SCIence outreach: The example of BIObanks in Europe

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The Need for Sample Quality in Biobanking

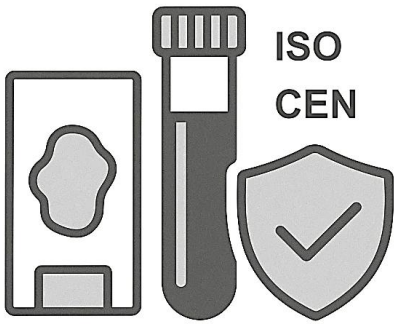

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Image: modified ChatGPT

SCIBIOEU course lesson

The Need for Sample Quality & Quality Management (QM) in Biobanks

- Target group:

  Young/early stage researchers and PhD students with limited knowledge about biobanking
  - to improve their own knowledge about biobanks, biobanking processes and major biobanking-related topics and
  - to enable them to pass on this information to patients, research participants, and the public.

- Learning objective:

  As course participant you are able to outline
  - What high sample quality means
  - Why quality of samples and data is important for diagnostics, biobanking and research
  - What is done to achieve high quality of samples and how biobanks contribute to it
  - Which quality standards are relevant for biobanking
  - Why the pre-analytical phase is crucial for quality and which elements it comprises

- What awaits you:

  This online course lesson is one part of a series of SCIBIOEU course lessons on biobanks and on the process of biobanking. This lesson teaches why it is important that biobanked samples are of high quality and what biobanks do to achieve this.
  The content is explained using information text and videos and is lightened up with an online quiz.
  The text and video content of the course take approx. 20 minutes reading time for the text handout and 5 minutes for the recorded presentation (video). Extra time should be allowed for the quiz and the links to films in the text below.

- Learning materials:
  - Recorded presentation (video)
  - Handout (text document)
  - Quiz

Biobank samples must be of high quality - why and how to achieve this

Human biobanks contain biological samples such as blood, swabs, saliva, urine or tissue for health research from patients or (healthy) citizens. Often these samples are collected at hospitals during diagnosis and treatment of a disease or by biobanks building population-based cohorts.

For health research, but also for diagnosis and treatment in healthcare, high quality of samples is a prerequisite for obtaining correct research and diagnostic analysis results. Particularly with the rapid development of modern, very sensitive analysis techniques and in personalized medicine, high sample quality is becoming even more important.

To achieve and maintain high sample quality, biobanks must adhere to international standards and best practices, and implement quality management. Biobanks possess expertise on how to correctly handle samples in the phase that precedes the analysis (the so-called pre-analytical phase). They

closely collaborate with medical professionals and clinicians during sample handling outside the biobank, train their biobank staff, but also advise researchers in pre-analytical matters during the set-up of sample collections.

With this commitment to quality management, biobanks support researchers to achieve reliable and reproducible research.

1. What is a biobank? What are samples?

An introduction to what biobanks are and which types of samples (and data) can be in a biobank is given in other SCIBIOEU course lessons (see below). In brief, human biobanks are facilities which collect, process, store, and manage high-quality human biological samples and accompanying data that are provided by people for medical and health research (1-3).

Among many different subtypes of biobanks, human biobanks can be broadly classified into the following two major types (3):

- Disease-oriented often hospital-associated (clinical) biobanks, which collect, process and/or store samples and data from hospital patients (1, 4, 32), and
- population-based biobanks, which collect, process and store samples and data from volunteering individuals from the general population of a certain country or region (1, 5, 32).

'Samples' can be almost everything that can be removed from the human body for diagnostics, therapy or special research studies:

- liquid samples, comprising various types of body fluids such a blood samples (venous whole blood, serum or plasma), saliva or sputum, urine, liquor/cerebrospinal fluid, ascites, etc.,
- solid samples, such as tissues (from tumours or other diseased parts of the body like inflamed appendices or tonsils) which may be removed by biopsy or surgical resection
- other samples, such as buccal or vaginal swabs, stool, or cells and nucleic acids isolated from samples.

