Biobanking for better healthcare

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ABSTRACT

Translational cancer research is highly dependent on large series of cases including high-quality samples and their associated data. Comprehensive Cancer Centers should be involved in networks to enable large-scale multi-center research projects between the centers [Ringborg, U., de Valeriola, D., van Harten, W., Llombart-Bosch, A., Lombardo, C., Nilsson, K., Philip, T., Pierotti, M.A., Riegman, P., Saghatatchian, M., Storme, G., Tursz, T., Verellen, D. 2008. Improvement of European translational cancer research. Collaboration between comprehensive cancer centers. Tumori 94, 143–146.]. Combating cancer knows many frontiers. Research is needed for prevention as well as better care for those who have acquired the disease. This

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1. Biobanking, a heterogeneous concept

Biobanks are developed in relation to a research question having its own strategy and specific demands on quality and annotation of the collected samples, resulting in a very heterogeneous concept in Biobanking. Even considering exclusively human samples-related banks for research, there are multiple designs according to the different possible goals. In a brief summary, human-driven biobanks include three mayor types (see also Figure 1):

A. Population banks. Their primary goal is to obtain biomarkers of susceptibility and population identity, and their operational substrate is germline DNA from a huge number of healthy donors, representative of a concrete country/region or ethnic cohort.

B. Disease-oriented banks for epidemiology. Their activity is focused on biomarkers of exposure, using a huge number of samples, usually following a healthy exposed cohort/case-control design, and studying germline-line DNA or serum markers and a great amount of specifically designed and collected data.

C. Disease-oriented general biobanks (i.e. tumour banks). Their goals correspond to biomarkers of disease through prospective and/or retrospective collections of tumour and no-tumour samples and their derivates (DNA/RNA/proteins), usually associated to clinical data and sometimes associated to clinical trials. Those data are usually not collected for a concrete research project, except in case of clinical trials, but from the healthcare clinical records. The amount of clinical data linked to the sample determine the availability and biological value of the sample (see also Figure 2).

Although these three major biobanks types have many aspects in common, it seems necessary to discriminate and develop a deeper knowledge and recognition of their differences and specific characteristics and challenges.

2. Harmonization

Before any research can be conducted, the bio-materials and the necessary associated data must first be collected, while research specific factors (number of samples required, the pathology being studied) can influence the duration of the collection process. The collection process typically takes years, and in some cases decades. This results in a risk that over time new scientific insights emerge causing the unforeseen experiments to change in their set-up that in the worst-case result in a shift in the desired end product. It is therefore recommended where affordable, to keep the scope of the end product as large as possible and the sample quality as high as possible. The gained advantage also is that the samples are probably useful for multi-center efforts that were perhaps not foreseen at the start of the collection.

However, to really enable harvesting the immense treasure of information hidden in the biobanks for healthcare (Oosterhuis et al., 2003) to its full potential it is important to have a research infrastructure facilitating multi-center research. Currently this is the only way to acquire the high sample numbers needed for statistical significant results in a reasonable time. Especially, the longitudinal studies on multi-factorial diseases like cancer to discover genomic correlations starting with a healthy population of volunteers need decades to obtain the needed critical mass of a certain (sub)type of cancer (participants in time acquiring the disease of interest in the population) to commence a study. However, also the clinical cohort studies face similar problems. For proper biomarker/profile description it is not enough to describe a discovery in one group of patients, but needs in addition independent rounds of validation in other independent patient groups.
Therefore, it is absolutely instrumental to work together in networks of biobanks (Morente et al., 2007; Yuille et al., 2008; Riegman and Llombart-Bosch, 2008). In Europe plans have been launched for an infrastructure of a pan European biobank network (BBMRI) that will be integrated in infrastructure for research on drug development (Yuille et al., 2008). This infrastructure is generated for all diseases including cancer.

Therefore, biobank managers need to monitor the latest developments in favour of harmonization and make an effort in joining networks. Especially when the involved biobanks have adhered to internationally accepted procedures, standardization and quality control (Morente et al., 2006; Mager et al., 2007), the materials can be exchanged between or among institutes, to be used in a high variety of experimental designs, whereas the origin of the samples is expected not to influence significantly the end results.

