Chapter 2: Biobanks in the Literature

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1. Introduction

Population genomics recognizes that in order to completely understand common disease risk and human health, basic data is needed on genomic variation and on lifestyle behaviours and environmental factors. Hence, there is a need to carry out studies of normal genomic variation across whole populations (Khoury 2004). This requires the collection of biosamples and data on a longitudinal scale. Prior public consultation and engagement are a *sine qua non*. While the ethical frameworks and scientific norms by which existing or new database resources can be networked together are now being established (see especially the Public Project in Population Genomics), the literature is still replete with continuing criticism of population biobanks.[2]

Our review of the literature on the ethical and regulatory aspects of human genetic databases reveals numerous outstanding issues pertaining less to the very creation of biobanks than to the issues of consent to the use of the samples (see below 2.), confidentiality (see below 3.) and potential commercialization (see below 4.). The laws and policies governing these large scale resources have been examined elsewhere (Knoppers, Abdul-Rahman and Bédard 2007); the goal of this literature review then is to discern whether these three areas of discussion in the literature reflect a gradual

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[2] Population biobanks are "collections of biological materials having the following characteristics: "i. the collection has a population basis; ii. it is established, or has been converted, to supply biological materials or data derived therefrom for multiple future research projects; iii. it contains biological materials and associate personal data, which may include or be linked to genealogical, medical and lifestyle data and which may be regularly updated; [and] iv. it receives and supplies materials in an organized manner" (Council of Europe 2006, art. 17).

acceptance of the "legitimacy" of the approaches taken by the population biobanks or whether outstanding issues remain.

2. Consent

Consent of participants is a core issue (Uranga et al. 2005) since two interests are perceived as being at odds; 1) the protection of data, considering informatic technologies and 2) the importance of data sharing and access by the scientific community. Indeed, "informed consent is one part of honoring the contribution that the person is making to [the] advancement of knowledge" (Clayton 2005, 19). Informed consent to research includes information about the purpose, methods, risks and benefits of the study (Lipworth, Ankeny and Kerridge 2006; Knoppers 2005), security and access policies, future uses and commercialization. Population biobanks have unique features however.

For example, the Declaration of Helsinki requires that consent be specific to a clearly defined research project. The Declaration states:

> In any research on human beings, each potential subject must be adequately informed of the aims, methods … the anticipated benefits and potential risks of the study and the discomfort it may entail (World Medical Association 2000, art. 22).

Yet in population biobanks, unlike clinical trials of specific drugs or devices, specific future research uses cannot be identified at the time of consent (Knoppers and Kent 2006; Gibbons et al. 2005). The literature has debated this central issue extensively as well as those associated therewith, that is, the possibility of recontact (see below 2.1.) and the right to withdraw (see below 2.2.).

2.1. Future Uses and Recontact

At the outset, it could be argued that the requirement of a specific consent is met even in these infrastructures. Their epidemiological objectives are described, their nature is

longitudinal, the conservation of tissues and the mechanisms for the security of data are explained and governance structures for access and ethics review monitoring are ongoing. In other words, specific consent is given for the creation of a public resource to be used for future research subject to these conditions. If a competent adult decides that these conditions and protections are sufficient, why would such a specific broad consent not be valid? Two approaches have been suggested in the literature; the first is supportive of a broad consent and the second, recommends a layered consent.

Some authors support the decision of the National Ethics Committees of France and Belgium and of the HUGO Ethics Committee, which endorse the use of broad consent in this context (Gibbons et al. 2005). They maintain that under a broad consent regime, research participants may agree to future uses, including uses that are unforeseen at the time, although making the argument that such a broad consent has not been legally tested within Europe (Gibbons et al. 2005). The same is true in the United States where authors have approved the 1999 National Bioethics Advisory Commission of the United States that a consent for all the possible uses can be obtained at one time and further consent would not be required (Trouet 2003, 417). Obviously, proper governance and ethics approval would have to be in place.

Others suggest "layering the consent". Under this approach, a participant could make choices, such as limiting consent to research on a specific disease or request recontact for consent to any other research (Trouet 2003, 411.). In fact, open-ended consent may not be acceptable to a certain type of participants who would not want their sample to be used for certain types of research (Lipworth, Ankenny and Kerridge 2006). Such research

could include for example, psychiatric diseases, sexual disorders or where the research is of a commercial nature (Lipworth, Ankenny and Kerridge 2006; Trouet 2003).