For more details on biobanks see SCIBIOEU course lesson on "General information about Biobanks" on https://training.scibioeu.eu

For more details on samples and sample types see SCIBIOEU course lesson on "How samples and data get into a biobank" on https://training.scibioeu.eu

2. What does 'high quality' of a sample mean? Why is it relevant?

Relevance

'Garbage In — Garbage Out' is a universal principle that also applies for biological samples to be used in any kind of analytical test. **A low quality of input (i.e., a biological sample) will lead to a low quality of the 'output' (i.e., the analytical test result).**

But what is quality – and particularly high-quality – with respect to a human biological sample?

Definition

High sample quality means that a biological, e.g., human, sample to be used in a certain diagnostic test or research study is 'fit-for-purpose', meaning it is suitable for its intended use which is the respective analytical test that detects or measures specific biological parameters. 'Fit' means, first of all, that the sample corresponds very well to its original state in the human body before it was removed. It must optimally reflect the real health or disease status.

Influences on sample quality

However, many process steps take place before the analysis can modify this original state of the sample. These process steps comprise the 'pre-analytical phase' (Figure 1). It includes all steps starting with the patient's anamnesis and patient 'preparation' (e.g., fasting before taking blood, or anaesthesia for a surgical intervention), followed by the sample collection, the proper labelling of sample collection containers (e.g. blood vials, or cryo tubes) and correct assignment to the patient/research study participant. It further includes the intermediate sample storage and transport to the laboratory/biobank, any processing of the sample (e.g., preservation such as freezing or formalin fixation and paraffin-embedding, centrifugation, aliquoting of the sample, or isolation of biomolecules such as nucleic acids (DNA or RNA), and short- or long-term sample storage until the analysis.

Figure 1 schematically illustrates the process steps of the pre-analytical phase using the examples of a blood and a formalin-fixed paraffin-embedded (FFPE) tissue sample.

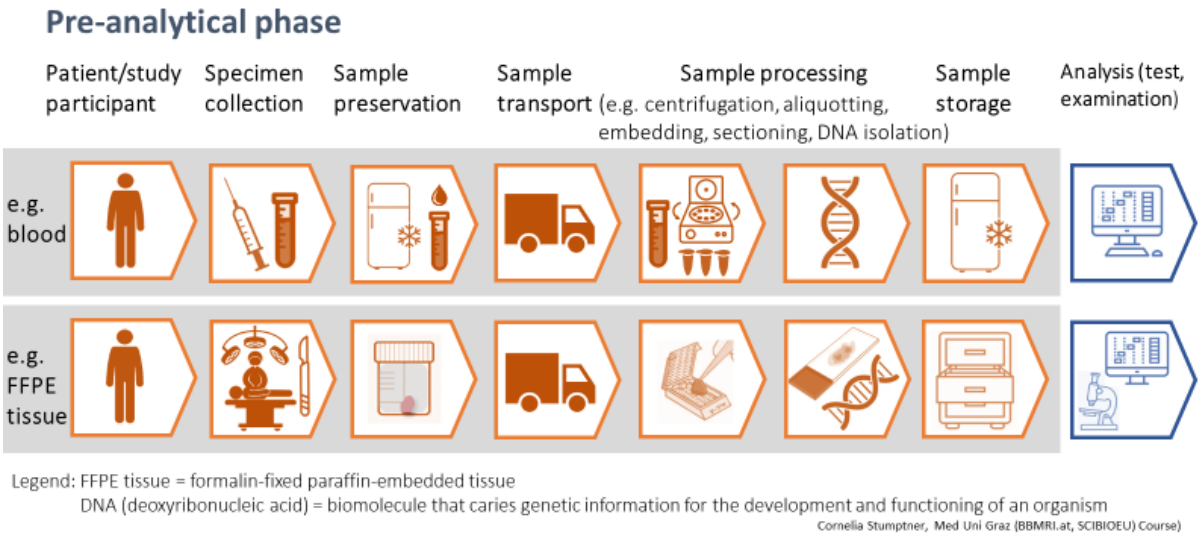


Figure 1: Pre-analytical phase using the examples of a blood and a tissue sample

Along the entire pre-analytical phase of a diagnostic, biobank, or research sample, there are numerous factors - called **'pre-analytical variables' or 'pre-analytical factors'** - that can impact the sample quality and thus the reliability of an analytical test result. (6, 7)

Figure 2 highlights the most important pre-analytical variables or factors that are considered in the literature and in international quality standards to be the most critical ones when handling diagnostic and research samples. (8-15, 31, 35, 37)

