

BIORESOURCE PAPER

The Integrated Research Biobank of the University Medicine Greifswald

Theresa Winter^{1,2}, Nele Friedrich^{1,2,3}, Sophia Lamp^{1,2}, Christian Schäfer^{2,3},
Mario Schattschneider^{1,2}, Stefan Bollmann^{1,2}, Diana Brümmer^{1,2}, Katja Riemann^{1,2},
Astrid Petersmann^{1,2} and Matthias Nauck^{1,2,3}

¹ Integrated Research Biobank (IRB), University Medicine Greifswald, Greifswald, DE

² Institute of Clinical Chemistry and Laboratory Medicine, University Medicine Greifswald, Greifswald, DE

³ DZHK (German Centre for Cardiovascular Research), Partner Site Greifswald, University Medicine Greifswald, Greifswald, DE

Corresponding author: Theresa Winter (Theresa.Winter@med.uni-greifswald.de)

The Integrated Research Biobank (IRB) at the Institute of Clinical Chemistry and Laboratory Medicine (IKCL) is the central biobank resource of the University Medicine Greifswald (UMG) for all biological materials collected within the framework of clinical and experimental studies carried out by internal and external researchers. The IRB is a core unit of the UMG and focuses on collection, processing and storage of mainly liquid biomaterials, e.g. blood, urine, saliva or swabs in established workflows and thereby securing highest quality standards. Aliquots are usually stored at -80°C in one of the two fully automated LiCONiC biorepositories or, if necessary, in one of the -80°C freezers. Up to now, the IRB stores more than 1.1 million liquid aliquots and the collection grows continuously. Currently, the storage capacity of the IRB is limited to 3 million aliquots.

Keywords: automation; centralized liquid biobank; high process quality; LIMS integration

Funding statement: European Fond for Regional Development (EFRE) funded by the European Union (grant INZ-EFRE 1503).

Study of Health in Pomerania (SHIP) is part of the Community Medicine Research net (CMR) of the University of Greifswald, Germany, which is funded by the Federal Ministry of Education and Research (grants no. 01ZZ9603, 01ZZ0103 and 01ZZ0403), the Ministry of Cultural Affairs as well as the Social Ministry of the Federal State of Mecklenburg-West Pomerania.

German Centre for Cardiovascular Research (DZHK) funded by the Federal Ministry of Education and Research (grant 81Z7400173).

German Biobank Alliance (GBA) funded by the Federal Ministry of Education and Research (grant 01EY1705).

National Cohort (NAKO) funded by the Federal Ministry of Education and Research (grant 01ER1301/18).

(1) Bioresource Overview

Project description

The University Medicine Greifswald (UMG) comprises the Medical Faculty of the University of Greifswald and belongs to one of the oldest universities in Germany (founded 1456). The UMG ranks among the most attractive and best universities with respect to medical education in Germany [1]. Apart from teaching and state-of-the-art medical care (approximately 1,000 beds) the 21 clinics and 19 institutes also put a strong emphasis on research.

The Integrated Research Biobank (IRB) is acknowledged as a core unit of the UMG and therewith the central institution for the storage of biomaterial. It ensures highly standardized processes that include the consideration of ethical, legal and data protection regulations. The IRB is a member of the German Biobank Alliance

(GBA), consisting of 18 biobanks that aim to establish common quality standards, cross-linked IT and legal as well as ethical guidelines for biobanking. The biobanking resources are available for internal as well as for external researchers.

Having started in 1997 with numerous freezers, a fully automated biobank (LiCONiC AG, Mauren, Liechtenstein) was established in 2012. The IRB's storage capacity was enlarged with a second automated system in 2017. Currently, three million aliquots can be stored at -80°C . Sample collection, processing, storage and distribution including laboratory analyses within the Institute of Clinical Chemistry and Laboratory Medicine (IKCL) is done in a highly standardized way and include aspects of the DIN EN ISO 20387. Up to now, 1.1 million liquid aliquots are stored within the IRB.

