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BIORESOURCE PAPER

Hospital-integrated Biobanking as a Service – The Interdisciplinary Bank of Biomaterials and Data Wuerzburg (ibdw)

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The ibdw was established in 2011 as one of 5 centralised national biobanks in Germany within the framework of the governmental funding program "Nationale Biobank-Initiative". The ibdw is a joint core facility of both, the University Hospital and the Julius-Maximilians-University Würzburg and acts as a faculty-wide service provider of human biological material for medical research. From the outset main emphasis was placed on comprehensive automation and seamless integration of sample collection in clinical routine workflows thereby securing highest quality standards. The ibdw collects fluid and tissue samples in parallel from patients, based on a broad informed consent, hence not limiting future research use.

Keywords: Centralized clinical biobank; broad consent; online consent management; LIMS integration; data warehouse; automation

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(1) Bioresource Overview

Project description

The Julius-Maximilians-University of Würzburg was founded in 1402; many eminent scholars and scientists have since researched and taught in Würzburg (14 Nobel Laureates, among them e.g., R. Virchow and W.C. Röntgen). Today, the University of Würzburg is particularly recognised among the medium-sized institutions of higher education in Germany. With respect to life and natural sciences it is ranked among the top 150 universities in the world and among the top 50 universities in Europe (Academic Ranking of World Universities) [1]. The hallmark of the University Hospital Würzburg is excellent medical care and top-level research to the benefit of its patients. The University Hospital consists of 19 clinics with polyclinics, 3 autonomous polyclinics (22 departments), and 4 clinical institutes taking care of about 60,000 inpatients and 250,000 outpatients per year (2015) [2]. Within the University Hospital a number of clinical centres have been established aiming at an integration of diverse clinical disciplines in close collaboration thus providing optimized treatment to patients; among these are e.g., the "Comprehensive Cancer Center Mainfranken" (CCCM), the "Comprehensive Heart Failure Center" (CHFC), and the "Center for Rare Diseases" (CRD). The close vicinity of research and clinical routine enables an immediate transfer of research results to clinical application.

Future advances in the diagnosis, treatment, and prevention of human diseases require the combined analysis of human biological material and related clinical and research data including "omics"-data. This is where the centralised Interdisciplinary Bank of Biomaterials and Data Würzburg (ibdw) comes in as a faculty-wide operating central service provider of human biological material for medical research. The concept of centralised biobanks is based on the experience that it is virtually impossible to provide consistent and reliable quality of samples and data in an environment with decentralized, independent units collecting, processing and storing samples and data on their own authority. Consolidating decentralized structures in a centralized unit enables comprehensive quality control and standardized procedures can be implemented, adapted and improved as required without delay. The ibdw is composed of a central database (biobank management system, BBMS, linked to the clinical data warehouse) and two central sample repositories, one for body fluids and one for tissue samples, respectively, and a limited number of specialized decentralized ibdw-subunits (e.g., Departments. of Dermatology, Psychiatry, and Orthopaedics) fully adhering to ibdw standards and rules. The Medical Faculty, i.e., the Julius-Maximilians-University and the University Hospital Würzburg together hold full responsibility for the ibdw, which is governed by its own steering committee (**Figure 1**).