Pre-analytical variables along the analysis workflow – Outside the laboratory

Chapters	Workflow steps	Preanalytical variables (examples)
- **Specimen collection**	Patient	Identity, demographics (age, gender, ethnicity, etc), informed consent, health/disease condition, medication & treatment BMI, life style (e.g. fasting, nutrition, stress, physical activity), etc.
	Specimen & Collection	Surgical procedure, biopsy device, type/origin of specimen, warm and cold ischemia time, blood collection device + procedure, labelling, etc.
	Stabilization	Stabilization method and compound: freezing, fixation (type of stabilizer, volume/specimen ratio, duration, temperature) etc.
	Storage	Specimen container, duration, temperature
- Transport	Transport	Transport container, duration, temperature

Stumptner et al; Crucial Role of High Quality Biosamples in Biomarker Development; Handbook of Biomarkers and Precision Medicine (2019)
Zatloukal, Stumptner et al; Biobanks in personalized medicine; Exp Rev Prec Med (2018)

Pre-analytical variables along the analysis workflow – Inside the laboratory

Chapter	Workflow steps	Preanalytical variables - examples
- Reception	Reception	Reception (person, date/time, condition, …)
- Pathol. Evaluation of, Fixation, decalcification, processing, embedding; **- Plasma preparation;** **- Freezing**	Specimen processing	Macroscopy/grossing of tissues, sample selection, fixation (duration, condition), decalcification, tissue processing, paraffin embedding; freezing method & reagents; centrifugation, aliquoting, etc.
- Storage	Storage	Specimen container, duration, temperature, etc.
- Isolation of DNA/RNA/prot **- Other pre-processing**	Pre-processing for analysis & storage until analysis	Sample region for isolation, (RNA, DNA, protein) isolation kit/method; quantity & quality assessment , storage conditions; sectioning of tissues, deparaffinization etc.

Stumptner et al; Crucial Role of High Quality Biosamples in Biomarker Development; Handbook of Biomarkers and Precision Medicine (2019)
Zatloukal, Stumptner et al; Biobanks in personalized medicine; Exp Rev Prec Med (2018)

Figure 2: Pre-analytical variables which may impair sample quality and modify analysis results

These variables shall or should be considered by biobanks, diagnostic laboratories and researchers **before and during handling human samples**; as well as planning for writing standard operating procedures (SOPs) and/or research study protocols.

Data about the pre-analytical phase and its variables also need to be documented (e.g. in databases) They also need to be linked to the respective sample to allow for determination of a sample's fitness-for-purpose.

Data associated with the pre-analytical variables include:

i) Data associated with the patient/study participant: These can be demographic data (e.g., age, gender), medical data (e.g., medication, family or personal medical history, diagnostic data from the health record such as laboratory test results, etc.) or life-style data (e.g., smoking, dietary habits, physical exercise).
ii) Data about the sample: for example, information on the type, origin and health/disease state of the sample, how it was collected and processed, and where and under which conditions it is stored (16).

To learn more about associated data that can be in a biobank go to SCIBIOEU course lesson on "How samples and data get into a biobank" on https://training.scibioeu.eu.

3. Why is the pre-analytical phase so relevant for high sample quality?

The pre-analytical phase is a very critical phase because at each step various factors can modify the sample and thus the analysis results so that it does not reflect the true situation in the human body anymore but is the result of pre-analytical sample handling.

As soon as a sample is removed from the body, the sample begins to change its state. The cells in the sample - for example in a blood or tissue sample - are still alive and suddenly face a completely different environment once taken out of the warm human body. The temperature drops to room temperature and with the interruption of the blood flow, the supply with nutrients and oxygen is terminated. This leads to stress reactions in the cells and can e.g. result in an increase, decrease or other modification of the biomolecules or biomarkers to be measured with analytical tests. These changes are, however, not related to a patient's health or disease status, but are caused by pre-analytical factors. (7, 11, 17-19)

Changes of the samples during the pre-analytical phase cannot always be avoided, since it may be a necessary part of the procedure: e.g.,

- the interruption of the blood supply (called warm ischemia) during surgery,
- the removal of a tissue from the body (called cold ischemia),
- the fixation and processing of a tissue which is necessary to preserve the tissue and allow examination of a tissue section under the microscope for diagnosis.