3. Guidelines and best practices for organization of the biobank core processes

The most important aspects involved when setting-up a biobank are described in guidelines and best practices. The OECD has described guidelines applicable to all forms of biobanks (OECD, 2001, 2007), whereas the NCI guidelines are more focussed on human materials (NCI, 2007). The International Society of biological and environmental repositories (ISBER) has recently released their 2nd edition of best practices (ISBER, 2008). Despite these guidelines describe all the aspects and result in the proper facilities and encourage harmonization, they leave many choices for the methods used by the individual banks to choose the best method that best fits the aim.

Although guidelines and best practices can be useful for harmonization, a serious caveat might be in place here. When setting-up the guidelines there must be a team of experts that are not only aware of the variety of biobanks, but are also well informed on the specific differences. A compilation of these aspects was recently described in a laboratory accreditation norm compatible format (Betsou et al., in press).

4. Standardization for organization of sample collection

An attempt to come to a minimum standardization was launched by an initiative of IARC/WHO in which many experts in the field have participated (Caboux et al., 2007). These
minimum standards also describe examples of sample preparation protocols that can be used. Recently, CTRNet also released a complete set of Standard Operating Procedures (SOPs) into the public domain and established a web-based forum to discuss biobank-operating procedures. However, further research is needed when engaging a research project on the basis of biological material it is always important to establish the robustness of the end-use technique and ensure it is compatible with the material collection and preservation methods used.

Pre-analytics of a sample include two distinct phases. The acquisition phase, where the specimen comes under the supervision and control of the biobank personnel and the pre-acquisition phase, where the specimen is not yet under supervision and control of biobank personnel. In the pre-acquisition phase there can be circumstances that can influence the final status of the sample upon retrieval. For example the donor may have been treated with drugs like antibiotics, certain anaesthetics or other pre-treatments. Development of quality control tools for assessing pre-analytical variations of the acquisition phase can be very useful. Such quality control tools can play an essential role for assessing the quality and therewith the usefulness of the sample when it is about to be used in experiments sensitive to such parameters. They will represent the only means for the biobank to prove conformity to a given collection/preparation SOP.

In the search for biomarkers, molecular targets and profiles, the community tends to look for a completely noise-free output. This of course facilitates the discovery of the desired marker or profile. However, an adverse effect might be the actual clinical performance of the identified marker. Leaving room for acceptable variation might make it difficult at the start of the experiment to see whether there will be a feasible end point, however, when successful, this will result in the end in a more robust marker, target or profile. The obtained marker or target is likely more easy to use in practice, because of its stability in slightly different situations. As an example, it has been shown that processing time of prostate tissue had only minimal effects on the protein profiles (Jackson et al., 2006).

Additional research into other quality factors in the major pre-acquisition phase is required. Process changes in the pre-acquisition phase both highlight the need for a multi-disciplinary approach and demonstrate the barriers to implementation. For example, for both the biobanker and the researcher, lag time, the time between removing the specimen from the body until freezing, is a critical variation factor and therefore a quality indicator. For the surgical staff, recording lag time is but a minor detail during an intense procedure. However, the current measurement of lag time may be misleading by not measuring the time the tissue was without a blood supply. While more research is required to determine if measuring lag time from the time of clamping would provide a significantly better quality indicator, it is clear that such a research project would need a multi-disciplinary approach. Although the multiple blood supply of most of organs complicates the discrimination of the concrete time of the start of warm ischemia, the estimations will present a more reliable lag time and become a significantly better quality indicator.

