



Trust Quality Experience Knowledge

Issue No. 6/2017

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EDITORIAL REPRODUCIBILITY AND RELIABILITY

Ensuring reproducibility and reliability of scientific work should be at the heart of medical science. It is thus an issue of great concern for BBMRI-ERIC and we are dedicated to working hard in order to facilitate both better quality of and accessibility to biological samples and data that is curated by the biobanks of our members. Ultimately, we will implement quality tools to support European biobankers and researchers in their daily work.

In order to do so, we have to challenge the definition of *excellence* for biomedical research, which still has a too high and therefore unacceptable level of irreproducibility: *“Pre-analytical errors still account for nearly 60% - 70% of all problems occurring in laboratory diagnostics, most of them attributable to mishandling procedures during collection, handling, preparing or storing*

*the specimens”*¹.

Consequently, there is increasing concern about the reliability of medical research results, with recent articles suggesting that up to 85% of research is wasted². In the article *“Standardisation is the Key in the Pre-analytical Field”*, Uwe Oelmüller describes the outstanding work the SPIDIA project (2008 - 2013) has done - and more is to come in the context of the SPIDIA4P project, which started by the end of 2016, page 33.

For their outstanding article *“The Economics of Reproducibility in Preclinical Research”* published in *In PLOS Biology*³, Leonard Freedman, Iain Cockburn and Timothy Simcoe of Boston University combed the literature of two dozen studies that tried to quantify how many biological papers are flawed because of specific problems. They estimated that 53% of all preclinical studies have errors and are thus not reproducible. The most common reasons included problems with reagents

and reference material (36%), study design (28%), data analysis and reporting (25%) and laboratory protocols (11%). Such difficulties are also highlighted in the article written by Prof. Kurt Zatloukal, page 16.

The waste of money can be enormous; In the United States, there is an estimated expenditure of \$28 billion each year on preclinical research that can't be reproduced by other researchers. For an average German hospital, pre-clinical error has been calculated to cost €347,000.

Taking these issues into account, I thus propose to redefine *excellence* by including specific characteristics such as a high level of organisation and the rigorous standardisation of methods and procedures in order to guarantee the reproducibility of research results. This can only be reached from within the community and by a large team effort. The details are described in the article *“Tremendous Teamwork within*

¹ Lippi G. *et al.* Preanalytical quality improvement: from dream to reality. *Clin Chem Lab Med.* 2011 Jul; 49(7):1113-26.).

² Stephen A Bustin. “The reproducibility of biomedical research: sleepers awake!” In: *Biomolecular Detection and Quantification* (2014), pp. 35-42

³ Plos Biology, Freedman LP, Cockburn IM, Simcoe TS. The Economics of Reproducibility in Preclinical Research. *Plos Biol.* 2015 Jun 9;13(6):e1002165.

BBMRI-ERIC improves Quality in Biobanking”, page 4. In fact, BBMRI-ERIC is one of the few organisations to have outlined a clear path to resolve the data reproducibility and reliability issue for medical research, ultimately relying on its 19 Member States and IARC for the implementation. The many activities taking place in this field in the respective countries are presented on page 24-32.

In particular, I would like to highlight two current efforts for improvement:

- Standards on pre-analytical workflow (described in this issue)
- New technologies for securing high quality samples

Moreover, procedures for collecting and using biobank samples are set to undergo dramatic changes in the coming years, necessitating efficient provision of support for users of the corresponding techniques. The costs of some analyses are decreasing by orders of magnitude making entirely new approaches realistic, whi-

le new classes of biomarkers that depend on new analytic technologies are continually appearing, and the types of molecules that are being targeted are steadily increasing. At the same time, growing numbers of individuals are being recruited as donors of blood and other samples for biobanks. This requires defining new data types. We have, for instance, started the MIABIS⁴ Working Group to define data types relevant for microbiome and include aggregated descriptions of microbiome biobanks to the BBMRI-ERIC Directory.

All these developments are consistent with the rapidly increasing interest in personal medicine. This means that biobanks and their users will need support to adapt to not only new technologies, but also study designs and research strategies, and finally to agree on preferred approaches in order to ensure that data can be combined across different sites and countries. That is the reason why we will now also focus more on the second “B” (biomolecular resources) in

BBMRI. An important role will be to help industry to access resources and to support industrial development of new technologies as well as biomarkers for applications in clinical care using retrospective sample material.

Ultimately, this will not only save a lot of money for our Member States, but also lead to better reproducibility and reliability of research results, provide added value for research and stimulate the innovation process in Europe.



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⁴ MIABIS paper: <http://www.bbmri-eric.eu/news-events/miabis-2-0-published/>

TREMENDOUS TEAMWORK WITHIN BBMRI-ERIC IMPROVES QUALITY IN BIOBANKING

by Andrea Wutte, MSc

“Quality is...”

“fitness for the intended use” - the researcher says,

“meeting users’ or customers’ expectations” - the biobanker says,

“conformance to specifications” - the lab technician says,

“Quality must be made measurable” - BBMRI-ERIC adds.

Medical researchers and biobankers are not usually accustomed to using the terms ‘customer’ or ‘product’. However, both terms are appropriate if understood in a non-commercial and service oriented sense. Hence - in the field of medical research - the researchers be-

for an immediate intended use (then stored and archived) or just for archiving purposes. In both models, the sample has been collected, transported, processed, analysed and stored according to specific procedures. The sample therefore represents the profile and in-

ture analysis purposes. The key in making a sample valuable for any future purpose however, is not to foresee the future, but to be able to provide a complete documentation of the entire process chain from “donor to storage” based on validated methods and standardised protocols.



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come ,customers’ when they reach out to biobanks for requesting access to the ,product’; the archived samples and/or the associated data. In biobanking, these human samples are removed from the body either

tegrity that is suitable for the specific use it was collected for. The rapid developments in analysing technologies make it difficult to foresee whether the current sample handling techniques are adequate for fu-

WHAT DOES THE CUSTOMER NEED?

The customer may require access to the samples/data or only to the data from downstream analysis. In either case, the biobank managers are expected to ensure that the sample handling is in compliance with the known requirements for the specific sample type throughout its lifetime and that

the provided data is accurate. Sounds easy enough, but it is not! Only a very comprehensive quality management in biobanks is able to provide such

services and medical/lab technicians that are together providing reliable and reproducible results to the customer. The most demanding position of all

The biobanks within BBMRI-ERIC are also implementing the newly published CEN Technical Specifications (CEN/TS) to further improve their pre-examination sample handling procedures to offer the customers even more standardised products in the future.



service for its customers. Based on available documents and records to track the sample handling processes, the customer can determine the usability of the sample and data. Customer satisfaction is therefore a matter of providing documentation with detailed pre-analytical process records rather than offering only the sample and/or data.

When successful, it reflects tremendous teamwork between operators such as biobankers, clinicians, nurses, courier ser-

vice is that of the biobanker as he/she is the interface between the customer and the rest of the operators.

The biobanks of today are willing and able to provide quality products and services.

This is indicated by more than 60% of the biobanks participating in the BBMRI-ERIC Expert Working Groups that hold, and/or working according to, certificates (e.g., ISO 9001, NFS96-900) or accreditation certificates (e.g., ISO 15198, ISO 17025).

BBMRI-ERIC - QUALITY MANAGEMENT SERVICE

In 2016, the BBMRI-ERIC Quality Service encouraged the biobanks to comply with the highest quality requirements available thereby serving the best interests of their customers. Consequently, the increased demand and usage of the high quality sample products and services places the biobanks in a central role for researchers from the basic and applied fields as well as for industry.

In order to provide solutions to better meet the sample quality requirements, BBMRI-ERIC set up 5 different Quality Expert Working Groups to develop a Self-Assessment Survey based on the pre-examination processes (CEN/TS). The Quality Expert Working Groups currently (12.2016) involve 89 experts and researchers from 18 different Member States and WHO/International Agency for Cancer Research (WHO/IARC)

(Fig 2.) therefore covering a wide range of biobank operators and customers all over Europe (Fig 1.). This is the first time the community has come together in such a way to demonstrate the need for quality improvement in biobanking. The expert working groups initiated their work by completing a joint intra-biobank and inter-biobank benchmarking against the CEN/TS 'Molecu-

lar in vitro diagnostic examinations - Specifications for pre-examination processes'. In the course of 34 web-conferences within 12 months, the benchmarking resulted in improved sample handling procedures and documentation throughout the community. Furthermore, the discussions and experience sharing encouraged and motivated the community to improve the

