Biobanking
Lecture: Master Molecular Medicine

SS 2023

Jena, 5th June 2023

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Please contact me if you have any questions regarding this lecture:
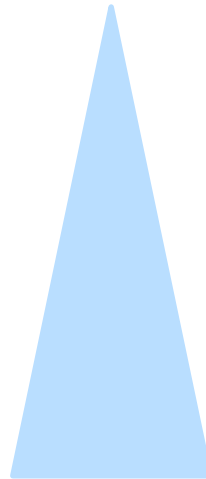
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Biobanking? – More than just a Freezer!

Biobanking is more than just storing samples in a freezer and getting them out for a measurement!

Storage Complexity

1 sample

100 samples

10000 samples
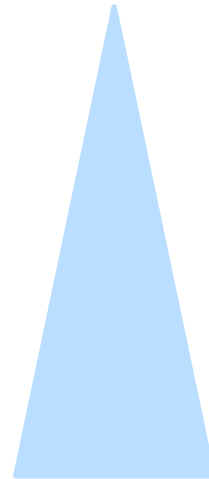
100000 samples

Complexity of storage

- Storage facilities

- Sample organization

- Data management

Biobanks offer professional sample storage and organization
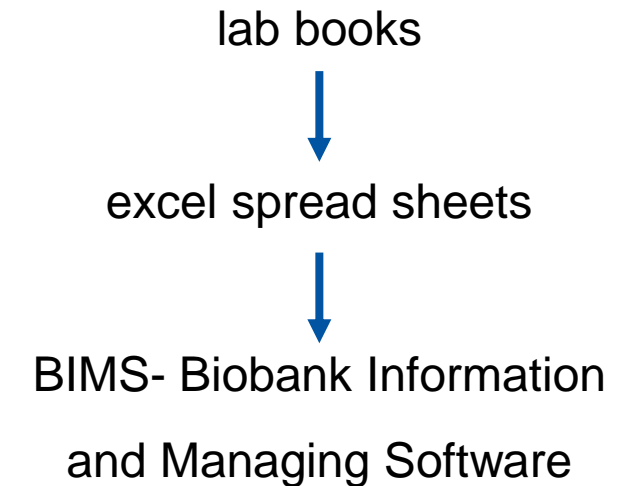
Data Handling Complexity

1 sample

100 samples

10000 samples

100000 samples

Complexity of storage

- Storage facilities

- Sample organization

- Data management

Professional data handling

lab books

↓

excel spread sheets

↓

BIMS- Biobank Information and Managing Software

Why Biobanking?

Guideline for quality- promoting aspects in medicine and biomedicine

Leitfaden für qualitätsfördernde Aspekte in der Medizin und Biomedizin

Erarbeitet von der Arbeitsgruppe „Qualität in der Klinischen Forschung" der Ständigen Senatskommission für Grundsatzfragen in der Klinischen Forschung der DFG

Published June 2021

https://www.dfg.de/foerderung/info_wissenschaft/2021/info_wissenschaft_21_54/index.html

Key Tasks for Biological Samples from Biobanks

Biomaterials from Biobanks should „reflect the biological or biochemical state of the donors at the time of sampling".
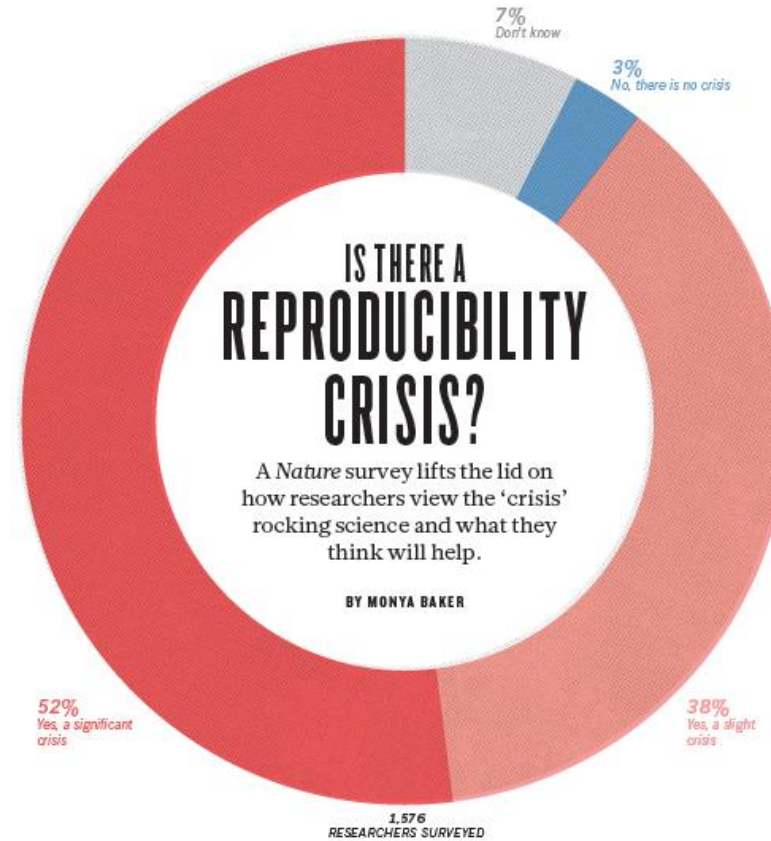
- Even after long term storage

Sample integrity plays a major role for downstream analysis!

But:

**There are multiple process- associated risks for biological samples endangering sample integrity!**

Gislefoss et al., Clin Biochem., 2014

Why Biobanking?

**Biobanks help storing samples
at optimal conditions**

7%
Don't know

3%
No, there is no crisis

IS THERE A
REPRODUCIBILITY
CRISIS?

A *Nature* survey lifts the lid on
how researchers view the 'crisis'
rocking science and what they
think will help.

