Biobanking of blood and bone marrow: Emerging challenges for custodians of public resources

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The Australian Bone Marrow Donor Registry (ABMDR) is a publicly funded company that is part of an international network that facilitates unrelated bone marrow transplantation. This role means that the ABMDR has access to a large biospecimen repository, therefore making it a highly valuable research resource. Recognising the potential value of these biospecimens for research purposes, the ABMDR is in the process of determining whether, and how, to share its biospecimens with other biobanks. While this would undoubtedly be of value to the scientific community, and ultimately to the wider community, it would also inevitably transform the role of an institution whose primary role is therapeutic, and would compromise the degree of control that a custodian has over donated material. This article describes the challenges confronting the ABMDR, and organisations like it, in balancing their duties to donors, patients, researchers and the general public. These problems have led inevitably to the use of “property” rights language in the discussion of these issues but notions of gift, ownership, trusteeship and transfer might also be considered.

INTRODUCTION

Biobanks (also known as tissue banks or biorepositories) are collections of human biological material. The blood, tissue (eg muscle), parts of organs or whole organs (referred to broadly as “tissue”) that make up biobanks may be removed from healthy donors, from patients in the course of medical diagnosis or therapy, or post-mortem. Biobanks provide a crucial resource for basic and translational biomedical research (biobanking research) and have been used extensively in genetic, genomic and molecular epidemiological research. This research has provided information about genes and other molecules (biomarkers) that can be correlated with the aetiology, prognosis and treatment responsiveness of diseases, and can be used as the basis of targeted therapies.

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The value of biobanks to medical research, to research communities and to public health has been widely recognised, and biobanks have been supported by philanthropic and public donations and by governments. In Australia, eg, biobanks have been supported through National Health and Medical Research Council (NHMRC) Enabling Grants to bodies such as the Australasian Biospecimens Network – Oncology Group (ABN – Oncology).2

Research utilising banked tissue has, however, become the subject of sustained scientific and ethico-legal critique. Those with an interest in the ethics and law of biobanking have focused on the means of obtaining consent for the long-term storage and future use of tissues, the management of donor (eg genetic) privacy, and the commercialisation and ownership of the tissue and the products of tissue-based research.3 Ethical disagreements frequently centre on the tension between individual autonomy and the “common good” 4 – a tension that is seen to be particularly significant in the context of biobanking research because this often depends upon the participation of large numbers of people (including healthy populations), many of whom are unlikely to benefit from the results of the research.5

These ethical and legal issues have become increasingly salient in the face of advances in medicine and changes in the research environment. For example, techniques such as whole genome sequencing make it more likely that biobanking research will yield incidental findings, and there is no clear consensus on how to address this issue.6 Likewise, the commercialisation of biomedical research means that biobanks are now valuable commercial resources, and pharmaceutical and biotechnology companies are increasingly creating their own biobanks as part of their basic research and clinical trial activities.7 Perhaps most significantly, biobanking is now a global endeavour. While individual research laboratories may retain their own tissue collections solely for their own use, it is increasingly the norm for biobanks to be “networked” and to be viewed as resources for any researcher in the world who is able to make use of the materials.8

Regulation has not kept pace with this rapidly changing medical and research environment. Regulation of biobanking research is enormously complex and there is little international regulatory harmonisation.9 This means that those administering biobanks need to be cognisant of a tangled web of existing regulations, and also need to be able to make principled decisions in the absence of clear regulatory guidance.

This article discusses the approach taken by the ethics committee of an Australian biobank – the biobank of the Australian Bone Marrow Donor Registry – to the question of whether and how its samples should be shared with other biobanks.


6Wolf SM et al, “Managing Incidental Findings and Research Results in Genomic Research Involving Biobanks and Archived Data Sets” (2012) 14 Genetics in Medicine 361.


8Catchpoole et al, n 2.

The Australian Bone Marrow Donor Registry (ABMDR) is a company funded by the Australian Government that is responsible for matching unrelated adult volunteer donors and stored umbilical cord blood units with patients in need of haematopoietic stem cell transplant (bone marrow transplant) in Australia and overseas.

