Critical Issues in International Biobanking

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Biobanking for clinical or research purposes includes the collection, processing, storage, and analysis of biological specimens. It is now well recognized that biobanking involves a complex array of technical and ethical/regulatory considerations. Biobanking policies and procedures are often documented by best practices that are usually voluntary but may be supplemented and reinforced by strict rules and regulations that govern informed consent, privacy, QC, and other critical issues. As biobanking has emerged as a global endeavor, with national networks and international collaboration becoming the norm, it has become even more critical that practices are coordinated and that quality standards are developed. Biobanking is also often a business endeavor, in that formal strategic and business plans need to be developed to ensure the long-term survival of the associated research programs. As new technologies are developed for using biospecimens to diagnose and treat disease, as well as to evaluate genetic risks, patients are becoming more aware of the importance and benefits of biobanking as part of the medical infrastructure. As a result, patients who donate biospecimens are becoming more interested in learning more about their own sample’s use and in seeing the actual results of the research. One of the aspects of these evolving attitudes toward biobanking was addressed in a previous Q&A concerning biospecimen “ownership” in the January 2011 issue of Clinical Chemistry (Gronowski et al.; Clin Chem 57:540–4).

From the broad array of issues that could be addressed, this Q&A focuses on a few critical issues that many biobanks are facing today: quality management; biobank network design; long-term sustainability; conveying the importance of biobanking to the public; and the return of research results to biospecimen donors. Five experts who are engaged in national and international biobanking programs discuss these complex issues here.

What are some of the important issues related to quality management in sample collection, processing, and storage?

Tim Peakman: Biobanks should aim to collect and store samples and associated data in the form most useful for scientific research. This means that they should represent the biological environment at the time of collection as closely as possible, and the introduction of variation through the way they are collected and processed should be avoided as much as possible. Where cases and controls come from different sources, this problem may be particularly acute (with the exception of purely genetic studies). In studies where samples are shipped to a different location for processing, the time delay between collection and stabilization may lead to loss of some unstable markers. Where samples are processed at local sites, maintenance of consistent intersite processing can be challenging. Odds ratios for many exposures are typically 1.2–1.5, so that introduction of uncontrolled or unmeasured variation may lead to weak associations being overlooked, spurious associations being further investigated, or significantly greater cost as sample size is increased to enhance power of the study.

For many studies the greatest source of variation is at the preanalytical stage, in other words the collection, transport, and processing before stabilization at low temperature or on matrices such as blood spot cards. This can be managed by the implementation of a proper quality program that aims to make the collection and processing of samples as consistent as possible. Formal quality schemes such as ISO 9001:2008...
may be suitable for larger studies, but whether a formal accreditation is obtained or a laboratory-based approach is taken, the quality management process should include full documentation of the sample processing trail (including dates, times, temperatures, location, operator, etc.), use of standard operating procedures (SOPs), training, audits, critical materials review, and so on. Practical steps to reduce introduced variability can be taken that aim to ensure the time from collection from the volunteer to stabilization is as consistent as possible across all samples and any preprocessing (such as clotting time for serum tubes) is standardized. Finally, quality of sample annotation should be ensured using approaches such as bar codes that maintain accuracy of sample attribution and avoid the risk of misidentification that can result in false positives.

It is also important to empirically determine the stability of the samples under the particular collection protocol and whether this is sufficient for the intended purpose. Many analytes are quite stable in blood if they are transported and processed at 4 °C and, with a few exceptions, those analytes that aren’t stable only degrade a small amount over 24 h. Establishing systems and processes to avoid this marginal loss may be expensive and unnecessary.

Peter Watson and Lise Matzke: Quality management (QM) is an essential component of operating and maintaining a biobank. At the end of the day, it’s “garbage-in, garbage-out,” or so they say. Operationally, biobanks must be able to track each biospecimen that is collected, processed, stored, and distributed from the facility to manage biospecimen quality and ensure effective future use. Quality is managed by an established system that verifies biospecimens are handled appropriately. Such quality systems involve the creation and maintenance of accurate process protocols, SOPs, and the activities that verify these protocols’ being followed by biobank personnel (staff education and training). Further, standards and best practices set by international organizations such as the International Society for Biological and Environmental Repositories and the National Cancer Institute set guidance around the issues, provide a reference point for content of this documentation, and facilitate harmonization by national organizations and down to individual projects.