A major variation factor, taking place in the pre-acquisition phase of tissue samples, might be to include the total clamping time of blood supply in the lag time. Now the lag time is defined as the time between removing the specimen from the body until freezing. But more realistic would be to record the time of real hypoxic conditions and determine a lag time from cutting of blood supply including the time of warm ischemia until freezing of the samples. However, the data is difficult to acquire due to the extra work and attention required from the surgical team and yet, if this could be accomplished, due to multiple blood supply of most of organs it will stay hard to discriminate the concrete time when the real hypoxia starts. Other more illusive influences on the sample status depending on the robustness of the specific technique/analyte combination may include parameters such as the kind of nourishment or the time that elapsed between the last meal and the acquisition or time of day.

Standardization is relatively easy to do with materials specifically collected for biobanking or those ones originally devoted to diagnostic and curative goals but clearly secondly used for banking like fresh frozen residual tissue samples, as described for OEG-TuBaFrost (Morente et al., 2006; Riegman et al., 2006). However, when the collection is dependent on material that was first meant for diagnostic purposes like FFPE material this becomes already more difficult due to the scarcity of tissue and other previous technical procedures. Two circumstances could be useful to exemplify the pre-acquisition phase peculiarities between different biobanking designs: population vs. disease-driven biobanks and blood collections.

Population and epidemiology-driven biobanks collect samples and data specifically for biobanking and then collecting activity can be done according to the biobank rhythms and agendas. Samples, usually ones as easily obtained as peripheral blood, can be handled directly for the study/banking characteristics and goals, and associated annotation, although comprehensive, can be collected directly from the donor by specialised personnel. On the other hand, disease-driven and hospital-based biobanks work with samples primarily obtained for diagnostic and therapeutic purposes. An appropriate diagnosis is the first and biobanking pass to be the secondary priority resulting in an independent rhythm, relapse in sample handling for banking, more complex specimens, data collections from the clinical records, post-sample-collection informed consent, etc. (Morente et al., 2006).

In case of blood collections the collection alternatives are too numerous to give common-quality sample, or plasma derivatives. Despite the wealth of choices, DNA has a high chance to yield usable end products. However, when looking for DNA amplifications or expression profiles of RNA or proteins it soon becomes very complicated. For this type of multi-center research this often results in making use of prospective collection with sound agreements on the collection procedures, annotations with high corresponding traceability.

Serum and plasma proteomics illustrate the difficulties establishing quality control and standardized protocols
suitable to assess proper cryopreserved samples. The major challenge is to fully identify and characterize the proteins and post-translational modifications at any given time in serum, because disease states may be associated with distinctive configurations of circulating proteins. Plasma contains most, if not all, human proteins, not only proteins that carry out their function within the circulatory system, but also proteins that are secreted or leaked from different cells and organs, and proteins from foreign microorganisms.

Quantitation of relative abundances in comparative proteomic studies is difficult, not only because of complexity but also because of the enormous dynamic range. The relative abundance of plasma proteins spans a range of over eight orders of magnitude in concentration (<pg/ml to >mg/ml). Even if ultra-high efficiency capillary liquid chromatography separation followed by ion trap-tandem mass spectrometry allows identification of more than 2000 proteins from plasma samples, more than 80% of the identified proteins interact with IgG or albumin. Moreover, clotting additives may compete or interfere with the binding of proteins on the surface of protein chip arrays used in MS. For lower abundance markers, profiling probably requires pre-fractionation to reduce sample complexity. Such pre-fractionation procedures will also need to get standardized, possibly as part of the biobank’s processing methods (Zimmerman et al., 2005).

The most important thing that biobanks should do, at the actual state of the art is to ensure complete traceability of the sample collection and processing, by recording all variables, such as time of sampling, type of primary collection tube, delays and temperatures of processing and storing the samples. The HUPO Plasma Proteome Project has also published guidelines in the same direction (Rai et al., 2005). It is recognized that detailed material traceability may be impractical and unaffordable for many biobanks, it is therefore recommended that as a minimum step biobanks capture the standard operating procedure (number & version) that can be mapped to the details of the SOP. For an example, see the CTRNet Advanced Tumour Information Bank (ATiM) application.