BY MONYA BAKER

52%
Yes, a significant
crisis

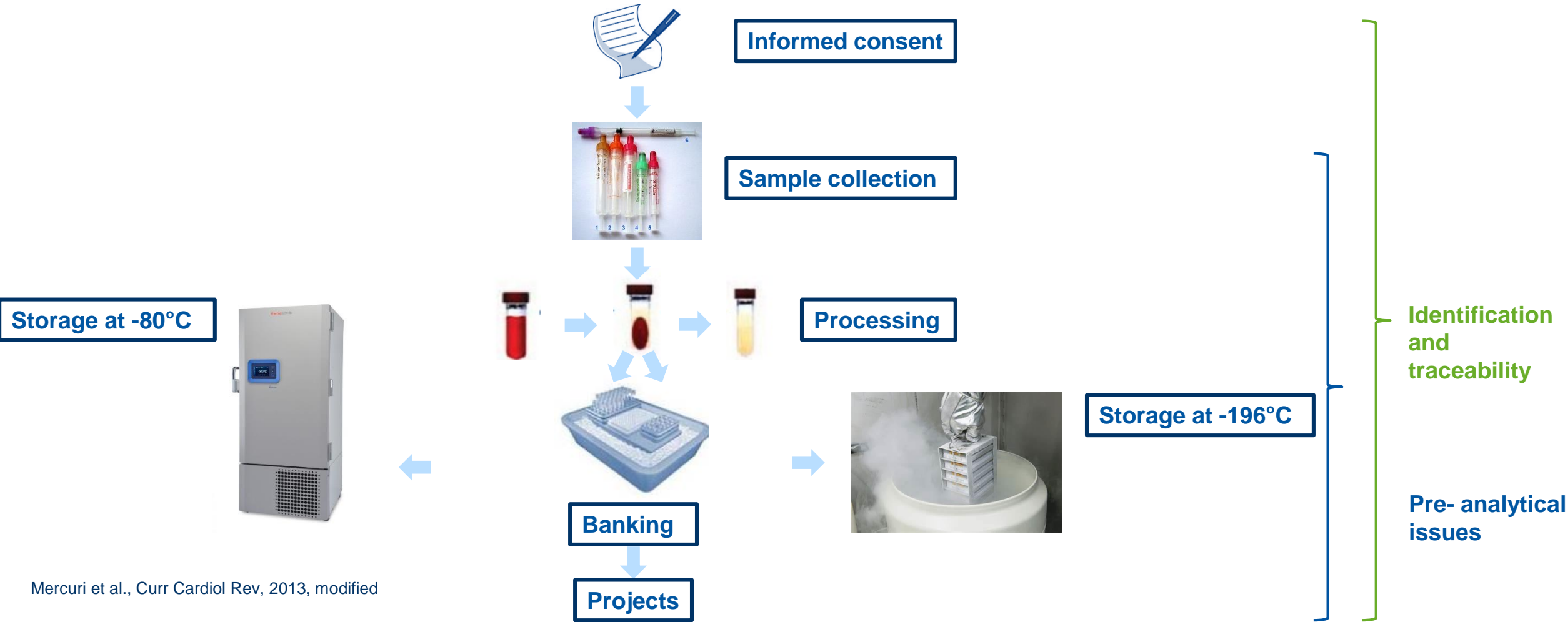38%
Yes, a slight
crisis

1,576
RESEARCHERS SURVEYED

Nature (Vol.533, Issue 7604., May 2016)

Estimated US Preclinical Research Spend and Categories of Errors that Contribute to Irreproducibility
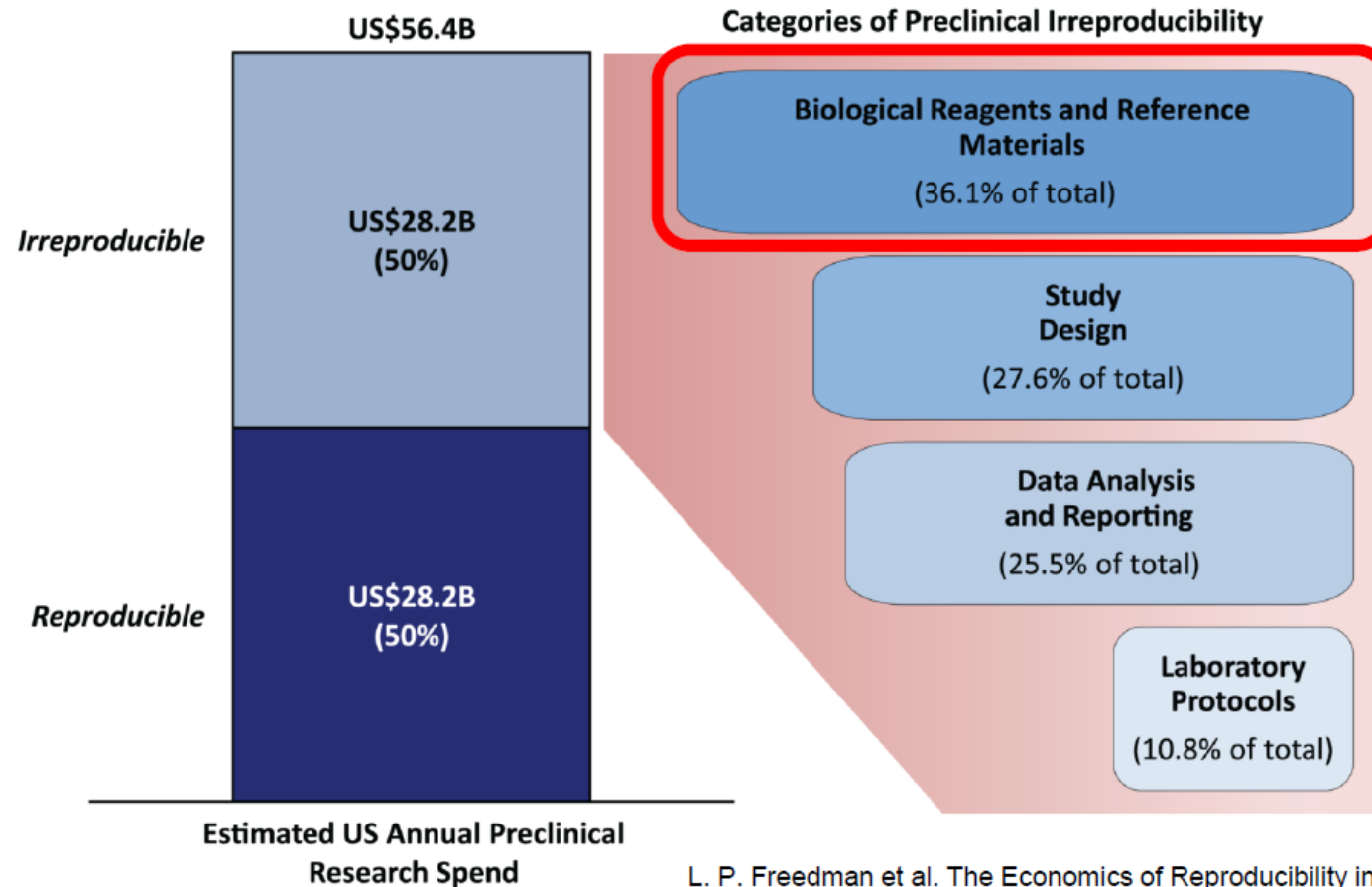
L. P. Freedman et al. The Economics of Reproducibility in Preclinical Research, *PLoS Biol* **13**, e1002165–9 (2015)

Process- associated Risks for Biological Samples- Overview

Informed consent

Sample collection

Processing

Storage at -80°C

Storage at -196°C

Banking

Projects

Identification and traceability

Pre- analytical issues

Mercuri et al., Curr Cardiol Rev, 2013, modified

Pre- analytical Issues

Preanalytical phase

Biological/ environmental factors

Time of day/ Season	**Coffee**	**Alcohol**	**Weight**	**Smoking**	**Medicine**	**Sunlight**

Technical factors
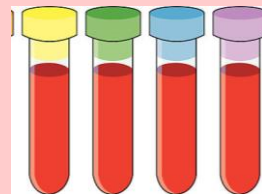
Collection	**Processing**	**Transport**	**Storage**	**High risk for sample integrity**
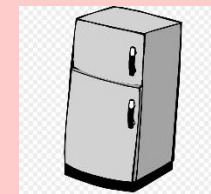
Analytical phase

Postanalytical phase

Ellervik & Vaught, Clin Chem, 2015, modified

Pre- analytical Problem- Processing

An MS-based metabolomics profiling on human EDTA plasma samples revealed that a high number of metabolites was significantly increased or decreased by preanalytical variation during blood and plasma processing

Short-term storage of blood either at room temperature or cooled on wet ice, hemolysis, and short-term storage of plasma for 5 or 16 h at room temperature resulted in statistically significant changes (4% to 19% of metabolites increased and 8% to 12% of metabolites decreased) of the human EDTA plasma metabolites.


