Was ist „Qualität“ und wie können Biobanken zu ihrer Verbesserung beitragen?

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Disclaimer

- Helmuth Haslacher
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  - No conflicts of interest

BBMRI.at Biobanking and BioMolecular resources Research Infrastructure Austria
BIOBANK MEDIZINISCHE UNIVERSITÄT WIEN
Wiener Gesundheitsverbund Universitätsklinikum AKH Wien

Why do we need biobanks?

Published OnlineFirst July 17, 2014; DOI: 10.1158/0008-5472.CAN-14-0925

Perspective

Cancer Research

The Increasing Urgency for Standards in Basic Biologic Research

Leonard P. Freedman[1] and James Inglese[2]

Open access, freely available online

Essay

Why Most Published Research Findings Are False

John P.A. Ioannidis

- Review of studies aiming to quantify the share of irreproducible studies
- Ranged from 68-89%!!!
- >65% of senior academic faculty had experienced being unable to reproduce published findings. If authors were contacted: In 60% of cases, indifferent, negative or no response from authors was received.

JOURNAL ARTICLE

An estimate of the science-wise false discovery rate and application to the top medical literature FREE

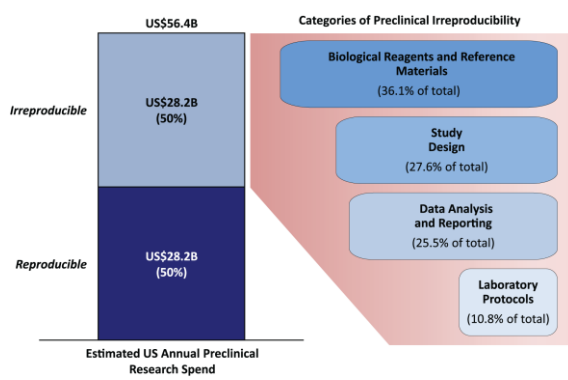
Leah R. Jager, Jeffrey T. Leek

Biostatistics, Volume 15, Issue 1, January 2014, Pages 1–12, https://doi.org/10.1093/biostatistics/kxt007

Published: 24 September 2013 **Article history**

Why do we need biobanks?

- High economic burden
- Annually USD ~30 billions wasted for non-reproducible research in the US alone



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

What is quality?

- **Quality**
  - "degree to which a set of inherent characteristics of an object fulfils requirements […] The term "quality" can be used with adjectives such as poor, good or excellent" (ISO, 2015)
    - "Needs, requirements and expectations are constantly changing.
    - Performance needs to be constantly changing to keep pace with the needs.
    - Quality is the difference between the standard stated, implied or required and the standard reached." (Hoyle, 2007)

What is quality?

- **Requirements**
  - Who are interested parties with requirements (active or passive)?
    - Users/Collaborators (1st party, 2nd party; academic, industrial)
    - Patients
    - Hospital
    - University
    - Funders
    - Legislator (FOG, KAG,…)
    - Ethics committee
    - Scientific community…

What is quality?

