Biobanking **Edited by: M. Kiehntopf**

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Biobanks for future medicine

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Abstract: The use of biospecimens for biomedical research is not a new idea. Many important developments for a better understanding of diseases have been made using patient samples and related data. In former times, this was realized by individual researchers and therefore not under controlled conditions. In early times, patients were not asked for their consent and quality of biosamples and data were assessed applying subjective criteria. This has changed significantly in the past two decades especially in terms of patient consent, ethical approval and data privacy. With respect to quality, it has been extremely difficult to establish clear guidelines due to the great heterogeneity of the downstream applications. Especially in the last decade, the impact and importance of well-defined and well-organized centralized biobank infrastructures was recognized globally and enormous efforts have been undertaken to establish and operate institutional biobanks in many of the medical centers. The most recent development refers to the cooperation of biobanks at different locations. Those biobank networks enable the query for biospecimens and data across biobanks in order to collect sufficient number of samples from small disease subgroups which would not be possible for single sites. To serve this need is of utmost importance as the advances in omics technologies allow a highly sophisticated subdivision of diseases into small molecular subgroups. Moreover, the existence of many disease subgroups, which can be ideally targeted with a tailored treatment, challenges the pharma industry: in order to support the development of personalized treatment options, biobank networks offering well-defined patient samples of high quality and with rich clinical information are becoming essential partners not only in academic research but also for companies developing diagnostic tools or new therapies.

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Centralized biobanks – the basis for everything

Stand-alone biobank activities in an institution are historically the roots of biobanking and have been an important resource of medical research in the past. Meanwhile, it is recognized that there are many drawbacks if sample collections are handled as an individual effort: these collections are often stored with insufficient backup solutions and no permanent control of the temperature. Technical failures lead to uncontrolled storage conditions and sometimes temporary thawing of samples. Such events have a major impact on the quality of the sample and need to be prevented or at least tracked so this can be considered for further use [1–3]. Research data generated on the basis of samples with undefined quality are prone to non-reproducible results [4]. Another important aspect of individual collections is related to patient consent and ethical considerations, which may not meet the requirements for broad and sustainable research purposes. In addition, data privacy appears to be difficult in cases where the researcher and clinician are represented in one person. Moreover, data and samples are often not available to other researchers and the sustainability of the collection is often not guaranteed – both are not in the interest of donors.

Centralized biobanks operating under well-controlled and defined conditions primarily act as enablers for biomedical research [5]. This is due to the fact that there is no own direct research interest of the biobank linked to the samples stored in the biobank and therefore it can be regarded as a neutral instance in the system. Trust is an important prerequisite to motivate researchers and clinicians handing over their precious biospecimens to the biobank. By definition, the biobank itself cannot collect and deliver biosamples and data without consent of the sample donors. This accounts for samples from clinical trials as well as for samples collected from patient care.

The general procedure of handling biospecimens needs to be described in the usage regulations of the biobank, whereas specific conditions for a project are regulated in a cooperation contract and a material/data transfer agreement between each project partner and the biobank. This procedure guarantees a maximum of transparency and provides an excellent framework for a trustful cooperation. It is important that resulting publications based on the biospecimens and data cite the respective biobank. The most appropriate place appears to be the Materials and Methods section where also quality criteria can be mentioned [6]. Only the provision of sample and data is not sufficient to justify a co-authorship of the biobank. However, if biobank co-workers contribute to the publication with intellectual input, co-authorship is considered to be adequate.

Centralized professional biobanks should have a certification according to the International Organization for Standardization (ISO) standards [7]. Accreditation is also possible but the norms currently available are not designed for application in biobanks. However, a specific biobank norm has been published recently and should be applicable in the course of 2019 [8]. In any case, the quality management of a biobank has the highest priority assuring that all procedures are carried out according to well-defined protocols. This includes documentation of all major steps of each workflow. Regarding storage, the equipment should be very reliable and run under conditions which guarantee constant temperatures. To demonstrate the secure operation, the temperature needs to be permanently controlled and documented. In the cases of failures, an alarm system is essential which allows paging of the responsible biobank co-worker. In order to prevent damage of the biospecimens, backup devices for all temperatures need to be in place which are pre-cooled available in case of an emergency. In this case, samples can be immediately translocated to an empty device without any delay. In the case of system failure of huge −80 °C storage systems, the relocation of samples is not an option. Therefore, the cooling system needs to have backup options allowing an immediate switching to the second compressor. In addition, backup cooling employing liquid nitrogen should be installed which also works in case of breakdown of electric supply for a longer period. Liquid nitrogen-based storage devices are less critical for failures due to the independency from electricity usually supplied by huge storage tanks with capacity for a long time cooling.

