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What Are the Most Oppressing Legal and Ethical Issues Facing Biorepositories and What Are Some Strategies to Address Them?

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Several major legal and ethical requirements that may greatly hamper the operations of biorepositories have only been proposed; however, in the future such requirements could negatively impact biorepositories as well as biomedical research in general. Two examples are the following:

1) *The return of research results to patients:* While this issue affects biorepositories worldwide, some of the legal issues that complicate this topic are national. One legal issue in the United States is that most research laboratories are not certified via the Clinical Laboratory Improvement Amendments (CLIA) and laboratory data provided to patients or their physicians must be performed by a CLIA certified laboratory. Thus, it is illegal to provide patients with most biomedical information generated in research. Most important, as the name implies, "research data" are not validated clinically. These data may be wrong (e.g., the methods used to collect the data may be invalid, mistakes may occur in analysis or interpretation, the data may be fraudulent or misinterpreted, bias may be responsible for the conclusions, and/or the data may only apply to one subpopulation). Of note, if such incorrect information is used in making medical decisions, harm may be caused to the individuals to whom the research information is provided. With whom does liability reside? This would be an unfunded mandate; who would be responsible and pay for the huge amount of work associated with the transfer of research data, for the development of the informatics systems needed for this activity and for costs of repeating and verifying results? Because human tissues as well as clinical information are supplied de-identified to investigators, the cost of these unfunded mandates would likely fall on biorepositories. Because biorepositories typically have no clinical relationship with the source of specimens, cold contacts with patients to provide research data would be very problematic, legally and ethically. Most institutions would not accept such potential liability, other risks, and costs associated with such requirements, so the number of human biorepositories would be reduced, which would result in a great reduction of research. I would not agree to return research results to patients.
2) *Informed consent for the use of all human tissues in research:* The second example is manifested by the recent proposal of the Office for Human Research Protections (OHRP) which might classify all research with human tissues, even when anonymized, as research that would require patient informed consent. Such a requirement is impracticable because the infrastructure to accomplish this does not exist and such a mandate would require over a million dollars per year per site to fulfill such a requirement. This requirement would prevent much current translational research.

Both of these are examples in which proposals have been advanced to late stages without being evaluated carefully or understood adequately by those putting them forward. Biorepositories are then forced to fight these proposals based on their impracticability. I would urge ethical and regulatory groups to evaluate the practicality of proposals before advancing them and to consider a reduction in research as an ethical consequence. Funding of any ethical/regulatory studies affecting biorepositories should require the inclusion in the ethical and regulatory groups of investigators experienced in biorepositories.

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Biobanks and, in particular, large population studies have been built, but what now? Optimizing access and use, ensuring sustainability, and supporting personalized medicine are the major challenges.

Fears of legal liability by the universities and institutions that house biobanks for possible misuse of data or samples

may well impede the future use of biorepositories. Paradoxically, even where participants have consented to broad access including international research, multiple ethics reviews and extreme data security may also thwart access. Likewise, if such resources are not sustained, then cost-recovery charges imposed on researchers could include the overall costs of recruitment, maintenance, and administration of the biobank, not just the preparation of samples and data for research. Again, this will affect access and use and perhaps lead to closure and possible loss of all the data and samples. Finally, researchers using biorepositories for disease-specific studies employing whole exome/genome sequencing will discover incidental findings that have clinical, "personal" significance and raise the thorny issue of the return of results (a minefield!).

Are strategies available to mitigate these issues or solve them? Not yet, but we should address them. First, we need to streamline, simplify, and customize access to such resources such that an internationally accepted approach is generally accepted in terms of policy (though local interpretation may differ). Second, such infrastructure science deserves and needs continuing public support especially if we wish to re-contact participants and update the data in these population reference maps. Third, personalized medicine can only happen if research results can be validated against these maps. So, personalized medicine ultimately depends on the population. The whole system of communication with participants must become dynamic, interactive, and ongoing. Only then will the return of results and incidental findings become "normalized."

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The consequence of technology advancements frequently includes ethical concerns. In the last decade, the biomedical community has become the focus of enormous public interest with advances permitting stem cell manipulation and genetic modification of organisms. More recently, the advent of rapid and relatively cheap high throughput genotyping has not resulted in as prominent a public interest as stem cells or GMOs. However, so-called Next Generation Sequencing (NGS) has the possibility to have very significant consequences for our community and, in particular, on biobanking involving human tissue.

Tissue banking from anatomical pathology is using material surplus for diagnostic needs. But now there are already several molecular tests becoming important in cancer management that requires pathology to use material that would have previously been placed into an archive, post diagnosis. In most instances, these are single gene tests, such as that for KRAS or BRAF. As more targeted therapies come onto the market, more tests will be required and NGS is already being tested to see if it is a practical and cheap means to sequence multiple genes. If this comes into more widespread practice then there is likely to be no "waste" any longer as there will be a necessity to use any material for primary diagnostic purposes.

