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International Biobanking Interface Service – A Concept for Health Sciences in the Digital Age

Christian Linke[1,2]***, René Mantke***[1,2]***, Reiner Creutzburg***[3,4]

[1] ***Brandenburg Medical School Theodor Fontane, Germany***
[2] ***Faculty of Health Sciences, joint Faculty of the Brandenburg University of Technology Cottbus – Senftenberg, the Brandenburg Medical School Theodor Fontane and the University of Potsdam***
[3] ***Technische Hochschule Brandenburg, Department of Informatics and Media, IT- and Media Forensics Lab, Magdeburger Str. 50, D-14770 Brandenburg, Germany***
[4] ***SRH Berlin University of Applied Sciences, Berlin School of Technology, Ernst-Reuter-Platz 10, D-10587 Berlin, Germany***

Email: christian.linke@mhb-fontane.de, mantke.mhb@klinikum-brandenburg.de, creutzburg@th-brandenburg.de

Abstract

Long term collections of human tissue or body fluids in biobanks combined with health-related data are important resources for medical research and the development of personal medicine in the future. At present, increasing number of clinical studies published new diagnostic, preventive options or treatment approaches of especially age related diseases such as diabetes, cancer or neurodegeneration.

For some years, a rapid improvement in the mutual exchange of data and common quality assurance policies between biobanks can be observed especially in western countries. However, global web-based interfaces suitable to search for disease-related information and biomaterial are not yet in practice partly due to differences in national private policy laws and missing cooperative efforts between health care IT systems.

In a new collaborative project between the Technical Hochschule of Brandenburg and the Faculty of Health Sciences, a joint Faculty of the Brandenburg University of Technology Cottbus-Senftenberg, the Brandenburg Medical School Theodor Fontane and the University of Potsdam, we try to fill this gap and review the technical and juristic requirements to accesses biomaterial and clinical data of US and European cancer patients ultimately leading to a concept for an international biobank network interface. Our aim is to provide instantly clinical data such as diagnostic and treatment approaches in real time that can be used by physicians and medical scientists from all over the world.

Introduction

With the overall aim to remarkably improve translational research, modern biobank structures have been established in the Unites States and European countries for around two decades. A biobank is a facility that collects samples of human body fluids as well as cells, tissues and organs, supplemented with clinical and scientific data from the test subject (e.g. patient) with the purpose to conduct biomedical or epidemiological research [1]. The value of the biomaterials stored in biobanks increases with the number and quality of the samples and the scope of the (research) data associated with them [2].

Since then, the biobank industry has grown to a remarkable discipline in biomedical research and evolved even further upon distribution of -omics technology among hospitals and clinical research facilities [3, 4]. Especially with a view to the upcoming era of personalized precision medicine, large scale, high-throughput analysis of disease-specific patient material comprise great opportunity to advance and improve modern health care approaches [5, 6].

The biobank field rose to prominence, to face major problems in preclinical research, such as the irreproducibility of research data due to low complexity, number and quality of the biomaterial and related information [7]. The collection of sufficient quality assured biospecimen and associated data but also developing more professional downstream procedures poses great challenges that are continuously under assessment [8, 9]. Concerns about quality of biomaterial and validity of related data become even more important, following a recent trend in the biobanking community whereby biobank networks facilitate the acquisition of a higher number of biospecimens [9].

Another important aspect in health research and human biorespositories are ethical principles and human rights that needs to be considered. Protection of donor privacy upon the use of identifiable human biological material and confidentiality of identifiable data as well as proposed research projects are most sensitive issues in this research field [10].

This article aims to review essential topics related to biobank organization, the use of human tissue in research and central aspects of bioethics. It will summarize key processes in biobank practice associated to material and data harmonisation, protection requirements, quality assurance, sample request and consent management that are essential to consider in order to develop an international biobank service.

Results and Discussion

The history of biobanking

Undoubtedly, the collection and use of animal and plant materials for the purpose of treating wounds and diseases has a long tradition in various human ethnics. The first archives for human cells and tissues, however, were established in the late 19th century in the context of modern pathologies and the study of cellular physiology initiated by Rudolf Ludwig Carl Virchow [11]. An important next step towards a sustainable collection of human

material was the generation of the first immortal cancer cell line in 1951. This cell line (HeLa), which derived from a surgery on Henrietta Lacks at John Hopkins Hospital, served as the first in vitro cancer model system and is still used in cellular research in almost every laboratory around the world [12].