Bone marrow transplant is an established treatment modality for many patients with acute or chronic leukaemias, lymphomas, or bone marrow failure syndromes. Haematopoietic progenitor (or stem) cells for transplantation may be sourced from umbilical cord blood or from adult donors. In adults, there are two types of haematopoietic progenitor cell donation: bone marrow and peripheral blood stem cell. Bone marrow donation involves a surgical procedure in which liquid marrow is extracted from the back of the pelvic bone. Peripheral blood stem cell donation is a non-surgical procedure in which haematopoietic progenitor cells are removed from the blood using a procedure similar to donating plasma. In each case, the cells are infused into bone marrow recipients following the administration of high doses of chemo/radiotherapy.

Ideally, haematopoietic progenitor cells are donated by related donors, who are immunologically "matched" to the recipient, thereby reducing the chance of rejection and other complications of transplant, notably graft versus host disease. Unfortunately, only around 30% of patients who require a bone marrow transplant have a matched related donor. For all other patients, haematopoietic progenitor cells must be sourced from unrelated donors. Unrelated donors are identified from cord blood and stem cell registries that store tissue-typed cord blood or blood samples from volunteers who are willing to donate their bone marrow or blood stem cells to any patient in the world in need of a transplant.

The ABMDR’s main purpose is to recruit unrelated volunteer donors and to administer the National Cord Blood Collection Network of public umbilical cord blood banks in Australia. Clinical information about potential donors is uploaded into an electronic system that allows national and international transplant centres to search and select a matched donor or cord blood unit for patients in need of a transplant. Once a donor has been selected, the ABMDR oversees the donation and post-donation process to ensure the wellbeing of the volunteer donor. Currently the registry has 175,476 donors and 1,117 donor-patient paired samples. Importantly, the ABMDR is part of an international network of registries and transplant centres. Collaboration among these organisations is fostered by the World Marrow Donor Association (WMDA), which currently consists of 67 stem cell donor registries from 49 countries and 46 cord blood banks from 30 countries. This network currently has more than 21 million potential donors.

ABMDR AS A RESEARCH RESOURCE

In addition to its core function in supporting bone marrow transplant, the ABMDR sees itself as the custodian of a “biobank” consisting of donor and matched donor-patient samples. The ABMDR recognises that this biobank is not simply a therapeutic resource but an important resource for research, and sees itself as having a moral obligation to support health and medical research by providing researchers with its material. And because the ABMDR is part of an international network of registries and transplant centres, it could potentially provide researchers with access to the largest “virtual” biobank in the world.

However, the ABMDR also sees itself as the “custodian” of its materials. Custodianship refers to the ABMDR’s moral and ethical duty to ensure its data and/or samples are used responsibly and respectfully in accordance with its purpose for the public good; and to ensure that research participants’ interests are taken into account. This custodian role is seen to be particularly important because the ABMDR’s biobank exists, and is funded by the Australian Government, for therapeutic, rather than research, purposes and because there is a perception that ABMDR material (samples and related data) is a public resource, which is “owned” in some way by the public.

With this in mind, a Human Research Ethics Committee (HREC) was established in May 1991 to assess applications for research using ABMDR material. To date, the committee has reviewed 82 applications for research use of ABMDR samples. Numbers of applications are expected to increase as researchers become more aware of the existence of the ABMDR’s biobank as a resource, for research not only into haematological diseases and therapies, but also for other diseases and therapies, such as therapies using induced pluripotent stem cells.

**ETHICAL CHALLENGES FACED BY THE ABMDR**

As mentioned above, biobanking research raises a number of ethical issues including consent, privacy and ownership. The ABMDR Human Research Ethics Committee is, therefore, charged with ensuring that donors’ bodily material is not used for research without their consent (unless there is an important reason for waiving consent), that donors’ privacy is protected, and that materials are not exploited purely for commercial gain. These roles are reasonably straightforward and there is clear legislative and regulatory guidance as to what is required.

