International biobanking regulations: the promise and the pitfalls

Anna Wagstaff

Banked samples of human tissue, blood and serum linked to the patient's clinical data are the raw materials of modern cancer research. A single infrastructure for Europe's rapidly evolving biobanks is urgently needed. But finding agreement on the ethics, language and operating standards is proving quite a challenge.

Moving towards personalised cancer therapy is about finding answers to questions like: Is this colon cancer aggressive or fairly indolent? Which type of chemotherapy will this breast cancer respond to? Does this person need to take preventative measures to guard against a raised risk of cancer?

Finding those answers involves looking at samples taken from aggressive and indolent (or responsive and non-responsive) tumours and identifying a biological 'marker' or 'biomarker' that appears to differentiate the two. Further samples, from newly diagnosed tumours, are then needed to test, in a prospective study, whether such 'candidate' biomarkers really can predict the behaviour of the disease and can thus be relied on to help guide the clinician towards the right therapy for their patient.

The raw materials for all this work are large quantities of quality-controlled and well-catalogued biological specimens linked to information about the person from whom they came, their health status and the trajectory of the disease. A shortage of these raw materials will slow down progress in improving cancer treatments.

Responding to this need, the research community has been steadily building up 'biobanks' as repositories of data-linked human biological samples. Systematic banking of samples for research is becoming increasingly common at major cancer centres and university hospitals and is now mandatory in many. Biobanking samples for research is also specified as an essential activity for members of the elite Organisation of European Cancer Institutes (OECI).

A European network for data-linked frozen cancer specimens TuBaFrost, was set up in Rotterdam in 2003, and is now in the hands of the OECI. Specialist networks, such as Conticanet for connective tissue cancers, are building up their own banks to identify molecular subtypes. A number of countries, including Sweden and the UK, have also embarked on projects to develop population-based biobanks, which should enable researchers to study samples from cancer patients (and others) that were taken while they were still deemed healthy, to look for biomarkers of early detection or risk.

A considerable number of data-

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linked biological samples have also been collected as part of specific studies. The MINDACT study, for example, collected and gene-profiled frozen samples as an integral part of the protocol, which aims to see how accurately the Mammaprint gene signature can predict who will benefit from adjuvant chemotherapy. Other collections come from 'correlative' translational research studies – ancillary protocols that research groups like the European Organisation for Research and Treatment of Cancer (EORTC) run alongside clinical studies, on the principle of 'no tissue, no trial'. This principle, put forward by ESMO's José Baselga – now Professor of Medicine at Harvard – holds that it is a waste of resources to organise a trial that answers the question: 'Is *a* better/no worse than *b*?', if it fails to gather biological samples that could answer the personalised therapy question: 'For which patients is *a* better/no worse than *b*?'

The blossoming of these biobanks is very good news, and yet their ability to serve the research community remains limited by their fragmentation. Each has grown up with its own set of norms, principles, quality

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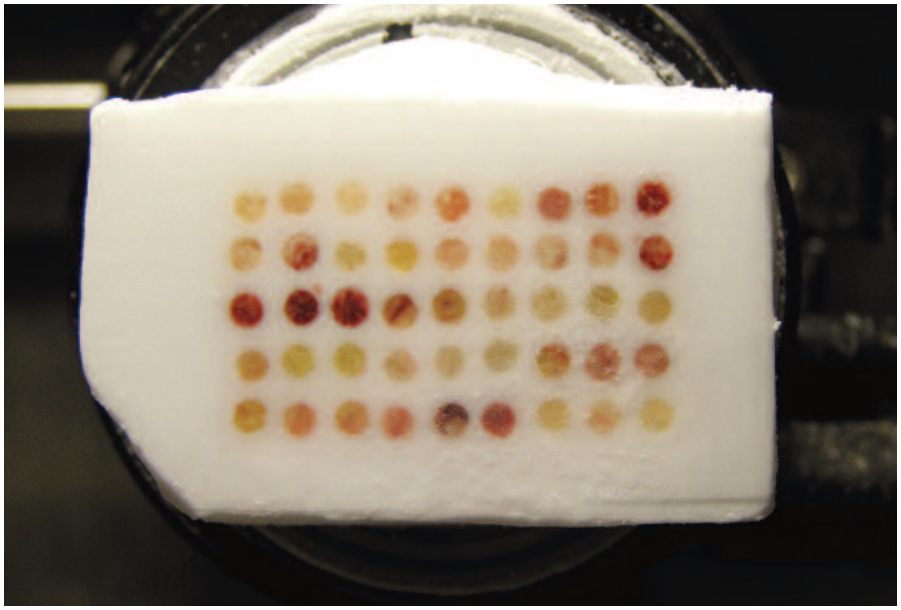
The principle that an individual should have a say over the use of their biological material is widely recognised