The foundation of the IRB was laid by the long-lasting expertise of the UMG in population-based cohort and patient studies with numerous participants and patients repeatedly investigated, which started in 1997. The main UMG related projects include the population-based cohort Study of Health in Pomerania (SHIP), with the baseline examination conducted between 1997 and 2001 followed by four follow-up investigations [2, 3], and the Greifswald Approach to Individualized Medicine (GANI_MED) [4]. Within the implementation of the GANI_MED project, the founding of the IRB and the steps towards a core unit were initiated. The collected biomaterials have been analyzed both with established methods in the field of clinical chemistry and laboratory medicine and with advanced different OMICS techniques. Together with the obtained clinical data these laboratory analyses allow complex integrated investigations and provide the basis for translational research to deduce better and personalized preventive, diagnostic or therapeutic strategies.

Apart from the mentioned studies, the IRB is heavily involved in structuring the sample collection, storage and use of biomaterials collected within the framework of the German Centre for Cardiovascular Research (DZHK) with the lead in the clinical scientific infrastructure. Beyond biomaterial storage, the IRB is substantially involved in the design and realization of the biobanking concept of the German National Cohort (NAKO) [5], Germany's largest long-term population study [6].

A majority of the stored aliquots have been analyzed in the IKCL. The remaining aliquots were analyzed in other laboratories within Germany or abroad. The IRB is closely associated, not only spatially but also structurally, with the IKCL. The IKCL is the core laboratory, executing most of the UMG's clinical analyses in the fields of clinical chemistry, hematology, hemostaseology, pediatric laboratory, biochemistry, immunology, diagnostic of cerebrospinal fluids and metabolomics, the latter applying NMR-spectroscopy in addition to mass spectrometry. Each year, about two million analyses are performed related to patient's health care. Additionally, the institute performs about one million analyses every year for research purposes.

Classification (1)

Human, animal (on request)

Species

n/a

Classification (2)

Biological samples

Context

Spatial coverage

The IRB mainly stores aliquots from participants investigated within the framework of population-based cohorts and patients of the UMG. The majority of samples originate from subjects in the region of Mecklenburg-Western Pomerania. The IRB also acts as storage partner for other research institutions, e. g. it is involved in multicentre studies.

Northern boundary: 54°41'5.5"N 13°25'32.1"E

Southern boundary: 53°6'32.2"N 11°23'45.1"E

Eastern boundary: 53°19'49.2"E 14°24'41.8"E

Western boundary: 53°21'59.0"N 10°35'47.5"E

Temporal coverage

The IRB represents a biobanking resource that is available for internal as well as for external researchers for, in general, an unlimited period. The storage of study-specific biomaterial started in 1997, when the baseline examination of SHIP was initiated. The IRB itself was founded officially with the start of the GANI_MED project in 2012. Both mentioned studies are ongoing. Collections for DZHK started in 2015 and for NAKO in 2014. Both studies are ongoing as well. Additionally, other internal and external studies are included continuously.

Temporal coverage for accessibility

Aliquots that are stored in the IRB are fully under the regulations of the corresponding studies for an unlimited period. In case of a consent withdrawal, all aliquots of the participant are destroyed in accordance to the study's regulations. The destruction is done and documented in accordance to IRB SOPs.

(2) Methods

As described above, the IRB is very closely linked with the IKCL, which is the core laboratory of the UMG for both in- and outpatients. Therefore, the arrival of study or patient biomaterial designated for biobank storage is also closely linked and integrated into the IKCL and its highly standardized fully automated laboratory workflows. All study samples are accompanied with a machine-readable study specific request form or electronically, allowing sample tracking procedures with all relevant key steps being documented via laboratory information system (LIS) documentation. Time stamps beginning from sample collection time, arrival in the IKCL as well as centrifugation time and freezing time are being provided and saved in the IRB aliquots management software.

Steps

Sample collection and obtaining the informed consent

The collection procedures depend on the corresponding study. The IRB is involved in the definition of sample collection procedures, selection of biomaterials and workflows to receive the biosamples in adequate time lines.

With respect to the UMG-related population-based studies such as SHIP and NAKO, subjects from the region are randomly selected and invited to attend. During their visit in the examination centre, multiple biomaterial samples such as blood, urine, saliva or swabs are collected and informed consent is obtained. All steps of the material and data collections are based on Standard Operating Procedures and done by certified staff. The informed consent is stored separately from the biomaterial and most importantly not in the IRB but in the transfer unit (TU, for details please see *Access criteria*), which is an essential partner in the Use and Access procedure for SHIP and GANI_MED samples as displayed

in **Figure 1**. Such study samples are accompanied with a study-specific request form and barcodes for the primary blood collection tubes ensuring a secured assignment of samples to each participant and allowing a fully integrated and automated sample and aliquot processing in the IKCL, once the samples arrive in the IKCL/IRB.

