathetic colleague or research partner. Our results bore this out, with contentious comments concerning networking, definitions and authorship in particular. For this reason, it was also important that we were able to offer and preserve strict anonymity for our interviewees.

Furthermore, the foundation for the empirical investigation was laid by extensive literature. This was a further essential step in developing the project, as it served to validate the research question, and fill in “background” details concerning international developments the responses of ethical committees to the shifting landscape in biobanking.

That both the theoretical and empirical parts of this study were unique and of value to the research community has been confirmed as the project moved forward. In 2012, a redrafting of the Declaration of Helsinki was undertaken. I presented our views to the World Medical Association Satellite Meeting in Rotterdam in June. In 2013, a revised version of the Declaration was published, which incorporates one of the amendments we discussed; the word “impractical” is now replaced by the stricter term “impracticable” in what is now Paragraph 32.¹

Drawing on empirical data from a previous study, we presented an analysis of the approach that a number of Swiss ethics committees took to requests for research with human tissue samples in 2010. Our findings indicated that sample requests are handled differently in different cantons, and that even within committees, confusion can exist about the committee policy on such requests. Since this

data was gathered, the Humanforschungsgesetz has come into force in Switzerland, which provides concrete guidance on correct protocol with human tissue samples.

That the issues identified in our empirical research are of importance in the biobanking field has also been validated by literature published in the past 12 months.

Wei and Simpson (2013) discuss the importance of biosample quality, emphasizing that consistent, standardized sample processing is essential for later use,² as do McQueen *et al* (2013).³ Solutions for global harmonization practices have also been put forward; there has been a move from suggested innovations to locally piloted practices which may be adapted to a larger scale.⁴⁻⁶

Other technological innovations include new Electronic Laboratory Notebooks to facilitate data sharing between labs, a preferable alternative to the older paper versions.⁷ The value of linking, for example between cohort studies and disease registries, is reiterated in articles such as that by Brescianini *et al* (2013), who report on the development of the Italian Twin Register, permitting statistically strong research on heritable disease.⁸ Finally, Brochhausen and colleagues (2013) detail their development of an “ontology”, a tool which enables numerous variables (in this case, the focus is on administrative aspects) to be sought from biobank databases.⁹

From the legal perspective, Soini (2013) details Finland’s new Biobank Act, in force from the 1st of September 2013, which, among other things, aims to facilitate the use of older samples and data, for which current consent standards may be lacking.¹⁰ There are also limits imposed on a biobank’s ability to restrict access to its database after it has been queried by researchers. Black *et al* (2013) also summarise 23 laws and guidelines which address the requirements for the disclosure of incidental findings, and examine the financial implications of this from the biobank perspective.¹¹ This is a potentially large added burden that many researchers may not have fully considered, and preparation for the need to disclose such findings is essential; careful checking of local ethical and organisational requirements is key.

Hofman *et al* (2014) specifically address the issue of making biosamples accessible, again with an emphasis on quality, although their article pertains to public-private partnerships, rather than general biobanking.¹² They explain that biobanks have different goals, and therefore, values, depending on the particular sphere in which they find themselves: public interest is for health care and research purposes, while private interests are in commercial drug and test development. This disparity is one cause of incompatibility of samples and data (which may be gathered, stored and recorded according to the foreseen use); another problem is the development of material transfer agreements which enable publicly collected samples to be put towards private ends. Accreditation of biobanks is also recommended to guarantee a level of “professionalism”, which allegedly brings with it assurances of quality and reliability.

Hirschberg, Knuppel and Strech (2013), in an innovative article, compare the consent forms of 30 German biobanks, and find significant variation in the content and wording of the documents.¹³ They note that this threatens biobank networking opportunities, due to the potential incompatibility of samples with institutional ethics requirements. That such problems persist, even at the national level, is an indication that the harmonization of biobanking practice continues to lag behind its technological development.

Finally, the argument that the needs of stakeholders, rather than the basics of biobanking, must be the focus of biobankers, is supported in an article by Simeon-Dubach and Watson, who suggest that the current generation of biobanks must enhance their value with regard to the requirements of stakeholders, and ensure their own sustainability.¹⁴ They suggest that greater focus on quality, stock management and accreditation are all important for the biobank, while researchers can play their part by reporting their research findings each time they use specimens from a particular bank. In this way, a system of mutual benefit, trust, and also professionalism is developed.

A number of other articles reiterate the issues identified in this thesis without making a new contribution to the discussion of solutions. The harmonisation of guidelines, and detailed attention to the ethical requirements of governing tissue sample transfer continue to pose a challenge;¹⁵ the underuse of samples is still a significant concern, as reported in a survey of 456 biobanks in the United States,¹⁶ and the trend towards broader consent with ethical committee oversight continues.¹⁷

This thesis is the first work targeting the obstacles specific to the evolution of biobanking, and collecting the experiences of those affected. The literature to date has supported the importance of troubleshooting in this area, yet concrete goals and solutions are still lacking. The results presented here are all points which must be considered in further efforts to harmonise biosample sharing at all levels. In the following sections, the practical importance of these findings is supported by a normative examination of the extent to which sharing can be required. Finally, the implications for future research are addressed.