Since then, the number of newly generated cell lines grew substantially and required specific institutions to monitor and preserve the origin and genetic property of each cell line, ultimately leading to the foundation of cell line biobanks [13]. Important examples of cell line repositories are the American Type Culture Collection (ATCC), the German Collection of Microorganism and Cell Culture GmbH (Leibnitz-Institute – "Deutsche Sammlung von Mikroorganismen und Zellkulturen" DSMZ), the Japanese BioResource Research Center RIKEN and the KCLB (Korean Cell Line Bank) [13, 14].

In order to further improve medical research and to translate scientific outcomes into drug and device approvals effectively, other sources of patient material have been utilized. Over time, systematic collections of human body substances (e.g. tissue, blood, urine saliva and stool) started as isolated biorepositories specific for a distinct research question [13]. These small human material collections, however, turned out to be insufficient to assure quality of stored biospecimen causing irreproducibility of preclinical research data [15]. As a result, a fast growing biobank community has been worked on the regulation, standardization and management of biobank activities in order to sustain high quality research [16, 17]. Moreover, technological and digital improvements such as large scale Multi-omics and innovative web-applications revolutionized biobanking. Nowadays, smaller archives of human biospecimens have been centralized and evolved to pivotal elements of clinical research that are considered to be crucial for the future of personalized medicine [18-20]. They provide not only human tissue and its derivates but also represent platforms for offering access to processed biomaterial such as serum, plasma, DNA, RNA, PBMC as well as applied research technologies that are linked to personal data and social-demographic information about the donors of the material [21]. This highlights a widely accepted opinion among researchers that the onset, progression and therapeutic success of a disease depends to a large extent on the patient's personal lifestyle, his individual genetic disposition and environmental factors. It is considered, that this personalized approach can be supported as best by biospecimen collected at multiple time points in the life time of individuals, thus ameliorating clinical research significantly.

In the last decades, several important research discoveries in clinical oncology have been made thereby highlighting the beneficial use of modern human biorepositories. Famous examples include the development of an antibody-based therapy with Trastuzumab targeting a deregulated gene (HER2) involved in breast cancer [22] as well as the tyrosine kinase inhibitor Imatinib used to treat certain types of blood cell cancer [23]. Additionally, large biobanks are of particular importance for identifying genomic changes suitable for therapy decisions also known as diagnostic biomarkers. A current example was the discovery of the chromosomal translocation of the ALK gene found in approximately 3-5% of non-small-cell lung cancer(NSCLC) patients but also observed in breast and colon cancer [24]. In clinical trials, successful treatment of patients with genomic rearrangement of ALK could be achieved with Crizotinib [25, 26].

More recently, large national multicentric biobanks have been established to support numerous clinical research projects. In this context, a project named Cancer Genome Atlas (TCGA) was initiated that aims to catalogue all known cancer-causing changes in the human genome [27].

An effective classification of molecular alteration in distinct cancer types and tumour subtypes is currently possible through large scale genome sequencing of patient specimens associated with clinical data.

Biobank classification and infrastructures

In the last years, large population-based biobanks have emerged but they almost exclusively collect liquid bio samples (mainly blood and blood components) and corresponding data from clinical tests. With the aim to study common risk factors, genetic disposition and external stimuli in the onset and progression of especially age-related diseases, they collect biomaterial from volunteers with or without specific exclusion criteria over decades [20]. Examples of population based biobanks are the UK Biobank, Estonian Biobank and Danish National Biobank [19, 28, 29].

In parallel, disease-orientated biobanks are embedded in universities, research institutes and hospitals to examine a specific disease pathogenesis as well as the potential of new diagnostics or therapeutic strategies [20]. To gain access to even larger numbers of biomaterial and related data, various network structures have developed, which have been increasingly promoted at national level [13, 18]. These so-called meta-biobanks such as the US-American National Cancer Institute (NCI) which is a consortium between 51 CCC, 13 Cancer Centers and 7 Basic Laboratory Cancer Centers are expected to initiate and conduct innovative clinical trials providing leadership and recruiting patients (`https://www.cancer.gov/research/nci-role/cancer-centers`). Following US example, the largest CCC network in Germany comprises 13 CCC and was founded to improve oncological care, standardize documentation systems and to optimize cancer registration, clinical research and education [30]. In this context, networking activities among researchers have been shown that the biomaterials used, in particular in terms of quantity and quality, are sometimes very heterogeneous and do not meet the requirements of current basic research standards [4, 31, 32]. In addition, retrospective analyzes of biomaterials that have already been used, showed incorrect or only to a limited extent reproducible data due to poor biomaterial quality [33].