Biosamples without accompanying data are not useful for biomedical research. To this end, linkage of clinical data to the biosamples is crucial. Currently, clinical information is mostly not structured and thus not directly linkable to the specimens. The use of this data for biobanks requires manual curation and structuring which is time consuming and requires data managers with profound expertise. Future developments in the frame of the German funding initiative “Medical Informatics” are expected to provide structured data which are able to enrich the value of existing and prospective samples [9].

The German Biobank Node/ BBMRI.de

The growing importance of biobanks is reflected by the establishment of an increasing number of centralized biobanks in Germany. To coordinate and harmonize biobank affairs, a central hub was needed which also represents the German biobank community in the Biobanking and Biomolecular Resources Research Infrastructure – European Research Infrastructure Consortium (BBMRI-ERIC). The German ministry for research Bundesministerium für Bildung und Forschung (BMBF) has started funding of a national biobank node in 2013 and the German Biobank Node (GBN) was subsequently established under the lead of Prof. Hummel (Charité, Berlin) [10, 11]. The first years of funding were designed to develop concepts for a national biobanking network. In addition, GBN is representing German biobanks in BBMRI-ERIC [12]. Due to the successful work of GBN, a second funding period was granted by the BMBF aiming to establish a network of biobanks which is building a common IT infrastructure and shares harmonized quality criteria. This German Biobank Alliance (GBA) is coordinated by GBN.

The German Biobank Alliance

The GBA is a consortium of 18 biobank sites (Figure 1). In addition, two IT expert centers (University Hospital Erlangen and Deutsches Krebsforschungszentrum, DKFZ Heidelberg) are part of the alliance to establish an IT network which enables queries for biosamples and data in all connected biobanks via a single entry point [13]. This requires the implementation of local connectors which host the respective biobank data and associated clinical information. In order to allow queries across different biobanks with different data structures and ontologies, mapping to a common standard is the most important prerequisite which is realized by a metadata