For studies with in- or outpatient participants within the UMG like GANI_MED the consent is obtained and documented in the hospital information system (HIS). The biomaterials relevant for clinical studies are generally sent together with the samples from patient care to the core laboratory of the IKCL. Depending on the study design, the primary blood collection tubes are either assigned separately for current laboratory analysis and biobanking or biobanking is done out of specified materials.

For external studies, the study principal investigators (PI) are requested to present an approved study protocol and/or positive ethics committee recommendation as well as the informed consent before the aliquots can be stored at the IRB. The informed consents are again stored separately from the biomaterial.

Workflow for liquid biomaterial

Cohort as well as clinical study samples and aliquots are all labelled with 1D or 2D codes and information is accompanied by a study-specific request form or electronically. These samples are delivered either via a pneumatic tube system or by courier within the UMG. All samples, independent of the kind of study, are registered once they arrive in the IKCL, ensuring a comprehensive time monitoring until final storage. Centrifugation of the samples is performed directly after the arrival in the IKCL and is completely integrated in the core laboratory's processes. After centrifugation study samples are transferred to the research laboratory of the IKCL. All further processing steps are performed there. Aliquoting of liquid samples is processed automatically by a pipetting robot.

The IRB is also located directly next to the research laboratory ensuring short distances between processing and final storage at -80°C . Storage usually takes place using 2D coded cryo tubes. However, some aliquots are additionally labelled with self-printed 1D barcodes for supplementary aliquot verification [8]. The fully automated (LiCONiC) as well as conventional (-80°C freezer) storage is integrated in the biobank laboratory information and management system.

Stabilization/preservation

Different studies send samples for processing and storage in the IRB. Therefore, we offer the service to handle and process a wide spectrum of primary tube containers and stabilization types:

- BD vacutainer, Sarstedt container as well as Greiner, Kabe etc.
- Additives: EDTA, Lithium Heparin, citrate and others

Type of long-term preservation

The number of processed aliquots can vary between the studies. The final number of aliquots and the used cryo tube volume is discussed and defined with the PI of

the respective study on the basis of the planned future research activity and plans for the samples. The majority of aliquots is stored in 0.5ml working volume tubes (external thread, 2D code on the bottom) in 96 well SBS racks (Brooks Life Sciences (formerly FluidX), Manchester, UK). As mentioned in the section 'workflow for liquid biomaterial', a self-printed 1D barcode is used in many cases as an additional label for several types of cryo tubes. On this barcode, further information concerning the respective study, type of material and ID is documented, which is fully compatible with the laboratory information system of the IKCL. This forms the basis for the automated analyses of the aliquots [8].

Storage temperature

Aliquots are usually stored at -80°C in one of the two fully automated LiCONiC biorepositories or, if necessary, in one of the -80°C freezers. The two LiCONiC biorepositories as well as all freezers are connected with a centralized temperature surveillance center ensuring a 24/7 temperature monitoring. A failure action SOP exists and is practiced regularly with all IRB and IKCL employees.

Shipping temperature from patient/source to preservation or research use

In general, the shipping temperature is room temperature ($18-25^{\circ}\text{C}$) for studies conducted at the UMG and with short processing times to freeze. For specific requirements and for example external studies aliquots are shipped, for instance, on dry ice.

Shipping temperature from storage to research use -80°C (on dry ice, if requested with a temperature logger).

Quality assurance measures

The IKCL and the IRB have successfully completed the EFQM assessment and were awarded the "Recognized for Excellence – 4 stars". A process orientated quality management system is well established in all laboratory and biobank areas. All used methods and processes are in line with the Rili-BAEK and include aspects of the DIN EN ISO 20387.

The quality assurance for sample-related clinical phenotype data is the responsibility of the corresponding study.

Source of associated data

The only data associated together with the samples, which is held by the IRB, is the study affiliation, study ID and number of aliquots, and, in many cases, gender and age. Other accompanying clinical data are available at the study coordination centre or in case of SHIP and GANI_MED in the TU (for details please see *Access criteria*). In case of external and smaller clinical studies, researchers have to contact the corresponding study centre or PI to get access to the aliquots as well as potential data.