However, these pre-analytical processes can be standardized and the pre-analytical parameters (called meta-data) documented. This is particularly important because - depending on the biobank type - many of the pre-analytical steps occur outside the biobank. For example, in hospital-based biobanks different medical professionals and hospital units (such as surgery, oncology, pathology, etc.) are involved in sample collection, transport and processing before the biobank finally receives the sample.

Knowing the pre-analytical data of samples (and the respective patient/study participant) helps to describe their quality and to determine their fitness-for-purpose. For biobanks this is crucial, since they store samples for future research, which may be performed several years after sample collection,

probably with novel techniques requiring well-defined sample quality to determine whether a sample is suitable for these techniques.

Standardizing the pre-analytical workflow will also help to avoid or reduce handling errors (e.g. labelling errors, incorrect collection procedures or use of inappropriate collection vials) (6).

High sample quality is pertinent for diagnostics, biobanking and research.
Several studies have shown that the pre-analytical phase accounts for approx. 50 to 70 % of all errors in diagnostic laboratories (Figure 3). And this has a tremendous impact: On the one hand it means harm to patients because it can lead to wrong diagnostic results, can make it necessary to take a new sample and repeat the analysis, or even lead to wrong therapy and in the worst case can cause patient death. On the other hand, it means enormous costs being a high burden for our health care system. A US study described that in an average-sized hospital pre-analytical errors led to unnecessary expenditures in the height of over 1 million US $.
Also, in research the pre-analytical phase accounts for wasted research money: Billions of US $ are spent on pre-clinical research that is not reproducible in the end (22). This coined the term reproducibility crises. (36)

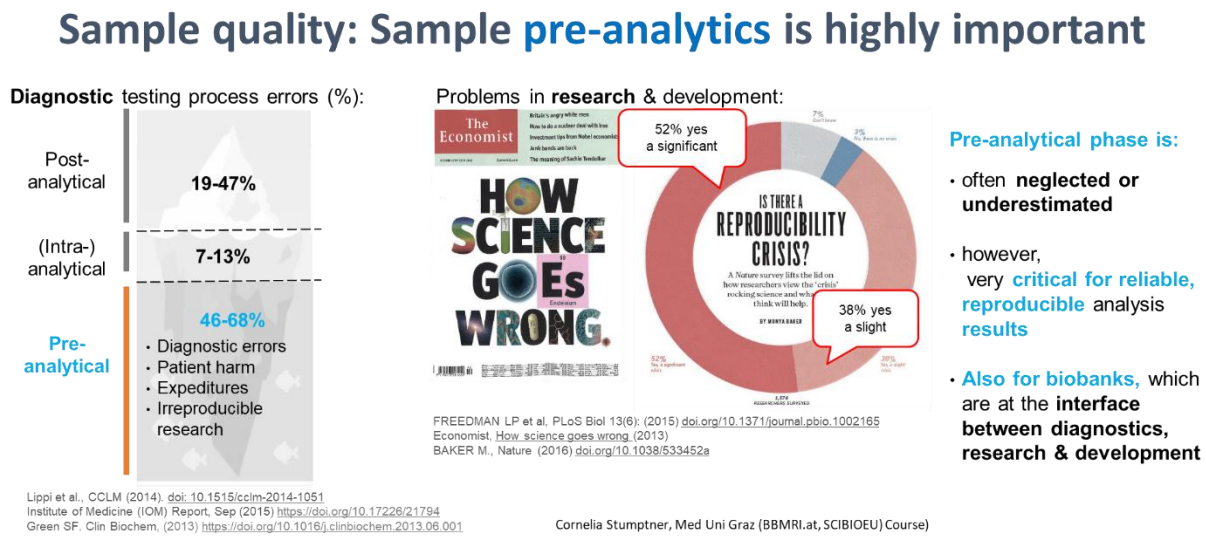


Figure 3: Impact of the pre-analytical phase in diagnostics and research & development

4. Why are high-quality samples crucial for diagnostics, biobanking and research?

Modern diagnostics and research use very sensitive methods and instruments to analyse samples and need to generate data (e.g., test results) of the highest precision. They aim at understanding complex molecular processes in the human body that are subtly different in disease compared to health. These processes can also vary from person to person and need to be identified and understood

so that hospitals can provide tailor-made prevention and treatment strategies for defined groups of individuals. (This is called personalized medicine or precision medicine). (20, 21)

