scripted

Volume 6, Issue 3, August 2009

"Deconstructing" Biobank Communication of Results

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Abstract

Biobanks have been troubled by a history of confusion and controversy around certain key concepts such as "broad consent", and, more recently, "return of results". This article analyses the return of results only as it pertains to the participation of (presumably healthy) volunteers in the creation of longitudinal biobank infrastructures for future unspecified research. Limiting ourselves to the trajectory of a typical protocol then that begins with: the arrival of volunteers at assessment centres for the collection of blood and the filling-in of extensive questionnaires on lifestyle, socio-demographic factors and family history; followed by long term storage; and finally the use by researchers accessing such biobanks (it is evident that it is necessary to distinguish between the different obligations that may arise at distinct moments in this trajectory). We posit that there are five types of communication, and we explore the best means of protecting the privacy of those involved in such biobanks, concluding that international policies are converging towards an ethical duty to return individual genetic research results to subjects, provided there is proof of validity, significance and benefit.

DOI: 10.2966/scrip.060309.677

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"… words full of sound and fury, signifying nothing …"

W Shakespeare, *Macbeth*, Act 5, Scene 5.

1. Introduction

For a decade, the conflation of concepts, principles and terminology surrounding biobanks has largely centred around the concept of "broad consent."[1] Today, it has moved to that of the return of results[2] with the same pattern of terminological confusion (if not cacophony) that accompanied the definitions of consent. This concept of a "duty" to return results is not without implications for a clear delineation of the ethical and legal obligations surrounding biobanks.[3]

The definition of a population biobank underlying this analysis is:

> A collection of biological materials that has the following characteristics:
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> I. The collection has a population basis;
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> II. It is established, or has been converted, to supply biological materials or data derived therefrom for multiple future research projects;
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> III. It contains biological materials and associated personal data which may include or be linked to genalogical, medical or lifestyle data and which may be regularly updated; and
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> IV. It receives and supplies materials in organized manner.[4]

This article analyses the return of results only as it pertains to the participation of (presumably healthy) volunteers in the creation of longitudinal biobank infrastructures for future unspecified research.[5] Such unique and modern biobanks are collective in that they rely on mass participation and are inclusive, prospective and purposively

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[1] M Hansson et al, "Should Donors be allowed to Give Broad Consent to Future Biobank Research?" (2006) 7 *The Lancet Oncology* 266-269.

[2] BM Knoppers et al, "The Emergence of an Ethical Duty to Disclose Genetic Research Results: International Perspectives" (2006) 14 *European Journal of Human Genetics* 1170-1178; V Ravitsky and B Wilfiond, "Disclosing Individual Genetic Results to Research Participants" (2006) 6 *American Journal of Bioethics* 8-17; P Affleck, "Is it Ethical to Deny Genetic Research Participants Individualized Results?" (2009) 35 *Journal of Medical Ethics* 209-213; BM Knoppers, "Return of 'Accurate' and 'Actionable' Results: Yes!" (2009) 9 *American Journal of Bioethics* 107-109.

[3] F Miller et al, "Duty to Disclose What? Querying the Putative Obligation to Return Research Results to Participants" (2008) 34 *Journal of Medical Ethics* 210-213; J Murphy et al, "Public Expectations for Return of Results from Large-Cohort Genetic Research" (2008) 8 *American Journal of Bioethics* 36-43; P^{3}G Observatory, "Model Consent Form" available at http://www.p3gobservatory.org/ (accessed 31 Aug 09).

[4] Council of Europe, "Recommendations on Research on Materials of Human Origin" (2006), available at www.coe.int (accessed 31 Aug 09).

[5] See generally, S Gibbons and J Kaye (eds.), "Symposium: Governing Genetic Databases: Collection, Storage and Use" (2007) 18 *King's Law Journal* 201-382.

indeterminate.[6] Limiting ourselves to the trajectory of a typical protocol then that begins with: the arrival of volunteers at assessment centres for the collection of blood and the filling-in of extensive questionnaires on lifestyle, socio-demographic factors and family history; followed by long term storage; and finally the use by researchers accessing such biobanks (it is evident that it is necessary to distinguish between the different obligations that may arise at distinct moments in this trajectory). We posit that there are five types of communication: immediate feedback during the assessment process; communication of general results at the extreme end; in between, re-contact for additional questions/samples for the biobank itself; but also if researchers accessing the biobank need re-consent in order to obtain different samples and/or questions; and, finally, the issue of incidental findings that crosses the whole trajectory.