A proposition on the best method giving the widest array of research options might give relief in this field. As a starting point in this discussion the proposed minimum standardization protocols published by IARC would be helpful. These discussions need to be taken up by the larger biobanking forums with a wide perspective as ISBER, Marble Arch International Working Group on Biobanking for Biomedical Research or P3G, preferably all forums together with participation of international initiatives as IARC, EORTC, BBMRI and others. Still this must not be a one-time decision but monitored in time, new techniques and insights might warrant for alternative choices.

5. Information technology and annotation

The scientific value of the sample is not only determined by the physical quality. Clinical, environmental and demographic data play an important role in the research capabilities of the sample. The planned research determines the (minimal) data set recorded by the biobank. In almost all instances the biobank data standards have evolved to include a combination of local and international standards that are established primarily to meet local requirements only.

International networking of biobanks reveals a full-blown annotation problem (Riegman and Llombart-Bosch, 2008). For large studies, shared data needs to be comparable and has exactly the same meaning and has been collected following similar coding practices and data controls. If not the scientific end result might get severely impaired. Therefore, networks need to describe and publish annotation rules, making use of coding lists where possible. Poor and incorrect annotation limits and unnecessarily delays research and in the worst-case results in erroneous research. When crossing borders, the language becomes a second barrier, which needs the addition of translation tables for all words that will be used. In addition, the use of international coding tables for topography and diagnosis, like Snomed or ICD-10, can be standardized differently (have a slightly different interpretation) in the countries involved. Instances where these coding tables are subject to a license can place a further barrier to implementation.

The ideal solution would be a compatible tracking system used in the local biobanks that forms a federation of data for a network, complete with translation tables on terms and languages enabling international sharing of materials and data.

The national efforts have resulted in a wide array of tracking both commercial and non-commercial software applications becoming available that may be the foundation of a solution. The free non-commercial packages vary from full-scale solutions including clinical annotation, inventory management, order entry and shipping to simple study specific applications. The best of these systems include query solution that permits the biobank manager solve many research questions in minutes.

Unfortunately, the implementation of any system highlights many of the process and data problems within the local bank. The situation becomes more challenging as the local bank networks with other banks. Additional complications arise within hospital security when data needs to be shared. A central web-based biobank network application actively downloading from a hospital database is not allowed and therefore an active upload procedure needs to be chosen.

Even with the existing national solutions an interim simplified solution providing an achievable minimum data set is required. This minimum data set would set the standards for the acquisition of data in either electronic or paper-based forms in a manner suitable to searching for and identifying suitable samples. Along with standards operating procedures for the collection, processing, storage, relative scientific value and distribution of materials, these systems would result in a significant improvement for researchers. Included in the minimum data sets, the standard operating procedures followed, consent procedure, storage conditions, available data and options to retrieve the data, scientific value of the collection, access procedures, etc. Instead of specifying every sample with exact clinical data in the network central database, the requestor has the task to specify the samples exactly to his needs and ask the national or international repository network or the involved collectors on the availability of such samples.
6. Sample logistics

During the lifetime of a sample the sample needs to be transported from one place to another. It actually starts with sample transport from the site where it is taken from the donor to the site where the sample is processed for long-term storage. Indeed this phase can be very critical for the overall quality of the sample and its future use. The type of biosample collected depend on the experimental design but it is mandatory that a tissue fragment must be kept on ice when resected from a patient until it can be snap frozen, particularly if the sample later will be used in molecular studies. This cooling or quick freezing procedure is not always necessary when collecting blood samples, depending on the needed derivatives.

7. Long distance transport of samples

In multi-center translational studies the quality of the sample is of paramount importance, therefore it needs to be shipped in proper conditions. If the biosample is not properly packaged it can get damaged during transport or can get held up in customs if the package is not according to IATA regulations and all the relative documents are not in the proper order.

In multi-center projects, the way to guarantee the best transport of the biosamples from the collection site to the processing and/or storage site, is to design a specific collection kit, containing the right collection tubes (vacutainers with the proper anticoagulant, ACD, LitHep, etc.) and packaging material and instructions as well as all the labels following the IATA regulations. IATA requires specific labelling on the outside of the package (e.g. UN 3373, Biological Substance, Category 2, etc.) and specific packaging material inside of the box (watertight primary and secondary receptacles, absorbent paper towels, sturdy outer packaging, etc.).