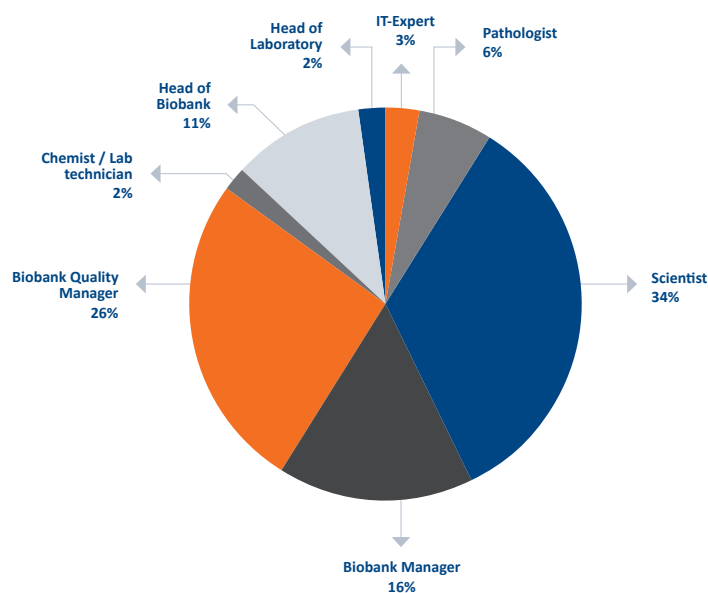


Fig 1. Composition of the representatives of BBMRI-ERIC Expert Working Groups and the expertise presented (12.2016)

Table 1 BBMRI-ERIC SELF-ASSESSMENT SURVEY
a complementary tool

- Specifications for Pre-examination processes for snap frozen tissue
– Part 1: Isolated RNA, CEN/TS 16826-1:2015
- Specifications for Pre-examination processes for snap frozen tissue
– Part 2: Isolated proteins, CEN/TS 16826-2:2015
- Specifications for Pre-examination processes for FFPE tissue
– Part 1: Isolated RNA, CEN/TS 16827-1:2015
- Specifications for Pre-examination processes for FFPE tissue
– Part 2: Isolated proteins, CEN/TS 16827-2:2015
- Specifications for Pre-examination processes for FFPE tissue
– Part 3: Isolated DNA, CEN/TS 16827-3:2015
- Specifications for Pre-examination processes for Venous whole blood
– Part 1: Specifications for Pre-examination processes for Isolated cellular RNA, CEN/TS 16835-1:2015
- Specifications for Pre-examination processes for Venous whole blood
– Part 2: Isolated genomic DNA, CEN/TS 16835-2:2015
- Specifications for Pre-examination processes for Venous whole blood
– Part 3: Isolated circulating cell free DNA from plasma, CEN/TS 16835-3:2015
- Specifications for Pre-examination processes for Metabolomics in urine, serum and plasma, CEN/TS 16945:2016

<http://www.bbmri-eric.eu/BBMRI-ERIC/quality-management/>

ENHANCING THE VISIBILITY OF BIOBANKS: THE SELF-ASSESSMENT SURVEY AND DIRECTORY

As of 2017, biobanks and sample collections may complete the Self-Assessment Surveys applicable for pre-examination processes and submit them to BBMRI-ERIC. The survey results can be informative for individual biobanks to improve their specific procedures and processes. BBMRI-ERIC will encourage biobanks to provide evidence of samples that meet the CEN/TS and QMS criteria as specified in the BBMRI-ERIC Self-Assessment Surveys.

In a first step, biobanks (respectively the comprehensive collections and their samples/ data) complete and submit the survey to BBMRI-ERIC together with a statement of compliance signed by the respective biobank manager. Second, BBMRI-ERIC reviews the completed survey which results in the BBMRI-ERIC Quality Grade following the given „shall/should“ criteria defined in the survey and based on the respective CEN/TS.

Finally, biobanks that fulfill the criteria of the Self-Assessment Survey will receive recognition by being flagged in the BBMRI-ERIC Directory as compliant to the specific CEN/TS e.g., „Conforms to CEN/TS 16826-1:2015 Specifications for pre-examination processes for snap frozen tissue - Part 1: Isolated RNA“. This will place the biobanks on the European map and makes the Directory a powerful tool enabling the researchers to find quality defined samples and data throughout Europe. Hence, BBMRI-ERIC promotes those biobanks that are able and willing to give access to high quality samples/ data. This is an added value and service for both biobanks and their customers.

FUTURE PERSPECTIVES

So far, BBMRI-ERIC has addressed the key priority shared by all biobanks: improving the quality of the sample will lead to better data reproducibility and reliability of research results. A comprehensive quality management of biobanks, however, entails a variety of topics such as management, resource and technical requirements, process requirements including validation and verification, quality control of the processes and the quality of the data. The work on quality is and will be a constant effort.

Within the next 2 years, the new ISO standard for biobanks (ISO/TC 276) will be developed and published, giving the biobanks a specific base on which to build their quality management. BBMRI-ERIC has an observer liaison with the ISO/TC 276 and ISO/TC 212 and is hence following and contributing to the work as well as acting as an information hub to communicate the latest developments and is exploring the possibility of setting up a BBMRI-ERIC Audit Programme helping the biobanking



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community to reach 3rd party certification and accreditation. Last but not least, BBMRI-ERIC is partner of the SPIDIA4P project, page 10 & 33, and will take its key role in facilitating pan-European supply of good sample quality by implementing the new standards. Even more this will underpin BBMRI-ERIC as being a trusted partner in the health care system. *“And that is what it is about, with our knowledge, our experience, supported by our highest quality demands, to contribute to the health and well-being of people, what a beautiful task!”*

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STANDARDISATION IS KEY IN THE PREANALYTICAL FIELD

SPIDIA¹ was a 54-month collaborative large integrating project started in 2008 within the EU 7th Framework Programme. SPIDIA addressed the objectives of the FP7 “HEALTH” section focus topic “Detection, Diagnosis and Monitoring”. The consortium united 7 private life science and diagnostic companies, 8 public research organisations, including universities and biobanks, as well as 1 standards organisation, the European Committee for Standardisation CEN. SPIDIA focused on the standardisation and improvement of procedures and development of new tools for pre-analytical workflows. The individual pre-analytical workflow steps, such as primary sample collection, stabilisation, handling, transport, storage, and analyte isolation were improved by new technologies and were standardised as integrated holistic processes for molecular applications. Where feasible, these processes support both, classical and molecular diagnostics. Molecular *in vitro* diagnostics has enabled significant progress in medicine. Further progress is expected

through new technologies analysing signatures of nucleic acids, proteins, and metabolites in human tissues and body fluids. However, the profiles of these molecules can change drastically during primary sample collection, transport, storage, and processing, thus making the outcome of diagnostics or research unreliable or even impossible, because the subsequent analytical test will not determine the situation in the patient but an artificial profile generated during the pre-analytical workflow. Therefore, the standardisation of



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the entire diagnostic workflow from sample collection to analyte measurement is needed (sample-to-insight workflows). Studies have been undertaken by SPIDIA to determine the important influencing pre-ana-

lytical factors in regard to blood, plasma, urine and tissue samples. The SPIDIA research studies' results were provided to the CEN/Technical Committee 140 for “In vitro medical devices” (CEN/TC 140) as the basis for developing the first CEN Technical Specifications (CEN/TS) for pre-analytical workflows (*Fact box 1*). SPIDIA project partners, experts from European national standard institutes, national and international professional societies, European and international research associations, a wider community of diagnostic manufacturers, users and researchers provided input to the content of the new CEN/Technical Specifications via a highly consensus driven process at CEN. Under the Vienna Agreement, these new Technical Specification documents were also presented to the International Organization for Standardization's Technical Committee 212 for “Clinical laboratory testing and in vitro diagnostic test systems” (ISO/TC 212). The further development to ISO Standards by the ISO/TC 212 with a worldwide impact is currently the next big step towards the improvement of healthcare systems. These ISO Standards are planned to be published in 2017.



Fact box 1: CEN/TS DOCUMENTS DEVELOPED FOR PRE-ANALYTICAL WORKFLOWS* <https://standards.cen.eu/dyn/www/f?p=204:105:0>

- CEN/TS 16826-1, snap frozen tissue
– Part 1: Isolated RNA
 - CEN/TS 16826-2, snap frozen tissue
– Part 2: Isolated proteins
 - CEN/TS 16827-1, FFPE tissue
– Part 1: Isolated RNA
 - CEN/TS 16827-2, FFPE tissue
– Part 2: Isolated proteins
 - CEN/TS 16827-3, FFPE tissue
– Part 3: Isolated DNA
 - CEN/TS 16835-1, venous whole blood
– Part 1: Isolated cellular RNA
 - CEN/TS 16835-2, venous whole blood – Part 2: Isolated genomic DNA
 - CEN/TS 16835-3, venous whole blood – Part 3: Isolated circulated cell free DNA from plasma
 - CEN/TS 16945, metabolomics in urine, serum and plasma
- * the synonyms “pre-examination processes” or “pre-analytical phase” are used as well

THE SPIDIA EFFECT

The big international success of the SPIDIA Project stimulated European and international efforts to continue. A roadmap discussed within SPIDIA, the CEN/TC 140 and other organisations laid the basis for the next project submitted to the EU Horizon H2020-SC1-2016-2017 programme. This new project has started on January 1st, 2017. It is cal-

led “*SPIDIA for Personalized Medicine - Standardisation of generic Pre-analytical Procedures for In vitro DIAGNOSTICS for Personalized Medicine*”, in short **SPIDIA4P**². SPIDIA4P will focus on pre-analytical workflows needed for personalised medicine. Progress in personalised medicine is limited by missing pan-European and international standard documents and insufficient guidelines for pre-analytical workflows. This situation does currently not

sufficiently prevent using compromised patients’ samples with post collection changes in cellular and extracellular biomolecules’ profiles, thus often making diagnostic test results unreliable or even impossible. To tackle this, SPIDA4P plans to initiate, develop and implement a comprehensive portfolio of an additional **14 pan-European pre-analytical CEN/TS and ISO/IS documents**, addressing the important pre-analytical workflows applied to

¹ EU FP7 SPIDIA project funded by the European Union Seventh Framework Programme [FP7/2007 2013] under grant agreement no 222916. For further information see www.spidia.eu.