Table 1. Number and percentage of statistically significant metabolite changes after applying defined preanalytical confounders out of 267 metabolites for the blood and 262 metabolites for the plasma processing experiment.[a]

Material	Preanalytical variable applied	Significantly changed metabolites (increase/decrease)[b]	
		Number	Percent change
Blood	Microclotting	31 (3/28)	12 (1/10)[c]
	Room temperature, 2 h	59 (27/32)	22 (10/12)
	Wet ice, 2 h	44 (12/32)	16 (4/12)
	Wet ice, 6 h	46 (17/29)	17 (6/11)
	Hemolysis, grade 1	47 (15/32)	18 (6/12)
	Hemolysis, grade 2	81 (50/31)	30 (19/12)[c]
	Contamination with buffy layer, grade 1	0 (0/0)	0 (0/0)
	Contamination with buffy layer, grade 2	8 (8/0)	3 (3/0)
EDTA plasma	4 °C, 0.5 h	0 (0/0)	0 (0/0)
	4 °C, 2 h	7 (7/0)	3 (3/0)
	4 °C, 5 h	16 (12/4)	6 (5/2)[c]
	4 °C, 16 h	30 (24/6)	11 (9/2)
	12 °C, 0.5 h	1 (1/0)	0 (0/0)
	12 °C, 2 h	7 (7/0)	3 (3/0)
	12 °C, 5 h	14 (11/3)	5 (4/1)
	12 °C, 16 h	37 (29/8)	14 (11/3)
	Room temperature, 0.5 h	4 (4/0)	2 (2/0)
	Room temperature, 2 h	28 (25/3)	11 (10/1)
	Room temperature, 5 h	47 (27/20)	18 (10/8)
	Room temperature, 16 h	61 (41/20)	23 (16/8)[c]

[a] Statistical analysis was done via ANOVA, the significance level was set to $P < 0.05$ and FDR < 0.2. Details are given in online Supplemental Tables 1 and 2.
[b] Including free hemoglobin.
[c] All 3 percentages are rounded to an integer, so the values in brackets do not necessarily add up to the total.
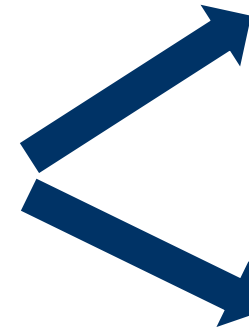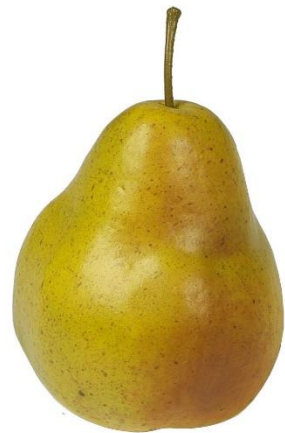
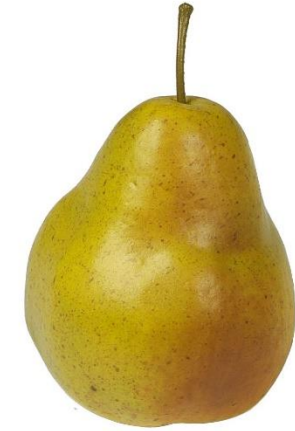Kamlage et al., Clin Chem, 2014

Pre- analytical Problem
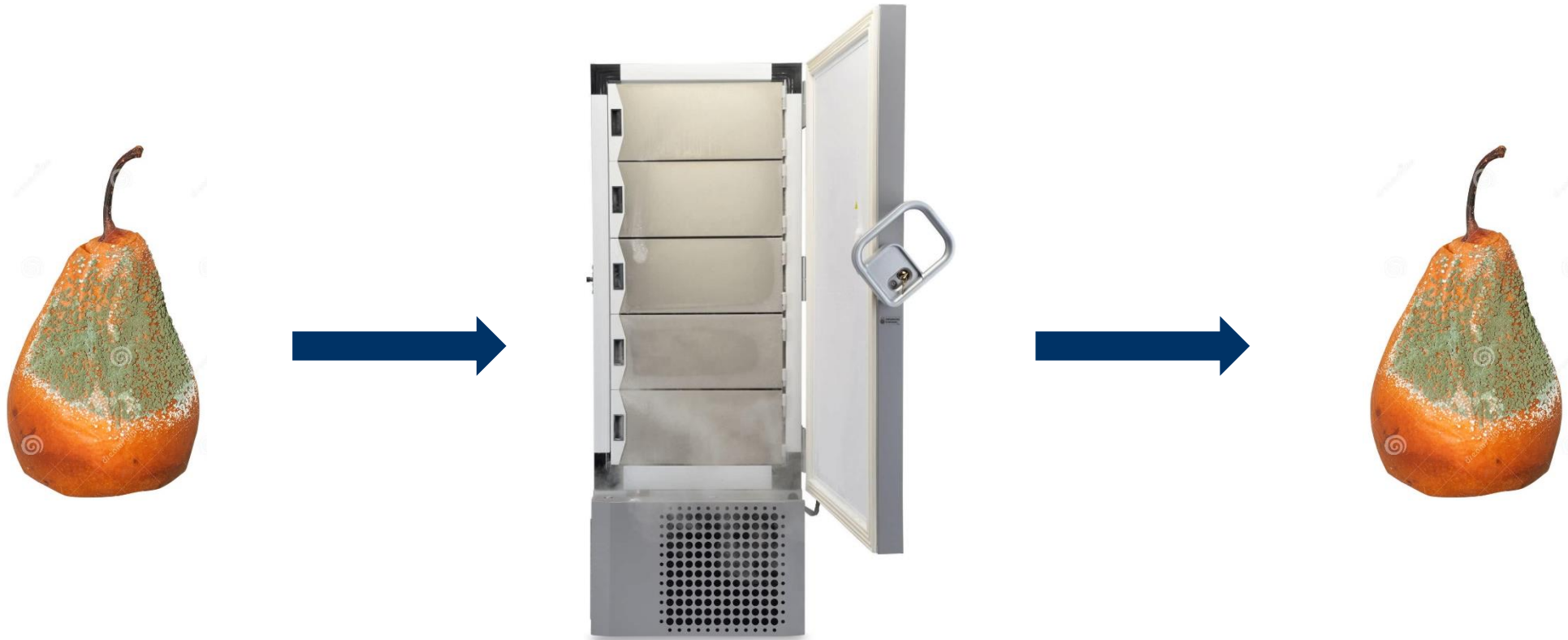
Pre- analytical Problem- Storage