Ethics Statement

A clinic wide broad consent does currently not exist. All local studies (e.g. clinical or epidemiological cohort studies) present their study design to the UMG ethics

committee. External studies need to present an existing and approved study protocol and/or a positive ethics committee recommendation before any aliquots are being stored in the IRB.

The studies are responsible for the informed consent and the subsequent use of the biomaterial (see *Sample collection and obtaining the informed consent*). In case of the SHIP and GANI_MED project, the participants are informed that their biomaterial can be used for analyses related to relevant research questions worldwide after a positive vote of the research board of the Community Medicine Greifswald (see *Access criteria*).

Constraints

n/a

(3) Bioresource description

Object name

Collection of liquid biomaterial of mainly epidemiological cohort and clinical studies of local and external collections/origin.

Bioresource name

Integrated Research Biobank
IRB

Bioresource location

Integrated Research Biobank (IRB)
University Medicine Greifswald
Ferdinand Sauerbruch Str.
17475 Greifswald
Germany

Bioresource contact

studylab@med.uni-greifswald.de

Bioresource URL

www.biobank-greifswald.de

Identifier used

n/a

Bioresource type

The IRB is a centralized clinical biobank (core unit of UMG) with a collection focus on epidemiological cohort and clinical studies. The clinical studies mainly focus on “cardiovascular diseases”, “infection and inflammation” and “abdominal and metabolic diseases”.

Type of sampling

Currently stored aliquots are collected within longitudinal cohort studies as well as clinical studies.

Anatomical site

n/a

Disease status of patients/source

The UMG is a maximum care hospital and a higher education institution. All kinds of diseases in all degrees are treated at the UMG.

Clinical characteristics of patients/source

No constraints

Vital state of patients/source

Alive

Clinical diagnosis of patients/source

Clinical studies focus mainly on “cardiovascular diseases”, “infection and inflammation” and “abdominal and metabolic diseases”.

Pathology diagnosis

n/a

Control samples

Samples for quality controls are within the biorepository. Many of the participants of the population-based epidemiological studies are suited to be age matched controls for patients with specific diseases.

Biospecimen type

Whole blood (DNA, RNA), plasma (EDTA, lithium heparin, citrate), urine, buffy coat, cerebrospinal fluids, saliva, throat swabs, periodontal pockets swabs, dried blood spots, RNA later stabilized feces.

Size of the bioresource

The IRB employs six persons (full and part time). Up to now, the IRB stores more than 1.1 million liquid aliquots. The collection grows continuously. Currently, the storage capacity of the IRB is limited to 3 million aliquots.

Release date

As a core unit of the UMG the IRB has been established permanently. Most stored aliquots are currently stored without a defined release date.

Access criteria

For clinical studies not related to SHIP and GANI_MED, all aliquots remain in the IRB until they are requested by their study PI or associated researchers. In the latter case the study PI must permit the aliquot transfer.

The biomaterials of UMG-related projects including SHIP and GANI_MED are provided to UMG's internal and external research partners all over the world in a standardized and transparent Use and Access procedure (U&A, see **Figure 1**). Biomaterial and associated data including clinical phenotypes are publicly available for scientific and quality control purposes by application at www.community-medicine.de.

In general, biosamples are provided together with clinical and demographic variables from the interview and study examinations and the research board Community Medicine (FVCM) regulates the access. In monthly meetings, the board of the community medicine network discusses all applications which can be submitted via the web page of the TU (fvcm.med.uni-greifswald.de):

- the applicant is asked to describe the research subject, the scientific background as well as the methods and planned analyses