Implementation of QM activities requires dedicated time and a resourcing strategy which can be very costly. Therefore the scope and scale of the program should be dictated by the scope and scale of the biobank and the nature of the research it is intended to support. A biobank supporting basic discovery research may choose a primary QM focus different from that chosen by a biobank that is intended to support multicenter validation studies. Adequate training and education of biobank personnel and a tracking mechanism to ensure training is current and role specific are essential parts of the overall QM strategy. This helps to ensure consistent and informed application of both quality assurance and QC measures. The process of review of a QM system allows for evaluation around what is and what is not working in the QM and the ability to make changes.

There are several types of external assurance programs that are offered on the international stage that are complementary strategies to raise the standards across the discipline of biobanking. Some define an upper standard and use an external assessment process and measurement of product quality, while the focus for other programs is to define a minimal standard and concentrate on education. An example of the latter approach, which ties all these components of QM together, is the concept of biobank certification, which is broadly applicable for all entities handling biospecimens and is offered by the Canadian Tumour Tissue Repository and UBC Biobank Resource Centre.

Helen Moore: Quality can mean very different things to different people. One might think of quality management as the process followed to determine that, in the end, you got what you set out to get. For biobanking, quality management would follow the complex set of procedures undertaken to enroll a research participant in biobanking and collect, process, annotate, and store biospecimens.

Nonstandard abbreviations: SOP, standard operating procedure; QM, quality management.
mens, and determine whether that process yielded biospecimens and associated data sufficient for the purpose collected. Foundational elements would include well-documented SOPs that are understood and accepted by those who are collecting, processing, and storing biospecimens, as well as training on SOPs and annotation of deviations from SOPs. Quality criteria must be set at the outset and suitable metrics and analytical tests used to evaluate the processes and determine whether the quality criteria have been met. Having a quality management plan in place for biobanking does not mean that perfection is expected; in fact, it is important that quality management be reasonable in scope and that errors be expected. For example, some level of biospecimen degradation may be unavoidable in some circumstances. Awareness of this possibility and being able to measure relative degradation is part of the quality management plan. Good quality management in biobanking at best can translate to higher quality and reproducibility of research results using the biospecimens.

Akin Abayomi: In Africa, where extreme ambient temperatures are the order of the day in conjunction with potentially large geographical distances that samples may need to travel, attention to detail is critical. Clear and comprehensible SOPs and frequent training activities, particularly at sample acquisition research sites, are key to ensuring sample integrity. The emphasis is shifting towards minimizing preanalytical variables, which necessitates the need to have the capacity to bring the process of stabilizing the physiology of the sample closer to the donor. This is possible with good logistics and strategic team activity dovetailing with synchronized operations between the researchers and the biobanking teams. Communication is critical in this process. Kit development and dispatch to sites of collection with good training and harmonized operational activity all along the route of the sample until it gets to its final storage site are mandatory in this process. Where cell-line creation is part of the menu of operations, then the sooner the blood mononuclear cells are isolated and either frozen or processed the better the outcome. This process can start at the collection site to stabilize the cells and completed at a central facility. Staffing at peripheral collection sites will need to be upskilled and infrastructure adapted to this objective. Use of emerging room temperature storage and transportation technology to stabilize the whole sample at time of collection or soon after isolation of nucleic acids may be useful options in some environments.

What are the advantages and disadvantages of centralized vs individual/local biobanks?

Tim Peakman: There is no right or wrong answer to whether a study should adopt centralized or local sample processing and archiving. This will depend upon factors such as size of the study, daily volunteer recruitment rates and sample acquisition, sample processing throughput, complexity of the processing protocols, available budget, and the expertise of the study team. As a general rule, once studies reach a certain size and certain sample accrual rate, centralized biobanking offers a number of advantages but this does depend upon the study. Use of automation allows much higher numbers of samples to be processed on a daily basis much more consistently and with a robust, secure anonymized data trail. Quality data are recorded as part of the process and, if sample storage and retrieval are automated, samples can be stored and retrieved quickly from very stable, low-temperature environments with complete accuracy. Balanced against this, central services cost a lot to establish and maintain and often samples need to be shipped from collection centers that introduce delays in processing (although the effects of this can be largely mitigated using temperature-controlled shipping conditions) and increase transport costs significantly. Smaller single-site studies may benefit from local processing which is as quick as possible (and is therefore likely to preserve as many analytes as possible), is suitable for very complex protocols, and doesn’t incur high setup or transport costs. This approach is limited to relatively small numbers of samples, and can encounter difficulties with process standardization and consistency (thereby introducing variability into the samples) and requires maintenance of a robust data trail especially for studies with long recruitment phases. From experience, we know that the cost per sample for large studies is also increased with local processing. Ultimately, investigators need to consider the pros and cons of each option for their study in their setting, with an understanding of the stability of the samples they are collecting and processing and the costs of different approaches.