References:

1. Declaration of Helsinki, amended by the 64th WMA General Assembly, Fortaleza, Brazil, October 2013. (2013).
2. Wei, B.-R. & Simpson, R.M. Digital pathology and image analysis augment biospecimen annotation and biobank quality assurance harmonization. *Clinical Biochemistry*.
3. McQueen, M.J., Keys, J.L., Bamford, K. & Hall, K. The challenge of establishing, growing and sustaining a large biobank: A personal perspective. *Clinical Biochemistry*.
4. Filocamo, M. *et al.* Telethon Network of Genetic Biobanks: a key service for diagnosis and research on rare diseases. *Orphanet J Rare Dis* **8**, 129 (2013).
5. Bravo, E., Napolitano, M., Santoro, F., Belardelli, F. & Federici, A. The Italian Hub of Population Biobanks as a Potential Tool for Improving Public Health Stewardship. *Biopreservation and biobanking* **11**, 173-175 (2013).
6. <http://www.datashaper.org/>.
7. Voegelé, C. *et al.* A universal open-source Electronic Laboratory Notebook. *Bioinformatics* **29**, 1710-2 (2013).
8. Brescianini, S. *et al.* An update on the Italian Twin Register: advances in cohort recruitment, project building and network development. *Twin Res Hum Genet* **16**, 190-6 (2013).
9. Brochhausen, M. *et al.* Developing a semantically rich ontology for the biobank-administration domain. *J Biomed Semantics* **4**, 23 (2013).
10. Soini, S. Finland on a road towards a modern legal biobanking infrastructure. *Eur J Health Law* **20**, 289-94 (2013).
11. Black, L. *et al.* Funding considerations for the disclosure of genetic incidental findings in biobank research. *Clinical Genetics* **84**, 397-406 (2013).
12. Hofman, P., Brechot, C., Zatloukal, K., Dagher, G. & Clement, B. Public-private relationships in biobanking: a still underestimated key component of open innovation. *Virchows Arch* **464**, 3-9 (2014).

13. Hirschberg, I., Knuppel, H. & Streh, D. Practice variation across consent templates for biobank research. a survey of German biobanks. *Front Genet* **4**, 240 (2013).
14. Simeon-Dubach, D. & Watson, P. Biobanking 3.0: Evidence based and customer focused biobanking. *Clinical Biochemistry* **47**, 300-308 (2014).
15. Staunton, C. & Moodley, K. Challenges in biobank governance in Sub-Saharan Africa. *BMC Med Ethics* **14**, 35 (2013).
16. Henderson, G.E. *et al.* Characterizing biobank organizations in the U.S.: results from a national survey. *Genome Med* **5**, 3 (2013).
17. Arias-Diaz, J., Martin-Arribas, M.C., Garcia del Pozo, J. & Alonso, C. Spanish regulatory approach for biobanking. *Eur J Hum Genet* **21**, 708-12 (2013).

4.2 2 IS THERE A DUTY TO SHARE? ETHICAL APPROACHES AND NORMATIVE IMPLICATIONS

Calls in the literature for increased biosample and data sharing emphasise the research possibilities which will follow such action.^{1,2} These appeals are made on pragmatic grounds, but must navigate obstacles which are not only logistical, but also ethical. This was validated by our findings with regard to territoriality and fair sharing practices. Consequently, there arises the possibility that action to increase sample sharing must consider another set of questions: is there an ethical duty to share samples and data? What is the basis of such a duty, and how far does it extend? What are the normative implications? And how does the duty to share conflict with other ethical requirements in biobank research?

To date, there has been to our knowledge no discussion of the questions posed above in relation to biobanks. Simple data sharing receives attention in the context of particular circumstances: in the case of the return of genetic results,³ or conceived as a responsibility to make one's genetic test data available for research purposes.⁴ There is also discussion of the placement of genomic data in a forum accessible to researchers on a global scale.⁵ It must be borne in mind that in the first two of these examples, the "sharing" in question is a form of "publication" of data, rather than an act of permission to use raw materials. In sharing biosamples and data for research purposes, a biobank or research is giving another party access to a resource that the party is likely to benefit from in a professional sense. By contrast, making data on incidental findings available to research participants will not have this effect. Moreover, ethical arguments are rarely used in these discussions.

A moral duty to share can be grounded in the values of solidarity⁶, justice and beneficence.⁷ The duty may be limited by other duties; in the case of biomedical research, duties of patient confidentiality and one's professional contract could have competing claims.⁸ In order to assign a duty of sample sharing to biobank stakeholders, the basis for that duty, beyond pragmatic grounds, must first be concretely identified, and then competing duties balanced.