It is far less clear what should be done when researchers ask not (only) to use samples for a specific research project, but (also) to store these samples and/or derive immortal cell lines from them for unspecified future research purposes and/or share these samples with other researchers. Such requests have become more frequent in recent years as a result of advances in science and technology that now enable scientists to store tissue samples for an extended period of time and to develop “immortal” cell lines.

The long-term storage of donated samples by researchers is made more complex by the fact that most biobanks are now networked both nationally and internationally. Thus material given to one biobank may be shared with others, and there is a point at which the original biobank (in this case the ABMDR) can no longer control the fate of its material. The challenge for ethics committees that have oversight of biobanks (such as the ABMDR’s committee) is, therefore, how to balance the potential good that could arise from allowing material to be stored in other biobanks, against the associated loss of control over the material and the implications this has for the custodial role that such biobanks have undertaken.

**THE ABMDR’S APPROACH TO NETWORKED BIOBANKING**

At present, ABMDR policy does not allow researchers to store bodily material. It has to be either destroyed or returned to the ABMDR at the completion of a specified research project. This policy is a conservative measure, aimed at ensuring the protection of ABMDR samples and donors, and at fulfilling the ABMDR’s role as a “custodian” of donated tissue (a particularly sensitive issue given the cultural significance attached to blood and the cultural status of blood banks and the Red Cross of which ABMDR is perceived to be a part).

In recent years, an increasing number of researchers have asked to retain samples beyond the life of a single project so that they can conduct further (currently unspecified) research. While the simplest response would be to simply deny such requests so that control over samples can be maintained, the ABMDR has also acknowledged that it has a moral obligation to support health and medical research, including biobanking research, consistent with the National Statement published by the National Health and Medical Research Council (National Statement).11

In addressing this issue, the ABMDR Human Research Ethics Committee is currently reflecting on the following questions:

- Is the ABMDR supportive of other researchers or organisations (“second parties”) establishing a new biobank or adding to an existing biobank using ABMDR-derived tissue samples, including through the immortalisation of ABMDR derived cells?

If so, is the ABMDR willing to allow the sharing of material by a “second party” with other researchers (“third parties”)?

To answer these questions, the committee is reflecting on the meaning of custodianship, and working to determine:

- What is the relationship between custodianship and ownership?
- Can custodianship be transferred?
- What conditions would need to be fulfilled in order for custodianship to be transferred? (eg does the recipient of the samples need to have particular governance processes in place)?
- To what extent (if at all) does the funding of biobanks matter? Is there a difference between public and privately funded biobanks?

One option that the ABMDR is considering is that, on approval of an application to bank ABMDR material, the ABMDR may entrust custodianship to a properly governed “second party” to store and share samples and data for research purposes. In these instances, the second party would be expected to use its own ethical and governance structure to evaluate access to their biobank for all subsequent applications, in accordance with NHMRC or other relevant guidelines for biobanking. The second party would also be required to report annually to the ABMDR Human Research Ethics Committee regarding its own use and transfer of the biobanked material. To satisfy consent requirements, donors to the ABMDR would need to be informed that samples may be made available to, or shared with, other researchers and laboratories, who may also store and share samples for future research. They would also be informed that they will usually, but not always, be re-contacted to provide consent for specific research projects using their tissue (as determined by the ABMDR Human Research Ethics Committee).

**DISCUSSION**

To adopt an approach to networked biobanking such as that described above would require two significant shifts in thinking. First, there would need to be explicit recognition that the scientific landscape is changing and that, if ABMDR material were to be used optimally for research, it would need to be accessible to researchers worldwide – not only through direct access to the ABMDR but also by being incorporated into other biobanks.

Secondly, there would be a need to stop (implicitly if not explicitly) equating custodianship of tissue samples with complete and everlasting control over these samples. This would necessitate trusting other properly governed researchers and research organisations to comply with NHMRC and other relevant guidelines for biobanking (provided they can demonstrate to the ABMDR that they have the necessary governance systems and processes in place). This would be consistent with the principles that have underpinned the shift towards approval by a single ethics committee of multi-centre studies.