For some time now, national governments focused on establishing quality-assured central biobanks at large research locations, increasing the degree of networking or organization of existing biobanks and to develop common "biobank standards" [6, 13, 31]. It is expected that the supply of high-quality biological samples improves clinical research projects in the long term [17, 34].

In conclusion, human biobanks are not only pure collections of bio-samples but also offer a wide range of special knowledge to support research projects in a best possible way. Selection of suitable quality-assured biomaterial and sample-associated data, but also processing, generating and interpreting the research data corresponding to the biomaterial can be important biobank-specific tasks [35]. Therefore, biobanks must be operated in an interdisciplinary manner with the involvement of clinics, pathologies

and research facilities. A close cooperation between multiple biorepositories will improve the connection between translational research, clinical research and health care.

Standardization, harmonisation and quality assurance

The properties of biomaterial preserved in different biobanks can be of great variability in terms of collection, processing, storage and quality control [36]. Without defined standards that regulate especially pre-analytical steps such procurement and storage of biospecimen, the outcome of downstream analysis in terms of reproducibility and therefore reliability is not appropriate resulting in inaccurate diagnosis and potential harm for patients [36]. Since human tissue obtained from surgeries or autopsies degenerated vastly, the time between resection and stabilization is crucial for maintaining its quality [13]. An important source of variation, that could alter parameter measurements significantly, remains tissue freezing. Today, samples of surgery tissues, body liquids and their derivates (e.g. DNA, RNA, proteins and other cellular components) usually are preserved at ultra-low temperatures ranging between – 80°C to 150°C his range, all metabolic processes are slow enough to preserve biomaterial for years [13].

To attain high quality biobanking standards, the US National Cancer Human Biobank (CaHUB) introduced validated protocols for biobanks in 2012 by defining standard operating procedures (SOPs). Similarly, in Europe, multiple national Biobanking and Biomolecular Research Infrastucture (BBMRI) formed a European Research Infrastructure Consortium (BBMRI-ERIC) with the main objective to increase biomedical research excellence by facilitating access to quality-defined human biological resources [17]. Therefore, the BBMRI-ERIC released SOPs and technical specifications but also supports education, and training programs to develop the best practice in the acquisition of high quality bio samples and data (`https://www.bbmri-eric.eu/services/standardisation`).

A fundamental step in the adoption of international harmonized standards for biobanking was the implementation of quality systems based on the ISO 2001 guidelines. With the increase in complexity of its infrastructure, administration and staff heterogeneity, in which clinicians, scientist, technicians, IT and QM are involved, the international scientific community agreed on the need of common strategies to further improve standardization requirements [21]. Hence, “General requirements for biobanking” were published according to ISO 20387:2018 in order to provide standardization of consenting, collection, procession, management, storage, distribution, research and sustainability of biomaterial and related data [13]. In this way, quality assurance in biobanks provides auditable tools to validate and verify the integrity of biospecimen ultimately leading to higher transparency in clinical research as well as robustness and reproducibility of data at international level.

Bioethics and legal issues

Historically, the most important guidelines influencing clinical research ethics and human rights were created as a result of the Nuremberg trials (Nürnberger Prozesse) between 1945 and 1947 after World War II. In response to the war crimes and unethical human experiments conducted by German physicians on prisoners in concentration camps, the judges raised ten points which became known as the ”Nuremberg Code” [37]. These points also provided the basis for a set of ethical principles proposed by the World Medical Association (WMA) in the Declaration of Helsinki in 1964, lately revised in 2013 [38]. The Code, which is essentially based on the Hippocratic Oath, states what medical experiments on human subjects require:

- A voluntary informed consent;
- A necessary purpose of the study beneficial for society;
- A study designed on initial animal research and disease knowledge;
- No avoidable physical and mental damage to the subject;
- No a priori suspicion of harmfulness;
- No unfavourable risk/benefit assessment;
- A proper designed experimental setup protecting the subject;
- Scientists with the highest degree of qualification;
- A right of cancellation;
- An immediate termination of the study due to health threatening concerns.