There is some precedent for the sharing of data-as-resource which is useful to consider in this context. Kaye *et al* (2009) describe the advances made in data sharing in genomic research, where resources such as the database of Genotypes and Phenotypes (dbGaP) supply researchers around the world.⁹ In this field, funders have come to require that study data be made accessible: "The rationale for these policies is that science and creativity are furthered by access to openly available data, and that data created by publicly funded bodies should be freely available in the research community." A moral duty is not directly appealed to; nevertheless, a requirement based on reciprocity is advanced, and it is one which overrides research-group interests to some degree.

Moral arguments come into play in an article by Langat *et al* (2011), which describes the difficulties of elaborating a data sharing policy in the context of public health emergencies.¹⁰ Crucially, they refer to the non-emergency context norm of scientists enjoying a "proprietary right" to the material derived from their own research efforts. The lack of internationally applicable documents on sharing have perpetuated a situation in which there is a tendency to shy away from data sharing, even in emergency cases of public health importance (the authors identify the example of the lack of international cooperation in the wake of the SARS pandemic in 2003).

Langat and colleagues advance three broadly consequentialist arguments against data sharing which they feel confident do not apply in the context of public health emergencies. First, that scientists

have some ownership over the data and samples that they have collected; second, that it would be unfair to force those who have exerted effort in collecting resources to simply give it to others who have not; and third, that the scientific landscape values commodities (essentially, publications) which sometimes require that data and samples be held by one research group only. Their counterclaims apply equally well to non-emergency situations: the authors point out that the “ownership” of research data is not a foregone conclusion, due to the public funding which supports it. Biobank material is therefore public in nature the way genetic material is “familial in nature”;¹¹ “Render unto Caesar,” etc. This public aspect demands a reshuffling of the concept of burden and fairness, entailing, in some cases, a duty to share samples in order to benefit the public. It is concluded that the nature of current scientific research, though it may depend upon publication figures, is also inextricably linked with collaboration, and cannot continue with it. Sharing by researchers is therefore not only not morally neutral; there exists a duty to share which, on this line of argumentation, clearly extends to biobanks and biosample collections.

Melton (1988), in an article which applies well to the particular case of biobanks, makes appeal to a moral argument based on openness being the gold standard of scientific research.¹² On this understanding, those engaged in this research are bound by a duty to openly share their data. Melton provides interesting challenges to this argument, and to the one above, citing authors who have suggested that privately funded research and the possible divergence of the interests of research participants and the general public make generalised claims for openness and sharing of data problematic. These counterclaims are compelling because they are made on moral, not pragmatic grounds. However, they do not inherently threaten the notion of a duty to share; rather, they refer to other duties which bind those engaged in research. In what follows, the question of competing duties will be examined.

It may seem a moot point to discuss a duty to share strictly in terms of biobanks (less official biosample collections are different, and the above arguments apply excellently). Biobanks are set up to share biosamples, after all. But two considerations must be remembered; first, the implications of a duty to share on the practice of biobanks, particularly those less well established, must be addressed; second, the conflict of a duty to share with other ethical duties will give rise to certain normative conclusions.

While a strictly deontological approach would be difficult to employ here, consequentialist and principlist theories of morality will have no difficulty embracing a duty of sharing. An ethical duty, grounded on public benefit, to share biosamples, requires that biobanks make their resources available to researchers who are able to demonstrate that they can carry out a potentially valuable research investigation using those samples. For biobanks set up to provide samples, this amounts to a negative duty to not prohibit access to suitable applicants. It is interesting to consider whether there might be a further, positive duty for biobank managers to ensure that their valuable resources reach as many interested parties as possible. A positive duty might entail some requirement to publicize the bank, a certain level of network involvement, and other strategies involving the bank as agitator.

It would be difficult to conceive of a positive duty of self-promotion for biobanks, and indeed on the practical level it would require effort and infrastructure beyond most existing banks. A negative duty, by contract, would seem to be an essential part of a biobank’s work, given biobanks’ status as publically supported, in part publically funded, research resources for public health. It is interesting

to consider, in light of Lagat *et al's* arguments, to consider to what extent such a negative duty can be extended to unofficial biobanks, sample collections of the type discussed in this thesis. If a duty to share on the basis of public good exists, can it be said to apply to all those who have potentially useful samples and data?

At several points in this thesis, the heterogeneity of sample collections has been commented upon, together with the consequence that this makes distinguishing biobanks from mere sample collections difficult, if not impossible. It has been suggested that intended use of the material (and again, this is tricky, given the unforeseeable nature of much biosample research) plays a role in determining the type of collection. Material for research purposes is fundamentally different from material for diagnostic, quality control, or as yet unspecified purposes. This is because the tissue donor has agreed to uses of the sample on the understanding that it may, if only to a small degree, contribute to useful findings on a particular research question. While this argument rests on the assumption that appropriate consent was obtained for the sample, it is plausible to suggest that in the great majority of research with human tissue and data, informed consent ought to be obtained, and its absence justified by suitably difficult circumstances, as discussed in Chapter 2.2 on the Declaration of Helsinki. Samples and data with research uses therefore fall into the category of material which can further the public good, and can therefore conceivably entail a duty of sharing.