² Spidia4P is funded by the European Union’s Horizon 2020 research and innovation programme under grant agreement n° 733112.

Fact box 2: SPIDIA4P LIST OF PARTICIPANTS

- QIAGEN GmbH (Germany)
- LGC Limited (United Kingdom)
- Technische Universität München (Germany)
- DIN Deutsches Institut für Normung e.V. (Germany), on behalf of CEN
- PreAnalytiX GmbH (Switzerland)
- Inivata Ltd (United Kingdom)
- Cambridge Protein Arrays Ltd. (United Kingdom)
- TATAA Biocenter AB (Sweden)
- Università degli Studi di Firenze, UNIFI (Italy)
- Consorzio Interuniversitario Risonanze Magnetiche di Metallo Proteine, CIRMMMP (Italy)
- Università degli Studi di Trieste, UNITS (Italy)
- Università degli Studi di Torino, UNITO (Italy)
- Biobanking and BioMolecular resources Research Infrastructure Consortium, BBMRI-ERIC (Austria)
- Luxembourg Institute of Health, IBBL (Luxembourg)
- Medizinische Universität Graz, MUG (Austria)
- Institut national de la santé et de la recherche médicale, INSERM (France)
- Erasmus Universitair Medisch Centrum Rotterdam, EMC (Netherlands)
- Fundacio Centre de Regulacio Genomica, CNAG-CRG (Spain)
- Fondazione IRCCS Istituto nazionale dei Tumori, INT (Italy)

personalised medicine. These are planned to be also applicable to biomarker discovery, development and validation as well as to **biobanks providing human specimens and human derived materials used for research**. This 48-months SPIDIA4P project brings together key experts of 19 stakeholder organisations (*Fact box 2 List of participants*), including BBMRI-ERIC, with the required critical mass in knowledge on pre-analytical and analytical procedures, on European and international standardisation organisations' processes (CEN and ISO), external quality assurance, quality management, ethics and regulatory demands. In addition, SPIDIA4P will work via a coordination action with other large initiatives in the field as well as with major stakeholder organisations.

All together, these highly experienced partners plan to carefully develop selected high priority pre-analytical CEN and ISO standard documents as well as corresponding External Quality Assurance (EQA) schemes and implementation tools (*Fig 3, Fact box 4, Fact box 5, Fact box 6*).

These are needed for **1)** reducing the number of sample-

based diagnostic mistakes,
2) reducing the number of non-reproducible pre-clinical and clinical studies, thus enabling **3)** improvement and speeding up of biomarker discoveries and validations for reinforcing the era of personalised medicine and innovations in patient care.

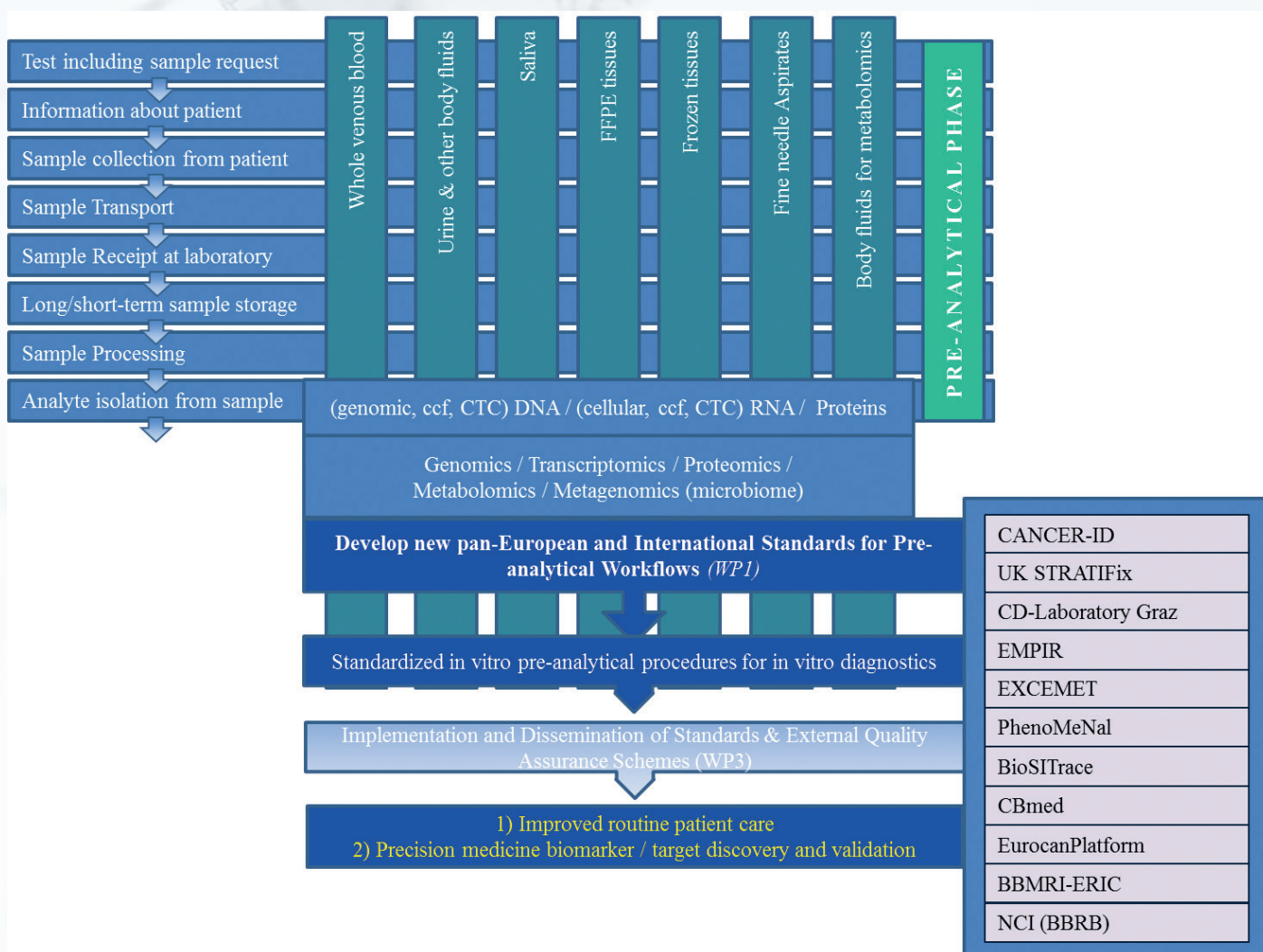


Fig 3. L. Mazuranok/ Copyright ACIES CG 2016 – 2017

Fact box 4:

12 PLANNED NEW PAN-EUROPEAN PRE-ANALYTICAL CEN TECHNICAL SPECIFICATIONS

- 4 new pre-analytical CEN/technical specification documents for in venous whole blood circulating tumour and organ cells (DNA, RNA, proteins, staining procedures)
- 1 for venous whole blood exosomes / cell free circulating RNA
- 1 for saliva (DNA)
- 1 for frozen tissues (DNA)
- 1 for urine and other body fluids (cell-free DNA)
- 3 for fine needle aspirates (RNA, DNA, Proteins)
- 1 for saliva and stool microbiomes (DNA)

13 new External Quality Assurance Schemes

13 new External Quality Assurance Schemes corresponding to the pre-analytical standards portfolio are planned to be developed and implemented (*Fact box 6*).

SPIDIA4P for biomedical and translational research as well as for biobanks

The SPIDIA4P partner BBMRI-ERIC plays a key role in facilitating a pan-European supply of good quality samples. SPIDIA4P plans therefore to develop the new standards not only for diagnostics but also for biomedical and translational research as well as for biobanks. The involvement of stakeholder organisations, SPIDIA4P's collaborations with other consortia and infrastructures as well as the alignment with the ISO/TC 276 for "Biotechnology" including biobanks will ensure this. Overall these positive impacts are intended to enforce Personalised Medicine through faster new molecular biomarker discoveries and developments as well as faster and more

THE SUMMARY OF SPIDIA4P OBJECTIVES

12 new pan-European pre-analytical CEN Technical Specifications

12 new pan-European Technical Specification documents for pre-analytical workflows are planned to be developed at the European Committee for Standardization (CEN) and planned to be implemented in European countries for in vitro diagnostics in Personalised Medicine (*Fact box 4*).