Peter Watson: But centralization of what? At the theoretical level, biobanks are the physical hubs of a complex activity called biobanking, and some components of biobanking need increased decentralization to reduce research bias (e.g., patient populations that capture regional variations of disease and biospecimen types) while others need more centralization to im-
prove quality (e.g., processing and storage), and still other components need both (e.g., governance of networks can be centralized in common virtual spaces but with stronger distributed representation from nodes and stakeholders). Nevertheless, at the practical level there are many logistical, economic, quality, and governance factors that influence what is a common decision facing organizations and research projects, whether to centralize or distribute their biobanks. A balanced appraisal of these factors, and the many pros and cons, have often been difficult to appreciate because of the bias created by the urge to compete.

Competition in research is an essential and healthy facet, but leakage of competitive motivation into decisions around shared infrastructure is unhealthy. The types of biobanks and research to be supported are other important factors. So there is no “best answer,” only important considerations. However, as recognition builds around issues such as reproducibility in health research and the need for increased scale and quality in biobanks (which can only come with professionalization, implementation of common standards, harmonization, and adequate resourcing), the need for more centralization and/or shared components and coordination of many types of biobanks becomes clearer.

Helen Moore: Centralized biobanks can offer advantages of increased control of biospecimens, with enterprise-wide systems for quality management, data management, and operations. Individual or local biobanks may provide advantages in flexibility and innovation. One way of combining these strengths is “federating” biobanks so that individual biobanks use the same, or at least interoperable, tools and approaches to biobanking, enabling the sharing of biospecimens across different sites in a networked or “virtual” biobank. An integrated quality management program across the system would be an important element of such a network and would include visits to different collection sites and a thorough understanding of collection and storage conditions that might be in place at different sites. It would be important to understand where approaches and processes could be aligned at different sites, and allow for differences (and annotate such differences) where they could not. A successful network would enable good communication and education about the common goals of the network, to answer such questions as: Why are we networking to do biobanking? What is the significance of the network’s work? Why is harmonization of approaches and quality management important to the final product? How do we facilitate better biospecimens and thus enable better research through this network?

Akin Abayomi: In Africa, where infrastructure is unreliable and electricity can be erratic, standardization through centralization is an attractive option with probably a more cost-effective long-term profile. Strategically placed central professional biobanks with effective outreach to peripheral collection processing satellite sites would serve the needs of the research team objectives and ensure samples are as close to that physiological state of the volunteer as possible. This would require stakeholder planning and investment. The centralized model lends itself more to the emerging principles of “biobankonomics” and biobanking 3.0, being more sensitive to the needs of potential clients and able to add value to samples before onward transmission. Economies of scale can be negotiated with vendors and courier companies on behalf of clients (researchers, institutions, or industry). This approach also serves to remove the burden of researchers individually acquiring biobanking facilities, which can have significant potential impact on sustainability and sample integrity, parameters that are becoming more attractive now and for future recipients of biological material. The ability to focus more on acquiring good samples, coupled with relevant phenotypically standardized data, lends itself to collaboration between studies and larger cohort size studies, which are attractive especially when one considers secondary use of biospecimens for epidemiological and population studies.

What are some of the issues facing biobanks in terms of long-term sustainability?

Peter Watson and Lise Matzke: Biobanks are expensive to establish, operate, and maintain. From collection of biospecimens to processing, storage, and release activities, the continuum of activities in a biobank is a costly endeavor. No two biobanks are the same: biobanks differ greatly in their purpose, scope, and scale. Further, as a unique translational research infrastructure, biobanks operate within a complex ethical and legal frame that is intertwined with biobank operations. Biobank sustainability is therefore a mixture of financial, operational, and social aspects. While financial sustainability usually dominates the debate, the importance of other aspects or domains should not be disregarded.