As noted above, other duties, long-established in medical research, are also a factor in research with human biosamples and resulting data. Doctor-patient confidentiality, respect for the limits of informed consent, and ethical requirements for proper study procedures all entail duties, indeed positive duties, to handle material in a certain way, and often that will place some *prima facie* limiting factor on sharing. In the case of biosample sharing, it has been argued that these duties might be less respected by secondary researchers, removed from the data collection and consent process, than by the initial investigators.⁹ This, however, is not an exceptional circumstance in medical research ethics; frequently, duties will conflict, such as in cases where beneficence appears to conflict with autonomy,¹³ or in case of incidental research findings not foreseen when the study was designed.¹⁴ A review of health care practices by the National Information Governance Board in England concludes that “The duty to share information can be as important as the duty to protect patient confidentiality.”¹⁵ Bioethics consists of analysing and balancing such duties, and the result is typically a guideline document presenting a consensus, and subsequent proper practice. The duty to share biomedical research material is, to date, missing from most guideline documents.

The reason for enshrining a duty in a document is not simply a recognition of its importance, but a sign that it is not to be violated, despite the fact that it may well be an individual's or a research group's interest to do so. Guidelines for biomedical research balance duties, yet also enforce them (in so far as possible) by placing duties before pure scientific interest in the hierarchy of research values. It might be of benefit to the public, in pure health terms, to allow unrestricted access to any biosample and data, without the requirement for informed consent, but this would violate numerous patient and practitioner rights, and consequently, it is forbidden. By the same token, it might be desirable for certain research groups to monopolise sample and data pools, and this might even lead to a significant discovery by that group; in the view of Cambon-Thomsen (2004), “...many restricted uses and opposition to sharing bioresources are a result of intellectual property rights or the control that scientists want to exert on the biobanks they have established with great effort, rather than ethical issues related to respect for the individual rights of donors.”¹⁶ It is, however, worth noting the

possibility that in many cases, the work of individual research groups may in fact be far less disadvantaged that might be assumed.¹⁷

In the presence of continued conflict, it is up to national and international bodies to weigh interests and safeguard patients; but for this to be carried out properly, the possibility that there is a duty to share biosamples and data must at the very least be considered.

References:

1. Marx, V. My data are your data. *Nat Biotech* **30**, 509-511 (2012).
2. Sharing public health data: necessary and now. *The Lancet* **375**, 1940 (2010).
3. Knoppers, B.M., Joly, Y., Simard, J. & Durocher, F. The emergence of an ethical duty to disclose genetic research results: international perspectives. *Eur J Hum Genet* **14**, 1170-1178 (2006).
4. Malm, H. Genetic Privacy: Might There Be a Moral Duty to Share One's Genetic Information? *The American Journal of Bioethics* **9**, 52-54 (2009).
5. Callier, S., Husain, R. & Simpson, R. Genomic data-sharing: what will be our legacy? *Front Genet* **5**, 34 (2014).
6. Harmon, S.E. Solidarity: A (New) Ethic for Global Health Policy. *Health Care Analysis* **14**, 215-236 (2006).
7. Lévesque, E., Joly, Y. & Simard, J. Return of Research Results: General Principles and International Perspectives. *The Journal of Law, Medicine & Ethics* **39**, 583-592 (2011).
8. Brakewood, B. & Poldrack, R.A. The ethics of secondary data analysis: Considering the application of Belmont principles to the sharing of neuroimaging data. *NeuroImage* **82**, 671-676 (2013).
9. Kaye, J., Heeney, C., Hawkins, N., de Vries, J. & Boddington, P. Data sharing in genomics [mdash] re-shaping scientific practice. *Nat Rev Genet* **10**, 331-335 (2009).
10. Langat, P. *et al.* Is There a Duty to Share? Ethics of Sharing Research Data in the Context of Public Health Emergencies. *Public Health Ethics* (2011).
11. Liao, S.M. Is there a duty to share genetic information? *J Med Ethics* **35**, 306-309 (2009).
12. Melton, G. Must researchers share their data? *Law and Human Behavior* **12**, 159-162 (1988).
13. Beste, J. INSTILLING HOPE AND RESPECTING PATIENT AUTONOMY: RECONCILING APPARENTLY CONFLICTING DUTIES. *Bioethics* **19**, 215-231 (2005).
14. Meacham, M.C., Starks, H., Burke, W. & Edwards, K. Researcher perspectives on disclosure of incidental findings in genetic research. *J Empir Res Hum Res Ethics* **5**, 31-41 (2010).
15. Dyer, C. Review recommends duty to share data when in patient's best interests. *BMJ* **346**(2013).
16. Cambon-Thomsen, A. The social and ethical issues of post-genomic human biobanks. *Nat Rev Genet* **5**, 866-73 (2004).
17. Prepublication data sharing. *Nature* **461**, 168-170 (2009).