2 additional new international pre-analytical ISO Standards

2 additional new International Standards are planned to be directly developed at the International Organization for Standardization (ISO) and implemented in European and international countries (*Fact box 5*).

successful in vitro diagnostic tests developments including their verifications and validations, as these all will be performed on clinical samples of not only higher but also comparable quality. Also, the implementation of in vitro diagnostic tests in healthcare including broad acceptance and market uptake will be speeded up due to reduced numbers of handling errors.

Finally and most importantly, the patients benefit due to reduced numbers of diagnostic mistakes enabling better patient stratification in personalised medicine and/or prognosis of disease outcome leading to improved clinical decisions.

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Fact box 5:

2 PLANNED NEW INTERNATIONAL PRE-ANALYTICAL ISO STANDARDS

- 1 for FFPE Tissues (in-situ staining procedures),
- 1 for Metabolomics (urine, blood plasma, blood serum)

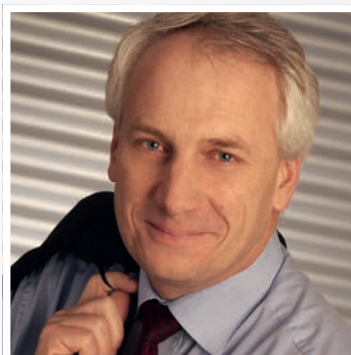
Fact box 6: 13 PLANNED NEW EXTERNAL QUALITY ASSURANCE SCHEMES

- Venous Whole Blood: Genomic DNA and cellular RNA, viable PBMC, Cell Free Circulating DNA (ccfDNA), Cell Free Circulating RNA (ccfRNA), Circulating Tumour Cells (CTCs)
- FFPE tissue: Genomic DNA, RNA, protein
- Frozen tissue: Genomic DNA, RNA, protein
- Saliva: DNA
- Stool: DNA

PRE-ANALYTICAL STANDARDS IN MOLECULAR DIAGNOSTICS AND BIOBANKING: TWO SIDES OF THE SAME COIN

Pre-analytical factors are the major source of error in molecular diagnostics contributing to approximately 60% to 70% of diagnostic errors resulting in ca 6% of deaths and 1% of total healthcare expenditures (Lippi et al., 2011¹ and The National Academies of Sciences, Engineering, and Medicine 2015²). This gained new attention, particularly in the field of personalised medicine where the effectivity of very expensive drugs relies on a molecular test (companion diagnostic) to select the right patient to treat. As a consequence, the European Commission funded a research program (www.SPIDIA.eu) to develop the scientific basis for European standards for the

pre-analytical phase of molecular in vitro examinations. The research work of SPIDIA led to the development of a series of European Committee for Standardization (CEN) Technical



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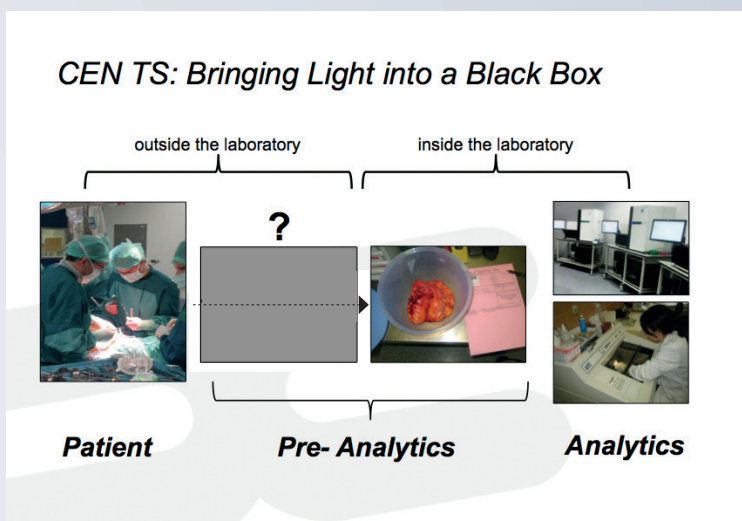
Specifications (TS) for molecular in vitro diagnostic examinations – specifications for

the pre-examination processes, which address specific pre-analytical quality requirements for human blood and tissue samples as well as the most relevant analytes (i.e., DNA, RNA, proteins and metabolites). The CEN/TS published in 2015 and 2016 are now being developed further to ISO standards. The CEN/TS are primarily developed for addressing needs in molecular diagnostics but are explicitly also relevant for biobanks as highlighted in the scope of the TS. The main goal of the CEN/TS is to improve the reliability of molecular analysis and molecular data, which are key for both medical diagnostics as well as research and development. Lack of reprodu-

¹ Lippi G, Chance JJ, Church S, Dazzi P, Fontana R, Giavarina D, Grankvist K, Huisman W, Kouri T, Palicka V, Plebani M, Puro V, Salvagno GL, Sandberg S, Sikaris K, Watson I, Stankovic AK, Simundic AM. Preanalytical quality improvement: from dream to reality. *Clin Chem Lab Med.* 2011 Jul;49(7):1113-26.

² National Academies of Sciences, Engineering, and Medicine. Improving diagnosis in healthcare. Washington, DC: The National Academies

³ Freedman LP, Cockburn IM, Simcoe TS. The Economics of Reproducibility in Preclinical Research. *PLoS Biol.* 2015 Jun 9;13(6):e1002165.



cibility of research data results in major financial loss of R&D spending. For example, the loss of expenditures of the US pharmaceutical industry because of lack of reproducibility of research data in pre-clinical development is estimated to be as high as 28 bn US\$ per year, and more than 30% of this loss can be attributed to reference material (Freedman et al., 2015³). The CEN/TS can improve this situation by defining standardisation requirements for the whole pre-analytical workflow from collection of a sample from a patient to transport, processing and stabilisation, and (interim) storage to isola-

tion of analytes. Since different parameters have to be fulfilled for various sample types and analytes, the CEN/TS request that all quality relevant steps and parameters have to be validated for fit-for-purpose and compliance with the validated parameters have to be documented for each sample collected. Therefore, the CEN/TS do define certain reagents to be used or maximal durations or temperatures for the various pre-analytical steps but leave it to the diagnostic manufacturer or user (scientist or diagnostic laboratory) to do so. Consequently, validation studies on pre-analytical para-

eters will create a novel and major need for samples representing a broad spectrum of well defined pre-analytical parameters. This creates a new opportunity for biobanks to become partners for diagnostic assay developers. At the same time only biobanks containing samples that comply with the CEN/TS (and future related ISO standards) can provide samples for biomarker research and development. Therefore, implementation of CEN/TS is important in enabling biobanks to provide samples that allow generation of reliable molecular data and to qualify for sustainable funding.

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QUALITY ASPECT IN ADOPT BBMRI-ERIC

The ambition of BBMRI-ERIC is to implement a world leading Research Infrastructure for biomedical research in Europe – a true gateway for health. A close collaboration between researchers, biobankers, patient advocacy groups, and the biotech and pharma industry is essential in addressing both common and rare diseases as well as societal concerns. Keeping in mind the need for better prevention, diagnostics, and therapy for all, we are aware that every single sample impacts our ability to comprehend disease and, thus, achieve our

goal for a healthier life. Acknowledging that the majority of samples stored in the various biobanks across Europe are currently underused, we believe

in the moral responsibility to ensure knowledge about and access to these resources for research, which have been entrusted to the scientific community by patients and donors for altruistic reasons of solidarity.

Imagine the countless possible applications for the billions of biological samples that are available from biobanks across Europe.

This will be achieved by defining criteria for high quality assured samples and their clinical data to be provided by members for selected disease entities (cancer) and by defining the quality of samples and data.

Statutes of BBMRI-ERIC
“BBMRI-ERIC shall establish, operate and develop a pan-European distributed research infrastructure of Biobanks and Biomolecular Resources in order to facilitate the access to resources as well as facilities and to support high quality biomolecular and medical research.”

ADOPT BBMRI-ERIC¹ has agreed on using colon cancer as the first fully implemented disease entity, where validated data and samples should be made available in the BBMRI-ERIC Gateway. **What is the BBMRI-ERIC Gateway?** Colon cancer is one of the most common cancers

and most National Nodes / Member States have colon cancer programmes to build upon them. Moreover, the quality of interoperable samples and data

¹ ADOPT BBMRI-ERIC is funded by the European Union’s Horizon 2020 research and innovation programme under grant agreement n° 676550.

is defined through implementation of standard operating procedures (SOPs) of each biobank and harmonisation among biobanks. Harmonisation, standardisation and validation of methods, samples and data are pursued to ensure that samples are collected, transported, processed, tested and stored in compliance with the procedures, which assure consistently high quality samples in compliance with international standards and consistently accurate data. Integrate evidence-based criteria and criteria that meet the “intended use” taking into account the different areas of research. In fact, the use determines pre-analytical condition requirement and several uses with special reference to new technologies (e.g., metabolomics, next generation sequencing, and omics data) applied to solid and liquid biopsies.