Nevertheless, biobanks are often characterized as not being financially secure because they rely on mixed, short-term or per-project funding. But it is perhaps the complexity and variation of scope, scale, and design that is the most important cause of this insecurity, and it is defining the metrics to evaluate the relative importance of individual biobanks and the importance of biobanks alongside other forms of health research infrastructure that represents the critical challenge. Funders of health research are diverse, fragmented, and
How can biobanks better communicate their potential value to researchers and the public?

Peter Watson and Lise Matzke: Communicating the potential value of a biobank requires the biobank to be clear on internal mission and vision and key messages (in other words the “brand” of the biobank). For the outward communication, knowing the audience and how to deliver key messages is important. Communicating value to researchers and the public will differ. To the researcher, we communicate that there is value in biospecimen banking for research, while to the public the emphasis is on the end product: biobanks are working for better health. Communicating these nuances requires a different communication strategy from delivery (public engagement vs scientific publication) to how we engage each group in the governance, design, and planning of a biobank.

Helen Moore: Biobanks are an essential foundation of the medical research enterprise, and the “value proposition” for investing and participating in biobanks must be elaborated upon and communicated. It is important for the public to understand that donation of research biospecimens, as well as the careful custodianship by biobanks of the biospecimens for current and future research, is fundamental to medical advances that may benefit the donors (or research participants) and their families. In the US, the concept of donating organs for the common good is presented to 16- or 17-year-olds who are applying for their driver’s licenses, when they are asked to note whether they would be willing to donate organs in the event of an untimely death. It is important now to educate the public about donation of biospecimens for research. Such education must be done across diverse cultural, socioeconomic, and age groups.

Akin Abayomi: Communication in the era of genomics has three dimensions: upward to the stakeholder policy makers and caretakers of national assets; horizontally to peers, collaborators, and potential clients; and downward to the populace from which samples will be derived. Each requires a different strategy and style of communication to fill the gap in knowledge. The greatest gaps will be from the recipients of the upward and downward streams. All thrusts are important.
to effective uptake and sustainable longevity. The gaps in knowledge at the three different levels can be quite significant and awareness should not be assumed. For the national stakeholders, the importance of the message is to bring awareness to the enormous advantages to be realized through bioenquiry, not just in terms of improved health of its populace but also creating economic growth opportunities. On the horizontal plane, convincing colleagues of the benefits of patronizing professional biobanks requires committed interaction. To the public the functions of community engagement committees are critical in defining an outreach strategy and form an important aspect of overall governance. An aware and informed public is easier to engage, but with this comes the evolving phenomenon of dynamic patient–public researcher relationships. The engaged public is more demanding and requires resources to fulfill expectations.

Please comment on the emerging and controversial role of biobanks in the return of research results to biospecimen donors, and the increasing likelihood that incidental findings will result from secondary review of slides and images by pathologists.

Peter Watson: The issue of “return of research results” has become perhaps one of the most dominant ELSI (Ethical, Legal, and Social Implications) issues facing research and research infrastructures in recent years. Key drivers are advances in electronic communication of data and the scale and depth of research data as exemplified by the dramatic changes in the capabilities of extracting DNA sequence data from biospecimens. The complexity and nuances of different donor–research scenarios are vast and the lack of understanding of the diversity and designs of biobanks that sit in between the donor and the research sides of the equation has created an interesting controversy. But above all else an important issue remains and is often lost in the debate: research by its nature and goals must be distinct and insulated to some degree from clinical care. There are both practical and theoretical imperatives to hold to this view. So research biobanks do not belong within the clinical care arena and should never be required to assume the responsibility for return of research results. That is not the same thing as assuming an ethical responsibility to raise issues or participate in the process of return of results when actionable incidental findings arise from research and become known to the biobank.