From a legal perspective, the Ethics Committee has been challenged to (re)think issues of the legal status of “gifted” material, consent, the legal conditions attached to the sharing of biospecimens and what the lack of a comprehensive legislative or regulatory regime for biobanking in Australia means in relation to the enforcement of those legal conditions.

In legal terms, the status of the biospecimens donated to the ABMDR is that they are the property of the ABMDR. While the res nullius rule ordinarily applies to samples of human tissue, the current authors believe that the ABMDR’s samples have been transformed into property by the addition of work and skill in their collection and storage, in accordance with the principle in *Doodeward v Spence* (1908) 6 CLR 406. The tissue is extracted by the ABMDR with care and skill and processed for the sole purpose of making it amenable to long-term storage and later use. These are the hallmarks of transformative work and skill.12

This is a different situation from that in *Yearworth v North Bristol NHS Trust* [2010] QB 1 where men who deposited sperm in a sperm bank were held to have possessory rights in their stored sperm

12 *Dobson v North Tyneside Health Authority* [1997] 1 WLR 596.
prior to the addition of work and skill. In that case, the sperm samples were stored on behalf of the men and they were entitled to use them later. This principle would not apply to the ABMDR’s donors as the donated tissue is not intended for use by the donors. Moreover, any rights that the donors might have had would be transferred to the ABMDR by the broad and unconditional terms of their agreement with the ABMDR. In property terms, donations to the ABMDR could be categorised as absolute and unconditional gifts of property.

The use of property language immediately creates challenges to the way that the ABDMR relates to its biospecimens, but it also provides opportunities for reimagining these relationships. For example, property law can immediately provide clarity in relation to the ABMDR’s concept of custodianship. As stated above, the ABMDR sees itself as having a moral and ethical duty to ensure its data and/or samples are used responsibly and respectfully in accordance with its purpose for the public good. This very much emulates the form of a charitable trust, where the legal title is held by a trustee to be used for purposes which the law deems to be charitable and in the public interest. The definition of charity has been found to cover gifts of property for the treatment of disease and disability, gifts to health-based institutions and research into health care. It would be relatively easy to mount an argument that the ABMDR’s biobank is charitable in nature. The advantage of such a conceptualisation is that it provides a legal framework for understanding the nature of the ABMDR’s custodian relationship towards the biospecimens. It also provides guidance on the ways in which the ABMDR can transfer its property to third parties, as charities can themselves transfer their property to third parties to further their charitable purposes. However, being a charitable trust also comes with added regulatory oversight via both the Supreme Court and relevant Attorneys General, who retain the Royal Prerogative over charitable institutions.

Another issue that can be resolved by the use of property language is the question of consent from donors to allow the ABMDR to transfer the biospecimens to third parties. As noted above, ABMDR policy currently does not allow biospecimens provided by it to others to be kept other than for the duration of an individual research project. In other words, participants are not ordinarily asked to consent for their samples to be used beyond a single research project. On one view, if the ABMDR is the owner of such samples, it is not necessary to seek further consent once the tissue has been gifted to the ABMDR. However, it may be more ethically acceptable to amend consent forms for those joining the ABMDR (as a donor or a patient) to encompass the possibility of sharing with second parties and beyond. Consent forms would need to clarify that, in line with any new policy, the ABMDR would not necessarily remain sole custodian of donated tissue samples in the long term. It could become property by their work and skill on it and the consent form should make it clear that ownership of this property may pass to third parties of whom the donor may have no knowledge. Importantly, this would be consistent with evidence about public attitudes to biobanking, which demonstrate high levels of support for biobanking, and a willingness to consider open-ended consent (i.e. consent to unspecified future research). It would also make it clear that the donation of tissue to the ABMDR is being given on the understanding that the right to alienate the tissue is also being granted to the ABMDR as part of the donation.