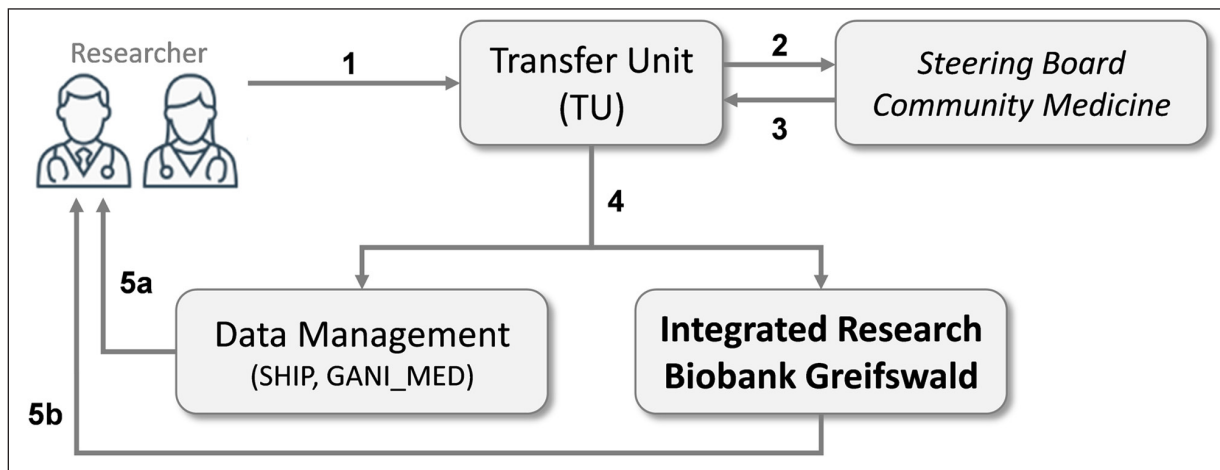


Figure 1: Simplified decision workflow for requests of SHIP or GANI_MED aliquots and/or data based on [7].

- the requested amount of material has to be specified in the application
- any additional variable (e.g. sex, age, blood pressure) needed for the research project can be selected from the same portal using the build-in data dictionary browser

The completed application [1] can be submitted to the TU which performs a basic plausibility check and [2] circulates the application within the steering board of the FVCM. For applications including biomaterial two reviewers are nominated by the speakers of the steering board. The reviewers are asked to assess the proposed analysis method as well as the requested amount of material. Based on the two reviews the steering board decides in a monthly meeting, whether the application is granted or needs to be revised. In case of a [3] positive decision from the steering board the TU prepares a data usage contract to be signed by the applicant and the head of the TU. After reception of the signed contract the TU gives clearance [4] for data [5a] and biomaterial [5b] transfer to the applicant. In case of a negative decision the applicant will be informed and specific reasons (e.g. imprecise research questions, missing variable selection) will be laid out and the applicant can re-submit the application after revision. The transfer of aliquots to the researcher is performed using a standardized Material Transfer Agreement (MTA).

(4) Reuse potential

The disclosure of samples is the responsibility of the respective study. Therefore, researchers have to contact the corresponding study centre or PI to get access to the samples as well as potential data. During the storing period the samples are under the ownership of the institution that conducted or organized the study. In general, the IRB will be contacted by the study PI if external researchers apply access to the samples. If researchers contact the IRB directly, we will forward their request to the PI of the corresponding study.

In case of SHIP or GANI_MED, aliquots are provided to a researcher for a specific research project. It is strictly prohibited to use these aliquots for other research purposes

or to pass these aliquots on to any “third party” researcher. Furthermore, all new data that are generated (e.g. new biomarkers) based on SHIP or GANI_MED aliquots must be forwarded to the study data management. These data will be entered in the study-specific database and will be available for other researchers in general after a two-year embargo period.

Since the IRB is part of the German Biobank Alliance, the aliquots are potentially accessible via the BBMRI Sample Locator, which can be reached under the following link: <https://samplelocator.bbMRI.de/> (currently this site is a developer version, but will remain at the same web address after its finalization).

Acknowledgements

The authors like to thank all staff that helped to build up the biorepository and the processes around this topic at the IKCL. In particular Markus Roser, former deputy of the head of IKCL, who introduced the LIS and structured the workflows within the laboratory, including the part of biobanking. Henri Wallaschofski, former deputy of the head of IKCL, assisted with the planning and implementation of the automatic biorepository as well as implementation and structuring processes around the sample preparation. Matthias Nauck (head of IKCL), Theresa Winter (head of IRB), Nele Friedrich (head of the IKCL’s research laboratory) and Astrid Petersmann (deputy of the head of IRB and IKCL, present affiliation: Institute of Clinical Chemistry, University Medicine Goettingen, Goettingen, Germany) currently supervise the biobank. Anke Hannemann, Kathrin Budde, Robin Haring, Sophia Lamp, Katja Riemann, Diana Brümmer, Carina Hojenski (scientific staff IKCL) support(ed) the implementation of processes around this topic. Christian Schäfer, Mario Schattschneider (both IT staff IKCL) and Stefan Bollmann (medical documentation specialist IKCL) support the IT-based workflows and documentation with their expertise. We also thank all technical assistants for their highly appreciated effort, especially Volker Hein, Hanka Zobel, Dolores Oldenburg and Katja Levin as well as Jutta Bruchnow, Anja Möller, Marie Nehrkorn, Juliane Doß and Laura Hamann.