4.3 IMPLICATIONS FOR FUTURE RESEARCH

Our data is exploratory, and we have presented our results in a descriptive form, as is appropriate to the aims and methods of our study. We set out to identify obstacles to biosample sharing in Switzerland, and met this goal. However, we have only briefly touched on the potential solutions to these problems; and, as with any research project, the answers that we found lead themselves to further questions.

First, our empirical data was drawn from a relatively small pool of individuals working in a single country. While, as we have explained, our interviewees in fact represent a large percentage of those working in the field in Switzerland, and the majority have had international work experience, we cannot generalize our findings to the global level. Hence, a fully comprehensive approach to the barriers to sample sharing must involve international data gathering. It would be extremely illuminating to compare the results of such a study to the results of our literature review.

Second, the issue of networking, both formal and informal, professional visibility (largely web-based), and the role of personal contacts, is perhaps the key theme of this dissertation. It is addressed in detail, and held in high importance, by our interviewees, and also plays a role in questions of fairness and authorship. Therefore, a detailed examination of biobanking networks, their aims, successes, failures, and future development, is crucial in the further development of the field as a whole. A large variety of networks already exists, and implement numerous harmonisation measures; however, the fact that even networks are numerous and diverse contributes to the fractured nature of biobanking. In a field that is driven by researchers, rather than oversight bodies, incentives for universal collaboration are essential, and networking systems promise this. The limitations of these organizations are likely to have a negative impact on biosample sharing. Further research into the optimal way to broaden participation in biobanking networks is therefore an important future avenue.

Our conclusions about future directions regarding authorship agreements for biosample use, and transparency of documents to ensure fair sharing, can be found in the Discussion sections of each of these articles. We have also recommended a definition that we feel is appropriate to ensure the regulation, not “strangulation”, of researchers who work with human biosamples.

Finally, in order to understand what researchers would benefit from in the biosample research, it would be beneficial to address not simply the obstacles to current practices, but the views of stakeholders about their desires for the development of their fields of research. Adopting this “positive” questioning tactic will allow for the development of new, perhaps unforeseen measures which might unite researchers with valuable biosamples, rather than simply seeking to make alterations to existing patterns of sample identification and requests. Examples of this approach include questioning stakeholders on the ideal sample size, type, and population for their research, and on the multidisciplinary expertise required to design new projects. Biobanking is in itself a new technique, enabling research on a scale which previously was virtually impossible. Thus, it is an ideal field in which to pilot new research methodologies; future research must take this into account, and foster its full potential.

4.4 CONCLUSION

A number of conclusions regarding the barriers currently affecting biobanking in Switzerland are made in this thesis. It is possible to classify them in two catch-all themes; transparency and information. We have suggested that clarity and transparency is required in the written material which governs human biosample transactions: this includes the wording of governing documents, inter-biobank transfer agreements, authorship agreements and the nomenclature used to describe samples; it extends to the definition of the term “biobank” itself. This must be promoted by consensus documents created by stakeholder groups and can be facilitated by the international networks such as ISBER and BBMRI. We have suggested that biobank stakeholders must be informed about the potential for collaboration, existing infrastructures, and potential research partners, and that ethical committees which deal with human tissue research must be informed about the appropriate regulations and content of this research. This is more difficult to accomplish, as it is not the responsibility of any party, other than the biobanker him or herself, to promote participation in networks and seek out researchers with common goals; hence, the risk is that those who are in the dark will stay in the dark as they remain unaware of the possibilities for broader networking. However, cautious optimism about the work of Biobank Suisse and ESBB is warranted, as these organizations actively seek to identify biobank stakeholders and encourage membership. A decision not to participate is at the discretion of the stakeholder. While other barriers to biosample sharing were identified, limitations to transparency and information encompass those which are truly significant for the stakeholders we interviewed. These are directions which require attention to minimize obstacles to biosample exchange, which should, in turn, allow for promising research to progress.

4.5 APPENDICES

4.5.1 INTERVIEW GUIDE

Intro for interviewee

To get started we will ask you questions about

1. yourself and the biobank(s) you are associated with, then
2. we will ask you questions about your experiences with and views on sharing samples and data, and finally
3. we will ask you about your views on fair and just sharing practices.

Our interview method is semi-structured meaning that we will ask you questions regarding a topic but you have a lot of leeway on how to answer. Of course, you don't have to answer all the questions if you don't have an opinion or don't have the information. Overall, we want you to tell us what you think is important about each topic so we want to hear your ideas even if our question may not have anticipated your answer. That being said, because we know your time is precious, and we don't want to over stay our welcome, we may sometimes guide you away from a theme or have to stop discussion about one topic in order to make sure that we get information on all the basic themes of our study.

Regarding confidentiality of the information you provide, we want to remind you that the link between your identity and your answers will be coded and the only persons with access to the code will be the researchers Heidi Howard, Flora Colledge and Bernice Elger.