The raw material of cancer research. Large numbers of fresh-frozen tissue samples like these, linked to clinical data, hold the key to learning about the biological differences between cancers, and understanding what these differences mean for the way a given cancer behaves and thus the treatment strategies that will be most effective

standards and IT and legal frameworks, often in response to specific needs. The question is how to move to a more harmonised system that would enable any authorised researcher with a study proposal to instigate a single search request across all relevant biobanks, together with agreed rules, guidelines and principles governing the collection, storage, transfer and use of these data-linked samples. As if this were not challenge enough, it has to be achieved within the relevant national and European rules and regulations, including those on data protection and on the rights of the individuals from whom the samples are taken.

No consensus on consent

The principle that an individual should have some say over whether and how their biological material is used is widely recognised within research fields and the wider community, but is interpreted in a variety of ways. As a result, one breast cancer tissue sample may be available for use in any well-founded research study, whereas a similar sample biobanked elsewhere may have tight restrictions on its use. Consent may have been given purely for use in the study for which it was originally collected, or for additional specified studies, or perhaps with the proviso that use in any studies beyond those specified on the consent form would require approval from an ethical review board. In some cases, researchers may even be obliged to re-contact the donor to get a new consent. This disparity in conditions attached to the use of samples presents a potential obstacle where, for instance, a research centre from a country with stricter rules wishes to join an international biobanking system where tissues could be transferred for use in a country with more liberal rules.

Debates over personal data

Biological material, important though it is, makes up only half the research equation. The other half is data that describe the donor (age, gender etc) and disease (eg stage IIIb non-small-cell lung cancer), as well as data that allow researchers to draw conclusions about the significance of biological differences with regard to disease progression, response to treatment or perhaps adverse effects.

Though there is a European Directive on data protection, the laws and practices governing the storage and use of personal data for research vary widely across Europe – as has been highlighted by the battles that have had to be fought in some countries just to get the go-ahead to set up a basic cancer registry that could link a person's cancer diagnosis to their cause of death.

As with the consent issue, there is a broad consensus around a general principle: namely that patients have a right to keep their medical details confidential, and that biobanks may therefore only store anonymised data. There is less consensus, however, on what this means.

Some countries interpret it in the tightest possible manner – each donor is assigned a code that is used to identify their data and their biological samples, and the link between the donor and the code is then destroyed to preclude the possibility that someone could access the banked data to illicitly look at an individual's private medical records.

This is fairly disastrous for the purposes of research, because it means researchers cannot go back to the treating oncologists to get updates on how a patient's disease progressed or how it responded to various treatments. They cannot even go back to ask for additional information – on side-effects for example – that might have been available at the time of anonymisation, but was not deemed relevant.

Many countries, however, do accept 'two-way' coded data as 'anonymised', if there are sufficient safeguards. With two-way coding the patient's oncologist, or a third party, keeps hold of the code book, thus retaining the possibility for researchers to request further information about the donor. How easy that process is depends on how stringently the system is safeguarded. In the chain of tissue and data, double coding (coding additional to the one done at the source institution) may be required and permission to decode may involve complex and possibly bureaucratic procedures.