Another issue that arises is the question of how the third party could be bound to use the tissue according to the terms and conditions set by the ABMDR. A Material Transfer Agreement could be employed to clarify the conditions to the third party’s use of the biospecimens given by the ABMDR and the ABMDR’s legal responsibilities. This could be done by a condition subsequent so that the
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conditions must be complied with after the legal title has passed to the third party. However, such conditions would need to be carefully worded (probably as determinable interests\textsuperscript{19}) so as to avoid the rule against restraints on alienation\textsuperscript{19,20} and the rule against perpetuities.\textsuperscript{20} It could also be a condition of transfer that the third party will not transfer the tissue to another party without notifying the ABMDR and contractually binding that fourth party to use the tissue under the same terms and conditions.

This type of contract model of transfer to third parties is a form of private regulation. Because Australia lacks a comprehensive legislative regime for biobanking, enforcement of the conditions imposed is to be left to the ABMDR and its own resources, practically meaning that compliance would depend upon trust rather than legal enforcement. It also is limited by the doctrine of privity of contract, which would mean that any fourth or further party would not have a direct contractual relationship with the ABMDR. While there are a numbers of ways around the doctrine of privity of contract, it would appear to be a major impediment to the enforcement of any original conditions imposed by the ABMDR, against fourth parties and subsequent transferees.

CONCLUSION

Regulation of biobanking in Australia by legislatures has not kept pace with the rapidly changing medical and research environment. In the absence of clear regulatory guidance, organisations like the ABMDR have to return to “first principles” and reflect on the tensions between their moral obligation to support health and medical research and their ethical duty to ensure that the use of their materials (samples and related data) is responsible, respectful, and in accordance with its purpose for the public good.

In recent years, sociologists with an interest in biobanking have argued that donor autonomy is relational and that trust, solidarity and community also need to be taken into account when thinking about the ethical problems of biobanking and their possible solutions.\textsuperscript{21} At the same time, sociologists have cautioned against the commodification or “marketisation” of the human body and the formation of tissue-based economies, on the grounds that these processes threaten identity, dignity, wellbeing, agency and kinship.\textsuperscript{22} However, these views do not take sufficient account of how property concepts can empower and protect identity and autonomy, by creating opportunities to place conditions on the use of tissue via concepts of trust and conditional disposition.

While there are clearly merits in moving to a more open and flexible sharing of human tissue for research purposes, there are also risks involved in such developments, and steps need to be taken to maintain public trust in research and research institutions. This, in turn, requires that there are appropriate processes for scientific and ethical review, that there are mechanisms to ensure that donors

\textsuperscript{18} A determinable interest ceases on the happening of some event: \textit{Hood v Oglander} (1865) 55 ER 733. For example, “to A on trust for B for life until B ceases to use the property as a hotel” creates a determinable life interest in B, which will be determined by B using the property as a hotel. See Radan P and Stewart C, \textit{Principles of Australian Equity and Trusts} (2nd ed, LexisNexis, 2013) p 393.

\textsuperscript{19} The rule against alienation on leasehold or life estate that once property has been transferred absolutely, any restraint that is inconsistent or repugnant to that transfer will be invalid: \textit{Public Trustee v Donoghue} [1999] TASSC 147; \textit{Brandon v Robinson} (1811) 34 ER 379.

\textsuperscript{20} This rule requires that conditional interests vest within a perpetuity period, traditionally set at a life in being plus 21 years: \textit{Cadell v Palmer} (1833) 6 ER 956. The rule has been modified or abolished in most Australian jurisdictions: \textit{Perpetuities and Accumulations Act 1985} (ACT), s 9; \textit{Perpetuities Act 1984} (NSW), s 8(1); \textit{Law of Property Act 2000} (NT), s 184; \textit{Property Law Act 1974} (Qld), s 210; \textit{Perpetuities and Accumulations Act 1992} (Tas), s 9; \textit{Perpetuities and Accumulations Act 1968} (Vic), s 6; \textit{Property Law Act 1969} (WA), s 103.


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and the general public are informed and engaged, and that there is equitable access to the knowledge, products and services stemming from biobanking research. Again, property concepts may prove helpful here in providing mechanisms for imposing limits on the use of tissue via contract and trust forms.