Work Package 2 is mapping

the well-established European biobanks with the aim of establishing the first BBMRI-ERIC-wide disease cohort for colon cancer, which will become a unique resource for future research in precision medicine. This joint effort is the first step towards the interoperability of European biobanks.



Prof. Marialuisa Lavitrano
National Node Director BBMRI.it
University of Milano-Bicocca

The Work Package aims at facilitating access to quality-defined human disease relevant biological resources including

associated data, in an efficient, quality controlled as well as ethically and legally compliant manner to foster high level research collaboration. This will be achieved by implementing the BBMRI-ERIC criteria for high quality assured samples and their clinical data to be provided by National Nodes for selected disease entities (e.g., colon cancer). This objective involves essentially all BBMRI-ERIC National Nodes and several biobanks within them and will demonstrate the power of being able to integrate resources established in different Member States following harmonised procedures and to make them accessible through the common access portal of BBMRI-ERIC. This is the major factor for successful operation of BBMRI-ERIC.

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NEW ISO STANDARDS FOR BIOBANKING IN DEVELOPMENT – ISO OBJECTIVES AND INVOLVEMENT

There is a new light on the horizon for the biobanking community! Within the International Organization for Standardization (ISO), action for the development of an ISO Standard on „*Biobanking — General requirements for biobanking*“ with the ultimate objective of enabling „high quality bioresources“ has been initiated resulting in a newly registered ISO project in August 2016. The project is part of the work programme of ISO/TC 276 „*Biotechnology*“ and will be internationally referred to as ISO 20387. It is handled in the working group „*Biobanks and bioresources*“ convened by Dr. Georges Dagher and consists of highly qualified experts from research, development, industry, FDA, accreditation bodies, etc. in the realm of biobanking. The Secretariat of

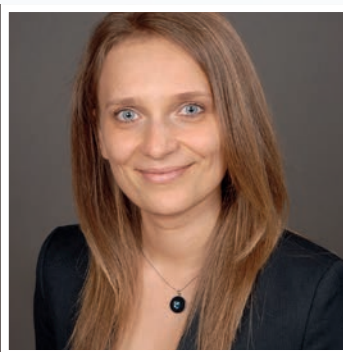
both ISO committees is held by DIN. ISO 20387 will be applicable to all types and sizes of biobanks, recognising that globally, biobanks vary greatly in size, application and emphases. The publication is envisioned no later than mid-2019.



The project was started by screening all relevant Standards and Guidelines (e.g., ISO 15189, ISO/IEC 17020, ISO/IEC 17025, ISO 9001, OECD, WHO), summing up the similarities and adding the necessary requirements for biobanking, which have been missing so far. ISO 20387 will set horizontal

requirements for a biobank's infrastructure, personnel competence, quality management system, equipment, quality control, and the procedures for sample handling, processing and storage, including the validation and verification of methods. It will also be developed with the objectives of providing a reference framework and a universal language for suppliers and customers, facilitating trade and technology transfer by eliminating trade barriers by, e.g., considering relevant legislation (Nagoya Protocol, etc.), and enabling the successful implementation of trade agreements. Furthermore, ISO 20387 will enable a biobank's competence assessment and accreditation leading to stakeholder confidence and assurance, as well

as the organisation's competitive positioning. In addition to ISO 20387, biobanks handling human bioresources should be looking out for three new ISO Standard series on „*Molecular in vitro diagnostic examinations — Specifications for pre-examination processes...*“ for targeted isolated analytes (RNA, DNA, ccfDNA, genomic DNA, proteins) in frozen tissue (ISO 20184), formalin fixed and paraffin embedded (FFPE) tissue (ISO 20166) and venous whole blood (ISO 20186). They are based on the three SPIDIA¹ originated European series of Technical Specifications, CEN/TS 16826, CEN/TS 16827 and CEN/TS 16835, which were published in 2015. The total of 8 ISO Standards share the aim of providing „*high quality biore-sources*“ by defining minimum



Dipl.-Ing. Lena Krieger
Project Manager
Secretary of ISO/TC 276
Secretary of ISO/TC 276/WG 2
Secretary of CEN/TC 140

requirements for each specific pre-analytic workflow starting from the specimen collection and ending with the isolated analyte, including storage, prior to the analytic examination. They are being developed in ISO/TC 212 „*Clinical laboratory testing and in vitro diagnostic test systems*“ in partnership with CEN/TC 140 „*In vitro dia-*

gnostic medical devices“.

ISO provides an international platform for all stakeholders to initiate and to take part in market relevant consensus-based standardisation activities aiming to result in one consented ISO Standard leading to worldwide acceptance followed by various trade benefits. Be one step ahead – the participation in standardisation is a strategic tool and catalyst for a biobank's business success in preparing for relevant future ISO Standards before they are publicly available and allowing their development to be influenced according to your needs and advantages.

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¹ EU FP7 SPIDIA project funded by the European Union Seventh Framework Programme [FP7/2007 2013] under grant agreement no 222916. For further information see www.spidia.eu.

CBMED IS THE FIRST EXPERT CENTRE OF BBMRI-ERIC

CBmed, an Austrian funded competence center, links excellent research infrastructure, scientific expertise, medical knowledge, national and international industry partners for systematic medical biomarker research. The Expert Centre brings together scientific experts with leading pharmaceutical, diagnostic, medical-technology and IT industry partners. Research projects will **identify new biomarkers, validate potential biomarkers and conduct translational biomarker research** for products to be used in clinical practice. CBmed has selected EFQM as its primary framework to achieve business excellence. The dynamic EFQM excellence model is designed to fit organizations of any size, sector or maturity. EFQM is a comprehensive, flexible system which enables CBmed management to view the entire organization from a strategic perspective and focus on continuous improvement.

EFQM is based on eight criteria, five enablers (leadership, people, strategy, partnerships &



From left to right: Dr. Franz Wurm, MedUni Wien/Supervisory Board CBmed, Prof. Jan-Eric Litton, PhD, Director General BBMRI-ERIC, Ing. Robert Fasching, CFO, CBmed and Univ. Prof. Dr. Thomas Pieber, CSO, CBmed

resources, processes, products & services) and four results (people results, customer results, society results, business results). Based on the RADAR logic (plan, do, check, act) the planned results, approaches, and deployment are assessed and thus a structured approach is taken that aims for long-term success. The implementation

of EFQM at CBmed was started in 2015 by specifying the eight criteria for CBmed (Fig 1.) both for management and CoreLabs.

Next steps for 2017 and 2018 include self-assessments (e.g. regarding laboratory relevant CEN standards) and an external audit by BBMRI-ERIC and subsequently Quality Austria.



Fig 1. EFQM @ CBmed

2ND EXPERT CENTRE OF BBMRI-ERIC: THE ATMA PLATFORM

ATMA PLATFORM, AN EXPERT CENTRE TO ACCELERATE CLINICAL RESEARCH WITH FOCUS ON BIOMARKER VERIFICATION AND VALIDATION.



From left to right: Dr. Dino Paladin, AB Analitica, Outi Törnwall, PhD, BBMRI-ERIC, Dr. Gianluigi Zanetti, CRS4 Sardinia, Dr. Giorgio Stanta, University of Trieste, Prof. Jan-Eric Litton, PhD, BBMRI-ERIC and Dr. Paolo de Paoli, CRO

ATMA-EC is a BBMRI-ERIC Expert Centre, a non-profit organisation with a public-private partnership with focus on Biomarker verification and validation.

ATMA set up a Quality Management System, based on ISO standards and the most recent international guidelines to meet both statutory (national and international-EU legislations) and regulatory requirements. ATMA has selected the International Standard Organisation Quality Management Systems as reference framework and in particular the ISO 9001:2015 Standard with i) a Process-based approach which enables the center to manage and control interrelated pro-

cesses and to extend the quality assurance strategies also to external parties. Moreover it allows also the rationalisation of activities, to prevent re-processing and errors and it supports a task-oriented organisation; ii) a Risk-based approach which is essential to determine the factors that may adversely affect the expected results, enabling ATMA to implement risk-containment strategies and to leverage risks as inputs for improvement and innovation. The continuous quality improvement model selected by ATMA is the PDSA or Deming Cycle, which is the elective model for the implementation of a process-based organisation. The phases of the Deming cycle can be summarised as follows:

The cycle begins with the Plan step. This involves identifying a goal or purpose, formulating a theory, defining success metrics and putting a plan into action. These activities are followed by the Do step, in which the components of the plan are implemented, such as making a product. Next comes the Study step, where outcomes are monitored to test the validity of the plan for signs of progress and success, or problems and areas for improvement. The Act step closes the cycle, integrating the learning generated by the entire process, which can be used to adjust the goal, change methods or even reformulate a theory altogether. These four steps are repeated as part of a never-ending cycle of continual improvement. (Source: *The W. Edwards Deming institute* <https://www.deming.org/theman/theories/pdsacycle>). ATMA also adopted a proactive approach to quality control, which include a systematic and periodic self-assessment against international standards of excellence, internal auditing and periodic external audits by BBMRI-ERIC management.