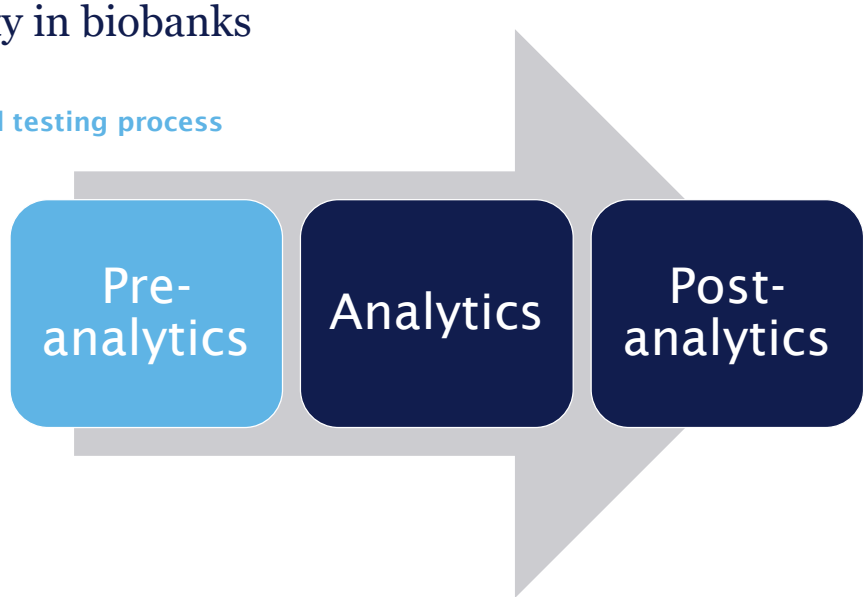
- **Requirements**
  - Who are interested parties with requirements (active or passive)?
    - Users/Collaborators (1st party, 2nd party; academic, industrial)
    - Patients
    - Staff
    - Safety officers/Labour inspectorat
    - Hospital
    - University
    - Funders
    - Legislator (FOG, KAG,…)
    - Ethic committee
    - Scientific community…

Quality in biobanks

- **Requirements**
  - Protocols / Guidelines

Quality in biobanks

The total testing process



Quality in biobanks

The pre-analytical phase

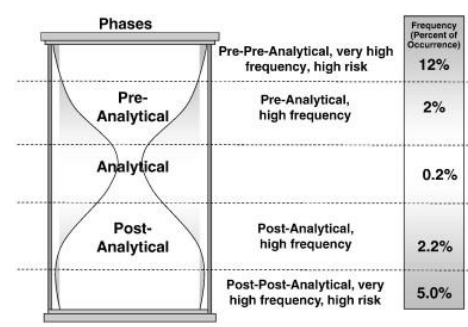
ELSEVIER
Clinica Chimica Acta
Volume 404, Issue 1, 6 June 2009, Pages 16–23
Errors in Laboratory Medicine and Patient Safety

Exploring the iceberg of errors in laboratory medicine

Mario Plebani

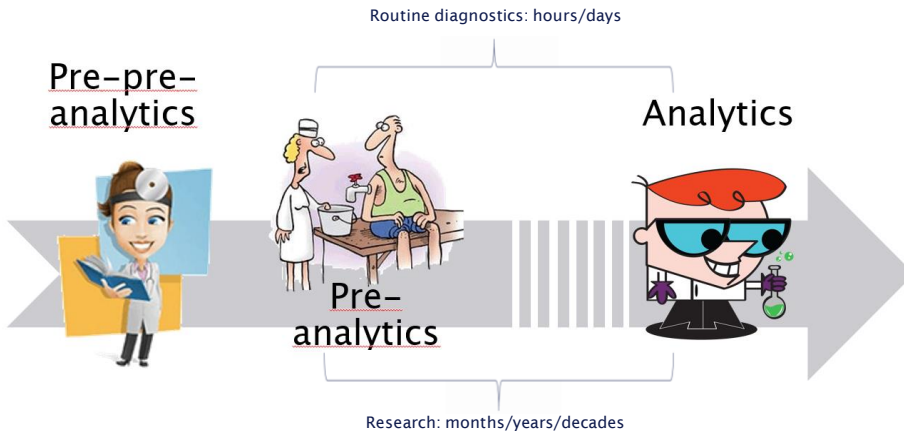
Table 2.
Frequency of errors (%) in the main phases of the total testing process.