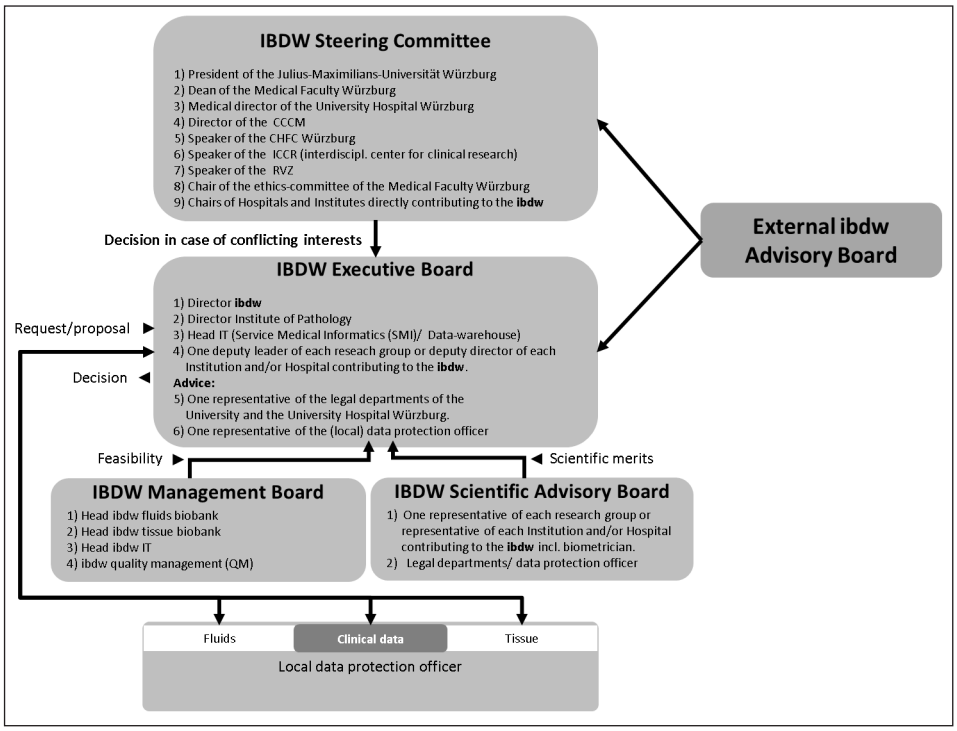

Figure 1: ibdw governance. The ibdw activities are supervised and controlled by the steering committee. The external advisory board assesses performance and development of the ibdw on a regular basis and gives advices for future development. The executive board and the internal advisory board are involved in the evaluation of sample and data requests.

The unique strategic concept of the ibdw comprises a systematic, simultaneous, and sequential collection of body fluids and tissue from patients and study participants of all 22 departments in the University Hospital [3]. Priority has been set towards a concerted establishment and sharing of ibdw resources consisting of high quality human biological samples collected according to current OECD (10/2009) [4] and ISBER recommendations (12/2012) [5], and access to all relevant information related to the samples through a clinical data warehouse. As one of the first large clinical biobanks in Germany, the ibdw has obtained certification according to the recently revised DIN EN ISO 9001:2015 in 08/2016. The IT infrastructure of the ibdw is part of the overall research infrastructure of the Medical Campus Würzburg and fully integrated with respect to the existing work- and dataflow concepts. This research infrastructure comprises a clinical data warehouse providing authenticated access to almost all kinds of analytical and medical data accomplishing all current data protection and safety regulations securing donors' privacy.

In addition the ibdw supports clinical and epidemiological studies by providing IT tools, equipment, logistics and laboratory services for collecting, processing, managing and storing samples.

Classification (1)
Human

Species
Humans

Classification (2)
Biological samples, related data and clinical core data.

Context

Spatial coverage
The ibdw collects samples from patients of the University Hospital Wuerzburg but also acts as service provider for clinical and epidemiological studies at the University and University Hospital of Wuerzburg, as well as other research institutions. Consequently, the majority of samples originate from donors in the region of Lower Franconia.

Northern boundary: 50°33′53.0″N 10°07′14.2″E
Southern boundary: 49°28′49.7″N 9°57′05.0″E
Eastern boundary: 50°08′31.9″N 10°52′45.8″E
Western boundary: 50°03′08.4″N 8°58′33.7″E

Temporal coverage
The ibdw was set up in 05/2011, and was fully operational in 07/2013. Since then the ibdw has provided services to studies like logistics, sample processing and storage. The studies' life-spans vary between 3 to over 10 years, depending on the particular objectives. The collection based on the broad consent of the ibdw started in 2013 and will be continued open-ended. Several legacy collections have been included insofar appropriate informed consent and documentation could be provided.