BBMRI-ERIC: OUR NATIONAL NODES AND QUALITY EXPERTS IMPROVE QUALITY IN BIOBANKING



AUSTRIA

High quality and data-rich samples are essential for future research. BBMRI.at works towards fulfilling this demand and puts its focus on excellent and harmonised sample, data and quality management. All BBMRI.at partner biobanks committed themselves to establish and, where this has already been done, maintain QM-systems according to ISO 9001. Key realisation processes are currently harmonised on the basis of CEN/TC 140 technical specifications (CEN/TS) on the pre-analytical phase. Cross-quality audits between BBMRI.at partner biobanks, starting in January 2017, will ensure further improvement by qualified mutual consultancy. BBMRI.at partners were involved in the development of the CEN/TS and share this knowledge regarding CEN/TS-conform sample processing in practical training courses.

Mag. Dr. Helmuth Haslacher
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Mag. Cornelia Stumptner
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BELGIUM



“Quality of samples and data is a crucial link between research and outcome. Only research performed with high quality samples and high quality associated data can be used for the identification of predictive and prognostic markers in patients.”

Dr. Annelies Debucquoy
National Node Director
BBMRI.be
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A quality driven approach is indispensable in all aspects of biobanking at the University Hospitals Leuven Biobank. It is elementary to assess the clinical quality by evaluating upfront which and how samples will be collected and used for meaningful research. Biobanking quality also relies on an evidence-based view of the numerous technical aspects. These efforts need to be carefully applied to avoid the quality paradox, e.g., that in the pursuit of quality the achievement of it is compromised.

Johan Klykens, Msc
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CYPRUS

“As we move ahead and invest more into Biobanking, quality of data and material matters more than anything else. Scientific soundness and high quality is a must for generating trustworthy results to benefit the patients and society.”

Prof. Constantinos Deltas
deltas@ucy.ac.cy

“Having in place a set of standardised procedures and protocols, that ensure the delivery of optimally preserved biological resources to the research community in Cyprus and Europe is our main objective.”

Prof. Kyriacos Kyriacou
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CZECH REPUBLIC

The effects of preanalytical factors on sample quality variation are crucial and need to be duly monitored. A focus on personnel resources and requirements (qualification, periodical training, etc.) helps to ensure that large numbers of high quality and well-annotated samples are collected, processed, and stored in standardised ways. All these processes were harmonised with national (NASKL) and international standards (ISO 15189) where applicable in clinical biobanks serving usually as source laboratories.

We conduct proactive risk management activities that identify and predict system weaknesses and adopt changes to minimise risks and maximise consistent quality through implementation of tools such as FMEA and periodical internal audits. Failure modes and effects analysis (FMEA) is an evaluation technique used to identify and eliminate known and/or potential failures, pro-



Long term cryostoring of biological material specimens in monitored area.

blems, and errors from a system/process before they actually occur.

RNDr. Martina Mrkvicová
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“Quality assurance is an essential part of good science. Keeping and controlling the process integrity in biobanking is a critical prerequisite in identifying clinically useful markers of disease, discovering new drug targets, and understanding the mechanisms of disease. Unless adhering to strict overall quality measures, results may be of no benefit to patients.”

Dr. Dalibor Valik
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ESTONIA

Ensuring sample quality is the primary consideration in all sample release procedures at the Estonian Genome Center. DNA sample picking is performed by an automated storage system in order to remove possible sources of error.

Prior to release, every single picked sample will go through both standardised and project-specific QC procedures, including assessment of DNA integrity, purity and quantity.

This contributes to achieving 99%+ first run success rates in large-scale sequencing projects and other research uses, and is instrumental in building trust in the biobank services.

Steven Smit, BSc
steven.smit@ut.ee



Dr. Andres Metspalu

“Estonian Genome Center of University of Tartu (EGCUT) maintains and develops the Estonian Biobank.

EGCUT is coordinating the Estonian Research Roadmap Program “Genome Center” together with the Estonian Biocentre and also coordinates the “Centre of Excellence in Genomics and Translational Medicine”.

EGCUT will participate in the “Estonian Program for Precision Medicine” coordinated by the Estonian Ministry of Social Affairs.”

Dr. Andres Metspalu
National Node Director
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FINLAND

There are 8 public biobanks in Finland, six clinical biobanks owned by the hospital districts and universities; a national hematological biobank and a population biobank of the National Institute for Health and Welfare (THL). Old samples (e.g., collected before the Finnish Biobank Act came into force) and associated data are the basic asset of especially clinical biobanks, whereas THL Biobank utilises blood-derived samples and data. New samples with high and uniform quality are constantly collected by laboratories, which are accredited according to EN ISO 15189 and/or EN ISO/IEC 17025 or certified according to criteria set forth by IAP. THL Biobank follows the EN ISO/IEC 17025 for sample collection and analysis. Biobank Quality Managers have constant discussions on topics related to quality.

Aulikki Santavuori, MSc
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“Finland aims to establish an official biobank consortium and implementation of common quality standards is an essential part of the national joint operations. It will be of great help to the Finnish biobanks that BBMRI-ERIC has taken up the excellent activity in establishing working groups of quality and aims to survey biobanks for CEN compliance as well as develop an audit programme.”

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FRANCE

“Increase quality, reduce costs.”

Dr. Georges Dagher
Convenor of ISO/TC 276/WG 2
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A French standard for quality management of biobanks was developed in 2008 and implemented in individual biobanks. There were 52 certified biobanks in 2015. To help the implementation of quality management in biobanks, the infrastructure published a guide book in French and English and trained 120 individuals. The infrastructure set up a basic training in biosafety and biosecurity, and published in 2015 a guide of good practices to harmonize existing documents and practices. The French infrastructure will pursue its endeavor in coordination with other BBMRI-ERIC national nodes to provide high quality biological samples to fit research and diagnostic purposes.

Biobanques
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GERMANY

The German Biobank Node (GBN, BBMRI.de) is developing a detailed quality management concept for liquid and tissue biobanks in Germany. Quality-oriented generic Standard Operating Procedures (SOPs), which are in line with recently published European Standards and harmonised with upcoming International CEN/TS for the pre-analytical phase, are being established. These generic SOPs will be made available by BBMRI.de to give guidance for both experienced and new biobanks in Germany to provide high quality biomaterials with associated medical and epidemiological data to academic and industrial researchers.

Dr. Cornelia Rufenach
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“One of the aims of the central contact and exchange point for the German biobank community, GBN (the German Biobank Node, BBMRI.de), is the development of and adherence to standards for quality assurance.”

Prof. Dr. Michael Hummel
National Node Director BBMRI.de
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ITALY

„BBMRI.it has implemented the Common Service Quality (CSQ), with the following objectives: monitor biobanks and bio-molecular resources, provide information on guidelines and best practices, harmonise operational procedures, develop criteria for the accreditation and certification of biobanks, implement the quality management system criteria of BBMRI-ERIC in the Italian network, improve interoperability, promote training on the issues of quality.

CSQ provides support to both Italian hospitals, universities and research institutes that are planning to build new facilities, and already existing research collections in the path to a fully established Quality management system. CSQ closely collaborates with regional and thematic networks as far as quality issues are concerned.”

Dr. Barbara Parodi
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Sample storage in the IRCCS-CROB Basilicata Biobank, Italy.

LATVIA

Genome Data Base of the Latvian population recognises quality as a main foundation for the sustainable development of biobanks. Our strategies to ensure quality include **1)** standardisation of procedures (SOP) based on published guidelines and our own experience of bio-sample management and **2)** laboratory information management system (LIMS) that support biosample circulation securing exact workflow and data tracking. We regard these aspects as crucial to enhance biobank quality, credibility, safety, compatibility and repeatability.

Vita Rovite, PhD
vita.rovite@biomed.lu.lv

“In a country where biobanking has been started from scratch relatively recently the quality management of samples and data is of crucial importance to maintain the integrity of bio-collections obtained under different conditions for successful use in research. Development and implementation of the common quality standards at the European level would help to increase the use of resources from smaller biobanks in collaborative studies.”

Dr. Janis Klovinš
National Node Director BBMRI.lv
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MALTA

At BBMRI.mt, we believe that harmonisation of pre-analytical procedures in human biobanking is the key to progress in the search for reliable biomarkers. This is why we are joining our many collaborating

“Like many biobanks, the Malta BioBank / BBMRI.mt has committed itself to ensure high quality across its operations because the quality image is important to encourage the participation of research partners and adds value to the sample collections.”

Prof. Alex Felice
National Node Director BBMRI.mt
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partners in the BBMRI-ERIC network to develop a common quality management system that meets the requirements of the recently published CEN/Technical Specifications for pre-examination processes. As a small biobank, the Malta BioBank can act as a prototype for biobanking quality practices.

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Joanna Vella, MSc
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THE NETHERLANDS

Within BBMRI-NL, the sample integrity working group has taken up the task of stimulating sample quality awareness, with focus on the pre-analytics during sample collection. Also the

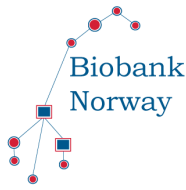
focus of the CEN Technical Specifications resulting from SPIDIA, which show sample metadata, is crucial to get a grip on the reproducibility of research results. Sample quality is the sum of the physical quality and the quality of the accompanying data including sample metadata and crucial for research. Therefore, BBMRI-NL plans to provide high quality biobanks through

data registration at the source and implementation of best practices and standards like FAIR.