Year	Author(s)	Pre	Intra analytic	Post	Reference
•1991	Ross et al.	45.5	7.3	47.2	17
•1997	Plebani et al.	68.2	13.3	18.5	18
•2003	Astion et al.	71.0	18.0	11.0	26
•2007	Carraro et al.	61.9	15.0	23.1	19



Quality in biobanks

- Pre-analytical phase is extremely extended in biomedical research



Quality in biobanks

ISO/TC276

Horizontal Standard (management aspects)

Vertical Standards (operations)

Vertical Standards (operations)

Vertical Standards (operations)

Vertical Standards (operations)

CEN/TC140

ISO/TC212

SPIDIA4P SPIDIA

QM standards

- ISO 20387:2018 Biotechnology — Biobanking — General requirements for Biobanking
  - Published in 08/2018
  - "developed with the object of promoting confidence in Biobanking"
  - "requirements to enable biobanks to demonstrate competent biobank operation and the ability to provide biological material and associated data of appropriate quality for research and development"
  - "applicable to all organizations performing biobanking, including biobanking of biological material from multicellular organisms (e.g. human, animal, fungus and plant) and microorganisms for research and development."

QM standards

- ISO 20387:2018 Biotechnology — Biobanking — General requirements for Biobanking
  - Chapter 1 Scope
  - Chapter 2 Normative references
  - **Chapter 3 Terms and definitions**
    - 54 definitions, e.g. for the terms "biobanking", "sample", "associated data", "traceability",…

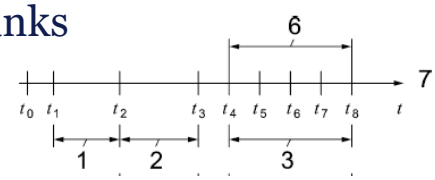
QM standards

- ISO 20387:2018 Biotechnology — Biobanking — General requirements for Biobanking
  - **Chapter 4 General requirements**
    - Requirement for impartiality (objectivity; absence of conflicts of interest) and confidence
  - **Chapter 5 Structural requirements**
    - Requirements regarding a biobank's management structure and governance
  - **Chapter 6 Resource requirements**
    - Contains paragraphs about personnel, environmental and infrastructural (equipment) resources
    - Regulates external (outsourced) processes, purchased products and services

QM standards

- ISO 20387:2018 Biotechnology — Biobanking — General requirements for Biobanking
  - **Chapter 7 Process requirements**
    - Deals with realization process ("operations")
    - Requirements for documentation (quality-related, associated data)
    - Sample collection procedure
    - Sample processing and storage
    - Access to and distribution of material and data
  - **Chapter 8 Quality management system requirements**
    - Fulfilled, if biobank runs a ISO 9001:2015 certified QMS/is included in an ISO 9001:2015 certificate
    - If not: requires to develop a QMS which is pretty close to ISO 9001:2015

Quality in biobanks



Key			
1	warm ischemia	t_1	vessel ligation
2	transport	t_2	surgical resection
3	experimental delay to freezing	t_3	freezing of the reference sample
4	cold ischemia	t_4	freezing of aliquot sample 1
5	experimental delayed cold ischemia	t_5	freezing of aliquot sample 2
6	different time points in the laboratory until freezing	t_6	freezing of aliquot sample 3
7	molecular analysis	t_7	freezing of aliquot sample 4
t	time	t_8	freezing of aliquot sample 5
t_0	start of surgery		

Figure A.1 — Overview of tissue collection

CEN/TS 16826-2:2015





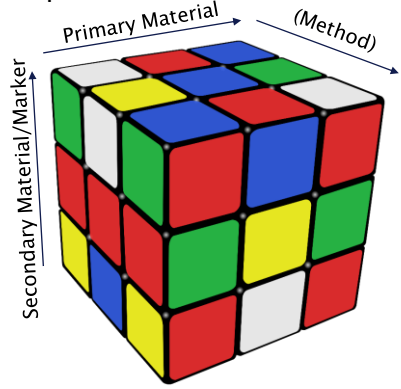




QM standards

- CEN/TS / ISO Standards on the pre-examination phase
  - Multidimensional approach