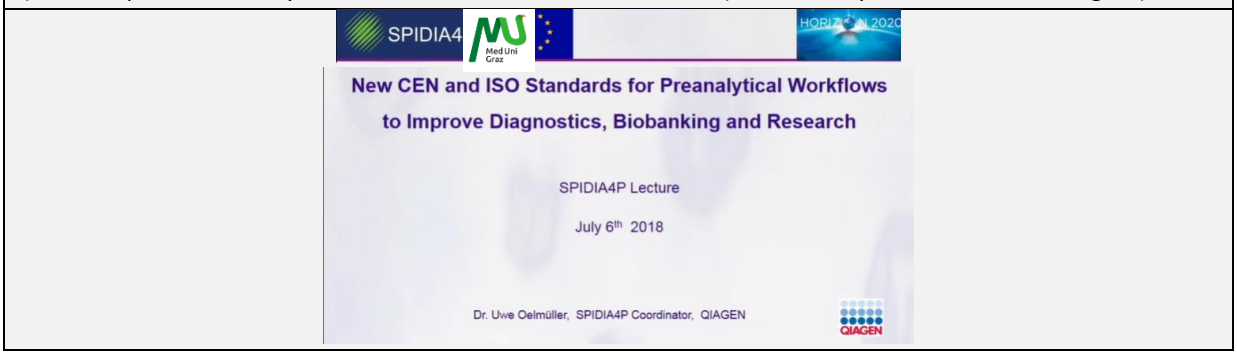
(Hospital-based) biobanks are at the interface between diagnostics/therapy and research: They often receive their samples from the diagnostic or therapeutic hospital workflow and **provide samples to researchers** for their studies. Researchers from universities, research centres and commercial organizations need samples of reliable, high and documented quality. They aim at **better understanding of disease mechanisms, identification of biomarkers for early disease detection, and development new diagnostic tests or drugs for disease treatment.**

Pre-analytical factors which impair sample quality were a major cause of failure of biomarker studies and of **research results that were not reproducible**, thereby wasting a lot of money and valuable samples. In healthcare, unreliable or wrong analyses might lead to wrong diagnoses, and as a consequence the disease of the patient might not be treated appropriately (22, 23, 36). Such errors become for example highly relevant in the context of biomarker development which are essential for diagnosing diseases and should help to define the best treatment for patients. There are observations that the pre-analytical phase accounts for the majority of errors in clinical laboratories (6).

OPTIONAL:

To learn more about the relevance of the pre-analytical phase in diagnostics, biobanking and research watch the following videos:

>New CEN and ISO Standards for Preanalytical Workflows to Improve Diagnostics, Biobanking and Research
(Video of presentation by Uwe Oelmueller, SPIDIA4P coordinator) recorded by Med Uni Graz; in English)



5. What do biobanks do to achieve high quality of samples?

To improve sample quality in medical diagnostics and biobanking, International Standards were developed by standardization bodies such as the International Standardization Organization (ISO) or the European Committee for Standardization (CEN) (24, 25, 31).

Diagnostic laboratories and biobanks follow these ISO or CEN quality standards, have implemented a professional quality management (QM) system and are ISO-certified or accredited.

QM Systems & Standards

Standards for QM systems give clear instructions for all operations of an organization, such as biobanks or diagnostic laboratories.

A QM system is defined as a formalized system that documents processes, procedures, and responsibilities for achieving quality policies and objectives. A QMS helps coordinate and direct an organization's activities to meet 'customer' and regulatory requirements and improve its effectiveness and efficiency on a continuous basis. (33)

QM standards for QM systems typically cover the overall management structure, the selection and training of the personnel, the standards that must be followed for individual processes, which material and devices to use, and also how to check the quality of the output. For diagnostic laboratories, a QM system is mandatory in most cases. Notably, whenever available, QM systems must adhere to existing standards on individual processes, such as those on pre-analytical processing of human biological samples.