The transport temperature is also very important. If the biosample must be shipped at room temperature (e.g whole blood which needs to be processed for establishing a Cell Line or extract DNA/RNA, etc.), the collection kit must be designed for room temperature shipping and must contain a temperature sensor to check the temperature variation during transportation. Instead if dry ice shipment is required (e.g. shipment of plasma, serum, cell lines, etc.) attention must be given to the quantity of dry ice placed in the box and on the courier chosen for the shipment. The proper shipping papers need to be filled out and the courier needs to be able to refill the box with dry ice in case the package gets delayed in customs. The most secure way of shipping biological samples is to use Liquid Nitrogen Vapour Shippers. The cost of shipping is higher but these shipments (depending on the size of the package) are IATA approved and can hold the –150 °C temperature for at least 15 days. It is of utmost importance that frozen tissue samples, are not shipped at a temperature higher than –80 °C, therefore the sample must be immersed in dry ice using a courier that can refill the dry ice during the transport if necessary. FFPE cannot be shipped in temperatures higher than 25 °C. Good isolation and coolant are therefore, nonetheless, necessary despite the fact these blocks can actually be stored at room temperature.

Recording of unforeseen temperature shifts during transport is mandatory to monitor the conservation of quality of the sample after transport.

8. Evidence-based biobanking: where biobanking becomes science

A new line of thinking is emerging in biobanking. The belief that research is needed to discover biomarkers for biobanking; an ideal biomarker should have an ubiquitous expression and show 100% loss or vice versa of activity upon inadequate processing, storing conditions and temperature variations. The biomarker that gives an on/off response could serve as quality indicator and can be used to show per sample if the sample has the quality to be used with a certain technique. Before using the sample a simple test can show the quality and usability of the specimen. In addition, these markers can reveal if during the lifetime of the sample it was kept up to the conditions as described in the SOP's. Biomarkers should be found for all types of samples or organs the sample was derived from as well as any desired derivative or end product.

This is how biospecimen research, leading to discovery of appropriate quality control tools, will help setting evidence-based standards for indirect validation of the core biobanking processes through direct validation of the samples. If standardization of preparation/processing methods is not attainable, standardization of quality control procedures, applying to materials, independent of the processing methods followed to process and sort these samples must be invoked to assure the appropriate quality of biospecimens for the research purpose. Simply put, biobanks must ensure that the biospecimens provided are fit for the research.

For example, too little is known on the impact of surgical lag time to the banking of materials. Currently lag time is based on the time the surgical specimen is removed from the patient until freezing. The lag time is frequently used as one of the critical estimators for overall material quality. However, the time the organ was clamped is not taken into account, but might be vital in setting the lag time for high quality samples and might to a certain point even clarify the differences seen between the different surgical specimens and the allowed lag time (Grizzle et al., 1998; Huang et al., 2001; Dash et al., 2002; Almeida et al., 2004; Blackhall et al., 2004; Spruessel et al., 2004; Micke et al., 2006). These types of experiments are too expensive for many a biobank budget to perform without proper funding, but nonetheless crucial for good biobanking. Ideal quality control tools are ubiquitous, show an on/off response and can be measured by widely accessible methods (Chaigneau et al., 2007; Langellé, submitted for publication).

However, not many attempts have been made by the journals on the reproducibility of experiments and therewith standardization of sampling. An enormous gain can be
made in the area of the very sensitive techniques using human materials like proteomics. Strong guidelines asking for specifics on the used samples as well as the used techniques for reporting results when preparing a manuscripts, as recently proposed for Molecular and Cellular Proteomics (http://www.mcponline.org/cpmeeting/ProGuidIntro.shtml), cannot only help to make results reproducible, but also make differences in results better understandable.