FFPE - Isolated RNA
FFPE - Isolated proteins
FFPE - Isolated DNA
FFPE - in situ detection techniques
Fresh Frozen Tissue - Isolated RNA
Fresh Frozen Tissue - Isolated proteins
Fresh Frozen Tissue - Isolated DNA
Venous Whole Blood - Isolated cellular RNA
Venous Whole Blood - Isolated genomic DNA
Venous Whole Blood - Isolated ccfDNA from plasma
Metabolomics in urine, venous whole blood serum and plasma
Saliva - Isolated human DNA
Isolated microbiome DNA
Venous Whole Blood Exosomes/Vesicles - DNA, RNA and proteins
Venous Whole Blood - Isolated ccfRNA from Plasma
Urine/Body Fluids - Isolated cfDNA
Venous Whole Blood circulating tumor cells - Isolated RNA
Venous Whole Blood circulating tumor cells - Isolated DNA
Venous Whole Blood circulating tumor cells - Preparations for analytical staining
Fine Needle Aspirates - Isolated genomic DNA
Fine Needle Aspirates - Isolated cellular RNA
Fine Needle Aspirates - Isolated protein



Quality in biobanks

- CEN/TS / ISO standards on the pre-examination phase

5.1.3 Primary venous whole blood sample collection from the patient and stabilization procedures

1. The identity of the person collecting the primary sample and the time of blood collection according to EN ISO 15189:2012, 5.4.4.3, f) shall be documented.

5 Outside the laboratory

5.1 Primary venous whole blood collection manual

5.1.1 Information about the primary sample donor

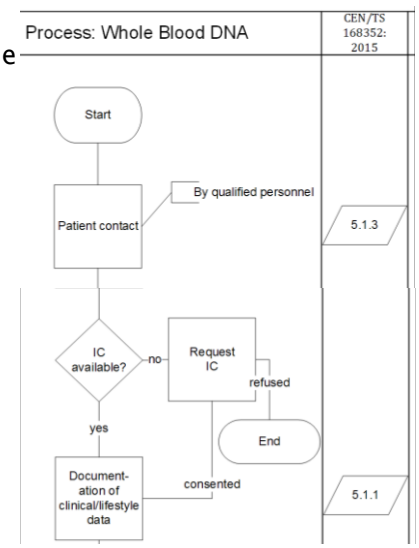
The documentation should include, but is not limited to:

a) the primary donor / patient ID, which can be in the form of a code;

b) the health status and relevant lifestyle factors of the blood donor (e.g. healthy, disease type, gender, age);

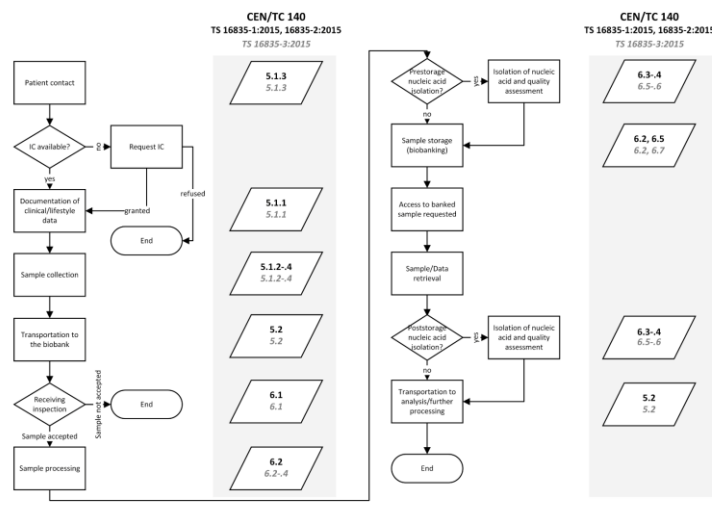
c) the information about medical treatment and special treatment prior to blood collection (e.g. anaesthetics, medications);

d) the type and the purpose of the analytical test requested.



