Biosample Provenance - What Researchers Need to Know and What Needs to Change

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What researchers need to know

According to the Merriam-Webster dictionary, the word 'Provenance' means the origin or source of something. In the world of antiques, it means the history of ownership of a valued object or work of art. In the scientific world when applied to biospecimens, it covers a number of categories of information: (a) sample processing history, (b) information about the donor and their medical history, (c) the geographic origin of the sample which provides information about environment and ethnicity, and (d) previous custodians which may include one or more brokers.

Reliable biospecimen provenance information is essential for reliable research. At the most basic level, knowing the identity of the biobank of origin allows researchers to decide whether samples are likely to be reliable. If that biobank has obtained appropriate licencing, certification or accreditation, this gives confidence about sample quality and reliability. Examples of this include licensing by the Human Tissue Authority in the UK, ISO certification (ISO9001 and ISO20387), US CAP Accreditation and CTRNet Certification.

Looking at a more detailed level, information on sample processing can be captured using a tool called the Standard Preanalytical Code or SPREC [1], which facilitates annotation of biospecimens with preanalytical factors that are suspected to impact the results of downstream analyses, and can be addressed using standard operating procedures (SOPs). SPREC data elements for fluid samples include for example the type of primary container, the pre-centrifugation delay, centrifugation conditions (temperature, time and g-force) and more. This tool has been implemented by professional biobanks around the world and illustrates the meticulous attention to detail that is important to fully account for the different pre-analytic variables influencing biospecimen quality.

Researchers who are unable to assess the reliability of their samples are at risk of producing research that is irreproducible. This is not only a waste of research funding on a huge scale, but it also delays the development of lifesaving therapies.

Why the procurement system is broken

Unfortunately, for researchers in industry, provenance information is often lacking. One reason is related to the fact that researchers in industry often obtain biospecimens through a commercial broker. These act as intermediaries between the hospital biobank where the sample was originally collected and preserved and the client in industry. They source the necessary samples for their client and charge a fee for this service. Generally speaking they do not want to allow free and unconditional communication between the researcher and the hospital biobank for one simple reason: this would risk their own circumvention and loss of profits. So many brokers will not reveal the precise origin of the samples with the result that the end-user may lack biospecimen provenance information.

Biosamples are needed by industry to study disease processes in patients and to relate the results of molecular analysis of these samples to the diverse characteristics of the corresponding patients and their own specific environments. So it is obviously vital for the researcher to have information about the medical history of the patient, their various diagnoses, treatments, responses to treatment and demographic information (age, race and sex). This information needs to be reliable and the best way of being sure of this is to deal directly with a source biobank with known credentials. Furthermore, it may be necessary to recontact the biobank for information on the patient's response to treatment, or for additional samples from the same patient. So again it is important to know the biobank identity for this.

It is also important to know the geographic origin of each sample for a variety of reasons. One is that the patient's environment and exposure to various risk factors (sunlight, temperature, altitude, diet, pollution, etc) may have a bearing on pathology and information on these factors may be needed to make sense of research findings. The need for this information is accentuated by the fact there is a great deal of international trade in patient samples. A recent survey by the Medicines Discovery Catapult agency found that diagnostics companies obtained 75% of their samples from abroad. This is partly due to the fact that in the UK and other countries in Western Europe, hospitals and biobanks are generally not comfortable to provide samples to commercial brokers. So these brokers need to look further afield for sources of samples, obtaining them from Eastern Europe, Asia and the USA instead. Some countries like China, India and Russia have laws that restrict the export of samples, so it is also important to be sure of geographic origin in order to avoid the possible use of illegally sourced samples [2].

The supply of clinical samples from different parts of the world may involve a series of commercial entities. For example there may be one company in Asia which supplies samples to another company with a distribution network in Europe and the USA. If a series of brokers are involved, then the reliability of information on patient consent and sample provenance obviously becomes less certain.

What can be done?

Information about sample provenance is clearly vital for a range of scientific, ethical and legal reasons, so what can be done to make sure that when industry obtains samples, they always come with reliable provenance information?

Regulatory authorities look likely to play a decisive role in the future. For access to the European market, the makers of medical devices including in vitro diagnostics must now show that the biospecimens used to validate their devices have undergone acceptable pre-analytic processing [3]. This is a requirement of the new European IVD Regulation (IVDR) which comes into force on the 26th May 2022. No doubt, other such regulations will follow and it can only be a matter of time before evidence of reliable and acceptable biospecimen provenance is required for approval of all drugs, diagnostics and vaccines for clinical use.

Together with the introduction of new regulatory requirements, there are promising technological developments that will help ensure reliable sample provenance information: blockchain for example allows secure and ethical tracking of the transfer of biospecimens from source to end-user through an incorruptible shared digital ledger [4]. Coupled with the SPREC tool mentioned above, this has enormous potential for improving the reliability of biospecimen-based research.

Another option is for brokers to modify their business practices and allow direct communication between the hospital source of samples and the end-user, but to require both parties to sign a contractual agreement to the effect that they will not circumvent the broker. Such contracts are indeed being used effectively by a number of commercial brokers. However, the fact they place restrictions on the freedom of companies and biobanks to form partnerships is not always acceptable to one or other of the potential partners.

Companies can independently build their own networks of biobanks to obtain the samples they require. Indeed, many long-lived pharmaceutical companies have done this, but it takes time. In the short term it is often very difficult to find suitable hospital biobanks with the necessary samples in stock. There are publicly available biobank directories that companies can consult, but these are generally designed with academic researchers in mind and may not indicate whether the biobanks are willing or indeed motivated to work with industry.

A recently established not-for-profit company called Biosample Hub (https://biosamplehub.org/) provides a further solution, through an online platform dedicated to partnering industry with academic biobanks. The platform presents companies with a ready-made network of biobanks all of which want to work with industry. The platform also includes a directory of companies, a directory of requests and networking features to allow members to communicate. So far this has been well received by academic biobanks in western Europe, providing industry with a route to previously inaccessible sources of clinical samples.

Final note

Where biospecimens are used in research to develop drugs, diagnostics and vaccines, it is vital that these are provided together with reliable and complete provenance information. Regulatory authorities have taken note as demonstrated by new European regulations affecting makers of IVDs. This development will most likely herald major improvements in the practice of biospecimen procurement for industry.

References

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