We are grateful to Heyo Kroemer (former dean of the medical faculty of UMG), Henry Völzke (head of Unit SHIP-KEF of the Institute for Community Medicine, UMG) and Wolfgang Hoffmann (head of Institute for Community Medicine, UMG), who always supported the idea of a faculty biobank.

Competing Interests

The authors have no competing interests to declare.

Author Roles

Winter T: head of IRB, corresponding author

Friedrich N: head of IKCL research laboratory, drafting of the manuscript

Lamp S: scientific staff IKCL, drafting of the manuscript

Brümmer D, Riemann K: scientific staff IKCL, proofreading of the manuscript

Schäfer C, Schattschneider M: IT staff IKCL, proofreading of the manuscript

Bollmann S: medical documentation specialist IKCL, proofreading of the manuscript

Petersmann A: deputy of the head of the IRB and IKCL, proofreading of the manuscript

Nauck M: head of IKCL, revision of the manuscript

References

1. **Stiftung für Hochschulzulassung.** Daten der bundesweit zulassungsbeschränkten Studiengänge an Hochschulen, WS 2016/17 Dortmund: Stiftung für Hochschulzulassung; 2016 [cited 2019 August 23rd]. Available from: https://zv.hochschulstart.de/fileadmin/media/zv/nc/wise2016_17/bew_zv_ws16_17.pdf.
2. **Völzke H, Alte D, Schmidt CO, Radke D, Lorbeer R, Friedrich N,** et al. Cohort profile: the study of health in Pomerania. *Int J Epidemiol.* 2011; 40(2): 294–307. DOI: <https://doi.org/10.1093/ije/dyp394>
3. **John U, Greiner B, Hensel E, Lüdemann J, Piek M, Sauer S,** et al. Study of Health In Pomerania (SHIP): a health examination survey in an east German region: objectives and design. *Soz Präventivmed.* 2001; 46(3): 186–94. DOI: <https://doi.org/10.1007/BF01324255>
4. **Grabe HJ, Assel H, Bahls T, Dörr M, Endlich K, Endlich N,** et al. Cohort profile: Greifswald approach to individualized medicine (GANI_MED). *J Transl Med.* 2014; 12: 144. DOI: <https://doi.org/10.1186/1479-5876-12-144>
5. **Wichmann HE, Hörlein A, Ahrens W, Nauck M.** The biobank of the German National Cohort as a resource for epidemiologic research. *Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz.* 2016; 59(3): 351–60. DOI: <https://doi.org/10.1007/s00103-015-2305-4>
6. **German Centre for Cardiovascular Research (DZHK).** Flow chart application procedure use and access Berlin: German Centre for Cardiovascular Research (DZHK); 2018 [cited 2019 August 23rd]. Available from: https://dzhk.de/fileadmin/user_upload/Flow_Chart_DZHK_Use_and_Access_Policy.pdf.
7. **Universitätsmedizin Greifswald.** Zentrum für epidemiologische und klinische Studien – Datenmanagement, -integration, -transfer Greifswald; 2019 [cited 2019 August 23rd]. Available from: <https://www.medizin.uni-greifswald.de/de/forschung-lehre/core-units/zentrum-fuer-studien/>.
8. **Winter T, Schäfer C, Westphal S, Böttcher C, Lamp S, Wallaschofski H, Roser M, Petersmann A, Nauck M.** Integrated Biobanks facilitate high quality collection and analysis of liquid biomaterials. *J Lab Med.* 2019; (in press). DOI: <https://doi.org/10.1515/labmed-2019-0171>

How to cite this article: Winter T, Friedrich N, Lamp S, Schäfer C, Schattschneider M, Bollmann S, Brümmer D, Riemann K, Petersmann A, Nauck M. The Integrated Research Biobank of the University Medicine Greifswald. *Open Journal of Bioresources.* 2020; 7: 2. DOI: <https://doi.org/10.5334/ojb.64>

Published: 26 March 2020

Copyright: © 2020 The Author(s). This is an open-access article distributed under the terms of the Creative Commons Attribution 4.0 International License (CC-BY 4.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited. See <http://creativecommons.org/licenses/by/4.0/>.