Although medical ethics and human rights have constantly been developed on an international level, the invention of more advanced technologies such as the “World Wide Web” and “omic” technologies challenges both in terms of privacy protection. Large collections of human samples and the storage of related clinical as well as genotypic data in databases raises the need to protect confidentiality and autonomy of each research participant. Insufficient protection of especially health data can lead to criminal misuse or human subject discrimination [39]. Therefore, in 2002, the WMA published the “Declaration of Taipei on Ethical Considerations regarding Health Databases and Biobanks” whereby a balance between human rights and the freedom of science was addressed [10]. With its last revision in 2016, it was stated that major risks in public accessibility of biospecimen and health data result from commercialization, cost-cutting and potential political abuse [10]. Primarily addressed to physicians and medical researchers, the declaration entitles individuals to exercise control over the use of their personal data and biological material permanently. Moreover, it was clearly pointed out that all people involved in handling the data and biomaterial are obliged to maintain its confidentiality as an obligation towards the donor. A novel guideline proposes the validity of a consent between donor and recipient (biobank or database) only if the latter one informed about the following points (`https://www.wma.net/policies-post/wma-declaration-of-taipei-on-ethical-considerations-regarding-health-databases-and-biobanks`):

- The purpose of the Health Database or Biobank;
- The risks and burdens associated with collection, storage and use of data an material;
- The nature of the data or material to be collected;
- The procedures for return of results including incidental findings;
- The rules of access to the Health Database or Biobank;
- How privacy is protected;
- The governance arrangements according to paragraph 21;
- That in case the data and material are made non-identifiable the individual may not be able to know what is done with

their data/material and that they will not have the option of withdrawing their consent;
- Their fundamental rights and safeguards established in this Declaration; and
- When applicable, commercial use and benefit sharing, intellectual property issues and the transfer of data or material to other institutions or countries.

In 2018, the European Commission launched a regulation on data protection and privacy in the European Union to harmonize differences among European national legal systems (https://gdpr-info.eu/). This "General Data Protection Regulation" (GDPR) provided a comprehensive framework of guidelines, provisions and requirements related to the property of personal data of individuals residing in the European Economic Area (https://eur-lex.europa.eu/eli/reg/2016/679/oj). The GDPR also addresses the transfer and procession of personal data outside the EU with the aim to simplify the regulatory environment for business processes (Chapter 5). Primarily, the regulation obliged controllers and processors of personal data to implement the highest possible safety standards to protect the data (Chapter 4) as well as to employ a data protection officer (DPO), who is responsible for managing compliance with the GDPR (Art. 37). Furthermore, it highlights the need to (at least partially) anonymize personal data if possible (Art. 25) and the right of an individual to revoke its IC at any time (Art. 17). To date, ongoing efforts are frequently made by the scientific community to improve bioethic principles, optimize consent documents and safeguards to protect personal information of individuals.

Another important ethical and legal issue in biobanking focusses on the property of biomaterials and related data. According to a current view, a human subject remains the rightful owner of his body material even if it is removed as part of a treatment (surgery, biopsy etc.) [39]. Although, in the recent past, a transfer of ownership for research purposes based on the subject's implicit agreement was common practice, modern biobanks prefer a model of custodianship to resolve the conflict of interests between freedom of their research and human rights [40]. In any case, the donor should have the right to withdraw from his consent at any time resulting in the proper destruction of the body material and related data.

Data access and IT-security

Large collections of data and human specimens are valuable resources and provide key elements in finding promising strategies, solutions and cures for a multitude of medical problems. Nevertheless, considerable risks of abuse and misuse of health data challenges biobanks in their practical application. With regard to the application of information technology and the ongoing process of digitalisation, which continuously changes all aspects of our lives, regulation and standardization of sample and data access become even more critical [41]. According to the policy of the BBMRI-ERIC, the main aspects for sharing biomaterial and data should include [13]:

- An access committee consisting of a scientific board that reviews internal and external requests;
- A veto right for researchers in charge for the original sample acquisition;
- A process of prioritization of biomaterial with a focus on its limitation and application frequency;
- A system to allow external researchers a better access to biospecimen and data, simultaneously honouring the biobank/researcher in charge for sample acquisition through citations, impact factor or other forms of recognition.

Up to now, there are several hundred local biobanks in Germany, which are highly heterogeneous with regard to their IT infrastructures [42]. As aforementioned, a major objective in the biobank community is to establish international biobank networks ultimately leading to increase scale and complexity of bio material and data. With the foundation of the US-American NCI or the European BBMRI-ERIC a first step was made but at the same time a couple of challenging tasks have been identified. A variety of local software systems and IT-components needed to be harmonized in a way that local IT infrastructures had to cover the issues of data protection compliance and quality assurance in these cross-location biobank infrastructures [43]. This process required the design and implementation of specialized IT components based on the needs of each individual biobank and its stakeholders but also the potential users. Essential topics to be supported with proper IT solutions comprised multicentric search engines for biosamples and data requests, traceability of biomaterial and data, administration of patient consent, communication with sample donors, compliance with data protection requirements and integration of standardized data [44].