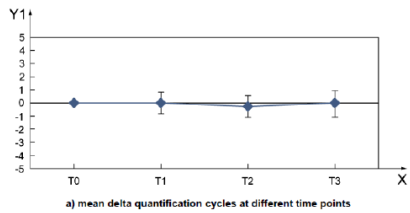
Quality in biobanks

- CEN/TS / ISO standards on the pre-examination phase
  - Goal:
    - Inclusion of all chapters into the process flow chart
  - Opportunities:
    - Identification of missing documents
    - Identification of quality indicators

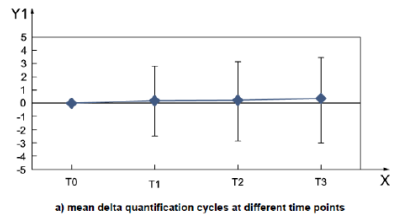


Quality in biobanks

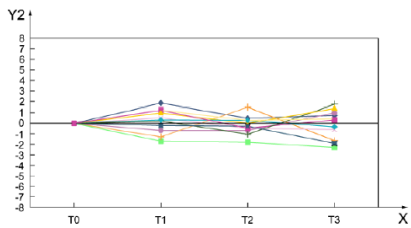
- Comparison of stable and unstable genes identified under ischemic conditions



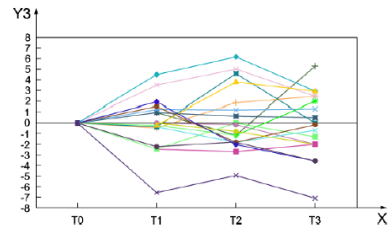
a) mean delta quantification cycles at different time points



a) mean delta quantification cycles at different time points



b) delta quantification cycles at different time points



b) delta quantification cycles at different time points

Key

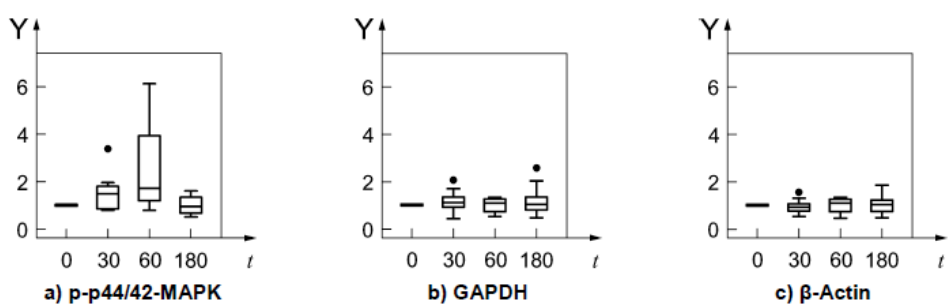
Y1	$\Delta\sigma q$ mean (mean delta quantification cycle)	T1	first time point during surgery
Y3	$\Delta\sigma q$	T2	second time point during surgery
T0	reference time point at the beginning of surgery (no ischemia control)	T3	time point after tissue removal including a short cold ischemia time (usual biobanking time point)
		X	time point

NOTE The results from T1 to T3 were normalized to the T0 time points to receive the $\Delta\sigma q$ values.

Source: CEN/TS 16826-1:2015

Quality in biobanks

- Cold ischemia: "condition after removal of the tissue from the body until its stabilization or fixation"

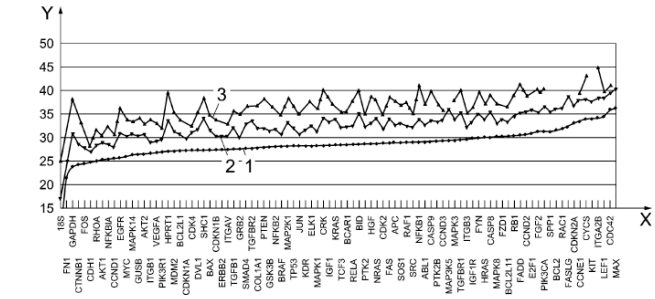


Y relative mean intensity t time (min)