Anatomical pathology practices already have an obligation to retain blocks under legislation or good practice guidelines and many are reluctant to release blocks for research even with patient consent. The advent of increased molecular profiling for diagnostic purposes will make pathology practices even more unwilling to release samples. Therefore, it is not inconceivable that there will be both an ethical and legal obligation for pathology labs to cease giving samples to researchers directly or indirectly through biobanks.

There is a silver lining to this possibility though, and that is the likelihood that when NGS becomes cheap enough it will become a part of routine clinical practice and pathology labs will become holders of a fantastic research resource by way of data held on each patient. The key ethical and legal issues here will be the way in which this information can be released to researchers. A way to manage this is to make biobanking a part of routine practice. This will require that "consent to research" become a part of the routine care of any patient having samples sent to a pathology practice. We have now been doing this as part of our colorectal practice for three years and it works well and solves many of the problems of custodianship and clinical obligations that may arise, such as through making incidental findings of clinically useful information. Pathology practices were once the sole "biobanks" and continue to hold the vast majority of cancer samples. Just as the microscope once did, perhaps NGS will lead regulators, healthcare managers and funders to embrace the idea that pathology is at the core of medical practice and research.

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The complexity of negotiating material transfer agreements (MTAs) for the use of the material stored in the biorepositories is routinely the most complex issue we encounter with reference to our biorepository. This is far more complex and time consuming than issues concerning patient consent and what the specimens can be used for. We specialize in the use of archival surgical pathology specimens—purely fixed tissue specimens from which cell lines cannot be derived.

We routinely encounter groups who seek to place substantial restrictions on the potential use of the biospecimens, not in relation to the consent of the patients from whom the tissue was obtained, or local laws, but driven by the institution and their desire to retain intellectual property rights or control of the biospecmens. The origins of these restrictions are poorly deployed intellectual property policies of the originating institutions and fail to acknowledge the altruism

of the donors. There is no doubt the donors of the specimens would be displeased to learn the gift was being conditioned without their input. Institutions routinely restrict the uses of these biospecimens, without reference to the original patient consents, with the goal of burnishing their reputation or claiming profit from discoveries which may be made by the use of these specimens. In our experience, it takes months longer to put the MTAs in place than it does to obtain appropriate IRB approval for the use of the biospecimens, and now routinely leads to project delays of 12 to 18 months.

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Responses to this question will vary significantly depending on both the nature of the samples held by a biorepository and the priorities of the potential end users. The perspective adopted in formulating the following response is that of the private sector, using non-human genetic resources prospected from multiple sources for commercial research.

A primary distinction may be made between biobanks holding samples of human origin, and those comprising non-human genetic resources. While the debate continues as to the precise property rights that may attach to samples of human origin, it is generally accepted that such samples are "donated" by the person from which they were derived, and that this "donor" should not derive commercial benefit—over and above reasonable expenses associated with the donation—from any subsequent use of the donated specimens. The equivalent position with plant, animal or other microbial specimens is quite different. Article 3 of the Convention on Biological Diversity, for example, establishes the principle that "States have sovereign rights over their own resources," making ownership and access rights to such materials a matter of national legislation in each territory. Article 15 of the same Convention also makes it clear that should such resources be commercially exploited, there should be a fair and equitable sharing of arising benefits with the originating party. Given that such biological repositories may include collections from diverse environments—such as marine habitats spanning high seas to territorial waters—unequivocally identifying the "originating party or parties" may not be a trivial matter. Similarly, species-specific collections of genetic materials may span many original donor countries, each with their own applicable national laws.

From the perspective of commercial entities, which may wish to access genetic resources for the development of new products, such as novel therapeutics, food stuffs, pesticides, industrial enzymes, etc., all of which involve significant financial investment and commercial risk, there is a need to seek legal certainty around title and access rights and the consequent extent of subsequent benefit sharing. While the Bonn Guidelines attempt to clarify this area, there is substantial focus on bilateral activities and little recognition of the challenge for the private sector in securing legal certainty where genetic resources from a number of sovereign states are utilized to further commercial research and development.

While the biorepositories are either directly responsible for collecting the samples or have dealt directly with other entities which may have done so, and are thus in the best position to identify the relevant "owners" in terms of originating sovereign states, it is the norm that any warranty as to title of samples is specifically excluded by the biorepository under the Material Transfer Agreement covering the transfer. This shifts the full commercial risk to the receiving entity, which has very limited potential to conduct the necessary due diligence to quantify or mitigate the associated risk. Future consideration should therefore be given to the obligations of biorepositories to secure, and provide evidence of title to samples held by them, to subsequent recipients.

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