It could be argued however, that contrary to a disease study, building a biobank for a large population study cannot be run with "individual" options. The participant would have to be contacted again and again with additional information for each new research project. Moreover, samples shared with other researchers would have to be labeled as to the type of research or the choice of diseases allowed (Lipworth, Ankenny and Kerridge 2006; Trouet 2003). Both requirements would be extremely onerous and impractical in longitudinal studies of large populations. Indeed, it is difficult to recontact donors who have died, or moved, or if alive consider it an invasion of their privacy or in some case may remind participants of a previous illness (W. Lipworth, R. Ankeny and I. Kerridge 2006). Finally, the possibility of research collaborations would be greatly narrowed under such an options approach.

In contrast, a one-time general consent "increases the scientific and social value of donated samples and lowers the costs of conducting research on them, eliminating the need to track the choices for each samples (W. Lipworth, R. Ankeny and I. Kerridge 2006). One-time consent allows for data-sharing and prevents constant recontact for new consent. This approach is strengthened by recent studies examining different consent options, in which 75-95% of the respondents were keen to give one-time general consent, while at the same time relying on ethics committees to decide on the use of their samples (Wendler 2006). At a minimum however, population studies should inform the public on a regular basis of the nature of ongoing research using the biobank. Furthermore, population studies may wish to update data and so should ask at the time of recruitment

for permission to recontact participants for this purpose. Such recontact would constitute a tacit renewal of consent and provides a renewed opportunity to withdraw.

2.2. Right to Withdraw

The Nuremberg Code explicitly established the right to withdraw (U.S. G.P.O. 1949-1953, art. 9), a liberty interest upheld in the Helsinki Declaration (World Medical Association 2000, art. B-22). Interestingly, the literature on biobanks is not unanimous on the exercise and extent of this right in the context of such population studies. Indeed, participants are often referred to as "donors" and so some would argue that as a "gift", samples and data cannot be returned or destroyed at the will of the donor, the gift having been transferred to the recipient biobank (*Washington Univ. v. Catalona* 2007). Furthermore, the absence of the potential of physical harm to the participant and considering that in contrast to clinical trials for example, such studies are considered minimal risk, the "right" has less meaning in this context (Helgesson and Johnsson 2005). Yet, the majority of authors would uphold the right to withdraw arguing that the corollary of a broad consent would naturally entail the right to withdraw over time considering the trust inherent in such longitudinal studies (Helgesson and Johnsson 2005).

Irrespective, there is a remarkable absence of discussion on the practical aspects of the exercise of the right. Data in population studies is longitudinal, aggregated and largely epidemiological in nature. The number of samples needed for statistical significance is enormous and on the whole there are no individual, clinically validated results. To that end, theoretically "withdrawal" can take several forms: destruction of remaining samples and no further use of data; anonymization of the samples and data but allowing future use and recall of any remaining samples including those that were transferred to outside

researchers as well as destruction of all data not already incorporated into datasets. This multiplicity of options may ultimately prove to be impractical in this context due to the sheer size and often indefinite length of population genomic studies. At the level of whole populations, it may be wise simply to state that data and samples will no longer be used in the future unless already published or in aggregated data sets. Indeed, for all intents and purposes, it is the protection of the confidentiality of the samples that in fact serves to counterbalance a broad consent.

3. Confidentiality

While unanimous on the need to protect confidentiality and put in place security measures, no field is more rife with terminological confusion and philosophical differences than that of the confidentiality of data (see below 3.1.). The mechanism chosen such as coding or anonymization can have great bearing on the possibility of communicating results (or not) back to participants (see below 3.2.).

3.1. Coding and Anonymization

All population studies have in place procedures to ensure the confidentiality of data, balancing possible "information" risks of identification of the participant against the need to have data useful for quality research (Uranga et al. 2005). A related issue (although not under discussion here) is that of access by third party researchers to protected data and samples (Knoppers, Abdul-Rahman and Bédard 2007).

Coding is a well-known and increasingly sophisticated mechanism involving encryption, bar codes, simple, double or triple codes. What defines it is the ability to retrace the participant. In contrast, anonymization entails the irreversible breaking of any possible links back to the participant, though some basic data accompanies the sample.

These two terms however have not been used or adopted in a clear and coherent fashion (Knoppers and Saginur 2005; see however ICH 2006). This is not without repercussions as the terms used determine not only possible future research uses by the study but by other researchers, that is, both the efficacy and utility of the study (Elger and Caplan 2006).