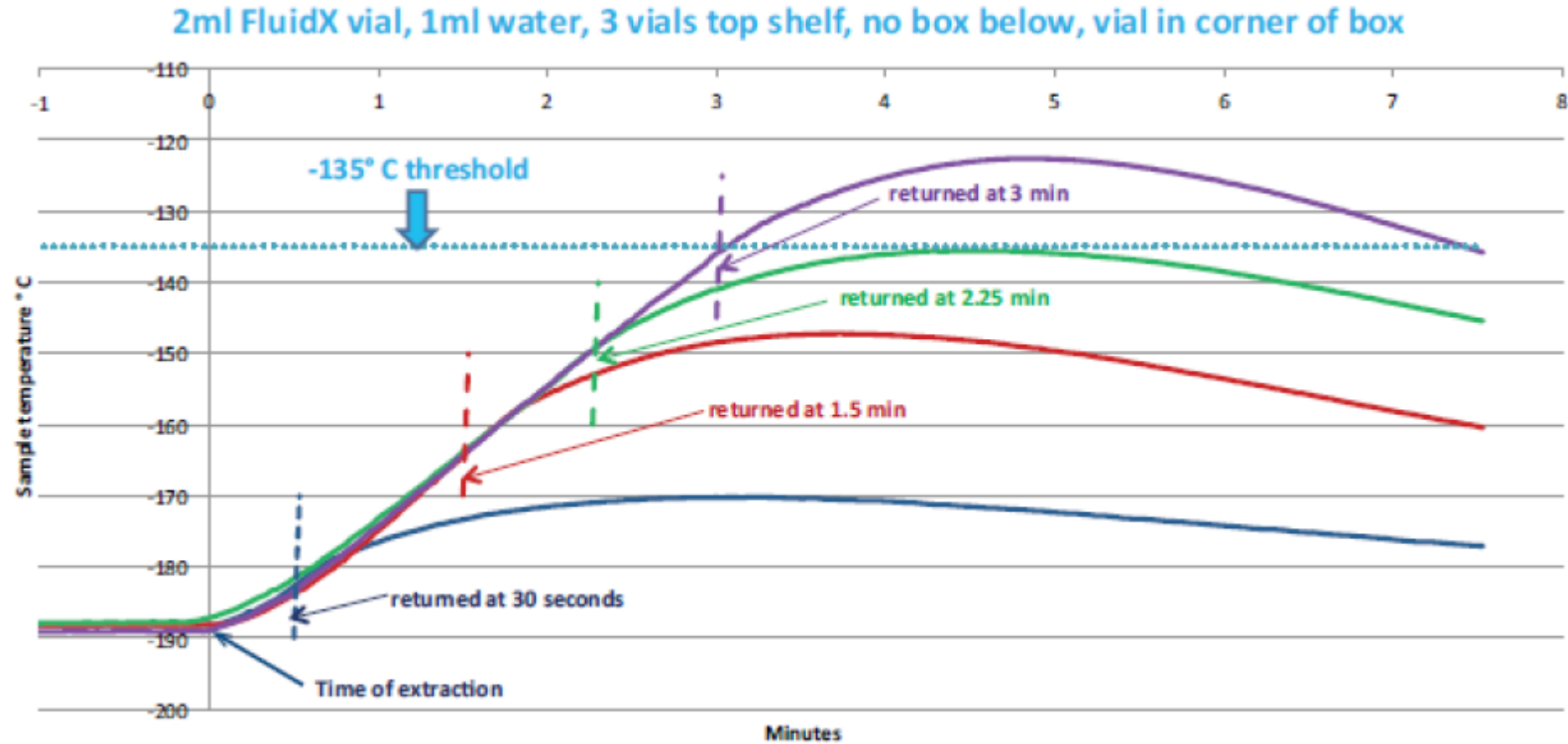**Problem: Storage is a kind of a black box for sample quality**
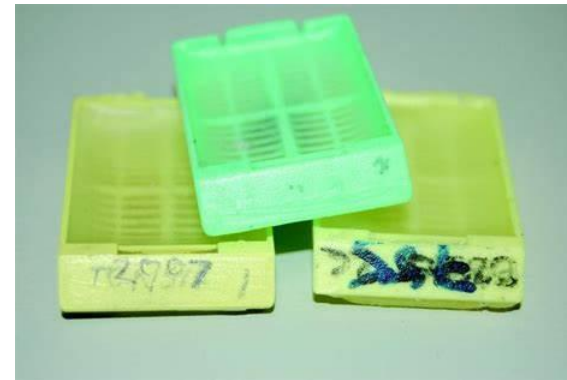

best case

worst case
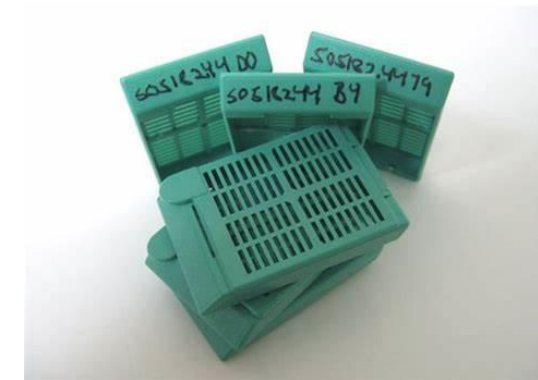
Pre-analytical Problem-Storage

Warhurst et al., Conference Paper *in* Cytotherapy, 2015

Identification and Traceability

Identification of samples- Problems arising from today's archives

Identification of labels!

Poorly labeled samples will lead to confusion and possibly misidentification.

Ambiguous cassette labels „S05", „50S", „505", „SOS"?

Identification of Samples

- Identification of samples is one of the key points in biobanking!

- It allows sample tracking and connection to sample and donor specific data.

- If a sample looses its identifier it is nearly impossible to save it.

- This has to be prevented as lots of work and money is needed to biobank samples!

- Also data protection plays an important role!