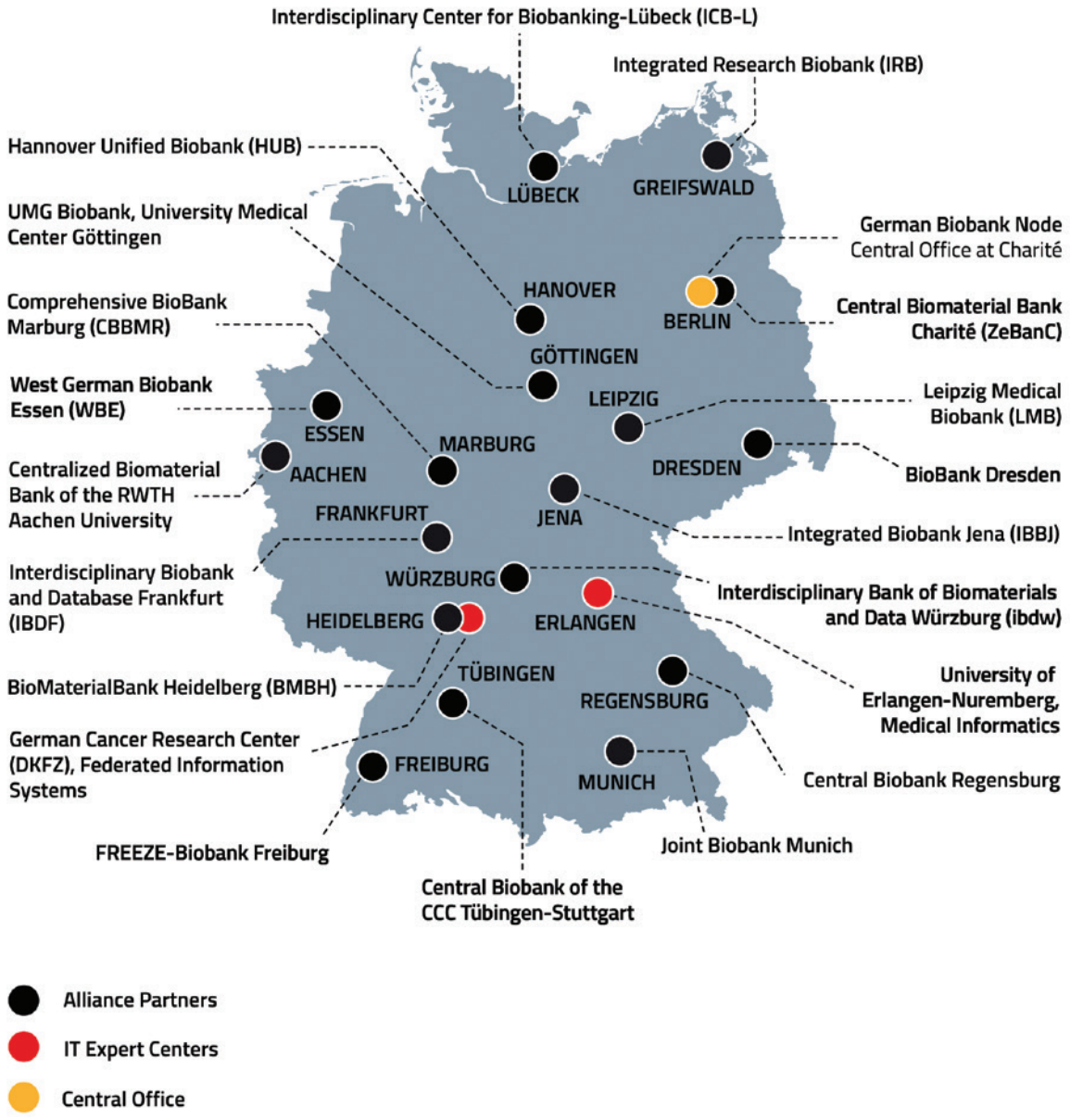

Figure 1: The German Biobank Node and Alliance.

repository (MDR). To support the set-up of the IT network, a decentralized core team of nine IT developers is supplemented by an IT expert at each of the 18 biobank sites.

Not only harmonization of the data structure but also commitment to common quality standards for the biospecimens is essential. To this end, common norms will be applied in all participating biobanks and ring trials will be performed to assess the compliance. Furthermore, an internal audit system is established to prepare the biobanks for accreditation according to the upcoming ISO norm. A first round of ring trials have already been carried out which indicate significant differences between the biobanks. Thorough evaluation of the results and individual feedback for the biobanks will be combined with educational and practical training tailored to the identified needs so that future ring trials should lead to more harmonized results.

All activities of the GBA will be aligned to the needs of biobank users. To identify the needs of various stakeholders, GBN has developed a series of activities addressing researchers, clinicians, industry and patients. To support biobanks in the communication with their stakeholders, a collection of services and tools is developed by GBN. In addition, GBN aims to identify reasons why

some researchers still prefer to run their own collections or biobanks. A group being neglected so far is the technical staff of biobanks. GBN identified their needs and is now establishing an educational program containing e-learning modules combined with practical on-site training sessions.

GBN and GBA are funded for 3 years by the BMBF. In addition to the developments at the national level, the German biobank community is also an important partner for the international network, especially in Europe. In this respect, a strong interaction between GBN and BBMRI-ERIC is of central importance. Right from the beginning, GBN has aligned its quality initiative with the corresponding activities at the European level. With respect to IT, a corresponding IT infrastructure is set up for the German biobank community as for the BBMRI-ERIC network. This facilitates an easy exchange of information and the establishment of joint collections [13].

The European Biobank Infrastructure – BBMRI-ERIC

The vision of BBMRI-ERIC is to facilitate access to biospecimens and data [14]. To this end, harmonization is essentially needed for ethical, legal and social issues ("ELSI") – including access –, quality and IT. However, this process is very complex due to enormous heterogeneity within the BBMRI member states. Since the beginning of BBMRI-ERIC, much progress has been made and tools have been developed to overcome the differences between the various member states.

ELSI

The clarification and harmonization of ELSI is key for access to samples and data across different biobanks – especially if they are located in different countries. In order to support the European biobanking community and to identify common rules, the BBMRI-ERIC Common Service ELSI was founded early on. A tool designated as "ELSI help desk" was developed by the Common Service ELSI which is available online. This way, European projects are supported in solving such issues. In addition, the Common Service ELSI was actively involved in shaping the now upcoming GDPR. As this data protection regulation has a major impact on the work of biobanks, the Common Service ELSI made a big effort during the creation of this regulation by extensive commenting and helped the community with the interpretation and implementation after the release. For access to samples and data, general rules were set up and synchronized with the Common Service IT which is responsible to establish an IT network of European biobanks. Finally, a database was established which consists of ELSI experts nominated by the national nodes of each BBMRI-ERIC member state. This database facilitates contacting ELSI experts of each member state to clarify very specific national conditions regarding all kinds of ELSI.

