A primer for managing international collaboration and legal compliance in biobank based genomics

Klingstrom, Tomas; SLU-Global Bioinformatics Centre, Department of Animal Breeding and Genetics, Swedish University of Agricultural Sciences

Bongcam-Rudloff; SLU-Global Bioinformatics Centre, Department of Animal Breeding and Genetics, Swedish University of Agricultural Sciences

Reichel, Jane; Faculty of Law & Centre of Research Ethics & Bioethics, Uppsala University, Uppsala, Sweden

Corresponding author: Tomas Klingström

Telephone: +4618-672126

E-mail: tomas.klingstrom@slu.se

Postal address:
Inst för Husdjursgenetik, Box 7023
75007 UPPSALA

Visiting address:
Ulls väg 26, Uppsala

Abstract

Legal & ethical compliance when sharing biospecimen across borders is a complex topic where few researchers can claim a high degree of competence. It is therefore common that major research projects contain a component with dedicated experts on research ethics. But despite this support it is impossible to fully delegate responsibility of biobank governance to external experts. For researchers it is therefore beneficial to learn about the most commonly encountered mistakes that prevent the efficient utilization of samples and take steps to avoid them.

Although laws regulating research oversight have been implemented differently in every country, there is a similarity of core principles founded on international charters. These core principles are based on the concept of consent and actions taken by the biobank in regards to sample usage rely on either an explicit or presumed consent. In interview studies among donors chief concerns among donors are focused on privacy, efficient sample utilization and if donors are given access to information generated from their samples. Despite a lack of clear evidence regarding which concern takes precedent among donors, scientific as well as public discourse has largely focused on privacy concerns and the right of donors to control the usage of their samples.

As a result biobank governance has taken a largely negative approach to uncertainties in sample utilization. This mean that sample usage is likely to be restricted if there is any uncertainty if the intended usage is in line with donor expectations. To help biobank professionals avoid making unnecessary mistakes we have developed this basic primer covering the relationship between ethics and law, the concept of informed consent and consideration for returning findings to donors.

Introduction

The risk of biobank samples being used in an inappropriate manner has received increasing attention in scientific discourse. In comparison the threat of under-utilization of samples or an inability to return the benefits of research to donors have received relatively little attention despite also being among the chief concerns of interviewed donors (Hoeyer, 2008). As a result biobank regulations largely focus on prevention of the inappropriate usage of samples rather than mechanisms to encourage their proper usage. Furthermore the genomic revolution means that pretty much any sample can be considered to contain potentially identifiable personal data in the form of DNA. Taken together these two have generated a research environment where biobank based research face an intricate extra-legal regulatory system complete with steering documents (ethics guidelines), overseeing bodies (research ethics committees) and formal procedures (informed consent)(Johnsson et al., 2014)

Although laws regulating research oversight have been implemented differently in every country, there is a similarity of core principles founded on international charters such as the Helsinki Declaration. Modern international consortia have translated these core ethical principles into policies, procedures, tools, and, governance that facilitate interoperability(Global Alliance for Genomics and Health)(Budimir et al., 2011). Enabling the scientific community to operate despite a lack of clarity and international agreements that may provide a stable and enabling environment for international collaboration (Knoppers, 2005)(“Data overprotection,” 2015).

As biobanks mature priorities tend to shift (Simeon-Dubach & Watson, 2014) and it is not uncommon that biobanks find themselves prevented from providing samples due inappropriate decisions taken several years earlier. These mistakes are often related to the relationship between the biobank and the donor in the form of obligations that the biobank has put on itself when creating consent forms and providing applications to institutional review boards. The primer therefore cover how these obligations are governed under international agreements and national law, the practice of establishing this relationship by the concept of informed consent and the difficulties on deciding when and what information should be provided to sample donors.

Hard and soft law, the key to international collaboration

The national legal framework of biobanking is often substantially different even between countries of comparable jurisdictional systems(Kiehntopf & Krawczak, 2011). To accommodate international collaboration it is therefore necessary to rely on “soft law” or extra-legal means to bridge the gap between the national legal systems which operate on a “one nation, one law, one project” approach(Kaye, 2011).

When dealing with such matters it is therefore important to understand and recognize how research is regulated by a combination of “hard law” and “soft law” where the terms can be defined as follows:

Hard law: Binding legal instruments, either in the form of international law (conventions, treaties or agreements) or national law (statutory law). International law is often drafted in a more general form and subsequently implemented in national law. For the individual researcher it is most often the national statutory law that regulates the legality of actions.