Temporal coverage for accessibility
Samples from studies remain in the biobank until requested or funding ceased. However, the ibdw offers continued storage of study samples provided that the

ibdw broad consent has been signed along with the study specific consent. Samples in the ibdw broad consent collection are meant to remain in the biobank until used. Access to broad consent samples requires an application (approved by an independent ethics-committee) which will be assessed and approved by an internal ibdw use and access committee (**Figure 2**). The destruction of samples is currently only specified when a donor has withdrawn the informed consent. The associated data are usually solely anonymized and only deleted if explicitly requested. As a matter of fact published data cannot be deleted. Only one consent has been withdrawn since the ibdw has become operational. As the corresponding consent pertained to a clinical study no patient related information had been stored at the ibdw.

(2) Methods

The acquisition of samples for the ibdw collection has been almost imperceptibly and smoothly integrated into clinical routine. Within the hospital information system (HIS) data fields specific for patient consent are provided (**Figure 3**). Thus any physician or surgeon can readily see whether a particular patient has signed the ibdw broad consent. Starting with the broad consent-based ibdw sample acquisition in 2013, we successfully implemented a complete sample tracking procedure with all relevant key steps being documented via time-stamps (including online temperature monitoring during sample transport (**Figure 4**). The high degree of automation reduces user interaction to a few pushes on a touch screen and barcode scans (**Figure 5**). On account of the effortless operation, an outstanding acceptance rate among the clinical and technical staff could be achieved.

Steps

Obtaining broad consent

After admission to the hospital a consent form can be requested from within the HIS. The consent forms for broad consent are generated electronically for each patient individually, with name, patient number and corresponding bar code already filled in (personalised patient broad consent form). The broad consent form is handed to the patient together with a comprehensive information sheet and a leaflet containing the key points for the patient in condensed and illustrated form. The signed original consent form is kept in the paper-based medical record, a copy is handed to the patient and a second copy is passed to a medical student assistant who checks the form for completeness and for consistency with the HIS data (using a person-specific HIS-view on the required data only). The documented broad consent unlocks the commissioning of biobank orders in the laboratory order entry system and the printing of labels for ibdw sample tubes (**Figure 6**).

Workflow for body fluids

As a general principle ibdw broad consent bio-samples are only acquired in the context of routine blood sampling. The ibdw request can be generated along with the routine sampling request in the order entry system (**Figure 6**) of the hospital's laboratory information system (LIMS) and all necessary labels are printed at once. The labelled sample tubes are packed according to their destination in liquid-tight bags earmarked with unique identification codes. The ibdw sample bags are passed together with the routine samples to the central laboratory of the hospital where the delivery is split for clinical analyses and biobank, respectively. Biobank samples are placed in a transport

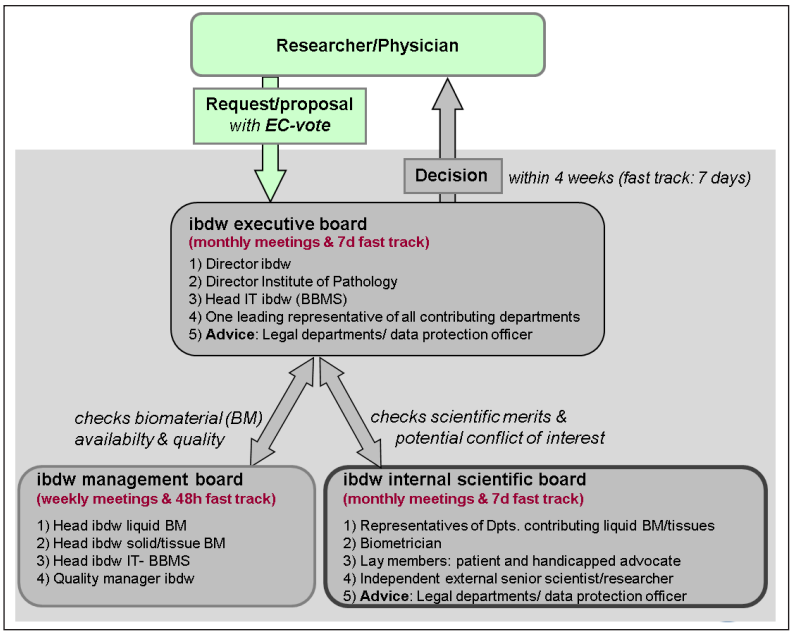

Figure 2: Decision workflow for sample requests. The request for samples and data has to be directed to the ibdw executive board. The executive board asks the management board to verify that samples of appropriate quality are available. The scientific (advisory) board reviews the request with regard to scientific merit and potential conflict of interest. In case of urgent need the decision process can be passed on a fast-track process.