Coding permits both the constant downloading of data during the life of a participant and the return of results by researchers to a keyholder in a way that enriches the biobank for further research. Like in all information systems however, there can be no absolute certainty against potential breach of confidentiality.

Anonymization is ethically and legally expedient in the sense that no participant is traceable. Hence, a decade ago this was often the preferred route (Knoppers 2005). Nevertheless, it greatly decreases the scientific and clinical utility of such initiatives as the data is static and not updated or dynamic. No rights can be violated because for all intents and purposes the person as an identifiable individual no longer exists. Certainly, no longitudinal study could function with anonymized data unless other highly informative databases provided demographic, administrative and other general, health data allowing perhaps for regional or sub-population profiling of some limited import. Where the current preference for coding may however turn into difficulty is as concerns the communication of results.

3.2. Communication of Results

The return of results has long been limited to the notion of publication and more recently, for clinical trials, to international registries (for example, WHO 2007). Obviously, in clinical trials involving drugs or devices the return of results is the norm. More

problematic however is the return of individual results in genetic research (Wilfond and Ravitsky 2006; Knoppers and Joly 2006) and hence in population genomic biobanks as well.

The literature on population biobanks is divided on this issue. The policy of "no-return" is supported by for example, the U.K. biobank (http://www.ukbiobank.ac.uk/) and CARTaGENE in Quebec (http://www.cartagene.qc.ca/). Certain authors argue that such initiatives which build infrastructures that are largely epidemiological in nature are not themselves involved in diagnostic tests of clinical validity and so have nothing to report (Knoppers, Abdul-Rahman and Bédard 2007; Knoppers and Joly 2006). The complexity, costs, impracticality and implications of attempting to do so are self-evident and could compromise the security mechanisms put in place and so endanger confidentiality and even lead to discrimination. It could also be argued that it is misleading and undue inducement to hold out the promise of an eventual return of individual results.

Others argue that, respect for autonomy mandates return of results (Roberston 2003) (even if they are only research results which by their very nature would be meaningless for the individual and unreliable) (Buchanan, Califano, Kahn, et al. 2002). Moreover, even if reliable, "the consent form should state who will make the determination of reliability, according to what standards, and who will have the responsibility of informing the subject … Other persons might find that always providing a subject that option is too costly to implement, but that recontacting with useful information should be pursued whenever feasible" (Roberston 2003, 305).

Nevertheless, considering the fact that some biobanks obtain ongoing access to the medical records of participants (e.g. Estonia), the issue of individual feedback is real. If

tests exist to validate research findings that may be clinically significant and treatment or prevention is available, procedures should be put in place for such exceptional circumstances (Johnston and Kaye 2004). In any event, the literature is unanimous that all population studies should have in place an ongoing public communication strategy not only while the resource in being built but also on the types of research protocols that use the data and samples (Robertson 2003). The presentation of the choice to be recontacted individually or at a minimum, notification of the biobanks' policy in this regard should be clear in the consent process. The same holds for eventual commercialization.

4. Commercialization

The debate on the characterization of genetic information – property or person – is classic (Chadwick 2001). It has also spilled over into the discussion of privacy which could be interpreted as a liberty interest or as a right of control (Rothstein 1997). Samples or data then are seen as either a proprietary right (Spinello 2004; Rule and Hunter 1999) or as an extension of personality rights (Le Bris and Knoppers 1997) (see below 4.1.). Neither seems to affect the issue of benefit sharing following commercialization (see below 4.2.).

4.1. Ownership of Samples

Twenty years ago, discussion in the literature largely stemmed from the infamous Moore case in California where unauthorized research uses of bodily materials led to a property claim by the donor (*Moore v. Regents of California* 1990; *cert denied* 1991). The economic inefficiency of such an approach to say nothing of the impact on altruistic donation of other elements of the body and organs was self-evident to the court. While Mr. Moore lost his property claim, the principle of obtaining an informed consent to research uses of samples and genetic information was established. Such a requirement

exists irrespective of the "property" or "person" characterization and allows a person to exercise a right of control. The exercise of property rights (and so potentially patent rights) could also create obstacles for biomedical research. Indeed, the recognition of upstream property rights could not only impede downstream therapeutic applications but lead to multiple owners with ensuing licensing fees, etc. (Boyle 2003).