It should be noted that communication of results in general depends on whether or not the identity of the individual is or can be known by the investigator. Because some form of de-identification is usually recommended to protect the privacy of participants and the confidentiality of their information, samples are coded. Irreversibly anonymising stored biological materials and data would render the feedback of results, and even withdrawal, impossible as individual participants could no longer be traced. Thus, whilst at a glance anonymising may be the best option to protect privacy, it is not widely endorsed as it prevents longitudinal follow-up, reduces the range of opportunities available to investigators and prevents participants from being re-contacted if therapeutic options become available. As mentioned, it also prevents participants from withdrawing. This is why assigning a code; removing all identifying information; storing specimens and data securely; restricting access to specimens/data; and providing firewalls between the subject identity and the recipient investigator, are preferred options for safeguarding privacy in population biobanks.

2. Communication During the Assessment Process

2.1 Physical Measures

It cannot be stressed enough that a population biobank infrastructure has to, as its main goal, provide a scientific resource for future research. Thus, throughout its activities the physician-patient relationship does not occur. Indeed, the assessment and measurements taken at the recruitment sites are not the equivalent of a clinical diagnosis. Yet even in the absence of such a relationship the nurses performing the basic physical measurements may encounter abnormal or even critical findings.

At the collection sites, prior to storage, the physical assessment and tests performed on fresh blood samples may reveal health information of value to participants. In some cases tests can also reveal infectious diseases that must be reported back to public health authorities[7] – resulting in a limited ability to protect participants' confidentiality. In other cases, they may reveal abnormal results, such as extremely high or low blood pressure or cell counts which may or may not be of medical

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[6] S Harmon, "Semantic, Pedantic or Paradigm Shift? Recruitment, Retention and Property in Modern Population Biobanking" (2009) 16 *European Journal of Health Law* 27-43.

[7] B Day et al, "Canadian Health Measures Survey: Ethical, Legal and Social Issues" (2007) 18 (Supp) *Health Reports* 37-51.

significance to participants. Should investigators include resources in their biobanks-strategies to support participants who choose to receive feedback or make it a matter of policy? What obligations, if any, do investigators have towards participants in such circumstances?

Participants recruited by population biobanks are asked to fill-out several questionnaires and provide physical measures as well as biological samples. Height, weight, muscle strength, lung capacity, bioimpedance (body fat percentage), arterial rigidity, bone density, partial electrocardiogram, hip and waist circumference are among some of the most common measures noted. While the measures taken may be similar to those taken during a medical check-up, unlike medical examinations, physical assessments in the context of population biobanks are not meant to serve as medical check-ups. More importantly, biobank participants are not patients, and biobank personnel are seldom doctors. For the most part, nurses are responsible for taking measurements and for collecting biological samples from participants. So, what, if any, obligations do nurses have towards biobank participants?

Nurses engaged in research do not have the same duty of care as they would have in a clinical setting. Nevertheless, in accordance with the *Code of Ethics for Registered Nurses*,[8] they must promote safe, competent, compassionate and ethical care, using guidelines for ethical research that are in keeping with nursing values. To promote and respect informed decision-making, they can provide individuals with adequate information should they chose to be made aware of results so that they are able to make informed choices with regards to the most appropriate course of action. As a result, it can be argued that nurses have an ethical duty to inform biobank participants in the event of abnormal results found during the assessment.

Reporting such values can be done through standard reporting, routine referral and urgent referral. When measuring blood pressure, for example, while normal levels can be reported to subjects in a standard way, elevated levels would usually be reported with recommendations for follow-up. Very high or critical levels, on the other hand, would require urgent and immediate referral to a medical practitioner.

Participants in the UK Biobank, for instance, receive feedback on a number of measurements made during their assessment centre visit – including blood pressure, body mass index, height, weight and lung function. These measures are reported against population standard ranges to give the individual an indication of whether or not they fall outside of the normal range. Thus, if an abnormal measurement or an incidental finding, such as melanoma, is found, individuals are advised to visit their doctor. It is interesting to note that in the UK results are not fed-back to physicians as was initially planned, but rather to the participants themselves.[9]

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[8] Canadian Nurses Association, "Code of Ethics for Registered Nurses" (2008) available at http://www.cna-aiic.ca/CNA/documents/pdf/publications/Code_of_Ethics_2008_e.pdf (accessed 14 Apr 09), at 9.

[9] UK Biobank, "Report: Public meeting of the UK Biobank Ethics and Governance Council," (2007) available at http://www.egcukbiobank.org.uk/assets/wtx050395.pdf (accessed 6 Apr 09). See also C Johnston and J Kaye, "Does UK Biobank Have a Legal Obligation to Feedback Individual Findings to Participants?" (2004) 12 *Medical Law Review* 239-267, at 240.