Such discrepancies between countries on the level of personal data protection presents another potential reason why some countries may not want their citizen's data to be internationally available through a biobank.

A PROLIFERATION OF GUIDELINES

Numerous guidelines and recommendations have been published regarding the ethical and social issues in biobanking.

- In 2003 UNESCO issued the International Declaration on Human Genetic Data. Among many other things, it set down the principle that "prior, free, informed and express consent, without inducement by financial or other personal gain, should be obtained for the collection of human genetic data," and that "Human genetic data, human proteomic data and biological samples linked to an identifiable person should not be disclosed or made accessible to third parties, in particular, employers, insurance companies, educational institutions and the family."
- In 2006 the Council of Europe issued its recommendation Rec(2006)4 of the Committee of Ministers to Member States on Research on Biological Materials of Human Origin, which laid down more stringent conditions for consent, particularly for unspecified future research, than those currently in force in many EU member states.
- In 2009 the OECD issued its Guidelines for Human Biobanks and Genetic Research Databases, which appears to have been written principally with healthy volunteers in mind. The level of detail required in the consent forms seems inappropriate for cancer patients, from whom samples are taken within routine diagnostic and treatment procedures, when they will have many other things on their minds.
- In 2010 the Organisation of European Cancer Institutes (OECI) published its ethical and legal recommendations, From the Biobank to the Research Biorepository, with an emphasis on building public trust and support. They recommend that biorepositories take the form of charitable trusts or other 'neutral' bodies with a mission to act in the public interest, and that they develop policies for the development of patents from research carried out on samples … "with the aim of protecting the public interest to enjoy new technologies for health at reasonable costs."

A CASE FOR HARMONISATION?

Getting EU-wide agreement on a single set of rules governing consent and data protection – or indeed other social/ethical issues such as duties to publish the results of any research done using these samples, and who should own the intellectual property rights – may seem the obvious solution. The Biobanking and Biomolecular Resources Research Infrastructure (BBMRI), an initiative to build an infrastructure for Europe's biobanks, is currently working on proposals to achieve this. Some, however, sound a note of caution. Evert-Ben Van Veen, an experienced medical lawyer at MedLawconsult in the Netherlands, points out that the Clinical Trials Directive was an exercise in harmonising rules and regulations across Europe – and look how that turned out.

Van Veen carried out extensive research on the various rules and regulations governing procedures for consent and data protection across Europe when the Erasmus Medical Centre in

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"Europe's approach to biobanking should be rooted much more firmly in solidarity-based values"

Rotterdam was in the process of setting up TuBaFrost in 2003. "The idea was that we would come up with a harmonised model for exchanging tissue: what would be accepted in one country would also be accepted in other countries." It wasn't long before a flaw emerged in the strategy. "I realised that if you want to make such a model, then you end up with the strictest regulations of the strictest countries, because what is accepted for the less strict will not be accepted by the stricter. That would be very harmful for research, especially for those researchers who have started their biobanks with lighter regulations."

The Council of Europe has, in fact, already agreed a 'Recommendation to Member States on Research on Biological Materials of Human Origin', Rec(2006)4, which Van Veen claims contains provisions considerably stricter than those operating in many European countries. The recommendation that any consent forms be "as specific as possible with regard to any foreseen research uses", for instance, appears to rule out asking patients to consent for their samples to be used in unspecified future research projects – an option widely seen as essential in cancer, where the rate of change in knowledge and techniques make it hard to foresee all possible research projects.

Any researcher wishing to use samples for a research project "not within the scope of prior consent", say the recommendations, should make "reasonable efforts" to contact the person in order to obtain consent to the (new) proposed use (with further conditions to be fulfilled if that fails). Given that the samples are coded, that many years may have elapsed since the original consent, and that it is cancer patients we are talking about here, this process would probably be not only complex and time-consuming, but may even cause distress to a cancer patient or family.