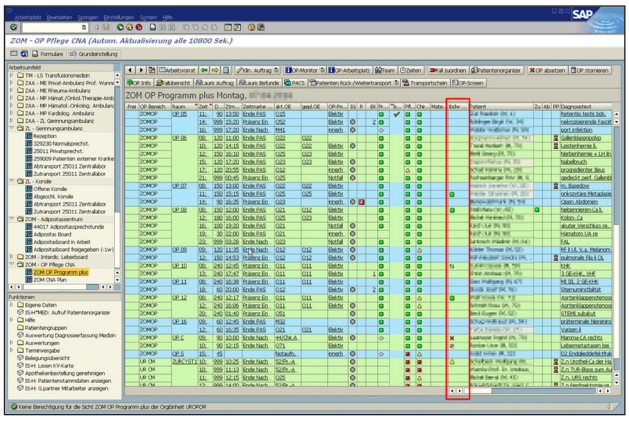

Figure 3: Consent management in the Hospital information system (HIS). In addition to standard information, the HIS provides a separate column indicating whether a valid patient consent exists.

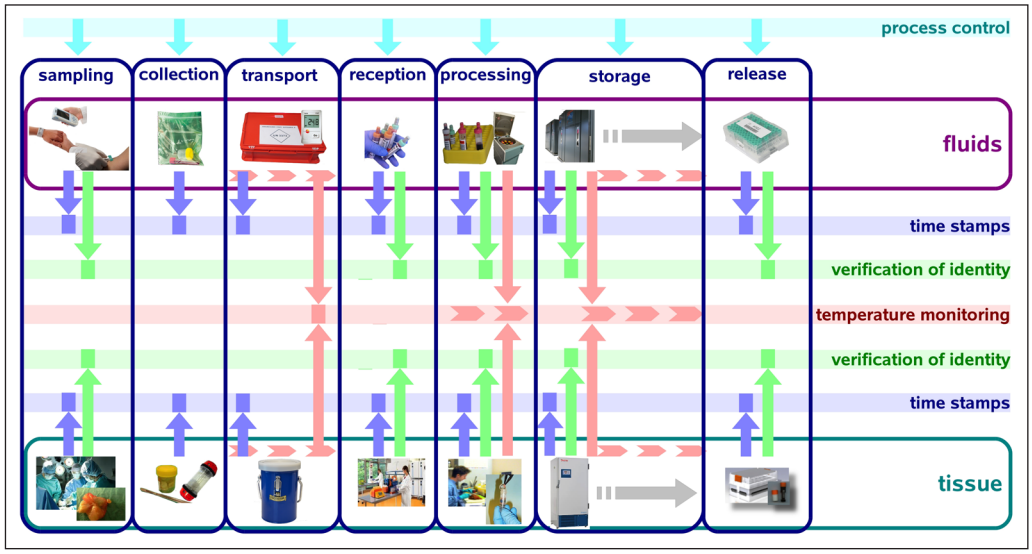

Figure 4: Workflow control and monitoring during the sample life cycle. The sample is monitored throughout its life cycle by tracking its position, generation of time stamps and temperature monitoring. The events and processes monitored are indicated by the coloured arrows (red: temperature monitoring, blue: time stamp, green: sample identity check).

box, which is provided by the ibdw and is equipped with a unique identification code and a mobile temperature monitoring device. Upon request the box is carried by a bicycle courier to the ibdw laboratory. There the box is registered by its code and the containing bags and samples are digitally associated with the box and thus the temperature probe. All samples received are checked for integrity and processed according to SOPs for the respective biological material.