2.2 Laboratory Results on Fresh Blood Prior to Storage

Although future uses for samples and data may not be explicitly defined in prospective biobanks, the standard tests that will be run on the biological materials prior to storage are usually known and should be disclosed to participants at the outset. Tests conducted on samples prior to storage are usually those that cannot be done subsequently, such as haematological analyses. They may reveal abnormal and sometimes even critical – that is, life-threatening – results. In Canada, the CARTaGENE project will contact participants if tests on fresh blood samples indicate the presence of critical values.[10]

Undeniably, the question of whether or not results from laboratory analyses should be disclosed to participants is an issue on many levels. First of all, what results if any should be disclosed? What are abnormal results? Do results necessarily have to be life-threatening to be reported? In the absence of a life-saving intervention, should critical results be disclosed to participants at all?

Results are considered abnormal when they deviate significantly from reference values. Moreover, they are considered critical when they will cause a patient to suffer a life-threatening event if not communicated and treated immediately. Some abnormal results might not be considered life-threatening and as a result might relieve biobankers of the duty to re-contact participants with feedback results. In particular, it should be noted that where participants have not fasted and the biobank does not include access to medical records, the risk of many "abnormal" results is so high in standard laboratory testing that the risks of false positives and needlessly frightening participants outweighs communicating such dubious results.

Yet, when results that could have specific and potentially important health consequences are detected, there might be an ethical duty to report back to participants. As such, if a biobank planned to conduct complete blood counts (CBCs), for instance, investigators who chose not to report results requiring the immediate attention of participants, or not to advise participants to consult a health care professional, might have trouble justifying their inaction. The decision not to feedback results of baseline laboratory analyses prior to the storage of a sample – where a serious condition for which intervention is possible – is problematic and in all likelihood actionable in countries where there is a duty to "rescue" a person whose life is in peril.

3. Communication of General Results

The very distinction between research and clinical care rests on the fact that research aims to produce generalisable knowledge for society at large, whereas clinical care aims to meet individuals' specific needs, interests and preferences. Yet, "[h]owever handled, the issue of notifying (or not) participants of results should be disclosed and agreed to in advance (i.e. on the consent form)."[11] The presentation of the choice whether to receive information about an individual genetic analysis or, at a minimum,

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[10] See http://www.cartagene.qc.ca (accessed 31 Aug 09).

[11] Knoppers et al, see note 2 above, at 1176.

notification of the biobanks' policy in this regard, should be clear in the consent process.[12]

There is consensus on the need to communicate general results to both participants and the population at large. Websites, newsletters and other public forums are foreseen. Outreach to the medical community and to health ministries of aggregate data that may be of importance for health surveillance or for general prevention is also part of their mission. Most biobanks provide notice on their website of research uses. Accordingly, "[s]ummary results arising from research conducted using the HBGRD's resources should be made available in easily accessible forms, such as through a newsletter or website."[13]

4. Re-Contact for Additional Questions/Samples

Consistent with the very scientific "value" of a biobank is the possibility to update questionnaires and, if necessary, samples. Longitudinal in nature, the updating of information on the lifestyle, environmental exposures, socio-economic and health of participants is crucial to the understanding by biobanks of gene-environment interactions. It is inherent in the longitudinal and gene-environment "mission" of modern biobanks to follow participants over time. Biobanks either foresee re-contact as a matter of policy or ask participants to opt to be re-contacted in the original consent. Thus researchers can also access the biobank data and samples as controls for validation, for replication, for comparison or for pharmacogenetic studies. This epitomises the very purpose of building such infrastructures. Such primary access and use are part of the broad consent. In short, updating via re-contact is foreseen as a matter of policy or as an option for participants in the initial consent. While this re-contact remains subject to an evaluation of the compatibility of requests with the aims of the biobank,[14] it does not require an explicit re-consent. Nevertheless, it goes without saying that the very process of re-contacting reaffirms the initial consent, since participants will be reminded of their inclusion and so also of their right of withdrawal. They can refuse to participate in such updates and leave only their original samples and data available for the research community. Re-contact also reminds participants of the possibility to verify what aggregate and findings data are reported on the website and what research uses have occurred.

5. Re-consent

In spite of the broad consent for future, unspecified, biomedical research, there may be researchers seeking access for studies that fall outside of the ambit of some biobanks, or that wish to access participants so as to obtain new samples or to ask different questions. It must be remembered that such requests need to be distinguished from "primary user" researchers. Indeed, as mentioned, those seeking to use or to

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[12] B Knoppers and M Abdul-Rahman, "Biobanks in the Literature" in B Elger et al (eds), *Ethical Issues in Governing Biobanks: Global Perspectives* (Aldershot: Ashgate Publishing Ltd, 2008) at 17, 13-22.

[13] OECD Committee for Scientific and Technological Policy, *Draft Guidelines for Human Biobanks and Genetic Research Databases*" (Paris: OECD, 2008).