Soft law: Non-binding instruments such as guidelines and codes of conducts that may lay down suitable and commonly accepted ways to deal with a matter. Soft law in different forms varies in form from very openly phrased to rather strictly defined rules, bearing close resemblance to hard law.

Hard law is codified in legal text which makes it relatively straightforward for a trained expert to access and identify the relevant laws. Soft law is on the other hand more flexible but makes it harder to find and understand the regulatory mechanisms as it allows governmental and non-governmental experts to update regulations and standards without requiring active engagement of law making bodies, often these experts may be specified in hard law as bodies tasked with providing legally binding regulations and decisions. Funding bodies are becoming an increasingly important source of soft law by enforcing contracts requiring certain guidelines or procedures to be followed by researchers given funding in order to be eligible for funding.

For European researchers, an important source of this kind of regulation is the EU funding program managed by the European Commission. It requires applicants to state in their proposal that they will conform to specific standards("Ethics - European Commission") where failure to comply mean that the researcher will not be eligible to receive the funds provided by the grant.

Similar approaches are not only used for international projects, but are also a way for national agencies to harmonize activities in nations where legislation is done at a regional or state level. For example, in the USA the National Research Council stipulates the following for the international transfer of embryonic stem cells:

If a U.S.-based investigator collaborates with an investigator in another country, the ESCRO committee may determine that the procedures prescribed by the foreign institution afford protections consistent with these guidelines, and the ESCRO committee may approve the substitution of some of or all of the foreign procedures for its own. (National Research Council (U.S.) et al., 2010)

These guidelines are defined by one selected group of experts (the National Research Council) who delegate decisions to another group of experts (the ESCRO committee) which is charged with deciding if there is a comparable set of checks and balances in the partner country in the form of a, yet to be identified, third group of experts. These guidelines are a good example of how a soft law approach with several layers reduces transparency in return for increased flexibility as guidelines, review committees and research practitioners make up an ever-changing system of stakeholders. Under such circumstances, collaboration is substantially more likely to be accepted between nations where the respective authorities have had the possibility to become familiar with each other's customs and traditions, and above all, where the legal requirements applicable to the matter have been enacted as a result of international agreements. A lack of trust, harmonization, or the local preferences of the committee may therefore significantly affect the outcome of an application for the transfer of data or samples. Decisions by judicial authorities covering one of the partners in a collaboration may also have an immediate impact on international collaboration as certain procedures are deemed to be in conflict with national law. The EU has for example chosen a very high standard for data protection, as seen in the recent *Safe Harbor*-ruling from the Court of Justice of the European Union (C-362/14), where the US level of protection was found not to uphold an adequate protection.

However, most modern national laws are based on an ambition to adhere to a common set of core principles derived from the declaration of human rights and international declarations such as the Declaration of Helsinki(Human & Fluss; "World Medical Association Declaration of Helsinki," 2013). This mean that even if there is yet little legal harmonization between countries there is a strong case for researchers to argue that before national institutional review boards that there is room for taking into account decisions from ethical review boards in other countries, in a soft version of a principle of mutual recognition.

Consent as the basis of international collaboration

The signed consent form provides a receipt that verify that the donor has been provided with sufficient information to make an informed consent when donating his or her samples. Modern regulations regarding informed consent were codified in an international setting by the Helsinki declaration and Nuremberg code (Weindling, 2001) as a result of the horrors in World War II and subsequent development. Respect for the autonomy of research subjects and their right to refuse participation in research does however have a much longer history in research (Vollmann & Winau, 1996) even if modern researchers may find certain practices troubling or even barbaric. For example, in the mid 19th century in America it was considered acceptable for a slave owner to obtain consent for invasive experimental surgery from slaves (Wall, 2006). While it for a modern person is hard, if not impossible to accept neither slavery nor the idea of "a consenting slave". From an academic context this intuitive protest can be interpreted as an example of how we instinctively respect that a person in a position of dependence cannot make a truly autonomous decision(Sjostrand et al., 2013). The concept of donors as autonomous agents is one of the key concepts of modern research and the question of identifying what information and freedom is necessary before a person can make an autonomous decision is therefore central to all forms of biobanking and genomic research with human participants.