Now, before we begin, may I ask you how much time you have scheduled for this interview today so that I can judge, as we progress through the questionnaire, how much time we have left.

QUESTIONNAIRE

Information about the Interviewee (part of this information will be pre-filled, so this may be more of a verification)

- 1- What is your Primary affiliation
- 2- How would you identify your primary work functions/activities as being:
 - a. Do you mainly do research? Clinical activities? Managerial or administrative tasks?
- 3- Number of years in post:
- 4- What field is your formal training/education in? Medicine, health science, humanities?

Information regarding the biobank and the interviewees role with the biobank(s)

1. What biobank(s) are you associated with/ work with?
 - a. If more than one, choose one or two to discuss, but make sure it is clear what scenario is being discussed
2. Can you tell us about the biobank and your role/involvement in it? (any documents, links, etc. are welcome)
 - a. See below for the specific information wanted re: bbk. If they don't answer all these questions on their own, ask directly.
3. Just to clarify, are you involved with an official bbk as well as being involved with the gathering of samples for a research or clinical lab?
 - a. Do you see these as being one in the same?
 - b. If not, when you answer the questions, please specify which scenario you are referring to.

Information about Biobank

2. What is the Name of bbk(s)?
3. What is the primary Location?
4. Is the BBK part of a larger network?
5. What is the main goal of the bbk?
6. Is it recognized as an official bbk?
7. How would you classify the bbk?
 - i. Are both samples and data banked?
 - ii. What type of data: clinical, molecular & lifestyle/environmental?
 - iii. What type of Samples: tissue, genetic
 - iv. Is the bbk a private or public entity?
 - v. Is the bbk for profit?
 - vi. Is the main goal of the bbk for clinical or research purposes?
8. *What type of biobank is it? In their own words*

9. Who collects/donates the samples?
10. Who makes the decisions about sharing samples/data?

How would you define a biobank? Basic

Questions re: Sharing/providing

Before we begin, please note that throughout we will be talking about the sharing of samples and/or data. If you feel like you want to distinguish between the two please let us know.

1. **Are you sharing** (define sharing as providing) biological samples and/or data from:
 - i. **your lab to other labs**
 - ii. your lab to a biobank
 - iii. from the biobank to other labs or biobanks

VIP!! with scientists, if not explained earlier, please specify the possible contexts of sharing: are you talking about sharing samples/data from your lab to other labs or a bbk? Or are you talking about how the bbk shares?

For the rest of the questions, it could be important to specify the context (i.e.: the researchers' view/practices vs. the bbk's view/practices

- a. **YES: Who do you share the samples with?**
 - i. A bbk? If so are you aware how the (the bbk) shares?
 - ii. With researchers Regionally, Nationally or Internationally?
 - iii. As part of a network(s)? which ones?
 - iv. Ad hoc? Organized?
2. **YES: If you do share, Why have chosen these partners/researchers?**
 - a. Are they part of the bbk?
 - b. Are they part of an organization?
 - c. Do you have an understanding with them? If so, what is it?
3. **NO: If you don't share, why not?**
 - a. What are reasons for you to decide not to share
 - i. via the formal channels (formal biobank)
 - ii. informal channels (colleagues and collaborators)
4. **Are you also borrowing (define as receiving) data/samples from a biobank or colleagues/collaborators?**

- a. Specify samples or data or both?
 - b. If yes with whom?
 - i. Regionally, Nationally or Internationally?
 - ii. As part of a network(s)? which ones?
 - iii. Ad hoc? Organized? Informal channels (with colleagues and collaborators)
5. **Do you feel like you have a responsibility to share your samples with other labs/bbks? What is the basis for this responsibility?**
6. **Could you give us a list of reasons/incentives/motivations why you share your samples/data?**
- a. via the formal channels (formal biobank)
 - b. informal channels (colleagues and collaborators from other labs)
7. **Are you aware of other motivations even if they don't apply to you personally?**
8. ***In practice*, what, according to you, is the most persuasive incentive to share samples and data?**
- i. Now, ***more theoretically***, can you think of any incentives, even if they don't exist at the moment, **that could encourage sharing?**
9. **Would payment** for access to your samples be an incentive for you to lend/share them?
- i. What about for other researchers/bbks
 - ii. Do you have (or plan for) a system of selling samples?
10. **Would authorship** on research publications be an incentive for you to share/lend your samples/data?
- i. What about for other researchers/bbks
- In practice, what do you expect to "get" or "obtain" when you share?**
- ii. Do you usually/always "get" this?
11. **Do you have reservations about sharing your samples/data?**

12. What, for you, are the disadvantages of sharing sample/data?

- i. Do you feel that sharing samples would/does involve a large drain on your time?

13. Why, in general, do you think researchers/bbks do not share samples/data?**14. What are the minimum conditions/criteria that need to be fulfilled in order for you to share data and samples?**

- i. Are there certain studies for which you would refuse to allow your samples/data to be used?
- ii. Have you ever denied anyone access to your samples? If so, what was the reason?