Handling and storage of the samples in the ibdw fluids biobank is carried out in an own building under constant ambient conditions permanently monitored electronically according to current OECD (10/2009) [4] and ISBER (12/2011) [5] guidelines. Whole blood, serum and urine samples in standard format are processed automatically by a pipetting robot, only exceptional biological material like cerebrospinal fluid (CSF) or bronchoalveolar lavage (BAL) are processed manually, but fully compatible with the automated process. Usually the samples are stored in automated –80°C stores (LiCONiC cryo-stores, Liconic Inc., Mauren, Liechtenstein), however for selected body fluids, particularly for delicate analytics (e.g. seromics, proteomics, metabolomics) or viable cells (e.g. PBMC) semi-automated storage is provided with cryo-tanks (gas phase of liquid nitrogen, –160°C). The automated and semi-automated storage are using the same 2D-coding, tracking, storage, and retrieval-system and are fully integrated in the biobank management system (BBMS).

Workflow for tissue samples

Handling and storage of tissue samples is carried out under qualified guidance and supervision by the Department of Pathology. Broad consent tissue samples are collected during surgical interventions or by biopsy and passed to the ibdw tissue lab utilizing the rapid section laboratory's workflow. Native tissue samples are stored in conventional freezers at –80°C using special 2D-coded tissue tubes (24-well format, suited for 1.0–2.0 cm^3 tissue specimens, FluidX Inc., or 48-well format, Micronic Inc., for biopsies). As a general rule, all snap frozen tissue samples are either directly processed in the ibdw tissue-bank next to the operation theatres (Center

Figure 5: Touch screen based process control and operation by the in-house developed ibdw application.

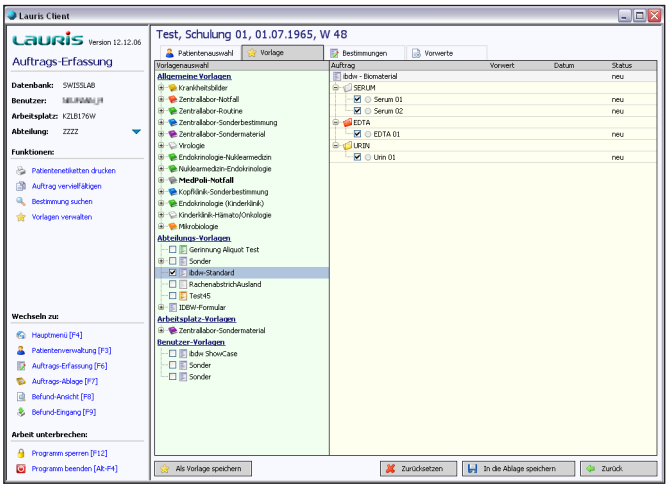

Figure 6: LIMS integration of the ibdw sample acquisition request. The ibdw sample acquisition request is integrated in the order entry system of the clinical laboratory. If the patient has consented, the clinician can place a request for biobank sample collection and storage alongside with the request for laboratory analysis.

for Operative Medicine, ZOM) or, for several other departments (e.g., gynaecology, neurosurgery, and maxillary surgery) processed in the Department of Pathology. Reference sections of the stored tissue samples are reviewed by the attending pathologist and handled according to the SOPs of the Department of Pathology for diagnostic samples (accredited by the German national accreditation body DAkkS (Deutsche Akkreditierungsstelle GmbH) in 07/2015 according to ISO/IEC 17020:2012).

Tissue and corresponding fluid samples are managed with the common BBMS using linked pseudonyms.

Stabilization/preservation

Blood samples are stored as either EDTA stabilized whole blood or plasma and serum.

Tissue samples and biopsies are snap frozen and stored at –80°C.