Peter Riegman, PhD
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“In order for personalised medicine & health research to really deliver on better clinical & public health outcomes, having the right level of quality assurance in place at all steps of the translational research process chain is critically important. This applies in particular for biobanks, as they are at the root of this process chain. Equally important it is to facilitate researchers, by providing them with dedicated IT tools that help them to efficiently conduct their studies, while at the same time making them comply with the right quality standards, e.g. compliance by design.”

Prof. Gertjan van Ommen
National Node Director BBMRI-nl
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NORWAY

Strategic actions taken include the establishment of a shared organisation called Biobank Norway (<https://www.ntnu.no/web/biobanknorge/biobanknorge>) which contains relevant information about the biobanks, international cooperation, contacts and a best biobank practice as a common ground.

A recent development is the opening of a service platform for biobank support to help share knowledge and good advice where we can use a broad network, including partners within BBMRI-ERIC to share experience and discuss solutions since every biobank has its own challenges and infrastructure.

All partners have contributed to establish a Best Biobank practice as a foundation for the quality work as a tool and base line. In addition, some biobanks have implemented relevant standards or accreditation depending on needs and rele-

vance. For example, the HUNT research center and the biobank at the National Institute of Public Health (FHI) are certified according to ISO-9001:2008 currently undergoing revision to the 2015 version. The biobanks has strategically chosen to put a lot of effort to the quality aspect as this is important for enabling research on a high level with valid and reproducible results. The Norwegian Node includes both population-based and clinical biobanks with long experience of collection, processing, retrieval of material and analysis. However, the biobanks have both concomitant and different tasks and procedures. Therefore, we try to meet and learn from each other and to harmonise how we can make our biospecimens more comparable in a national and international context.

Ida Ericsson, MSc
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“Standardised routines and a well-established quality management system gives a foundation for sustainable and comparable research globally”.

Prof. Kristian Hveem
National Node Director BBMRI.no
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-20 automated storage NIHP-Biobank Oslo




Christine Currat National Node Director BBMRI.ch, Laurence Chapatte and Sofiane Nacia from the Swiss Biobanking Platform.



POLAND

Polish Node BBMRI.pl started working on quality issues in 2015 by participating actively in the BBMRI-ERIC expert group led by Andrea Wutte. On top of that, the consortium of Polish Biobanks applied for funding to the Ministry of Science and Higher Education which is expected to support the development of a fully functioning biobanking network in Poland. One of the major milestones included in this project is Quality Assurance. Initially Poland is planning to work out tools suitable for Polish biobanks and introduce them in 7 biobanks as a pilot trial. Once they are validated they will be available for every biobank working in the Polish network. All steps have been based on the BBMRI-ERIC action plan for quality.

BBMRI.pl quality assurance group



“Quality plays a crucial role in many aspects of biomedical research, but in biobanking it is the way of living. We may invest a lot of money in modern biobanking technology, but it is pointless if not connected to quality assurance criteria.”

Dr. Lukasz Kozera
National Node Director
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SWITZERLAND

Promoting sample sharing and improving comparability of samples is of central importance for the Swiss Biobanking Platform (SBP). Improvement of sample quality by reaching compliance with international quality and implementation of Quality Management Systems are essential to fulfill these tasks. Different services are therefore developed to support the biobanks:

- Documentation such as quality policy, quality handbook and templates
- Training to upgrade stakeholder skills on biobank QMS
- Inventories, pre-audits and internal audits

Moreover, six local SBP coordinators will support biobankers in this quality strategy implementation.

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UNITED KINGDOM IARC

BBMRI.uk is committed to establishing an understanding about what makes samples re-usable.

Quality of samples and data remains a key component to ensure that the re-use of samples can be achieved. We are glad we have been able to contribute the previous work of the Confederation of Cancer Biobanks to the wider European network.

Quality cuts across all aspects of our work at IARC. We pay particular attention to recording and documenting the different processes and activities related to the life cycle of biological samples and their associated data. For us, quality means developing and adopting fit-for-purpose protocols to manage and govern our biobank in accordance with international guidelines.

We focus on standardisation and harmonisation of practices for collaborative studies conducted worldwide, including in low and middle income countries, for which biological samples and data are stored and managed within the IARC biobank.

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“Standardised routines and a well-established quality management system gives a foundation for sustainable and comparable research globally.”

Dr. Phil Quinlan
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THE SPIDIA4P PROJECT PARTNERS¹

“Because analytical test results are dependant on the quality of the tested sample, it is of utmost importance that the handling and documentation of the primary sample during the pre-analytic phase is done in a standardised manner. For this to be facilitated and widely spread, in order to enable the urgently needed improvement in the pre-analytic field, standardisation is key.”

Dr. Uwe Oelmüller, SPIDIA Coordinator

Publisher: Andreea Gulacsi – © CEN & CENELEC - September 2014



Picture kindly provided by the SPIDIA4P coordinator QIAGEN GmbH



LGC LIMITED

“LGC is an international life sciences measurement and testing company and the UK’s national measurement laboratory for chemical and bio-measurement. As a leader in genomic measurements LGC is proud to support SPIDIA4P’s development of quality standards for biobanking and precision medicine. Increasingly, measurement at trace levels in complex biological matrices using novel technologies such as NGS, compounded by poor sample quality, can

result in errors. Improved quality and standardisation of sample collection, storage and (pre-) analytics is key for enhanced measurement reproducibility in precision medicine. In SPIDIA4P LGC represents European Metrology (EMPIR), provides nucleic acid materials to EQA schemes and contributes to CEN and ISO standards development.”

Helen Parkes, Bsc
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TECHNISCHE UNIVERSITÄT MÜNCHEN

“One of the special activities of the biobank of the Technical University of Munich (TUM) and the hospital Klinikum rechts der Isar (MRI) in Munich was to establish a unique tumor tissue collection for quality control and biomarker stability testing. The distinctive feature of this tissue collection is that the samples have been exposed in a controlled fashion to different ischemic conditions from zero up to 180 min before freezing or formalin fixation. As partner of SPIDIA and the m4 Munich Cluster of Excellence, the TUM/MRI biobank - in particular the Institute of Pathology - contributes to CEN Technical Specifications and ISO International Standards.”

Prof. Karl-Friedrich Becker
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¹ Spidia4P is funded by the European Union's Horizon 2020 research and innovation programme under grant agreement n° 733112.



TATAA BIOCENTER AB

“Being part of SPIDIA and addressing the various challenges in the pre-analytical process and contributing to the writing of the CEN and ISO guidelines was most instrumental to us at TATAA Biocenter. It guided our development of quality control tools such as the RNA and DNA spikes, InterPlate Calibrator, ValidPrime for genomic background subtraction, and the Damp assays to assess RNA integrity. We can now provide our customers with high quality and exceedingly robust data in their biomarker discovery and validation processes.”

Prof. Mikael Kubista
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tataabiocenter



UNIVERSITA DEGLI STUDI DI FIRENZE

*“Department of Biomedical Experimental and Clinical Science, University of Florence, Italy
Within the FP7 EU Project SPIDIA, 6 EQAs, specifically designed for monitoring the performance of the pre-analytical phase of DNA, cell free DNA and RNA testing in blood samples, have been implemented. More than 320 applications from 220 laboratories of 30 European countries were obtained. At the SPIDIA laboratories the DNA, RNA and cell free DNA samples obtained from the participants were tested for quality/quantity/integrity and stability. From the SPIDIA-EQAs, the most critical steps in the pre-analytical procedure were identified; the results of these studies enabled the development of 3 European Technical Specifications (CEN/TS, published) and 3 ISO documents (under revision).”*

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CONSORZIO INTERUNI- VERSITARIO RISONANZE MAGNETICHE DI METALLO PROTEINE

“CIRMMP has been involved in a number of activities aimed at tackling the use of metabolomics in biomedicine. In the FP7 SPIDIA project, CIRMMP contributed the conceptual basis for the development for the CEN Technical Specification CEN/TS 16945:2016 “Molecular in vitro diagnostic examinations - Specifications for pre-examination processes for metabolomics in urine, venous blood serum and plasma”. Within SPIDIA4P, this document will be developed into ISO Standards. CIRMMP will also foster the interactions of SPIDIA4P with the H2020 metabolomics e-infrastructure PhenoMeNal and with the international consortium EXCEMET, which is aimed at promoting metabolomics for the evaluation of sample quality in biobanks.”

