Biobanking

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Integrated biobanks facilitate high-quality collection and analysis of liquid biomaterials

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Abstract: The collection and storage of biomaterials is essential for medical research. The aim of biobanking is the safe extension of the preanalytical phase. However, not all quality aspects are clearly defined nor accepted by the whole biobanking community. Samples for large or complex trials have to be collected and stored according to well-defined, rapid and reliable processes. In a comparable manner, also the post-storage phase needs well-defined, rapid and reliable processes which have to be implemented in order to guarantee high-quality samples as an inevitable basis for accurate analytical results. The time span between the sample removal from the biobank and analysis seems not to be in the focus of a biobank especially when it is run independently of a laboratory.

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Sample analysis represents the core responsibility of laboratories. But the quality of samples can be impaired by all process steps in the preanalytical phase, including preparation for analysis after the freezing period. Biobanks may contribute to high-quality standards in the retrieval and handling of samples before storage. They can offer electronic tools for data entry in parallel to sampling allowing a tight control and documentation of the preanalytical phase directly in the laboratory information system. In case of a biobank independent of the laboratory, which performs the measurements, the biobank's responsibility ends with the transport. A closer link between the two institutions, however, could significantly improve sample quality and laboratory results. Integrated biobanking combines long-term sample storage with optimized laboratory processes, thus facilitating high-quality analytical results.

Keywords: automation; integrated biobank; preanalytic; sample quality; standardized processes.

Introduction

The collection and storage of biomaterials is essential for medical research. The aim of biobanking is the safe extension of the preanalytical phase – as part of the whole analytical process. Biomarker research needs biobanking tools when performing clinical trials or epidemiological studies. Preanalytical process steps associated with biobanking, including, for example, sample collection, transport, centrifugation and aliquoting, influence sample quality [1–5]. Recently, the DIN ISO 20387 “Biotechnology – Biobanking – General requirements for biobanking” has been published [6].

However, not all quality aspects are clearly defined nor accepted by the whole biobanking community and are still a subject of extensive discussions. Especially preparation of aliquots for analysis after long-term storage is frequently not included and defined in the biobanking procedures. Sample analysis, often referred to as the analytical phase, represents the core responsibility of

laboratories. Therefore, the time span between the sample removal from the biobank and analysis seems not to be in the focus of a biobank especially when it is run independently of a laboratory. Integrated biobanks, i.e. biobanks closely associated with medical laboratories, are capable of providing services for the preanalytical phase between storage and analysis. It is important to point out that the quality of samples can be impaired by all process steps in the preanalytical phase, including thawing and preparation of biobank samples for analysis. Once the sample is damaged, all preceding efforts regarding the sample are worthless.

State-of-the-art biobanking for complex or large trials represents a challenging task: samples have to be collected and stored according to well-defined, rapid and reliable processes. After storage, well-defined, rapid and reliable processes have to be implemented as well, in order to guarantee high-quality samples as an inevitable basis for accurate analytical results in health care research. In a best practice biobank site, key process steps are thoroughly defined in advance and structured in a laboratory information management system (LIMS) to guide processing and ensure detailed documentation. The documented information for each sample and thereof generated aliquots can encompass basic information, such as type of primary sample (serum or plasma), number of aliquots and their sample size or presence of hemolysis. Furthermore, a series of details on the handling process such as the time spans between sample collection and laboratory entry, centrifugation or the time to freezing are documented as well (see Figure 1). These time-related data and impacts on sample quality are currently intensively discussed and evaluated by the German Biobank Alliance

(Working Package 3). The documented process details in the LIMS about quality impairing effects can be taken into account and thus biobanks can assist in identifying samples best suited for a specific research project in terms of preanalytical aspects.

Collection of samples

Samples from patients and probands become valuable through the standardized clinical characterization obtained in a given study and build the basis for biomarker research. Biobanks can support researchers by offering electronic tools for data entry in parallel to sampling. This allows a tight control and documentation of the preanalytical phase directly in the LIMS in real time already at the site of sample collection. When implementing these tools, laws and regulations have to be followed, e.g. data protection and correct handling of informed consent. It is important that the electronic ordering and documentation process are transparent and easy to handle for the study personnel.

Choice of cryotubes

Nation and worldwide many different cryotube types are in use. They differ in many aspects, for example, in size, cap type, applied torque to close or remove the cap and rack design. Racks may have a side barcode and/or a so-called 97th barcode at the bottom to identify the rack itself. Racks filled with tubes may also differ in total height and number of tubes, ranging from the widespread 96-well-format SBS

Figure 1: Processing chain of designated biobank material. Starting from sample collection, which takes place in or outside the laboratory and biobank, for instance, in study centers or on clinical wards. Afterwards, samples are transported and processed involving several steps, e.g. centrifugation of primary samples, aliquotation and labeling. Afterwards, the biomaterial is stored in the biobank. Exemplary time points and additional information obtained at different processing steps in the laboratory and the biobank are marked.

(SBS: Society for Biomolecular Screening) to highly condensed racks or racks for larger tubes.