Type of long-term preservation

Usually 6 aliquots of each body fluid are stored in 350 µl aliquots in V-bottom, screw-capped, internal thread, 750 µl tubes with Datamatrix code on the bottom on 96 well SBS racks with 1D barcode on the side (Micronic Manufacturing B.V., Lelystad, The Netherlands). Tissue samples are stored in 3 ml tissue tubes with screw-cap, Datamatrix code on bottom on 24 well SBS racks with 1D barcode on the side (Brooks Automation GmbH, Jena, Germany). Biopsies are stored in 1 ml tissue tubes with screw cap, external thread and Datamatrix code on the bottom on 48 well SBS racks with 1D barcode on the side (Micronic Manufacturing B.V., Lelystad, The Netherlands).

Storage temperature

Usually –80°C (body fluids in automated storage, tissue manual storage); –160°C manually implemented (gas phase of liquid nitrogen; cryo-tanks, Cryotherm

GmbH & Co. KG, Kirchen/Sieg, Germany) and available on special request.

Shipping temperature from patient/source to preservation or research use
Room temperature (18–25°C) (fully monitored).

Shipping temperature from storage to research use
–80°C (on dry ice) (monitored).

Quality assurance measures
The ibdw is certified according DIN EN ISO 9001:2015, the Department of Pathology is accredited according to ISO/IEC 17020:2012. The methods used are in line with the recommendations of WHO, IFCC and other professional societies.

Source of associated data
The ibdw holds only a core data set to each sample, consisting of age, sex, ethnicity, main diagnosis and date of consent. Additional clinical data are kept in the data-warehouse where data from electronic health records, tumour registry, and other sources (including research data) are merged.

Ethics Statement
Following the recommendations of the German Ethics Council [6, 7], in 2011 the ibdw management board together with the ibdw steering committee, the legal departments of the University and University Hospital, and the respective data protection officers have developed a model for an "as broad as possible" informed consent for patients and study participants donating biological material and clinical and/or health data for unrestricted medical research purposes. This "broad" informed consent was approved by the ethics committee (EC) of the Medical Faculty of Würzburg in 10/2011 and follows the concept of the German Ethics Council (GEC) for a virtually unlimited use of biological material and data for medical research. The concept is based on five pillars, namely biobank secrecy, permissible use, involvement of ECs, quality assurance, and transparency [8]. In addition, the ibdw assures that (a) any research proposal has received approval by an independent EC, and that (b) any actual transfer of samples and/or data is controlled by comprehensive access regulations including the commitment for feedback to the ibdw and – when appropriate – honoring the contribution of the ibdw to research results [3, 9]. The ibdw is the first faculty-wide operating, centralized German biobank that has fully implemented broad consent management and integrated into the University Hospital's Information System (HIS). This add-on permits hospital personnel to generate personalized consent forms, check the actual status of the patient consent based on a readily identifiable "traffic light" representation (green: consented, yellow: decision pending, red: broad consent refused) and to generate biobank orders (**Figure 3**).

Constraints
To date, the ibdw has no procedure in place that would allow obtaining broad consent from incapacitated individuals or children. As a consequence apart from study-specific collections of the Department of Paediatrics and the Department of Anaesthesia, the ibdw currently does not hold any paediatric samples or samples from incapacitated patients for "broad use" in biomedical research.

(3) Bioresource description

Object name
Clinical data, body fluids, tissue sections and/or biopsies from patients of the University Hospital of Wuerzburg.

Bioresource name
Interdisciplinary Bank of Biomaterials and Data
ibdw

Bioresource location
Interdisciplinary Bank of Biomaterials and Data (ibdw)
University Hospital Wuerzburg
Straubmuehlweg 2A; Bldg A9/A8
97080 Wuerzburg
Germany

Bioresource contact
ibdw@ukw.de

Bioresource URL
http://www.ibdw.ukw.de

Identifier used
n/a

Bioresource type
Centralized clinical biobank with disease focus on cancer and cardiovascular diseases.

Type of sampling
Samples are collected in clinical routine care and/or in clinical studies.

Anatomical site
Corresponding to the focus of the ibdw cancer tissue and biopsies from digestive, urogenital and respiratory organs as well as brain tumors are collected. The anatomical site of each collected tissue is documented in the BBMS.