- Don't use donor identifying codes (names, adress)

Identification of Samples- Examples from the IBBJ

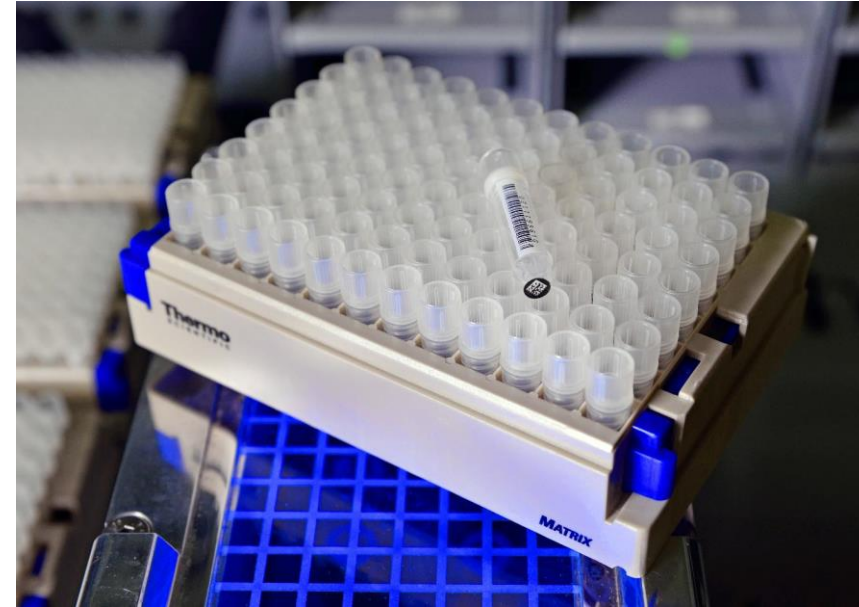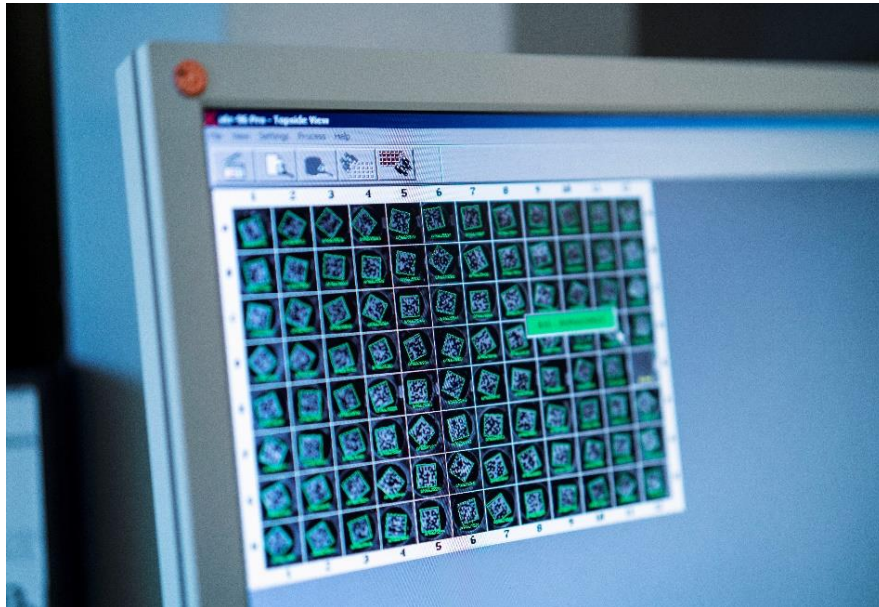Barcode and human readable label (optional)

Data matrix code

Barcoded rack showing data matrix orientation code on underside

Identification of Samples- Examples from the IBBJ

Key to efficient sample management is automatisation:
All tubes (samples) are tracked by barcode scanning

- Standardized racks with tubes on a barcode scanner
- Scan position of tube on rack and storage in central data base
- Automated cryo storage: Cherry picking of single tubes and output

Requirements for Automatisation

- Automated tube handling

- Tubes must be made for automatisation (opening/ closing)

- As much standardisation as possible

- Barcode identification

- Sample ID is automatically read out by a scanner and is stored together with the sample position in the managing software

Automated Biobank Work Flow

Fully automated blood fractionation

Plasma Fraction

Buffy Coat

Reference

RBCs

a. Fraction analysis
b. Aliquoting in 2D- coded target tubes without cap
c. Capping target tubes
d. Transport in -20°C freezing unit for short term storage
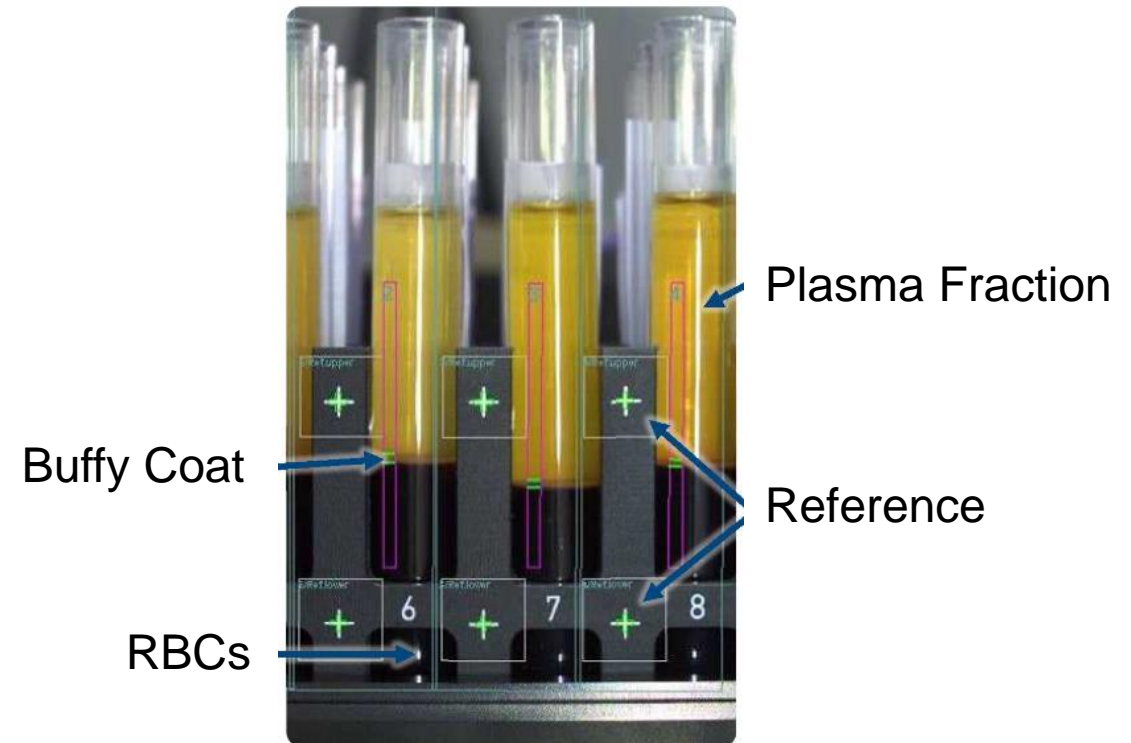
Traceability- Automated Storage Systems