Figure A.2 — Analysis of proteins and phosphoproteins during experimentally delayed cold ischemia

Source: CEN/TS 16826-2:2015

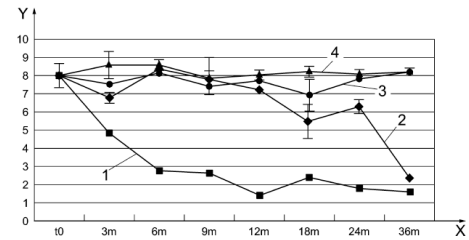
Quality in biobanks



Key

X	different tested genes	1	snap frozen liver tissue sample
Y	c_t values	2	FFPE liver tissue sample after 6 months
		3	FFPE liver tissue sample after 1 year

Figure A.3 — c_t values for 92 genes from snap frozen and FFPE human liver tissue



Key

X	months (m)	2	storage temperature 4 °C
Y	RIN value	3	storage temperature -20 °C
t_0	beginning of storage	4	storage temperature -80 °C
1	storage temperature 22 °C		

Figure A.4 — RIN values of RNA extracted from FFPE rat spleen tissue samples stored at different temperatures

Source: CEN/TS 16827-1:2015

Quality in biobanks

- Data quality dimensions

Dimension	Explanation
Accuracy	The extent to which data are correct, reliable and certified. Example: *Heart rate = 92 /min* – it‘s only an approximation (HR will not be exactly 92 during the whole examination process)
Currency	Is it up-to-date?
Completeness	Is all required information present to make an informed decision?
Readability	e.g., written data; also resolution of images, etc.
Reliability	Can you trust the data? (e.g., „cause of death“ inserted by general practitioner or certified pathologist)
Usefulness	For biobanks of less importance (you don‘t know, whether the data might be useful or not)
Cost-effectiveness	Do the costs outweigh the usefulness of the data?
Confidentiality	Is it only available to authorized persons?

Quality in biobanks

- Data quality dimensions

Dimension	Explanation
Consistency	Is the data comparable to real-word state, or are there relevant deviations?
Timeliness	Are the data sufficently up-to-date for a task? E.g., if a medication has to be prescribed body-weight-dependent, how recently was BW measured?
Relevance	Is the data useful to answer a specific question?
Granularity	To what detail has the data been collected
Specificity	Are the data categories corresponding to real-word data?
Precision	How exact are the data (e.g, ~90 kg or 89.5 kg)? Used a rapid test or a more reliable diagnostic test?
Attribution	Where does the data origin?
Volatility	How fast is the data changing, how stable is it?

Take home messages

- Biobanking has no purpose in itself – requirement of the scientific community (fighting non-reproducibility)
- For this, biobanks generate the environment in which samples and data are processed in a way to be „fit for purpose“
- Many different materials, many different purposes – many different standards applicable
- Sample quality, but also data quality!

Thank you for your attention!

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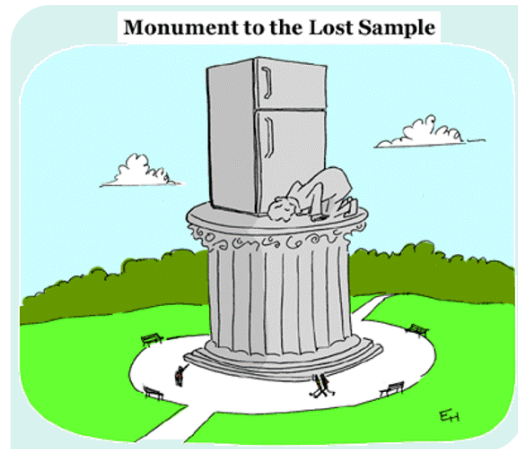

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