15. Do you (or the bbk you work with) have a “sharing” policy? If so,

- i. what is the policy?
- ii. What is it based on? Who designed it?
- iii. Is it official/formal/strict?
- iv. What “jurisdiction” does this policy have?
- v. In this policy, what do the researchers who donate samples get in return for sharing?
- vi. Do you have a policy on awarding publication credit for those who share/collect samples?
- vii. Do you think your policy (on publication credit?) gives fair recognition for the effort put in?
- viii. What do you think about your policy? What do you consider to be the good/bad things about your policy.

16. Have you, personally, encountered problems with sharing/borrowing (from your lab or from the biobank)?

- i. Can you give concrete examples of problems?

17. Are you aware of other problems even if you did not experience them personally?**18. What do you think are the biggest barriers to sharing samples/data?**

- i. Do you think these are the same for different contexts?
- ii. Why don't researchers share with bbks?
- iii. Why don't biobanks share with researchers?
- iv. Why can't researchers obtain samples/data?

19. Who do you think is responsible for the process of sharing and borrowing in biobanks?

- a. Who do you think has the responsibility of resolving problems?

20. In general, how do you see the present way of sharing data and samples?

- a. What is positive about it?
- b. What is negative about it?

Although some questions above have already addressed some of the issues concerning fair and just sharing, now we want to ask about your views specifically about justice and fairness of sharing

21. Do you find the present way of sharing data and samples “fair” within your bbk/lab?

22. In general (among other bbks and labs) do you think sharing is happening in a just way, or is it always the biggest labs who get the good samples? Is that fair?

- i. Is access to samples and data fair and equitable for all labs/researchers/bbks?
- ii. Are people getting the right amount of credit for the work they are doing?
- iii. Have you ever shared your samples/data and felt you were not properly recognized for this?

23. What do you consider “fair” sharing?

24. If it is not already the case, How could “fair” sharing be realised?

Now, we have almost completed the questionnaire, but before we end I have two last questions:

Are there any themes you feel we have not addressed about barriers to sharing that you think we should address?

Are you aware of any other Swiss Biobanks and/or of other persons that could provide us some information about sharing?

4.6 CURRICULUM VITAE

FLORA COLLEDGE BA (Hons.), MA

flora.colledge@unibas.ch
0041 (0) 7864 76749

Grellingerstrasse 64
4052 Basel, Switzerland

Education

- 2013 – Present **Departement für Sport, Bewegung und Gesundheit, Universität Basel**
Research Assistant & Lecturer
- 2011 – 2013 **Institute for Biomedical Ethics, University of Basel. PhD: 6 (summa cum laude)**
Doctoral Project: *A study of the barriers to sample and data sharing between biobanks in Switzerland.*
- 2009 – 2010 **King's College London. MA Medical Ethics and Law: Distinction**
Dissertation: *Moral particularism: a new approach to medical law, an unsuitable approach to medical ethics.*
- 2006 – 2009 **University of Reading. BA(Hons.) Philosophy and Politics: First Class**
Dissertation: *Can a system of private charity satisfy the Rawlsian difference principle more effectively than a welfare state?*
- 2004 – 2006 **University College Falmouth. Journalism Studies**
- 1999 – 2004 **European School of Brussels III. European Baccalaureate: 81.84%**

Awards

- 2015** Berner Suchtkongress Poster Prize: Implementation of a sports programme in opiate substitution therapy: experiences in heroin-assisted and methadone maintenance settings
- 2010** Eleanor Betsey Scowen Prize for Top Dissertation
Sir Eric Scowen Prize for Top Student
- 2009** Award for Top 3 grade in Politics
- 2008** Academic Achievement Award for top 10% of class
- 2007** Academic Achievement Award for top 10% of class

Languages

English native speaker, fluent in French and German, basic spoken Dutch.

Teaching

- 2013 – present:** Lecturer in Sport and Psychological Health
Seminar leader in Research Methods in Sports Science
- 2011** Coordinator and Lecturer for Biomedical Ethics course
Lecturer for Contemporary Debates in Bioethics course

2010 Tutor for Medical Ethics and Law seminars

Speaking & Presentations

2016 May European Opiate Addiction Treatment Association: “Qualitative and quantitative findings from a randomized controlled pilot study of exercise as an adjunct therapy in a heroin assisted treatment setting.”

2016 February Sportwissenschaftliche Gesellschaft der Schweiz: “Qualitative and quantitative findings from a pilot randomized controlled study of exercise as an adjunct therapy in a heroin assisted treatment setting.” (poster)

2015 July European Congress of Sport Psychology: “Physical activity as an adjunct treatment for opioid dependence: preliminary results of the PHAST study.” (poster)

2015 June Berner Suchtkongress: “Implementation of a sports programme in opiate substitution therapy: experiences in heroin-assisted and methadone maintenance settings.” (poster)

2012 November Joint Congress of the ESBB and Spanish National Biobank Network: “What’s in a name? Examining different definitions of the term biobank.” (poster)

2012 June WMA Satellite Meeting – Thinking Ahead – The future of the Declaration of Helsinki: “The impact of paragraph 25 on informed consent for biobank samples.”