IBBJ 2.0: Automated -80°C Storage for 1.5 Mio tubes

Traceability- Automated Storage Systems

Running aliquoted samples into the automated storage

Cap/ Decap tubes

Aliquot samples

Traceability- Automated Storage Systems

IBBJ: Perspectives 2023

- Implementation of a fully automated cryostorage
  system for storage of
  > 360.000 vials at -150°C N_2 vapor phase for
  newly founded **Leibniz Center**
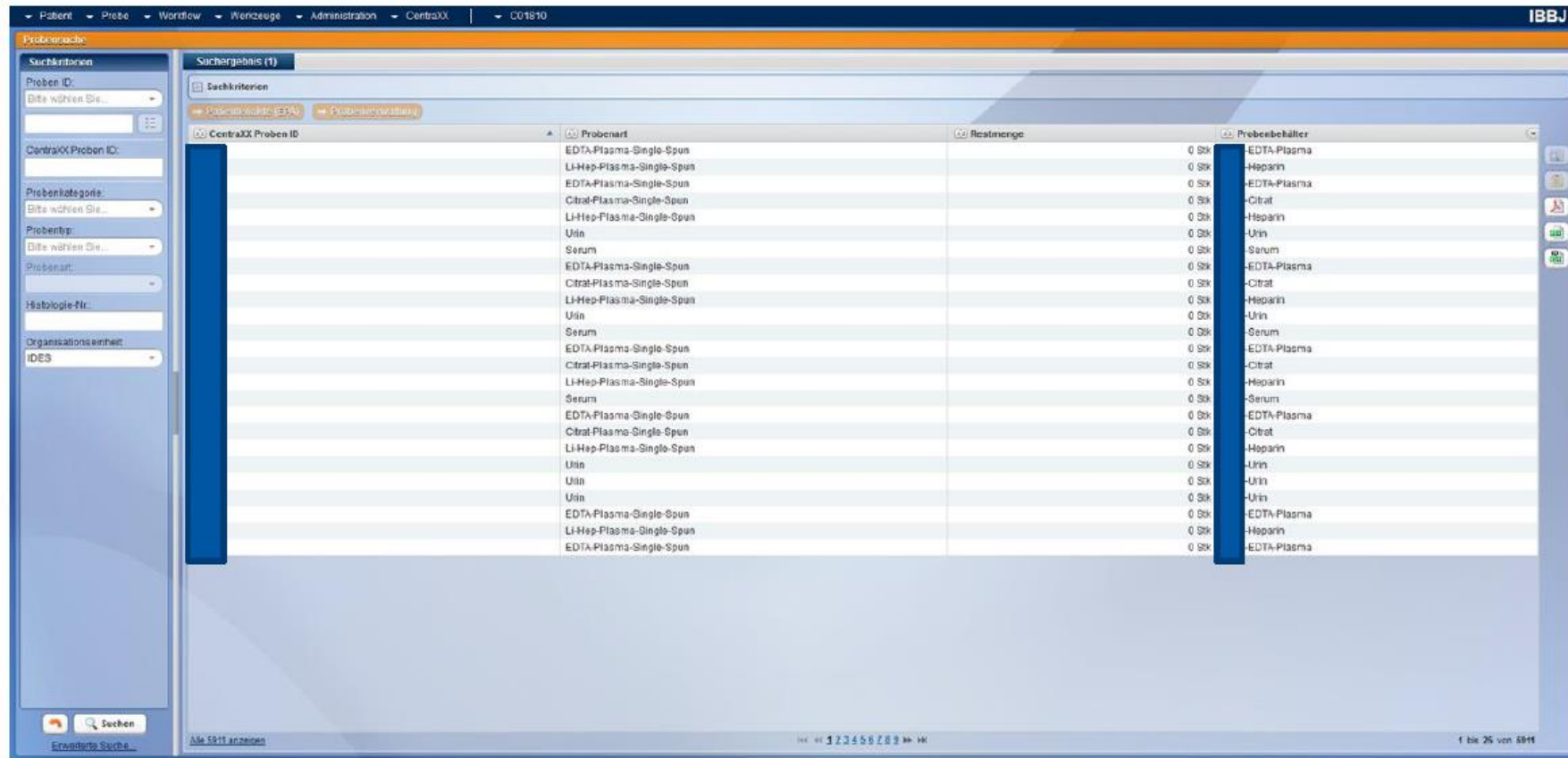 *for* **Photonics** *in* **Infection Research (LPI)**

The IBBJ BIMS *CentraXX*

The Biobanking Information and Management System (BIMS) is especially designed for sampling data handling

The IBBJ BIMS *CentraXX*

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The IBBJ BIMS *CentraXX*

All processes from sample arrival to aliquotation, storage and shipping are documented

Data is automatically updated when a sample barcode is scanned

The database can be searched for:

- Sample category

- Sample name

- Storage place

- Associated study

- Every other data attached to the sample

✓ For every sample infomation about the aliquotation status and the remaining number of aliquots is available

✓ Detailed history for the sample including its former storage places is available

Data Protection

Peter Meyer

Date of birth 12.05.1965, Address Jena, Sample ID 125656, Diagnosis
  Diabetes II, ... Freezer 3 Box 37.

Accumulation of data is convenient but not always legal!

Need for Data Protection

Peter Meyer

Date of birth 12.05.1965, Address Jena, Sample ID 125656, Diagnosis Diabetes II, ... Freezer 3 Box 37.

Examples of types of data:

- **MDTA:** medical or research data

- **OrgDat:** place of storage, freezing date

- **ProbDat:** sample data: results of assays, measurements

- **IDAT:** patient identifying data (name, health insurance number)

❖ It is not allowed to store IDAT in the Biobank

❖ Every employee should always only see the data he needs to know

❖ Pseudonymisation of samples: no sample is stored under patients name but a sample number.

MDTA: Material and Data Transfer Agreement

Every time someone requests sampes from the biobank a MDTA is needed to:

- Ensure that the recipient complies to data protection laws

- Specify the allowed usage of the material (an ethics committees vote is always needed)

- Agree on the usage of produced data (publication, patents)

- ...

The IBBJ

IBBJ

… is part of the research infrastructure of the University Hospital Jena.

Its mission is to support medical research through the quality-assured, standardized and fiduciary collection, storage and provision of liquid and non-liquid high-quality biomaterials and corresponding clinical context data.