In order to ensure bilateral biomedical research projects, a central task for an international application interface will be the invention of a user-friendly and reliable request software solution. In this process, the requesting scientist and the responding biobank are interested in identifying suitable samples for a planned research project. Since a scientific review board of the corresponding biobank providing the data and material needs to evaluate the project idea, an exchange of information between both actors requires mutual trust. Moreover, that automatic feedback on data records does not necessarily means a complete availability due to the complexity of ownerships [13]. To take these circumstances into account, a process was designed in which sample and data request management functions as a central mediator between requesting researcher and the biobank [43]. In this process, the applicant sends his request to all biobanks connected to the network via a central portal. Then, a central interface software calculates the availability in each participating biobank and report it back to the requester. The requester receives a maximum of the aggregated number of samples that meet the search criteria (material type, preservation type, patient diagnosis/therapy etc.) as well as a positive consent status of the respective donor. Hereafter, the requesting researcher contacts all biobanks potentially harboring the desired material and hands over the project description with exact details about the required material properties, data and the planned investigations in the project. Once, the corresponding review committee made a decision whether the project is feasible and can be lunched, both partners negotiate compensation for expenses and additional services. At the end of the process, a material transfer agreement between biobank and researcher is signed and the transfer of the biomaterial and associated data can be performed [45].

Concept of an International Biobanking Interface Service

Large collections of patient samples linked to well-annotated (pre-) clinical data represent an indispensable resource for modern biomedical research, life sciences and bioinformatics. To establish an interface cross-connecting the existing biobank networks in the United States and European countries, the above mentioned administrative prerequisites and IT components need to exist in each participating biobank:

- A harmonized data repository including the description of biomaterial and clinical data (data warehouse);
- A search portal handling biosample and data request management;
- An online portal suitable to give the donor subject the right to access his data, to inform about the use of his "property" as well as to cancel his consent;
- A common digital consent management ensuring that all stored samples and data are available in accordance with the sample donor;
- An access committee reviewing the requests of an applicant;
- A quality management based on the appropriate ISO norms also assuring compliance with data protection requirements.

A lot of research work needs to be done in this field. We are looking for interested prospective partners for establishing an international biobank network.

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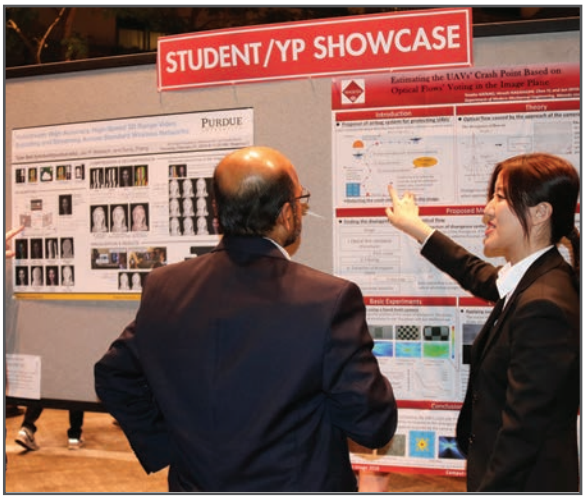

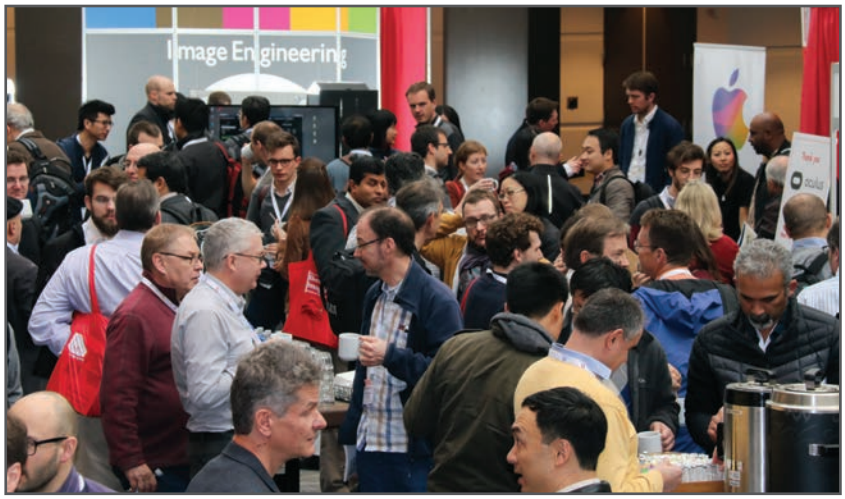

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