9. Ethical, legal and social implications

The importance of ethical, legal and social issues in human tissue research is widely recognized in both society and in the research community specifically, as evidenced by the focus reputable journals place on the understanding and resolving the issues. Towards, the goal of addressing the issues, the journals now ask evidence of research approval by a Medical Ethical Review Committee (MEC) or Internal Review Board (IRB) approval.

On a national level the rules for biobanks which require MEC or IRB approval are governed by complex evolving legislation and lack standardized procedures. Therefore, differences in decisions can be found already on a local level. To understand the issues on an International level sometimes means a biobank manager needs both legal and ethical advice. The extent and variety of laws and regulations, along with the differing study circumstances, warrant a (too) vigilant attitude towards exchange of materials and data. The most frequently observed example identified on the legal variation is that of “consent” with regard to residual materials. In some countries “consent” is assumed with or without the requirement of participants to be able to “opt out”, some countries accept “general consent”, others require “signed consent” and yet others require “informed written consent”. In a few isolated incidents, legislation has not been invoked to address the issue.

There is a continued long debate on what the various levels of consent mean, what is required to obtain those levels and what activities are permitted within consent (Salvaterra et al., 2008; Lunhof et al., 2008; Cambon-Thomsen et al., 2007; Hansson, 2007; Helgesson et al., 2007; Maschke, 2006; Wendler, 2006; van Dese, 2002; Homon, 2001). Adding to the complexity, the laws governing privacy and ethics continue to evolve and are subject to jurisdictional impetration. While the importance of the issues are well understood there is general agreement that the trade-off between increasingly more complex legislation and the marginal benefits derived from the new protection measures afforded individuals is not sufficiently understood in the context of the public good derived from research. Clearly this is just one area that would benefit from additional research and leadership directed towards resolving the issues in a practical way.

The OECI-TuBaFrost European Code of Conduct for residual material (van Veen et al., 2006), although in principle based on European legislation on home country control and honest international competition rules, has in fact touched upon an important issue. The code speaks to many as being very logical, because it in fact also respects the rules and legislation of the country of origin. This is also the country of the donor, where a democratic process has, or even in some cases deliberately has not formed these rules and thus represents the general will of the donor. This code was originally designed for residual material, but could form a basis for exchange of all human material for medical or healthcare research. This would mean that if samples are moved to a country with other or even stricter rules the rules of the home country apply and no further demands need to be met. Local IRB or METC approval is sufficient. A disadvantage could be that in case of multi-center studies, where several countries are involved would result in many different rules to be applied.

As described above a signed informed consent is not always needed and can save scarce research resources, money needed for research nurses helping the donors to fill out consent forms. Material Transfer Agreements are generally used and accepted as binding contract when samples are exchanged from the bank to research. Demands on intellectual property rights find their way more and more into these MTA’s.

The scientific community is not always aware of the fact that the pathology archival material is in most countries material part of the diagnostic process and must therefore be kept in storage for a certain time period. The institute/department is legally responsible for the proper storage. A typical example would be a period of at least 10 years. This implies the original lesion must stay intact, when the material is used for research purposes. However, sometimes blocks given out are not returned or are no longer contain the original lesion. One option is to close the archive for further medical research; however, this is not really contributing to better medical care. A second option is to only allow researchers to handle the block on the pathology department under supervision. This is also very restrictive and also isolates the institute from good multi-center translational research projects. In order to make sure the blocks are returned in good condition and on time, a clause can be taken up in the MTA in case the block(s) are not returned in time or are mistreated a fine can be claimed per day per block and any following juridical or financial consequence of this act are to be forwarded to and claimed from the institute and department of the recipient. This is of course not necessary between partners that can trust each other in respecting the integrity of the archive. In addition, in such cases good settlements can be made to keep the material elsewhere and send it back without delay and questions when it is asked for by the institute of origin.