Among the most important quality standards are those according to which (human) biobanks or (medical) laboratories can be accredited or certified, such as:

- ISO 20387 – (ISO 20387:2018 - Biotechnology – Biobanking - General requirements for biobanking) a standard specific for biobanks (for accreditation)[1]
- ISO 15189 – (ISO 15189:2022 Medical laboratories - Requirements for quality and competence) a standard for medical laboratories (such as blood laboratories or pathology laboratories) (for accreditation)
- ISO 9001 - (ISO 9001:2015 Quality management systems - Requirements) – a general ISO standard (for certification)

Certification is the provision by an independent body of written assurance (a certificate) that the product, service or system in question meets specific requirements. (34)

Accreditation is the formal recognition by an independent body, generally known as an accreditation body, that a certification body operates according to international standards. (34)

There is a family of pre-analytical sample quality ISO and CEN standards "Molecular in vitro diagnostic examinations — Specifications for pre-examination processes" **for different sample types intended for different analysis types.** They specify requirements and give recommendations for the collection, handling, documentation, transport, storage and processing during the pre-analytical phase (see above and Figure 1) of various sample types (such as frozen tissue, FFPE tissue or blood for RNA, DNA or protein analysis or for human specimens for microbiome DNA analysis). These standards for pre-analytical sample quality supplement quality management standards such as ISO 20387 and ISO 15189.

See Figure 4 to learn for which sample types pre-analytical standards exist. These standards are relevant for the different medical actors/institutions relevant for and/or applied in biobanking.

[1] Currently under systematic revision; the new version of ISO 20387 is expected for 2025/2026

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EXAMPLES OF IMPORTANT ISO STANDARDS IN BIOBANKING

ISO STANDARDS – FOR 'QUALITY MANAGEMENT SYSTEMS'

- EN ISO 20387:2018 - Biotechnology – Biobanking - General requirements for biobanking
- EN ISO 15189:2022 Medical laboratories - Requirements for quality and competence
- EN ISO 9001:2015 Quality management systems - Requirements)

ISO STANDARDS & CEN TECHNICAL SPECIFICATIONS (CEN/TS) - FOR PRE-ANALYTICAL SAMPLE QUALITY

Molecular In Vitro Diagnostic examinations – Specifications for Pre-examination Processes for:

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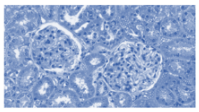


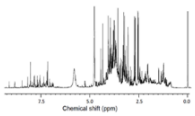
- EN ISO 20166-1: 2018 (former CEN/TS 16827-1), FFPE tissue – Part 1: Isolated RNA
- EN ISO 20166-2: 2018 (former CEN/TS 16827-2), FFPE tissue – Part 2: Isolated proteins
- EN ISO 20166-3: 2018 (former CEN/TS 16827-3), FFPE tissue – Part 3: Isolated DNA
- EN ISO 20166-4: 2021 FFPE tissues - Part 3: In-situ detection techniques ... Coordinated by K. Zatloukal / C. Stumptner (BBMRI.at) / B. Sheppard

- EN ISO 20184-1: 2018 (former CEN/TS 16826-1), frozen tissue – Part 1: Isolated RNA
- EN ISO 20184-2: 2018 (former CEN/TS 16826-2), frozen tissue – Part 2: Isolated proteins
- EN ISO 20184-3: 2021 (former CEN/TS 16826-3), frozen tissue – Part 3: Isolated DNA

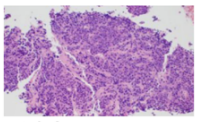
- EN ISO 20186-1: 2019, (former CEN/TS 16835-1), venous whole blood – Part 1: Isol. cellular RNA
- EN ISO 20186-2: 2019, (former CEN/TS 16835-2), venous whole blood – Part 2: Isol. genomic DNA
- EN ISO 20186-3: 2019, (former CEN/TS 16835-3), venous whole blood – Part 3: Isol. circ. cell free DNA from plasma

- CEN/TS 17626: 2021, human specimens – microbiome DNA ..... Coordinated by K. Zatloukal/C. Stumptner (BBMRI.at)

- ISO/TS 7552-1:2024 (former CEN/TS 17390-1:2020, circulating tumor cells (CTCs) – Part 1: Isolated RNA
- ISO/TS 7552-2:2024 (former CEN/TS 17390-2:2020, circulating tumor cells (CTCs) – Part 2: Isolated DNA
- ISO/TS 7552-3:2024 (former CEN/TS 17390-3:2020, circulating tumor cells (CTCs) – Part 3: Preparation for analytical CTC staining