When establishing a new biobank it is important to rely on forward-looking consent procedures to ensure the future viability of the sample collection. A large number of different forms of consent have been proposed in scientific literature. But in practice, consent forms likely available to a biobank would need to result in a presumed, broad or specific kind of consent (see table 1). In bio-ethicist literature, concepts such as "tiered" or "dynamic" consent are suggested as compromises between specific or broad forms of consent. In practice these forms of consent can either be broad or specific depending on whether the components of the consent is widely or narrowly specified. It is however not always possible or feasible to obtain information from a known, informed and willing donor. In some cases a presumed consent is necessary and several ethicists also argue that a consent can never be truly informed unless strict requirements are met (Salvaterra et al., 2008; Hofmann, 2009; Master, Campo-Engelstein & Caulfield, 2015).

When looking at large biobank infrastructures a broad consent is favored among the major infrastructures(Hansson, 2009) (Petrini, 2010)(Simon et al., 2011) even if there still is debate among ethicists on how broad a consent can be while still maintaining the autonomy of the donor (Master et al., 2012). The dominance of broad consent in infrastructures based on soft law is in this context a good example of how soft law solutions allow society to adapt more quickly to new possibilities and risks compared to hard law where important laws may be debated for years before implementation("Data overprotection," 2015).

Specific consent is by its nature reactive as it is impossible to request specific consent for purposes not yet foreseen. As a response to this issue, proponents of specific consent have made numerous proposals where modern communication technology makes it possible to repeatedly (or dynamically) ask donors for consent(Karlsen, Solbakk & Holm, 2011). Thus, initial consent only needs to cover foreseeable research while new projects are made possible by a renewed consent. Thereby, in the opinion of its proponents, creating a balance between maximizing the value of samples and the necessary safeguards to ensure that consent is truly informed.

However, research rarely takes place in clearly defined modules and there is often a continuum where it is hard to define the acceptable threshold for clarity which requires new consent (Shickle, 2006). In practice this means that a biobank will require a similar independent ethics review board regardless of if the biobank operates under a legislation requiring specific, broad or any other form of consent.

Recent research further underlines the support for a broad consent among biobank experts(Master, Campo-Engelstein & Caulfield, 2015) but even a broad consent is limited in how much freedom may be given to researchers to initiate new projects. That an administrative framework remains in place for the sample collection and that the new research does not change the overall aims, governance, are core conditions and may be regarded as a minimal set of regulations (Steinsbekk, Kåre Myskja & Solberg, 2013). For European needs, Carlo Petrini at the Bioethics unit of the Presidents office in Italy has conducted bibliographical study of European documents on the necessary conditions to operate a biobank under a broad definition of consent with the following conclusions(dei Ministri):

- Adequate sample coding procedures are employed.
- Adequate procedures for personal data protection are employed.
- The importance of the research aim is sufficient to justify conducting the study and is evaluated on a case-by-case basis by an ethics committee.
- The sensitivity of the data is evaluated on a case-by-case basis. Genetic information varies in sensitivity based on its significance, ranging from very stringent protection to a lesser degree of protection.
- Generic research results are always released without specifically identification of individual subjects.
- “Opt-out” consent is allowed for subsequent or secondary studies. Every subject must be guaranteed the possibility of withdrawing consent at any time.
- Participants must have adequate means of involvement, such as encouraging participant consultation or communicating information through the mass media prior to project initiation. The multiple modes of involvement should be complementary as opposed to mutually exclusive. It is especially important that forms of direct participation also be available, for example by having population representatives serve on the ethics committees that will decide on the approval of the research before it begins.
- Measures to ensure transparency and supervision must be in place. Adequate supervisory, procedural, and technical systems are necessary to guarantee information protection. Further, it is highly advisable to have external and independent supervisory bodies monitoring procedural correctness.

The reporting of planned or incidental findings

Another controversial subject with far reaching consequences for sample availability is whether researchers should be obliged to return information on findings to the donor(Christenhusz, Devriendt & Dierickx, 2013). There is currently no overall consensus on when to tell and when not to tell participants of incidental findings(Viberg et al., 2014). Careful planning of procedures to satisfy local or national expectations are therefore necessary to ensure that donor interests are managed properly.

Based on the conflicting opinions described by researchers conducting systematic reviews of the field it would be foolhardy to claim that practitioners and ethicists are anywhere near a consensus in the field (Christenhusz, Devriendt & Dierickx, 2013) (Viberg et al., 2014). It may however be possible to break down disclosure into two dimensions to separate situations where researchers are closer to consensus from areas where there still is severe disagreement (figure 1).