Were those recommendations given legal status, this would hinder efforts of the countries most actively promoting biobanking, some of which, the UK and Sweden for example, do give patients an option of allowing residual tissue to be used in future for unspecified research. Some even have an 'opt out' system, whereby patients are not asked for consent, but instead are given an opportunity to indicate that their tissue should not be used for research purposes. This system operates in Belgium and Denmark, with the Netherlands expected soon to follow suit.

Biobanking is a social activity

Van Veen is highly critical of what he sees as the 'paternalistic' and 'conflict-based' approach taken by most documents on regulating biobanking, including the OECD's 2009 Guidelines for Human Biobanks and Genetic Research Databases (see box, p25). They are, in his view, driven by the instincts of civil servants to regulate everything, they lack any democratic basis, and above all they fail to recognise that citizens don't just want protection, they also want, and will benefit from, progress in medical research. He says that patients are often very keen to be partners in research, pointing out that in Belgium and the UK, two countries where proposed legislation sparked wide public debate, the laws that were finally passed were much more research-friendly than the original drafts.

He believes Europe's approach to biobanking should be rooted much more firmly in the solidarity-based values that underpin the continent's healthcare systems, such that "the healthy contribute part of their income to the sick, the younger to the older, etc."

"What is wrong with expecting someone to contribute to observational research when it does not affect their personal lifeplan and other patients will profit in the longer run?" asks Van Veen.

This approach is apparent in the OECI recommendations for the operation of research bio-repositories, which says that, "to ensure compliance with the wishes of donors," every biobank should use the samples in the public interest. "In no way can samples be considered, or become, owned by private for-profit entities." It also recommends that every biobank should "disclose its rules, activities and results to the scientific community and the general public… to promote a culture of solidarity and consent to donations."

Rather than asking the EU to pass yet more rules and regulations, Van Veen suggests it should instead adopt a general framework for good research governance based on key principles consistent with a solidarity-based health system. These should encompass issues of transparency, accountability and the non-profit basis of biobanking, the right to opt out as a minimum, as well as "how the general results of research will be disseminated, 'conflict of interests' policies, how the issues of intellectual property rights are dealt with,

how the confidentiality of personal data of donors is maintained, etc." Above all, he argues, this should not become an extra bureaucratic layer.

This leaves the question of how countries with more strict conditions could agree to participate in an international biobank where samples may be used in countries with less stringent requirements. The answer, Van Veen suggests, is to use the 'coordinating principle' adopted by the TuBaFrost project, which states that, wherever the research samples are actually used, they must be handled in accordance with the regulations of the country where the tissue was taken from the patient and originally stored. This would permit unhindered exchange of biological samples without putting unwanted barriers in the way of biomedical research. Avoiding a new set of EU regulations would also make it easier for individual countries to review their own rules through their own democratic procedures.

A common language

If it is best to leave ethical and social details to countries, there are other aspects of biobanking for which the reverse is true. One big challenge will be establishing a common 'language' for cataloguing samples to ensure that what appears in the search results corresponds to what the researcher is looking for.

This issue has been preoccupying many cancer research leaders, including Angelo Paradiso, who is himself deeply involved in the effort to find biomarkers for early diagnosis and for predicting response to treatments. Paradiso is the coordinator for all of Italy's cancer centre biobanks, together with the Istituto Superiore Sanità in Rome, and he runs the biobank at the National Cancer Centre at Bari, southern Italy, which systematically collects and banks data and biomaterials from every patient. This system, he argues, is far more valuable than collecting samples only from specific trials, because it assembles samples from the entire cancer population, rather than only from patients selected by age, or disease stage or other criteria.

Paradiso recently completed an exercise that has introduced a single 'language' and software system throughout the network. He is now looking to work in collaboration with other national and pan-European networks to establish conditions for moving towards a similar level of harmonisation across Europe and beyond.

The term 'language' covers many issues that the clinical research community has wrestled with for years. Different hospitals may use different thresholds for judging a tumour to be ER-positive, or different tests for establishing the HER2 status. Even menopausal status may not be defined in the same way.