- EN ISO 23118: 2021 (former CEN/TS 16945) urine, plasma, serum for metabolomics
- EN ISO 4307:2021 (former CEN/TS 17305:2019), saliva – Isolated human DNA



- CEN/TS 17688-1:2021, fine needle aspirates – Part 1: Isolated cellular RNA
- CEN/TS 17688-2:2021, fine needle aspirates – Part 2: Isolated proteins
- CEN/TS 17688-3:2021, fine needle aspirates – Part 3: Isolated genomic DNA

- CEN/TS 17742: 2022, venous whole blood - isolated circulating cell free RNA from plasma
- CEN/TS 17747: 2022, exosomes & other extracellular vesicles in venous whole blood - DNA, RNA and protein´s
- CEN/TS 17811: 2022, urine and other body fluids – isolated cell free DNA

UNDER DEVELOPMENT

- ISO/TS 18701, human specimens – microbiome DNA
- ISO/TS 18702, exosomes & other extracellular vesicles in venous whole blood - DNA, RNA and proteins
- ISO 18703, venous whole blood - isolated circulating cell free RNA from plasma
- ISO 18704, urine and other body fluids – isolated cell free DNA

(March 2025)

NOTE: an updated list of ISO and CEN standards can be found at the BBMRI.at website>

Figure 4: Examples of important standards relevant for biobanking

Further relevant standards include for example

- ISO 21899:2020 for validation and verification of biobank methods (i.e. ISO 21899:2020 - Biotechnology — Biobanking — General requirements for the validation and verification of processing methods for biological material).

- CEN/TS 17981-1:2023 or ISO 25379-1, In vitro diagnostic Next Generation Sequencing (NGS) workflows — Part 1: Human DNA examination
- CEN/TS 17981-2:2023 or ISO 25379-2, In vitro diagnostic Next Generation Sequencing (NGS) workflows — Part 2: Human RNA examination

Third party quality assessment & support of biobanks

Biobanks (and medical laboratories involved in biobanking) which have implemented a QM system and are certified (e.g., according to ISO 9001 – see above) or accredited (e.g., according to ISO 20387 (26) – see above) undergo periodic third-party assessments.

These third-party assessments. assessments are quality audits performed by QM authorities, which, when passed, demonstrate compliance with the respective ISO standard(s). This supports the constant quality of all processes along the biobanking workflow. It requires extensive training of all persons involved in biobanking (e.g., medical/hospital, laboratory and biobank staff).

One way to test the quality of biobanking processes is participation in ring trials or proficiency testing. These are tests where samples from an identical source material are processed at different biobanks/laboratories and are then sent to one reference laboratory for analysis which assesses the quality (27). The term ring trials/proficiency testing is often used interchangeably with **external quality assessment (EQA)** and defined as 'a system for objectively checking the laboratory's performance using an external agency or facility. (28)[2]

Quality standards are an important element of such a QM system because they give instructions on how to manage a laboratory or biobank, how to become competent in laboratory or biobanking methods and how to process samples during the pre-analytical phase. Proper control and documentation of sample and data origin and processing are central to these standards.[3]

Biobanks within the European Biobanking Research Infrastructure BBMRI-ERIC are supported in QM matters by BBMRI-ERIC (BBMRI.QM>) and its national nodes (e.g. BBMRI.at[4]; BBMRI.de, BBMRI.ch, BBMRI.be (29)). They offer educational events, supportive QM tools, biobank quality audits (30), and contribute to the development of international ISO and CEN standards.

OPTIONAL:

To learn more about how professional biobanks can support researchers what the following film generated by the Austrian Biobanking Research Infrastructure BBMRI.at, the German Biobank node (GBN) and the Swiss Biobanking Platform SBP):

Unveiling Biobank Power: A Film by the Austrian, German, and Swiss BBMRI Nodes

[2] https://www.who.int/publications/m/item/overview-of-external-quality-assessment-eqa
[3] https://academic.oup.com/clinchem/article/70/9/1140/7704627
[4] https://www.bbmri-eric.eu/wp-content/uploads/Clinical-Chemistry-and-Laboratory-Medicine-CCLM-Quality-management-a....pdf

See also **LinkedIn BBMRI.at** www.linkedin.com/company/bbmri-at/

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