In general, biobanks, especially automated biorepositories, can handle only a limited number of cryotube types, including automated capping and recapping of the cryotube prior to storage. Of note, each automation in combination with a specific capping tool needs to be evaluated whether it appropriately opens and caps a given cryotube type. Incorrect applied torque, for example, might result in either damage of the cryotube or insufficient capping, both causing a leakage and consequently impaired sample quality. Unfortunately, these damages often cannot be spotted with the naked eye. Manual handling of cryotube types with different dimensions, caps or torque, which cannot be handled by a given capper/decapper, may at first glance appear to be an alternative. However, it meets its limitations when standardized handling of large numbers of samples is required. Automated cryo biorepositories can only be adapted to optimal handling of a limited number of cryotube types. Currently, without fine-tuning of robots in automated biorepositories for specific cryotubes, failure rates, e.g. for sample picking, are too high and samples may be lost.

It is therefore challenging for a biobank to obtain samples filled in cryotubes which do not fit with its processes and automation. Even cryotubes from the same manufacturer may differ to an extent that they cannot be processed over the same automation. A possible work-around could be storage of samples in commercially available classical freezers, contradicting, however, all benefits that arise from using automated biorepositories. Sometimes it is possible to store such samples on standardized racks in an automated biorepository without using automated sample picking. For this purpose, cryotube dimensions need to be compatible with the inner biorepository architecture, e.g. pitch height. Both circumstances are far from optimal in terms of sample handling. All automated biorepositories will hesitate to store external racks if the compatibility is unclear and the risk of malfunction or rack crashing might occur. This emphasizes the need for further standardization of cryotube types as well as the need for technical improvements of biorepository robots to allow for more flexibility.

Handling of cryotubes for further analysis

Sample removal and transport to external research laboratories are simple on the biobank side. In case of a biobank independent of a laboratory, the biobank's responsibility covers the documentation of sample removal in its LIMS

and, as far as requested, the initiation of transport under appropriate conditions, e.g. dry ice. It has to be kept in mind that the above detailed challenges play a role for the laboratory receiving the samples. These aspects may lead to increased hands-on time and costs, impaired quality or prolonged time until measurement results are available. In view of the purpose of biobanks, these difficulties can be overcome by linking the biobank closely to a laboratory and its processes.

The Integrated Research Biobank Greifswald (IRB) is part of the Institute of Clinical Chemistry and Laboratory Medicine (IKCL) at the University Medicine Greifswald. A frequent request issued to the IRB is the combined retrieval and measurement of samples from the local epidemiological Study of Health in Pomerania (SHIP) and the cohort study "Greifswald Approach to Individualized Medicine" (GANI_MED) [7, 8]. One retrieval and measurement request may encompass up to thousands of aliquots and combines and utilizes processes from both biobanking and medical laboratory.

The possible throughput of biobank samples which can be retrieved, prepared and measured on a working day can be estimated. Dummy samples are used to simulate the workflow prior to the retrieval of study samples. Additional quality assurance measures are implanted such as extra validation lists in the LIMS. Daily retrieved samples are thawed according to an agreed protocol. As these samples are stored in a cryotube type that fits the complete equipment of the IRB and IKCL, the process is aided by automation. The thawed and centrifuged cryotubes are automatically decapped. At the IRB, only cryotubes with a unique two-dimensional (2D) code at the vial's bottom are used since 2010. A special feature of the IRB is the additional labeling of specific cryotubes with classical one-dimensional (1D) barcodes prior to filling with biomaterials. Due to the additional 1D barcode label, cryotubes can be placed directly into commercially available analyzing platforms using custom-made adapters. Based on the 1D barcode, measurement results will be reported into the LIMS. Based on the 2D barcode, the biobank can communicate with the LIMS, thus combining both information in one system.

If, on the other hand, this link is missing, additional steps and hands-on time are required to obtain measurement results for the retrieved samples. Depending on the laboratory, this generally involves pipetting of samples from the cryotube into a vial suitable for the use in the analyzing platform. However, when thousands of samples have to be processed, this is not only a challenge for resources such as personnel or costs, but also for data integrity as the risk of errors increases when many

samples are handled without or with only limited information technology (IT) assistance. In addition, the time from sample retrieval to measurement is unnecessarily high, with negative aspects in view of sample quality. Pipetting from one vial into another, the handling of low sample volumes has implications to concerning dead volumes and sample evaporation. Therefore, these manual handling procedures should be avoided as far as possible.

Efforts can be made to automatically pipette samples from the original cryotubes. Again, this is resource consuming in the set-up phase, but will pay off through decreased hands-on time and decreased risk for sample confusion errors afterward. Programming, of course, has to be established for each study and cryotube type. Depending on the sample volume available and also on the cryotube type, automatic pipetting sometimes is not possible at all, even though the sample material volume is sufficient for the analyzing platform.

Conclusions

Biobanking can support medical research by assisting standardized collection and storage of biosamples. Electronic tools guide and document essential and detailed information on the preanalytical phase while the sample is obtained by the study personnel and processed by the biobank staff. Integrated biobanking is an efficient approach to process the samples between storage and measurement as safe as possible. The post-storage phase is currently ignored in most discussions about the sample quality and results gained from aliquots stored in biobanks. Harmonized processes and a tight connection between biobank and laboratory avoid interruptions of the processes especially in the post-storage phase. Such interruptions bear the risk of impaired sample quality. In addition, they are costly and require time for workarounds. Integrated biobanking closely links the long-term storage to laboratory processes facilitating high-quality measurement results for the collected study samples.

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