[14] P^3G, "P^3G Sample and Access: Core Elements", available at http://www.p3gobservatory.org/ (accessed 31 Aug 09).

update the biobank data or samples do not need to obtain a re-consent, as such work is the very purpose of the bank!

The biobank's review process serves to determine if there is a need for re-consent.[15] Where sample or data requests are not consistent with the informed consent provided by the participant, the process of re-consent should be initiated for those who agreed initially to be re-contacted for this very purpose. Ideally, it should be the biobank that re-contacts participants for re-consent. Thus "[t]he operators of the HBGRD should have in place a defined mechanism to review applications for access to human biological materials and/or data."[16]

Another possibility is to seek a waiver of re-consent from the ethics review committee.[17] However, considering the fact that the consent is very broad – as are the purposes of biobanks – such a waiver would be exceptional. It would require proof of necessity, impracticability and proportionality.[18]

6. Incidental Findings

As mentioned in the introduction to this paper, incidental findings can occur across the spectrum of biobank activities. What characterises their "incidental" nature is their unforeseeability, the fact that they are outside the very scientific objectives of a biobank and thus of the consent provided. Participants contribute to the furtherance of basic knowledge and ultimately to public health strategies. They are made aware that such infrastructures for research are not the equivalent of health-care or clinical trials. Hence, the understanding by participants that, in the absence of critical values and the public communication of general results, there will be no individual results forthcoming – including, thereby, incidental findings. To do otherwise would be to send mixed messages to potential participants, which would undermine the proper understanding of the very nature of such resources and thus the consent itself. Nevertheless:

> *Increasingly, tissue sample biobanks and DNA databanks are being set up to facilitate ... large-scale genomic epidemiology often pursued as "discovery research". In such discovery research it is harder to identify what might be an [incidental finding], as any genomic pattern correlating with pathology may be captured and studied. However, if the declared aim of genomic research analysis is to study certain pathologies (*e.g.*, cardiac illness, high blood pressure, or asthma), genomic patterns suggesting other clinical*

[15] OECD, see note 13 above, at §3.2.

[16] *Ibid*, at §7.2.

[17] *Ibid*, at §4.3.

[18] Interagency Advisory Panel on Research Ethics, *Draft 2nd Edition of the Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans* (Ottawa: Interagency Secretariat on Research Ethics, 2008).

> *concerns for an individual may be considered [incidental findings] IFs.*[19]

It is when researchers use the biobank to study specific diseases that incidental findings are likely to arise rather than in the primary collection and analysis. Accordingly, it is not unreasonable to limit attempts to re-contact participants, as concerns incidental findings, to those offering a strong net benefit that is "information revealing a condition likely to be life-threatening …. Or [one that is] grave [and] that can be avoided or ameliorated."[20] Nevertheless, this position admits that there have been no studies of incidence in the research context of genomic micro-array analyses.[21] Indeed, some have argued that "a general policy of offering incidental findings to unsuspecting people who had not previously thought about the issue does not seem right."[22]

7. Conclusion

The Council of Europe's 2006 Recommendation on research on biological materials of human origin stresses in its preamble that "[t]he full benefits for which the subjects gave their samples will be realised through maximising high quality, collaborative, research. Therefore, there is an ethical imperative to promote access and exchange of information."[23] It is for this very purpose that large population biobanks were funded: to provide reliable, baseline data for more specific research in the future. Imposing the return of results that is applicable in disease research or in clinical trials into the broader resource mission of population biobanks will undermine their longitudinal goals (to say nothing of the creation of untoward legal liability. Most importantly, it would create unrealistic expectations and harm the credibility and transparency of population biobanks. As stated in the draft OECD:

> *Non-validated results from scientific research using an HBGRD's human biological materials and data should not be reported back to the participants and this should be explained to them during the consent process.*[24]

In contrast, the issue of communication of results must be addressed by the researchers accessing these infrastructures for more specific studies. Indeed, international policies are converging towards an ethical duty to return individual genetic research results to subjects, provided there is proof of validity, significance and benefit.[25]

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[19] S Wolf et al, "Managing Incidental Findings in Human Subjects Research: Analysis and Recommendations" (2008) 36 *Journal of Law, Medicine & Ethics* 219-248, at 223.

[20] *Ibid,* at 235.

[21] *Ibid,* at 223.

[22] E Clayton, "Incidental Findings in Genetics Research Using Archived DNA" (2008) 36 *Journal of Law, Medicine & Ethics* 286-312, at 290.

[23] Council of Europe, see note 4 above.

[24] OECD, see note 13 above, §4.12 *et seq*.

[25] Knoppers et al, see note 2 above.