Prof. Paola Turano
turano@cerm.unifi.it





**UNIVERSITA
DEGLI STUDI
DI TRIESTE**

“One of the major interests of the laboratory is standardisation of pre-analytical conditions of tissues, this is one of the reasons for its participation in the ESP-OECI Working Groups for preanalytics and now in the European project SPIDIA4P, which is a recently approved H2020 project. Pre-analytical conditions of tissues are crucial for correct and reproducible analyses in clinical tissues. Preanalytical conditions cover all the phases of tissue processing, from warm (in the surgical theatre) and cold ischemia (after tissue removal from the body) to fixation and extraction procedures, but also for in situ methods, in which the lab is especially interested. These studies were part of the BBMRI-ERIC programme on quality management of tissues aiming to harmonise CEN Technical Specifications for European biobanks.”

Prof. Giorgio Stanta
stanta@impactsnetwork.eu



**UNIVERSITA
DEGLI STUDI
DI TORINO**

“The pre-analytical phase of surgical pathology can be considered the “Cinderella” of the whole process of tissue-based diagnosis and research studies. Optimal fresh tissue-specimen preservation during transfer to the pathology lab is a crucial factor in obtaining adequate material for any type of morphological or molecular analyses. However, due to the lack of guidelines, this often fails to take place. We are working on the validation of technologies for fresh tissue transfer and preservation. This endeavour will lead to additional CEN/Ts to be used by different stakeholders, with the final aim of improving the confidence in the quality of the generated analytical data.”

Dr. Anna Sapino
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**LUXEMBOURG
INSTITUTE
OF HEALTH**

“As a biobank and bioservice provider, IBBL has put enormous emphasis on quality and built its whole operations around a formal Quality Management System (QMS). This strategy paid off as IBBL is today ISO 9001 and NF S96-900 certified, as well as ISO 17025 accredited. The results of our biospecimen research flow directly into our QMS and our bioservices are heavily quality-focused, including e.g., validated processing methods, QC assays and a proficiency testing (PT) programme. We are proud to be part of the efforts to improve pre-analytical quality on a larger scale by developing new PT schemes for SPIDIA4P and by participating in the ISO/TC 276.”

Dr. Fay Betsou
fay.betsou@ibbl.lu





**MEDIZINISCHE
UNIVERSITÄT
GRAZ**



INSERM

“The Medical University of Graz has already been member of the FP7 EU Project SPIDIA as lead of the work package “Validation of tissue-related technologies and documentation for standardization activity” and contributed to the development of the already published CEN/TS. The Medical University of Graz is also partner of the H2020 project SPIDIA4P which started in January 2017 and leads the work package “Implementation and Dissemination of Standards & External Quality Assurance Schemes” and two tasks which aim at developing an ISO standard for in-situ staining on FFPE tissue and a CEN/TS for microbiome DNA from stool and saliva. In addition, the Medical University of Graz contributes to the generation of three other CEN/TS. Since the Medical University of Graz hosts the National Node BBMRI.at, it will link the available expertise of BBMRI.at partners to the SPIDIA4P consortium.”

Prof. Kurt Zatloukal

kurt.zatloukal@medunigraz.at

Dr. Penelope Kungl

penelope.kungl@medunigraz.at

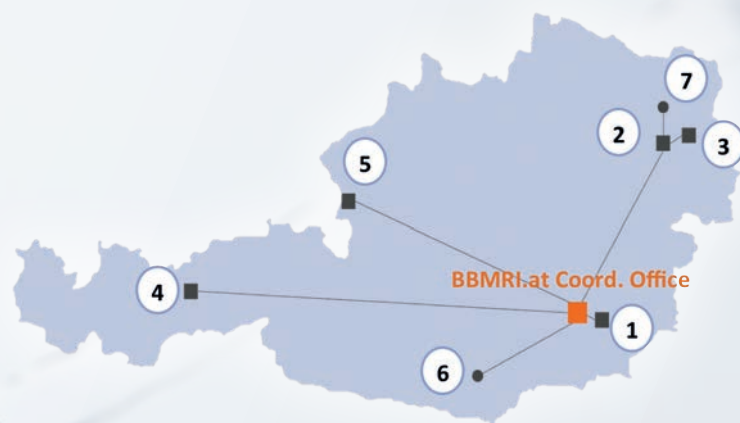
Mag. Cornelia Stumptner

cornelia.stumptner@medunigraz.at

“INSERM is also involved in the newly funded SPIDIA4P project and will contribute to the development of 12 new CEN/TS as described in this magazine. It will also explore the possibility of funding their implementation.”

Dr. Georges Dagher

georges.dagher@inserm.fr



BBMRI.AT PARTNERS AND BIOBANKS

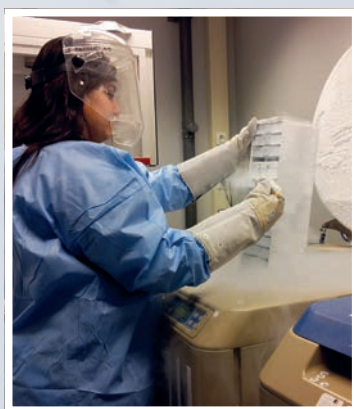

- ① Medical University of Graz (coordination) with Biobank Graz
- ② Medical University of Vienna with MedUniWien Biobank
- ③ University of Veterinary Medicine with VetBiobank
- ④ Medical University of Innsbruck with Innsbruck Biobank
- ⑤ Paracelsus Medical University (biobank planned)
- ⑥ Alpen-Adria University Klagenfurt
- ⑦ Life Science Governance Institute



ROTTERDAM ERASMUS UNIVERSITY

“The new partner Erasmus Universitair Medisch Centrum Rotterdam makes tissues, collected during the routine diagnostic pathology process, available for medical research through secondary use. The tissue bank is completely integrated in the diagnostic process and therefore imbedded in the department ISO 15189:2012 accreditation. Extra focus is placed on frozen and FFPE tissue sample quality issues, QA and QC due to participation in the SPIDIA project. This resulted in the composition of the published CEN Technical Specifications (CEN/TS) and SPIDIA4P. Where new CEN/TS will be developed and CEN/TS are brought to the ISO level with preparations for implementation.”

Peter Riegman, PhD
p.riegman@erasmusmc.nl

CENTRO NACIONAL DE ANÁLISIS GENÓMICO

“The success of the work done at genome centers such as the Centro Nacional de Análisis Genómico (CNAG-CRG) depends critically on upstream and efficient biobanking infrastructures and the correct handling of biomolecular resources.

BBMRI-ERIC is a clear example of outstanding performance in this regard and gives researchers high quality support.

We are very lucky to have BBMRI-ERIC as one of our partners. Their valuable work is crucial to advance the already fast-paced field of genomics, moving us towards the goal of improving human well-being.”

Dr. Ivo Gut
ivo.gut@cnag.crg.eu




FONDAZIONE IRCCS ISTITUTO NAZIONALE DEI TUMORI

“Within the SPIDIA4P project, the team of Dr. Verderio, at the Fondazione IRCCS Istituto Nazionale dei Tumori of Milan, will supervise all the statistical-methodological aspects among the involved consortia in order to strive for joint cooperation and continuous interaction between SPIDIA4P partners, in addition to data integration and harmonization with the final aim of presenting data in the right statistical manner in our upcoming CEN/TS and ISO/IS.

This implies a common quality framework based on a set of indicators of good statistical practice aimed to improve both methodology and effectiveness of the implemented methods. Dedicated procedures will be developed and routinely applied for checking data collection, data entry and coding as well as for assessing and validating sources of data, intermediate results and statistical outputs.”

Dr. Paolo Verderio
paolo.verderio@istitutotumori.mi.it

QUALITY MANAGEMENT SERVICES

WHAT IS THE QM SERVICE ABOUT?

BBMRI-ERIC provides tools and expertise, as well as knowledge and experience sharing on quality management for biobanks and research on biomolecular resources.

WHO IS THIS SERVICE FOR?

The service offers support on quality management related to biobanking activities. It is primarily intended for users located in Member Countries of BBMRI-ERIC.

HOW CAN I ENGAGE?

Sign up for the e-Newsflash!
Sign up to our QM expert Working Groups. See QM info & experts at a glance!
<http://bbmri-eric.eu>

WHO TO CONTACT?

Andrea Wutte, MSc, Quality Manager BBMRI-ERIC, andrea.wutte@bbmri-eric.eu

KEY QM SERVICES

- ✓ QM consultancy programmes (for Guidelines and Standards)
- OECD Best Practice Guidelines for Biological Resource Centres
- Common Minimum Technical Standards and Protocols for Biological Resource Centres dedicated to Cancer Research
- Guidelines for Human Biobanks and Genetic Research Databases (HBGRDs)
- ISO* Standards of Series 9001, 15189, 15190, 17025, 19011
- CEN**/Technical Specifications (TS) 16826-1/2; CEN/TS 16827-1/2/3; CEN/TS 16835-1/2/3; CEN/TS 16945:2016

Others to be forthcoming

- ✓ QM monitoring and audit programmes on demand
- ✓ QM training and education formats
Expert working groups, webinars, web-conferences
- ✓ QM documentation and assessment
Documents and tools for biobanks

* ISO (International Organization for Standardization),

**CEN (European Committee for Standardization)

Stockholm, Sweden | September 13-15, 2017

GLOBAL BIOBANK WEEK

Towards Harmony
in Biobanking

www.globalbiobankweek.org

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