IT

The findability of biological material and data is a prerequisite for subsequent access and use for biomedical research projects. There are two options to facilitate findability: (i) a directory of aggregated data and (ii) a federated search tool which enables queries at the sample level. The Common Service IT of BBMRI-ERIC has set up a Directory of more than 500 European biobanks which enables a query of the aggregated biobank data. This query results in a list of biobanks which fulfill the search criteria. The Directory is constantly upgraded and new information is added, for example, about the quality of the biospecimens [14]. The federated search tool is called "Sample Locator". This tool will allow a distributed search across many biobanks in different countries at the sample level without using a centralized database hosting all biobank data. To this end, a "Connector" has to be installed locally in each biobank which hosts the local data. This Connector is not directly accessible from the outside. Instead, external requests are processed locally and search results are communicated back merely in an aggregated format. In a first step of the process, only a number of cases fulfilling the search criteria are provided to the requestor. This highly aggregated information has no privacy issues whatsoever. In case the requestor needs access to samples and data, a second process is started which will be supported by the BBMRI-ERIC Negotiator. The Negotiator allows direct contact between a biobank and a requestor for further refinement of the request and to grant access to samples and data according to the rules of the respective biobank [15]. The Negotiator will also support the Directory queries to accelerate contacting the biobanks and refinement of the requests. The establishment of the processes for findability of samples and data is however not sufficient. One major obstacle is the use of many different ontologies to categories of diseases. A BBMRI-ERIC Metadata Repository will be established which helps to create compatibility across the many European biobanks.

Quality

The quality of the samples is essential for the establishment of cross-biobank collections for research. Only biospecimens with comparable quality are eligible for inclusion in research collections fed from various biobanks. Therefore, BBMRI-ERIC has initiated quality assessment tools and several working groups which consist of experts from the various national nodes. They have jointly commented the new quality standards which have been established in the ISO Technical Committee 276 (ISO 20387) as an international effort. In parallel, an audit program will be established which should help biobanks to fulfill the prerequisites for future accreditation.

The colon cancer data collection

To demonstrate the applicability of products designed by the activities of BBMRI-ERIC, e.g. for ELSI, IT and quality management, a colon cancer collection was initiated which consists of available samples of at least 10,000 patients enriched with clinical data. The harmonization of the clinical data was a major challenge but now an agreed compromise exists for detailed clinical information about diagnosis, treatment and clinical course. Tools for mapping of different ontologies were developed and uploading of data from contributing biobanks was possible via manual data entry or via uploading of XML or XLS files. Most data elements were mandatory whereas some elements were optional. The entire collection of more than 10,000 data sets has been finalized at the end of 2018.

Future directions

National biobank nodes should be permanently anchored as umbrella organizations to pool the national expertise and act as the driving force for the European biobanking research infrastructure BBMRI-ERIC. By establishing partnerships with further research infrastructures, researchers will get better access not only to biospecimens and rich clinical information but also supplementary data such as omics and imaging data. Biobanks will thereby form an integrative part of all disciplines within biomedical research. Furthermore, the support of interventional as well as observational clinical trials will constitute an increasingly important field for biobanks. Biobanks will essentially become the "home" for biospecimens and the trustees for the use of samples and data also beyond the end of the trial periods. This will ensure the long-term use of highly valuable samples and data acquired under well-defined structured conditions. By implementing uniform legal and ethical conditions for cooperation with industry, the biobank network will also be a strong partner for pharmaceutical/diagnostic companies. Thus, biobanks will contribute decisively to the accelerated development of diagnostic procedures and personalized medicine.

Summary

Reproducible research data are indispensable for the development of diagnostics and new therapies in the frame of precision medicine. The quality of biospecimens used in research and their associated data provide the most essential contribution to gain reliable research results. Well-organized central biobanks operating under defined conditions ensure that the material used for research meets the highest quality requirements. Networks of biobanks allow a federated search for suitable and sufficient number of biosamples even for rare disease subgroups. To this end, biobanks provide an essential contribution to the accelerated development in the context of precision medicine.

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