The Use of Human Body Material for Research Purposes

İnsan Vücudu Materyalinin Araştırma Amaçlı Kullanımı

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ABSTRACT Human body material is an important resource that enables researchers to challenge their research hypotheses. This paper outlines the importance of sample quality and the presence of associated data in view of reducing statistic variability, privacy issues and the rights of the patient. Important sources of samples and their benefits and drawbacks in view of their fit for purpose and required resources are situated.

Keywords: Human body; biomedical research; biobank; incidental findings

ÖZET İnsan vücudu materyali, araştırmacıların araştırma hipotezlerini test etmelerini sağlayan önemli bir kaynaktır. Bu belge, istatistiksel değişkenlik ile mahremiyet ve hasta haklarıyla ilişkili sorunları azaltmak amacıyla örnek kalitesinin ve ilişkili verilerin varlığının önemini özetlemektedir. Bu yazıda, numune kaynakları, bunların amaca uygunlukları ve gerekli kaynaklar açısından yararları ile sakıncalarına yer verilmiştir.

Anahtar Kelimeler: İnsan vücudu; biyomedikal araştırma; biyobanka; tesadüfi bulgular

Researchers often rely on the availability of human body material (HBM) to answer their research questions. It is however important to realise that such HBM needs to be fit for purpose. This means the researchers ideally have a very good understanding of the analyses they would like to perform. Indeed, as an example, whole blood aimed at molecular research would be captured in a different collection tube compared to such blood aimed at isolating live cells targeted to establish cell lines.[1] Components present in the blood collection tube such as EDTA or heparin, commonly used as anti-coagulant by binding calcium or antithrombin respectively, correspondingly impact negatively on cell viability or PCR reactions. The need to understand your research objectives is most important when one aims to establish a lengthy and costly prospective study aimed a collecting such material. Indeed, many PhD students embark on a sample quest at the start of their PhD, only later realising that they will only be generating meaningful results from these samples when they are over half way with little or no room for collection protocol modifications, at least not without meaningful impact on the downstream analyses and power of the study. Similarly, the sample processing protocol needs upfront consideration. Qualitative sample processing, executed within well-defined time or temperature boundaries, can significantly reduce the variability of the downstream generated research results. This is especially important if one considers, the inherent variability present within the patient population. Reducing experimental variability can therefor mean the difference between being able to report a tendency versus to come to a statistically significant conclusion.

Apart from prospective trials, there are of course other sources of samples. Biobanks are great sources of samples as they often collect high quality samples using well defined sample processing protocols. They might even have collected meaningful numbers of samples for rare diseases. As most biobanks register all important sample processing parameters such as the needle to freeze time, processing and intermediate storage conditions, the researcher has a good upfront knowledge of whether the samples are fit for the research question. As the researcher has no control on these parameters, this fit for purpose needs thorough consideration prior analysis as not to waste these valuable samples. Another source includes the use of residual samples post diagnostic use. Indeed, most clinical biology or pathology labs only partly use patient samples for their primary diagnostic purpose. Therefore, blood, urine or other samples can often be sourced from the clinical biology lab. However, as most clinical biology labs store these samples for several days in the fridge enabling potential reanalysis of the sample, there fit for research needs careful consideration and these samples are mostly not usable for research on molecules that more readily degrade. Then again, these samples might be of particular value to validate diagnostic tools, using the diagnostic value obtained in the clinical biology lab as comparator. Pathology labs archive tissue, often paraffin embedded, for future investigations in the framework of continued patient care. Parts of these so called FFPE (Formalin-Fixed Paraffin-Embedded) blocks can sometimes be obtained from the pathology lab. When part of an academic centre, additional FFPE blocks or even fresh frozen material is often stored, specifically aimed for scientific research. To complete the list, the secondary use of samples from clinical trials after they fulfilled their primary purpose or left-over samples from tissue banks post therapeutic use might be fit for certain research questions.

Given the current advances in the various omics fields and the rise of big data, the need arises for very large sample collections, often exceeding the amounts of samples present in a single biobank. Sourcing such numbers is difficult. In Europe, the European Commission enabled the establishment of the European research infrastructure for biobanking (BBMRI-ERIC) which brings a large number of European biobanks together in a virtual infrastructure.[2] The BBMRI website hosts a sample negotiator tool enabling researchers to enter sample specifications, resulting in a list of biobanks that have such samples in custody.[3] The researcher can then easily contact these individual biobanks and request the use of these samples. Given the lack of harmonisation of biobank legislation across Europe, obtaining these samples from the individual biobanks, however often remains a burden.

The value of the samples for research to a large extent depends on the associated data. These can for example be medical records, personal data or research data. When patients allow the use of the samples, they often also allow the use of their personal, including medical data. In Europe, provision of these data is regulated via the GDPR (General Data Protection Regulation). According the GDPR a legal basis is required to process the data. In many cases, this legal basis is embedded in the informed consent form that the patient signs when providing the samples. It is however important to note that the informed consent in itself if there to protect ethics and that this "consent" is thus not always identical to the "consent" under GDPR which is protecting privacy. Without specific clauses related to the use of the data, the informed consent can thus not serve as "consent" under GDPR. Then again, in some case, the informed consent cannot fulfil this legal basis at all. As GDPR defines consent as "Consent of the data subject means any freely given, specific, informed and unambiguous indication of the data subject's wishes by which he or she, by a statement or by a clear affirmative action, signifies agreement to the processing of personal data relating to him or her", other legal bases might be required for certain patient populations. As an example, a very sick patient can hardly refuse to consent for the data generated in a last resort trial. Such consent would not be considered "freely given" and another legal bases such as "You need to process the data to save somebody's life" might be a better fit. Apart from this informed consent, some European countries allow for the use of presumed consent for both the sample and the associated data. In such case, the patient is informed of the potential use of the samples via an information leaflet or other document/source. Instead of actively providing a consent, presumed consent entails that the patient is thought to have provided consent, unless he actively objected against it. It is important to note that any protocol that makes use of samples and data obtained under presumed consent still requires an approval by an ethics committee and as such is under scientific, ethical and legal scrutiny.

To further protect the patient, samples are often pseudominised. This means the personal data of the patient are replaced by a unique code. The decoding table, allowing to couple the patient to the samples and data usually remains with the physician that enrolled the patient. This allows the researcher to work with certain relevant medical data without being able to identify the individual

patient. This coding system also benefits the patient. In case the researcher identifies something that is of medical relevance to the patient, this can be communicated back to the patient via the physician holding the decoding table. Not all of such "incidental findings" will be communicated back to the patient. In most cases, the data need to be generated using a validated test, often not the case for academic research. In addition, the data need to be of relevance to the patient or his relatives. A high risk for certain cancers would be communicated, an influenza infection discovered two years after obtaining the samples would not. Most notably, incidental findings are discovered in the fields of genomics and medical imaging. Genomic shotgun analyses readily result in an incidentalome, the genome of potential medical risk factors. There is however no consensus on this incidentalome as the risk to the patient and the potential to act on that risk are often limitedly understood. This is more clear for incidentaloma, tumours found by coincidence through medical imaging and which would require immediate action toward the patient.

It is clear that the act of providing a sample, in most cases, does not benefit the patient directly or individually. However, the provision of human body material and associated data is a very important source of research results that are of benefit to the community and allow to advance the medical field as a whole. Biobanks are important stakeholders in the interaction between the patient, the physician and the researchers as they enable the sourcing of the samples and data and both streamline and safeguard the ethical and legal requirements, facilitating research while protecting the patient.

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