Disease status of patients/source
All kinds of diseases with all degrees of disease-severity treated at a University Hospital covering all medical specialties (tertiary care facility) with a focus on patients suffering from cancer or cardiovascular diseases.

Clinical characteristics of patients/source
Patients aged 18 or more

Vital state of patients/source
Alive

Clinical diagnosis of patients/source
The disease focus of the ibdw is on cancer and cardiovascular diseases. The major diagnosis is stored along with fundamental patient data.

Pathology diagnosis

The pathological diagnosis of each collected tissue is determined and documented by the Department of Pathology based on standard nomenclatures and catalogues (WHO, TNM, SNOMED). The diagnostic laboratory is accredited according to ISO 17020:2012).

Control samples

Available in the frame of a currently implemented collaboration with the Bavarian blood donor service and the collaboration with a population-based local epidemiologic study following 5000 residents of Lower Franconia/ the town of Wuerzburg.

Biospecimen type

Tissue, biopsies, whole blood, serum, EDTA plasma, citrate plasma, urine, CSF, BAL

Size of the bioresource

The ibdw employs 15 persons (full and part time).

Currently the ibdw stores 250,000 fluid samples and 2,000 fresh frozen tissue samples. The ibdw collects samples under the broad consent in perpetuity. At present the storage capacity is limited to 1.2 million samples.

Release date

As a central facility of the University Hospital and the University of Wuerzburg the ibdw has been installed permanently. Samples collected for funded studies are stored until requested by the study or funding ceases. In the latter case the ibdw offers to transfer the study specific samples to the broad consent collection, provided an appropriate consent is available. Samples collected under the broad consent can be stored indefinitely.

Access criteria

Samples in the ibdw collection are available to any researcher worldwide provided the intended research project has been reviewed and approved by a competent ethics committee. Any request for samples and data is received by the ibdw executive board which asks (a) the ibdw internal scientific board (that is, use and access committee) for an evaluation with regard to scientific merit and possible conflicts of interest, and (b) the ibdw management board for availability and appropriate sample quality. If the request has been positively evaluated the executive board instructs the ibdw to release the samples requested (**Figure 2**). The transfer of samples and/or data to third parties is performed using standardized Material Transfer and/or Data Access Agreement forms (MTA/DAA). Samples and data requested for basic research purposes by a non-profit organization are provided with a non-profit MTA/DAA.

(4) Reuse potential

a. Delivered samples may not be used by other ("third party") researchers except previously specified (name/purpose) in the initially submitted application.
b. Study-samples after end of funding may be used/ reused by other researchers, when an ibdw broad consent has been obtained together with the informed study-specific consent.
c. Tissue sections from a snap frozen "broad consent" specimen can be delivered to researches on request/application.
d. In case of missing consent or if donor re-contact is not possible, the ethics committee of the Medical Faculty Wuerzburg may approve reuse of data/samples for specific purposes (in general when any benefit for the general population and/ or specific disease entities is to be expected).
e. Data (clinical and research) can be reused by all researchers requesting access.
f. In case of previously performed external analyses (research, genetic, etc.) we plan to provide the respective contact information (individuals/institutions) and type of analysis performed. Data generated beyond the quality control of the ibdw are not stored at the ibdw as the ibdw cannot take any responsibility for the data quality.

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We would like to thank the Dean of the Medical Faculty, Prof. M. Frosch, the President of the University of Wuerzburg, Prof. A. Forchel, the former Medical Director Prof. Reiners, the current Medical Director Prof. Ertl, the Commercial Director of the University Hospital, Ms. A. Simon, and our Steering Committee members for continuous support.

We are indebted to our external advisory board for oversight of project development and implementation and their continuous helpful advice and encouragement.

We thank the ibdw staff as the success of the ibdw owes to their commitment.

Competing Interests

The authors have no competing interests to declare.

Author Roles

Geiger J.: Manager of Fluids Biobank
Both S.: Quality Manager
Kircher S.: Manager of Tissuebank
Neumann M.: IT Manager
Rosenwald A.: Chair of Pathology
Jahns R.: Director

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