Helen Moore: In today’s world, larger and larger cohorts of research participants have become part of medical research, and high-throughput technologies for genomics and proteomics applications play an important role in analyzing biospecimens. Such modern technologies, as well as established analysis approaches such as pathology review, can generate some unexpected results that are discovered as incidental to the original research intent. In some cases the incidental findings are of no or unknown clinical relevance, but in other cases the findings may have potential clinical relevance and/or be medically actionable. Traditionally such findings, if discovered in a research rather than a clinical setting, were considered to be nonclinical and researchers or biobanks were not considered to be responsible for returning the findings to research participants and/or their physicians. However, as more is discovered about actionable genomic variations and high-throughput genomic studies are conducted for medical care, the lines between research and clinical findings are blurring. The ethical responsibility of researchers and biobankers to return incidental findings is currently a topic of much debate. Central themes are the consideration of what incidental findings are medically actionable, and the potential benefits and potential harms of communicating the incidental findings to the research participants and/or their physicians.

Akin Abayomi: This is a complex clinical dilemma that will move closer to the fore of debate as the concept of personalized medicine becomes more of an expectation. It is conceivably unethical to withhold potentially medically useful information from a donor or the community. However, the main constraints are human resources and the ability to adequately and accurately transfer derived association data in an evidence-based manner to the donors. The concept of dynamic consent will probably emerge as a more appealing option to our patient base as information and access to patients becomes more implementable through modern broadband technology.

Briefly comment on one or two major challenges or emerging issues that you believe will have significant impacts on the future of biobanking

Tim Peakman: One of the major challenges for biobanks will be data management. This is likely to come from three sources:

- Data generated from use of the resource—many studies release data and samples to other researchers (particularly open access biobanks) and typically this arrangement involves the return of research data to the biobank once the work is complete. The great advantage of this is that it enhances the resource for future users. However, because of the range of scientific questions that can be asked using these resources and the technologies used to interrogate them, biobanks will need to address data standards, metadata...
requirements, data quality, and how data are stored and accessed in a “future-proof” way.

- In-house data generation—many large biobanks are turning their expertise and resources to initiatives to generate large data sets on their entire sample collection. For example, UK Biobank is currently genotyping the entire 500 000-person cohort, is measuring about 40 biomarkers in the plasma, serum, and urine of the whole cohort, and is piloting an approach to collect multimodal imaging data on 100 000 people. These data sets are very large and heterogeneous and present challenges of storage, accessibility, and use. Keeping them current, both from techniques such as genetic imputation and new analytical approaches and from analyses done by users, will be a major data management challenge.

- Avoiding gaps in the data—one of the great attractions of large open access biobanks is the breadth of studies than can use the resource. Care should be taken to avoid using the inventory of nonrenewable resources in a piecemeal way that creates gaps in the data set. It was on this basis that UK Biobank sought funding to genotype the entire cohort with the expectation that in three or four years it will be feasible to sequence the DNA of all of the 500 000 people. This creates a digital record of the genome so that the remaining DNA can be used for other types of emerging analyses (e.g., epigenetics). We are currently considering high-content screening approaches for the proteome and metabonome.

Helen Moore: Data sharing across biobanks and research programs will be very important in the future of medical research to better understand individual differences in disease development, progression of disease, and response to treatment. Enabling such data sharing while protecting the privacy of individual research participants is a major challenge for the future.

A better understanding of biospecimen science, i.e., the effects of different biospecimen collection, processing, and storage methods on the molecular integrity of biospecimens, is something we need to pay attention to now so that we can develop evidence-based biospecimen practices for different analysis technologies. We also need to be recording the methods by which biospecimens are handled, and storing this information with the biospecimens in biobanks. This approach will be even more important in the future so that there will be some assurance that collected and stored biospecimens are suitable or “fit for purpose,” for advanced research and detection of specific biomarkers as analysis technologies progress.

Akin Abayomi: DNA fingerprinting will become an important aspect of governance into the future as a means of tracking samples and derived data. Through unique demographically related single nucleotide polymorphism algorithms, highly defining biomarkers can ensure the ability to track samples from origin to publication and development. Similar to how sound bites regulate the use of copyright in the music industry globally, we should be able to trace a biological specimen from a research site to primary or secondary users and the benefit that is derived in contributing to a bioconomy. This will become particularly important with the increasing use of cell-line technology in terms of both a quality assurance and a means of tracking and governance. It will also serve as a means to embody confidence in the scientific process and perhaps start the building blocks for beneficence modalities on a macroscopic level.

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