Biobank Competence Network Sepsis

Biobank Centre for Innovation Competence (ZIK) Septomics

Biobank Center for Sepsis Control and Care

The Integrated Biobank Jena (IBBJ)- Expansion to the UKJ Biobank Infrastructure

Sample Numbers and Capacities*

Liconic: 1.5 Mio*
UTKs 21 = 1.88 Mio*
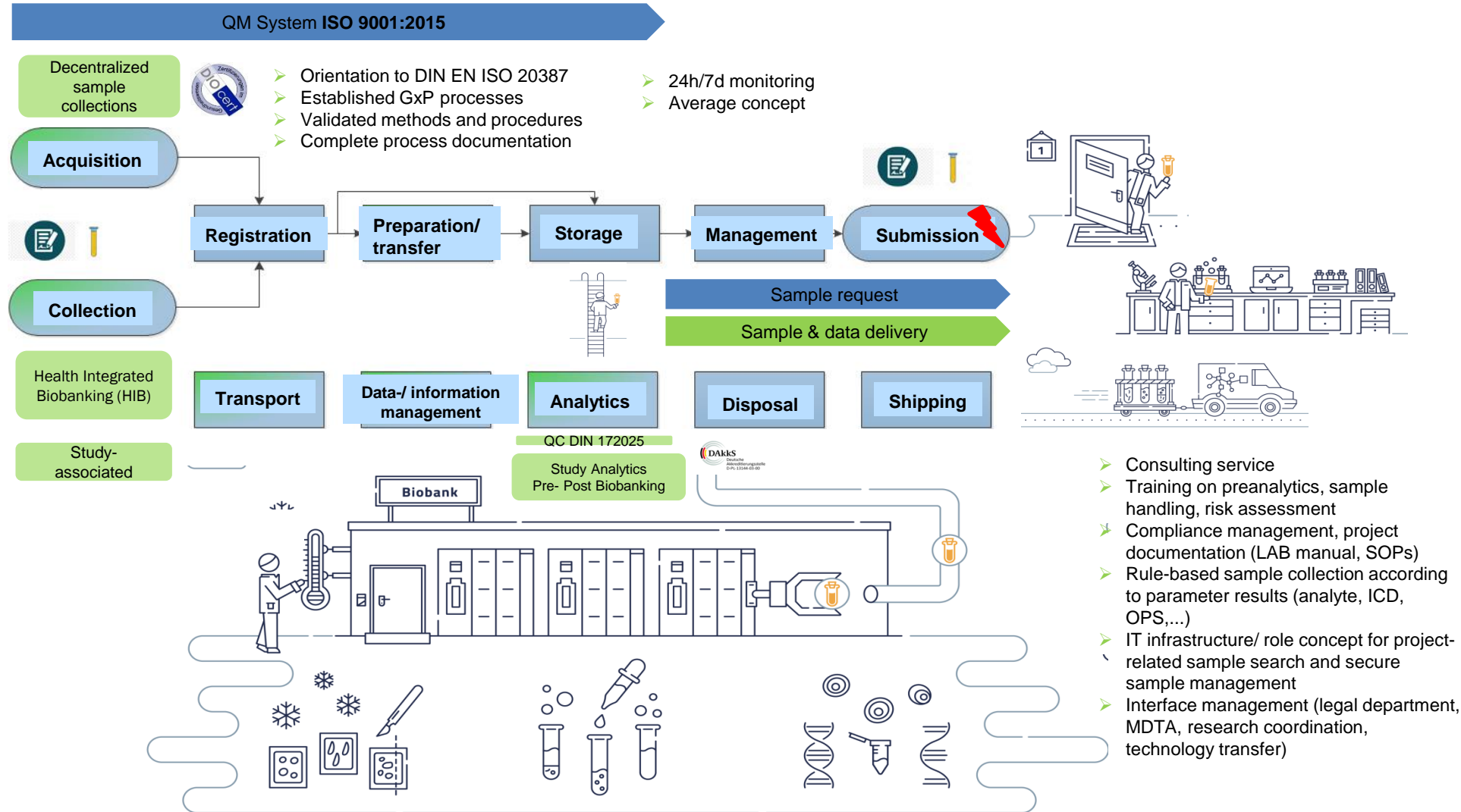**LN$_2$ 8 = 0.55 Mio***
ASKION = 0.38 Mio*

* 500 µL Tubes
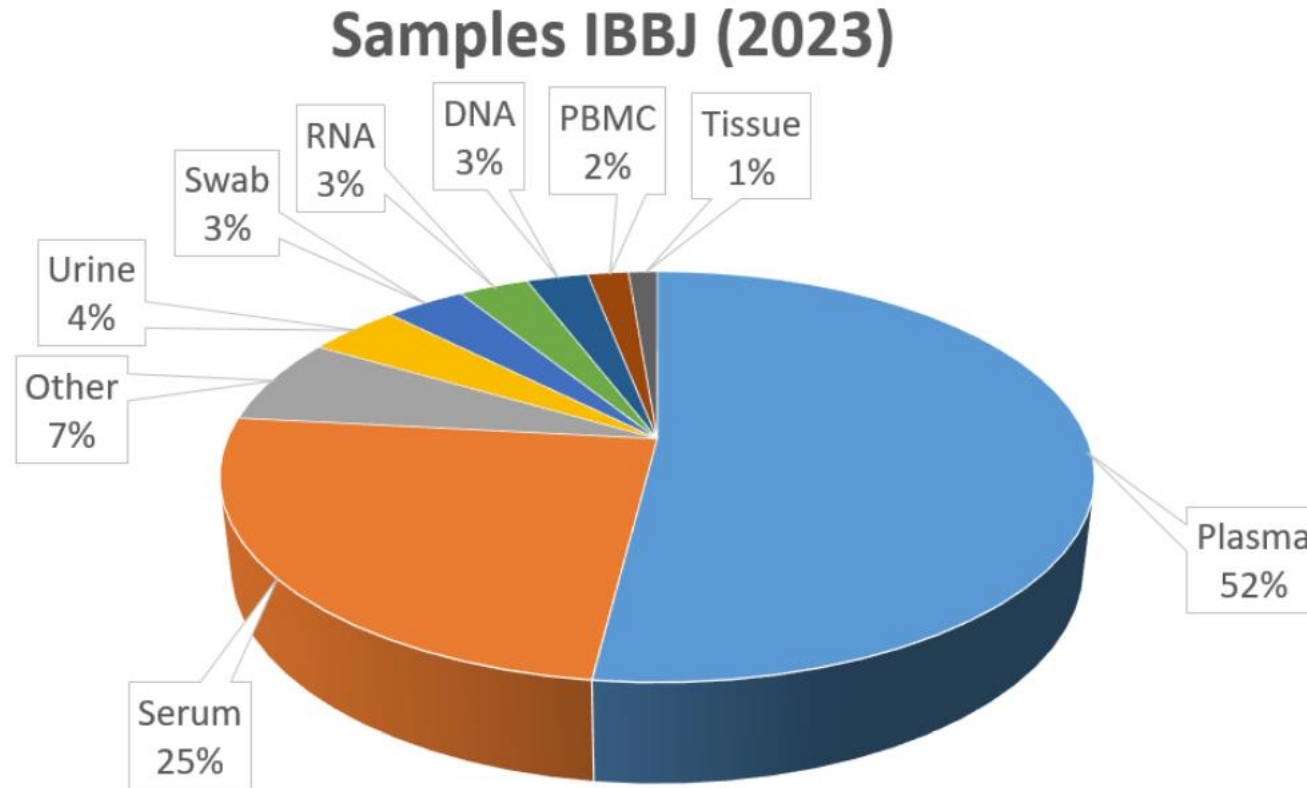
91 collections

Total sample size: 860.000

Samples IBBJ (2023)