Paradiso mentions also the stage of disease: "If I want to compare the characteristics of my sample with others coming from other tumour banks, I have to classify the tumour stage, histological diagnosis and cytohistological grade in the same way."

Then there is the question of how far you go in defining a tumour for the purpose of a searchable catalogue? Even a relatively rare cancer type such as sarcoma is now known to consist of more than one hundred biologically distinct diseases (see cover story), and it is becoming increasingly apparent that different biologies behave very differently.

Standards for handling and storing

Agreement on basic quality standards and quality control of the collection, storage and transfer of samples is another essential element, so researchers can be confident that, no matter where the samples originated, their studies will not be confounded by poor-grade samples.

Sophisticated techniques for gene profiling or proteomic and metabolomic studies can be highly sensitive to small

Paraffin-embedded or fresh-frozen?

Fresh-frozen tissue is needed for screening approaches like gene expression profiling or proteomics, which are used to search for biomarkers or to learn about the mechanisms of disease. These techniques are highly sensitive and strict criteria are needed about collection and storage.

FFPE (formalin-fixed paraffin-embedded) blocks used in standard pathology are far less sensitive to discrepancies in the way they are collected and stored. They are useful because large collections already exist from trials going back decades.

The initial research behind the Oncotype DX multi-gene assay that gives risk scores for certain breast cancers was done using gene profiling in frozen tissue, but much of the validation work was done retrospectively on FFPE tissue blocks.

If samples are to be catalogued and exchanged across borders, there has to be an agreed classification system

EORTC is developing templates for what it considers to be the key information for different sample types

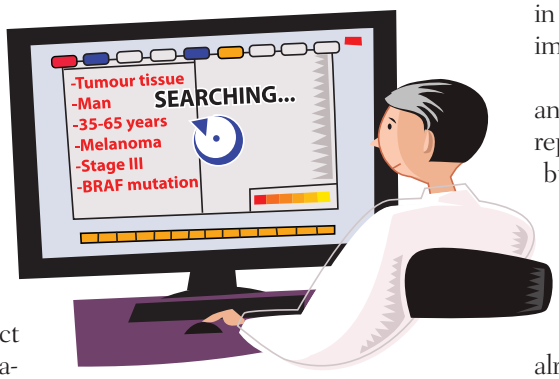
differences in samples. The minimum standards recommended by IARC/WHO in 2007 are widely accepted as a good starting point. However, they do not cover issues such as what drugs (not just cancer drugs) the patient may have been on at the time the sample was taken, or the techniques used for the sampling. Furthermore, these types of study all require fresh-frozen tissue, with the time from 'harvesting' to snap freezing being one of the quality parameters, and questions are now being asked about whether the time should be measured from the point of excision or from the point of clamping during the operation, as depriving the tissue of oxygen induces rapid changes. This in turn raises the question of how much you can ask of operating teams, for whom annotating samples is not their top priority.

Towards international biobanking

The goal of reaching agreement between Europe's biobanks might seem hopeless, given the disparities in practice and the difficult balancing act between cataloguing 'essential' information without demanding too much of the pathologists and data processors – not to mention the disparities in the software used to input that information. But Paradiso is confident it can be done. "When you talk about biobanks, you should talk about networks," he says. While harmonising every biobank for every disease in every European country might seem a big ask, if it is done network by network, working from the national level up, the task becomes a lot more manageable.

The framework for these networks has already been developed at a European level by the BBMRI in the form of 'hubs' that group different types of biobank at national and then European level. "Take Italy, you now have the hub for population-based biobanks, the hub for cardiovascular, for cancer, for genetic diseases and so on. This is the first level. The second is at the international level, where all national hubs take part, connected in a common platform, in which all kinds of communication is possible – within a hub and also between hubs."

As has happened in Italy, each of the hubs at national (first) level will of necessity work towards a common 'language'



and set of minimum data and quality standards, from the bottom up, with all of them hopefully following the international discussions and trying to move towards a harmonised system that could function internationally. "Discussion and agreement has to be reached, first at one level and then the next," says Paradiso.