Given this four-field breakdown and preceding information ethicists are at least approaching a consensus on the lower left and upper right corners. Which mean that incidental findings with a high level of actionability and clinical validity should, if possible, be reported back to the donor(Bradbury, McCormick & Robson) and findings of low validity and actionability should not be reported to the donors. There is however no consensus on whether it is a moral necessity to actively look for such genes in genetic data and many researchers also feel uncertain when judging if specific markers are actionable and clinically valid(Bradbury, McCormick & Robson). To support clinicians the American College of Medical Genetics have taken initiatives to support researchers to reduce these difficulties with lists of valid and actionable genetic biomarkers(Green et al., 2013) which can be consulted by clinicians to determine if incidental findings should be reported. The procedures for how and if findings are to be reported to the donor should be outlined to the donor at least by the time of consent. Thereby helping to set donor expectations and define their future relationship with their donated samples

This means that the researchers, when developing the consent form, must take care to ensure the long term viability of the biobank and balance their obligations to donors with the scientific needs of the project. A high level of reciprocity can for example not be offered in a biobank where a large portion of the research is expected to be conducted by external researchers limited to anonymized data to maintain privacy. It is therefore necessary that researchers make important decisions such as coding(Hunter et al., 2012) versus anonymization before contacting potential donors for consent. Failure to do so may otherwise result in major issues in the future as national laws on privacy or obligations outlined in the consent form may prevent the efficient usage of biospecimen.

Concluding remarks

International collaboration relies on soft law connecting national legal systems, which creates an environment which is inconsistent, unfair and often lacking in transparency. But replacing the soft law with hard law may be even worse since a codification of overly restrictive standards into law may stifle or outright halt scientific progress in regions within the jurisdiction of such laws("Data overprotection," 2015). Furthermore, it is unlikely that hard law solutions would be able to possess the necessary flexibility to keep up the pace with the rapid advancement of research and genomics.

As a researcher it is easy to become frustrated and avoid engaging in such a complex, and ever-changing field of work. But despite calls for harmonization it is unlikely that issues will be solved in the immediate future. There are significantly different legal traditions(Zika et al., 2010)(Watson et al., 2011)(Chen & Pang, 2015)(Lind, Reichel & Österdahl, 2015) as well as variation in public perception(Gaskell et al., 2013)(Ewing et al., 2015) of research. Taken together this makes it a perhaps insurmountable task to reach harmonization of national laws regarding biological samples and data protection. The legal obligations of biobank professionals concerning consent and reciprocity are therefore likely to change over time and remain areas associated with a high risk of interfering with the individual goals and aims of researchers.

In this context adhering to best practices contribute to the long term value of samples as new implementations of soft law instruments and codified law are likely to take established best practices in consideration. Guidance and templates provided by international organizations such as ISBER, Global Alliance for Genomics and Health, the Asian Network of Research Resource Centers, BBMRI-ERIC and H3Africa here form a platform for harmonization as well as generating the opportunities to build the mutual trust necessary to enable the transfer of samples or data. The role and function of these soft law tools must however take into account the constitutional aspect of the bioethical framework involving several human rights.. Traditionally these rights, and especially the limiting of the rights, are usually thought to be best regulated by democratically elected parliaments(Reichel). These international soft law tools do thus not supersede national authorities and courts, but their status as internationally recognized authorities may provide considerable support in achieving approval from institutional review boards acting under mandate from national laws.

It is therefore in the best interest of researchers to respect and promote core principles codified by international conventions and organizations. Connecting local interpretations on law to an international context also makes it easier to compare decisions and encourage the development of trust that is necessary for collaboration using sensitive genomic data. It is therefore advisable for biobank builders to adopt a system of governance where:

- The ethical standards set forth by the Global Alliance for Genomics and Health are upheld(Global Alliance for Genomics and Health).
- Samples are stored and managed in accordance with the internationally recognized ISBER standards for best practice(Campbell et al., 2012) .
- Sharing is handled in a manner compliant with the International Charter of principles for sharing bio-specimens (Mascalzoni et al., 2015).

This does not preclude researchers from having to abide by the national law of each state involved in international research collaborations and is far from an exhaustive list of tools to support international sharing of samples. But it may provide an international research project with a common foundation and framework, which make the project more easily acceptable to the national authorities charged with reviewing projects.

The inherent adaptability of soft law also mean that international collaboration through soft law mechanisms may steadily improve as experience is gained among stakeholders and thus alleviate the need for global governance via codified hard law solutions within the field. If given time to adapt, researchers and associated organizations might instead be able to contribute to a bottoms-up harmonization of a soft global bioethical framework.

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