- Plasma 52%
- Serum 25%
- Other 7%
- Urine 4%
- Swab 3%
- RNA 3%
- DNA 3%
- PBMC 2%
- Tissue 1%

Core Services

The IBBJ:

➢ It is partner for the conduction of studies and collections

➢ It is being run by a Steering Committee and sample access will be organised via a Use and Access Committee

QM System **ISO 9001:2015**

Decentralized sample collections

- ➤ Orientation to DIN EN ISO 20387
- ➤ Established GxP processes
- ➤ Validated methods and procedures
- ➤ Complete process documentation

- ➤ 24h/7d monitoring
- ➤ Average concept

Acquisition

Collection

Health Integrated Biobanking (HIB)

Study-associated

Registration → Preparation/transfer → Storage → Management → Submission

Sample request

Sample & data delivery

Transport | Data-/ information management | Analytics | Disposal | Shipping

QC DIN 172025

Study Analytics Pre- Post Biobanking

Biobank

- ➤ Consulting service
- ➤ Training on preanalytics, sample handling, risk assessment
- ➤ Compliance management, project documentation (LAB manual, SOPs)
- ➤ Rule-based sample collection according to parameter results (analyte, ICD, OPS,...)
- ➤ IT infrastructure/ role concept for project-related sample search and secure sample management
- ➤ Interface management (legal department, MDTA, research coordination, technology transfer)

Summary

- Biobanked samples are important for clinical research and medical progress

- Sample integrity plays a major role for downstream analysis and data interpretation as time point of sampling is linked to data acquisition

- Sample integrity can be impaired by an interplay of pre- analytical factors and loss of identification and traceability

- How to solve the pre- analytical problem:

- ❖ Standardized working with standard operating procedures

- ❖ High grade of automation

- ❖ Documentation of processing times and all deviations from protocol

Further Information

German Biobanks are organised in the
German Biobank Alliance (GBA)
and part of the European Network
BBMRI-ERIC
ABIDE

These Biobanks offer a centralised
sample search and aim for a harmonization and
standardization of biobanking processes and protocols.
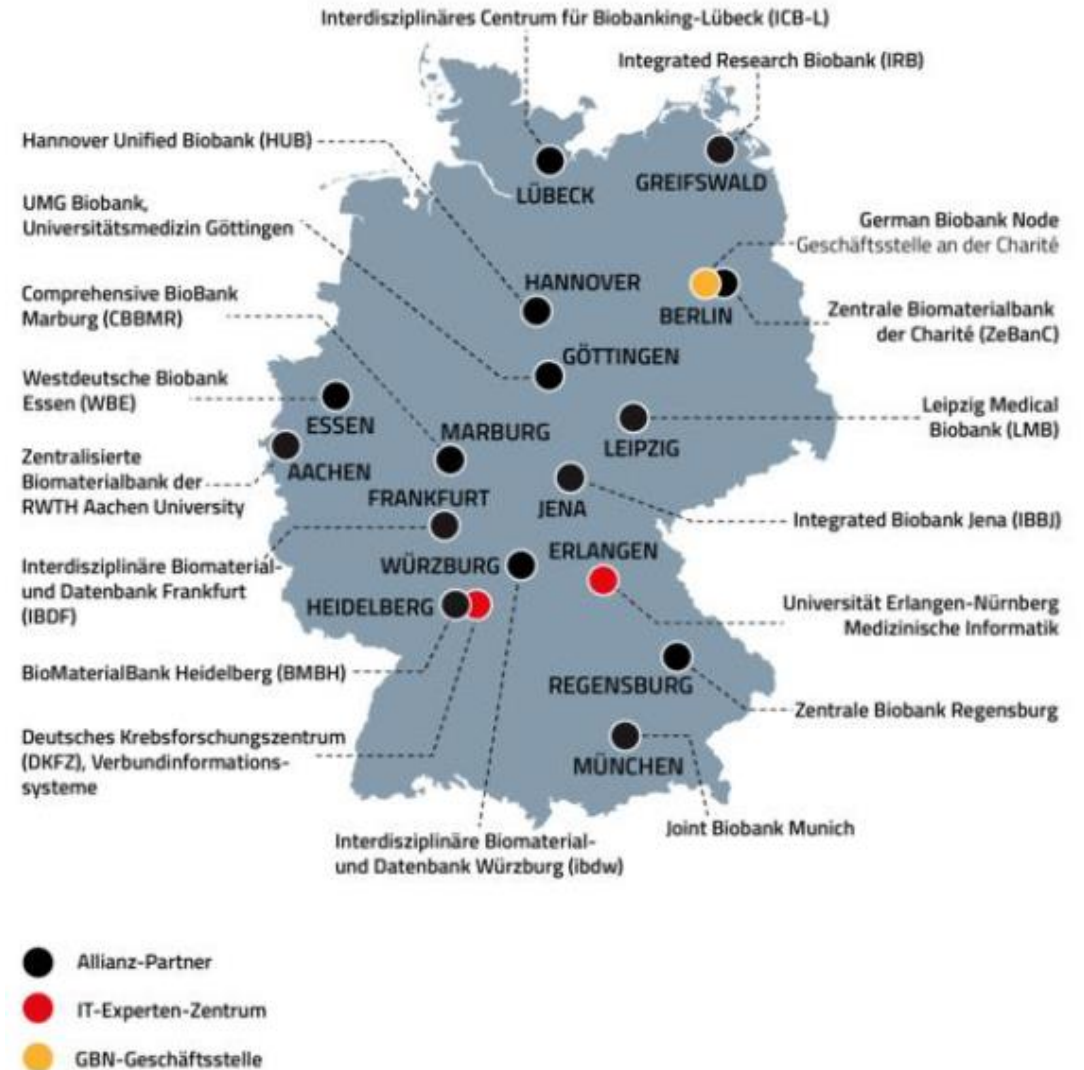
Biobanking offers access to samples to other researchers

- Biobanking enhances the visibility of sample collections by displaying them on their websites and national or international sample search sites like the BBMRI-ERIC Directory: https://directory.bbmri-eric.eu/menu/main/app-molgenis-app-biobank-explorer/biobankexplorer

- Using preexisting sample collections can be more cost effective and much faster than setting up your own collection. In addition, it reduces the overall amount of samples obtained from patients.

Movies and Links to some large Biobanks

Movie about Biobanks produced by the German Biobank Alliance

 (showcasing the ZeBank at the Charité)

https://youtu.be/njmeLYZujZo

Germany NaKo Gesundheitsstudie (Nationale Kohorte; NaKo)

https://nako.de/infomationen-auf-englisch/

UK Biobank

https://www.ukbiobank.ac.uk/

Thank you for your attention!

Daniel.Barth@med.uni-jena.de

IBBJ Tour