In short, a property approach is legally unworkable. Furthermore, while not denying the possibility of eventual intellectual property some countries such as France have explicitly denied the possibility of "patrimonial" interests in the human body or its constituent parts. Whether the right of property or the right to personal autonomy is invoked, what is important then is the exercise of control. It should be noted however, that in the case of a "gift", ownership passes upon donation (*Washington Univ. v. Catalona* 2007). If samples and data are provided altruistically for research and a test or a product is developed, is that the "benefit" that donors derive from the "gift" of their DNA?

4.2. Benefit-Sharing

The concept of benefit-sharing dates back to the Rio *Convention on Biodiversity* of 1992. Having forsaken the common heritage of humanity approach for that of State Sovereignty over biological resources (plant and animal), balance was sought through the Bonn Guidelines that ensured the concept of benefit-sharing. In contrast, while upholding benefit-sharing, the Human Genome Project has largely adopted the common heritage approach. Thus, while undue inducement through compensation was foresworn, this did not mean that recognition and gratitude for the altruistic participation of citizens through benefit-sharing was not forseen (HUGO 1996 and 2000).

The literature has largely seen this as a reasonable approach (Andrews 2005). Obviously, the notification of commercialization in the consent process warns participants that they will not share in eventual profits (if any) and so "no ethical issues arise" (Roberston 2003, 304). This may hold true for the large population genomic studies that create infrastructures for eventual research. Such projects are generally for population health surveillance and research and only secondly, for profit research by industry (with the exception of deCode in Iceland) (Williams and Schroeder 2004). The "benefits" here are at the level of the population in terms of improving health care systems and providing a database for validation and replication to ensure better quality of science and health care generally.

In contrast, when companies collect samples and data for disease gene hunting, "some patient or family groups may be unwilling to cooperate in setting up a biobank or research archive unless they have rights of access to final products, to licence patents, or even to share in royalties" (Robertson 2003, 304). Patent-sharing by families or groups may lead to lower costs for tests but could also in the long run create the same monopolies as industry would do in the case of exclusive licensing. To that end, a balance needs to be struck where the altruism of participant is "matched by a moral responsibility to use the resource, at least in part for the common good" (Williams and Schroeder 2004, 97). It is in the mechanism used to recognize in an equitable way, the solidarity of citizens that benefit-sharing begins (Chadwick 2001). For companies, this can take the form first suggested by HUGO in 1996 and again in 2000, but for the population databases, the "benefit" would be that such primary data could be considered to be part of the public domain so as to enhance research opportunities (HUGO 2002).

5. Conclusion

This review of the literature on population biobanks while concentrating on the three main areas of discussion: consent, confidentiality, and commercialization, reveals both convergent and divergent positions.

There is convergence in the sense that the same issues are identified as requiring clarification. Thus, in the domain of consent, the question of the legitimacy of broad consent is now accompanied by the ancillary issues of the need to recontact for future uses and the exercise of the right to withdraw. The former is often subsumed in the broad consent question while the latter is upheld albeit without much direction as to the modalities of its exercise. Likewise discussion on the protection of confidentiality is centered on traceability through coding or the lack thereof with anonymization. But the modalities of communication of results remains unresolved. Moreover, on this issue there is a certain confusion with the norms governing the return of results in clinical trials. At the outset there are no "individual" results in longitudinal, population studies which by their very nature are not concerned with individuals and not organized to produce "individual" results. That being said, there is no doubt that over time such results may become possible.

The area where there is the most agreement is on the need to notify participants that there may eventually be commercialization by researchers accessing the biobank for specific protocols. As such they relinquish any "property" rights they may have in their material. Interestingly, the debate on gene patents has not entered the population biobank literature. This is probably due to the fact that such resources are not gene-hunting endeavours but epidemiological in nature. Nevertheless, in spite of their non-commercial

nature, the concept of benefit-sharing is applied largely due to the tremendous public investment in such infrastructures. Thus researchers accessing these infrastructures are usually required to return their results to the biobank so as to not only enrich the data for use by others but also to ensure the quality of the data therein in order to speed potential use for population health.

The literature in these three areas is often ahead of the policies, the latter being the result of necessary compromise and consensus and sometimes drafted by individuals with little contact with the practical world of biobanks to say nothing of population genomics. In short, the need to move away from relying solely on individualistic ethics is evident in the literature on population studies which have communitarian goals (Knoppers and Chadwick 1994). The need to eschew anonymization but strengthen security and access mechanisms is self-evident given the longitudinal nature of such studies. The need to recognize and ensure access by researchers to these very public endeavours is crucial to their utility and success. Public investment, public participation and public trust demand no less.

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