To aid this process, he adds, there are already tools that make it possible to accept data from any of the software commonly used in hospitals and biobanks. Software, however, is no substitute for agreement between the major networks. To this end, the Bari Cancer Centre hosted a meeting for biobank networks last November, attended by representatives from more than 30 organisations in Europe, Asia and Africa. It was organised by the OECI together with ESO, under the auspices of the EORTC and endorsed by ISBER (the International Society for Biological and Environmental Repositories).

"The main aim," said Paradiso, "was to share experiences from all these groups, and to discuss the main possibilities for biobanking from a clinical perspective. What do biobanking organisations need in terms of minimum standards and minimum data requirements?"

These can be easy questions to answer, comments Jacqueline Hall, who represented EORTC at that meeting, but only if you know what study you want to carry out. "If you know, for instance, that you are going to be collecting a serum sample to be used for proteomics profiling, you know already what the goal is and you can already have in mind key variables you might want to collect about how that sample was taken from the patient or how it was processed, because there are known factors that can influence the proteomics profile.

"In the case of unspecified future use it becomes more tricky, because you have to find what is practical for the local pathologists and hospital staff to provide, and what is practical for managing the data here at EORTC HQ, and balance that against the needs of the research effort. As soon as you start

collecting more data it is more work and more cost. So we try to find a trade off."

Collecting samples is now a permanent concern for the EORTC and a priority for their research studies. In January the organisation released an updated policy on Human Biological Material Collection, Storage and Use, that covers sample collection for both specified and unspecified use (see Policy page at eortc.be). This policy includes making available for 'secondary use' the data-linked samples it holds in an independently run biobank facility in Milan, as well as at various institutions that participate in EORTC studies. Hall says it is also developing templates for what it considers to be the key information for different sample types. "We discuss these variables with the people involved in the studies, the pathologists who collect the samples and our own pathobiology group, in the context of international collaborations. We also look to information in the public domain about which variables people find important for different activities, and then we have an internal discussion to find out which will be the key variables for the different sample types in the context of that study."

With groups like this sharing experiences and discussing common positions on language, key associated data, and minimum quality requirements, the foundations are being laid for a biobank that can operate on a truly pan-European level. But Paradiso has set his sights on reaching further.

Present at the Bari meeting were representatives from Egypt, Tunisia, Israel and Jordan, all keen to develop biobanking in their countries. A follow-up meeting has been scheduled next year in Romania, with a focus on promoting a biobanking culture in central and eastern Europe, and beyond.

The best scenario is that the efforts being put in now will result in existing biobank networks gelling into an international system. As new biobanks join, this will transform the access researchers have to data-linked samples and significantly speed progress in understanding cancers and how to detect, diagnose and treat them.

For this to happen, guidelines and regulations must not only harmonise the biobanks. They must also inspire confidence in the public, in patients and in the clinicians and pathologists who are at front line of collecting samples, that the whole enterprise is based on the principle of solidarity, where the gains from these voluntary donations are disseminated and used for the public good.

BIOSOCIAL CITIZENS

Half a million people – around 1 in 50 aged between 40 and 69 – responded to the invitation to 'join the Biobank UK project' (www.ukbiobank.ac.uk). They attended 21 centres across England, Scotland and Wales to give blood, urine, saliva, and a variety of clinical measurements and filled out questionnaires on their lifestyle and medical history. Trust in the public service values of the NHS, which supports the Biobank, played an important role in motivating people to take part. The central message focused on the opportunity to take part in an exciting research project, and the idea that samples may be used for an unspecified purpose in future was presented as an opportunity rather than a threat: "In 10 or 20 years' time the things that we will be able to analyse in the samples may well be things that scientists have not yet thought about. The next generation of scientists, who might still be in primary school today, will actually use new tests and new methodologies to be able to unlock new secrets in terms of how we prevent diseases."

Guidelines and regulations must not only harmonise the biobanks, they must also inspire public confidence