10. Access rules

Again a variety of access rules are found between biobanks, dependent strongly on the embedding of the biobank and the relation with the stakeholders. Attempts to harmonize, easily strand when considering population/environmental banks to harmonize with disease-oriented/clinical banks. The access rules differ too much on one point to become completely harmonized. The main stakeholders in a population bank are the donor and the biobank with a committed research team, whereas in clinical biobanks the clinicians and a variety of researchers also belong to the stakeholders. An
important note is that without the cooperation of the clinicians there will be no collection at all. Therefore, this group needs to be involved on the decisions to issue collected samples to other requesting parties and this process needs to be repeated for all incoming requests, either from within the institute, or from external parties.

The Biological Resource Centers of the future need to have an open access to the sample collections according to the future network of biobanks in Europe in the Biobanking and Biomolecular Resources Infrastructure project (BBMRI) (Yuille et al., 2008). However, the above described access procedure for the clinical biobanks cannot simply be omitted, for the simple reason the biobank would lose local support and as a result would cease to exist.

The donor’s interest is to be involved in meaningful medical research. However, in these times of dynamic and fast developments it would become impossible to do research and unethical towards the donor to be re-contacted every time when new research perspectives and questions arise. Especially in clinical collections many of the persons involved might be already deceased, causing heartrending reactions amongst the surviving relatives. The biobank manager is in this process the honest broker between donor interest, clinician and scientist protecting all involved interests.

In networks often a review board is active to review requests. However, due to the stakeholders at institutes such review boards can only issue an advise to the institute and leave the final decision to the institute committee. Besides the internal committee is the only body that can take into account the institutional gain or loss when giving out samples to external parties and can decide on cooperation, co-publication or reimbursement. During this process of deciding to give out samples for research internally or externally it is of the highest important to in addition evaluate the composition of the research team involved in the research. Such a team must be appropriate and usually must consist of a multi-disciplinary team; the involvement of clinicians (e.g. pathologists and surgeons), statisticians, epidemiologists, molecular biologists and biobank managers appears to often hold the key to success (Riegman et al., 2007).

All the tasks summed up here makes clinical biobanking itself a multi-disciplinary occupation, which centralise around the biobank manager. The tasks typically involve knowledge of standardization and quality control, insight in the latest research developments on biospecimens, information technology, legislation, ethics, transport of infectious material, cost recovery, clinical and diagnostic processes, logistics, contacts with stakeholders, external contacts. Sometimes even negotiation skills are needed especially when multiple parties show common interest in the same samples. The tasks are performed dependent on the size of the clinical biobank minimally by a biobank manager and a research technician dedicated to the biobank often complemented by a research nurse when informed consent is needed.

- The timelines for research usable materials typically require in excess of 5 years.
- Grants are given to establish the biobank infrastructure, but fail to provide ongoing operating financing.
- Reimbursement of banked samples is mostly excluded from funding in research projects.
- Where cost recovery is invoked to comply with legislation in most countries prohibiting human specimen profit, pricing is typically calculated on average sample cost and significantly over valuing unused inventory.

Such an environment can easily lead to devastating financial situations, where it can become impossible to sustain the biobank both in the short and long term. In the short term, retrospective collections are unusable for most research and prospective biobanks are tied to specific research projects that prohibit the use of material for other research initiatives. In the long term both types of biobanks are challenged with the current mantra that biobanks can somehow achieve self-financial sustainability, however, unlikely.

The long-term survival of biobanks depends on host institutional support. To secure this support institute funded biobanks frequently provide scientists conducting within the institution with 100% discount. In recognition of funding from public sources, external users are often charged a user fee that deducts the institutional support towards complete cost recovery. This leads to a level product and service pricing complexity that a biobank manager requires to conduct complex and difficult cost calculations. The choice in cost models is already difficult and chasing for hidden costs even worse. However, it is necessary to have a good idea what the cost per sample is.

In addition, the full pricing can be to shown to those scientists who do not have to pay the samples have beyond a scientific value to demonstrate that a substantial financial value is represented. Presenting the bill showing the discount of 100% to also those who do not have to pay can alter the respect for the input of the biobank.

11. Cost recovery/sustainability

The financial situation of biorepositories for medical research has been far from promising so far. This is due to:

Acknowledgements


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