2012 May ISBER Annual Meeting: “Barriers to Sharing in Biobanking: A Qualitative Analysis of Obstacles to Sample and Data Sharing Amongst Biobank Stakeholders in Switzerland.”

2011 October SAKK State of the Art Symposium in Oncology Research – Ethical Considerations: “Approaches and attitudes of ethics committees to research protocols involving human biological material (biobanks).”

Publications

Peer-reviewed articles

M. Gerber,* F. Colledge,* U. Pühse, E. Holsboer-Trachsler, S. Zimmerer, S. Brand. (*both authors contributed equally to this article) Sleep quality, sleep EEG pattern, mental wellbeing and cortisol secretion in patients with ruptured aneurysm post-treatment: A comparison with post-surgery meningioma patients and controls. *Neuropsychobiology (in press) (Impact Factor 2.26)*.

S. Brand, F. Colledge, N. Beeler, U. Pühse, N. Kalak, D. Sadeghi Bahmani, T. Mikoteit, E Holsboer-Trachsler, M. Gerber. The current state of physical activity and exercise programs (PAEPs) in German-speaking Swiss psychiatric hospitals – Results from a brief online survey. *Neuropsychiatric Disease and Treatment (in press) (Impact Factor: 1.74)*.

M. Gerber, S. Lemola, F. Colledge, N. Kalak, E. Holsboer-Trachsler, U. Pühse, S. Brand. Validation of the German Version of the Insomnia Severity Index in Adolescents, Young Adults and Adult Workers: Results from Three Cross-Sectional Studies *BMC Psychiatry (in press) (Impact Factor: 2.21)*.

F. Colledge, B. Elger, Impossible, impractical, and non-identifiable? New criteria regarding consent for human tissues research in the Declaration of Helsinki. *Published in Biopreservation and Biobanking (Impact Factor 1.5)*

F. Colledge, B. Elger, H. C. Howard. A review of the barriers to sharing in biobanking. *Published in Biopreservation and Biobanking (Impact Factor 1.5)*

F. Colledge, S. de Massoungnes, B. Elger. Consent requirement for research with human tissue : Swiss ethics committee members disagree. *Under review in Kennedy Institute of Ethics Journal (Impact Factor 0.96)*

D. Shaw, B. Elger, F. Colledge. What is a biobank? Differing definitions among biobank stakeholders. *Accepted for Publication in Clinical Genetics (Impact Factor 3.944)*

F. Colledge, B. Elger, D. Shaw. “Conferring authorship”: Biobank stakeholders’ experiences with publication credit in collaborative research. *Published in PLoS ONE (Impact Factor 4.09)*

F. Colledge, B. Elger. Getting a fair share: Attitudes and perceptions of biobank stakeholders concerning the fairness of sample sharing. *Accepted for publication in Bioethics (Impact Factor 1.333)*

F. Colledge*, K. Persson*, B. Elger, D. Shaw (*both authors contributed equally to this article). Sample and data sharing barriers in biobanking: consent, committees and compromises. *Accepted in Annals of Diagnostic Pathology (Impact Factor 1.085)*

Gerber, M., Brand, S., Herrmann, C., Colledge, F., Holsboer-Trachsler, E., & Pühse, U. Increased objectively assessed vigorous-intensity exercise is associated with reduced stress, increased mental health and good objective and subjective sleep in young adults. *In press in Physiology & Behaviour (Impact Factor 3.16)*

Book chapters

I. Otte, F. Colledge et al., 2012. Research with animals. Ethics and Law in Medicine and the Life Sciences: Practical Examples in Biology, Clinical Practice and Research. B. Elger, N. Biller-Andorno, B. Rüttsche(eds.)

F. Colledge et al., 2012. Plant ethics. Ethics and Law in Medicine and the Life Sciences: Practical Examples in Biology, Clinical Practice and Research. B. Elger, N. Biller-Andorno, B. Rüttsche(eds.)

Educational training undertaken during PhD

-“Bioethics Research: Contemporary Debates 2011.” Institute of Biomedical Ethics, Basel (2ECT)

-“Biomedical ethics.” Institute of Biomedical Ethics, Basel (3ECT)

-“Empirical research in bioethics: qualitative and quantitative methods I.” Institute of Biomedical Ethics, Basel (2ECT)

-“Bioethics Research: Contemporary Debates 2012.” Institute of Biomedical Ethics, Basel (2ECT)

-“Conducting Qualitative Research in Health: An Introduction to Qualitative Research Methods.” Swiss School of Public Health (1ECT)

-“The Development of Biomedical Ethics in Switzerland.” Institute of Biomedical Ethics, Basel (4ECT)

The following lecturers were involved in this training:

Prof. B. Elger

Dr. H Howard

Dr. Karin Gross

Dr. C. Jung

Dr. S. Engel