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Pre-analytical requirements for in-vitro diagnostic medical devices

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Declaration of Conflict of Interest

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Qiagen	Research funding
Google	Research funding
AstraZeneca	Lecture funding
Roche	Lecture funding
Zatloukal Innovations	Founder & CEO

Impact of Errors in Medical Diagnostics

- 12 million adults experience a diagnostic error each year in US; about half of these errors could be potentially harmful.

  Singh et al., 2014

- 10 percent of patient deaths can be attributed to diagnostic errors
- 6 to 17 percent of adverse events in hospitals are related to diagnostic errors

  Institute of Medicine
  SEPTEMBER 2015
  Improving Diagnosis in Health Care
  The National Academy of Sciences.

- 46% - 68% of diagnostic testing process errors are in the pre-analytical phase

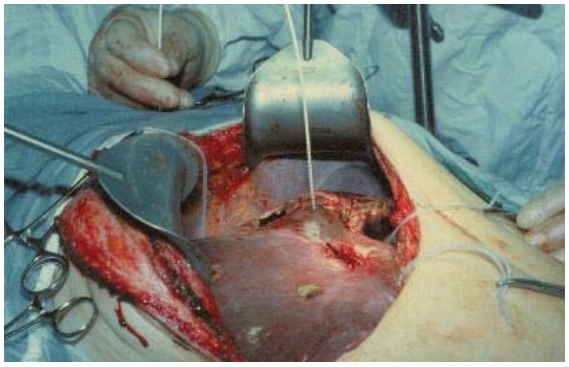
  Plebani M, Clin Chem Lab Med. 2006

How Pre-analytics May Affect Diagnosis

Examples

- Ischemia, fixation, processing, storage
- RNA-based analyses
- DNA-based analyses (PCR)
- Immunohistochemistry

Warm and Cold Ischemia Effects



Clinical study in Pringle manoeuvre liver surgery

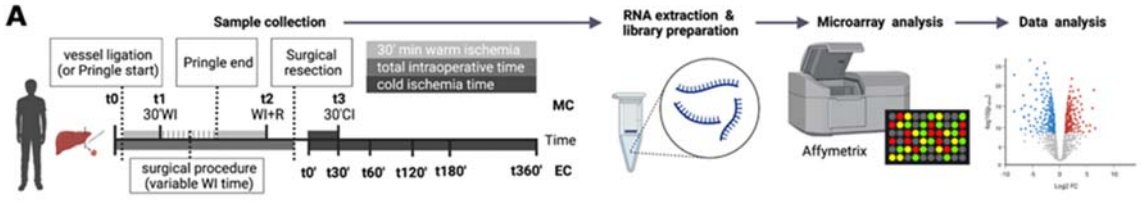
Snap frozen liver samples collected at :

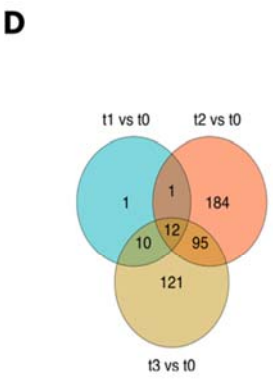
- **T0** sample before Pringle start: **medication**
- **T1** sample 30min after Pringle start: **warm ischemia**
- **T2** sample 30min after Pringle ending: **ischemia- reperfusion**
- **T3** sample after resection: **cold ischemia**

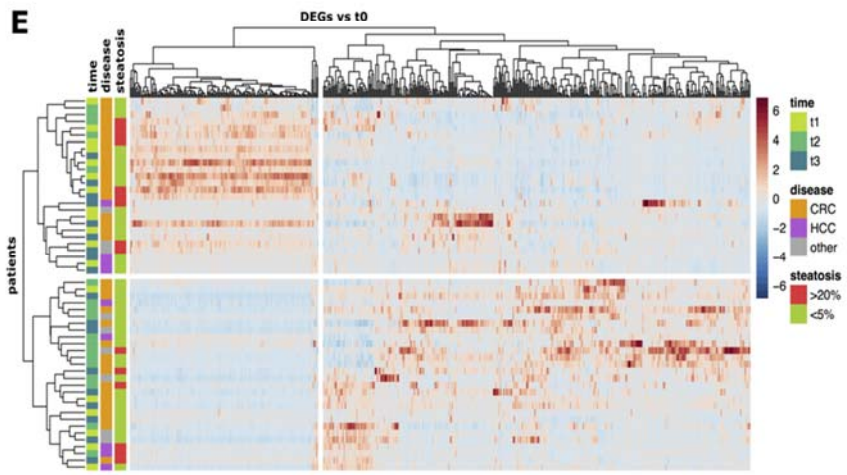
SPIDIA

GEN-AU
GENOMFORSCHUNG IN ÖSTERREICH

Ischemia and Gene Expression







Silvia Groiss[1], Christian Viertler[1], Marcel Kap[2], Gerwin Bernhardt[3,4], Hans-Jörg Mischinger[3], Anieta Sieuwerts[2a], Cees Verhoef[2b], Peter Riegman[2], Mogens Kruhøffer[5], David Svec[6], Robert Sjöback[7], Karl-Friedrich Becker[8], Kurt Zatloukal[1*]

Affymerix HG-U219

Individual Variability in Ischemia Response

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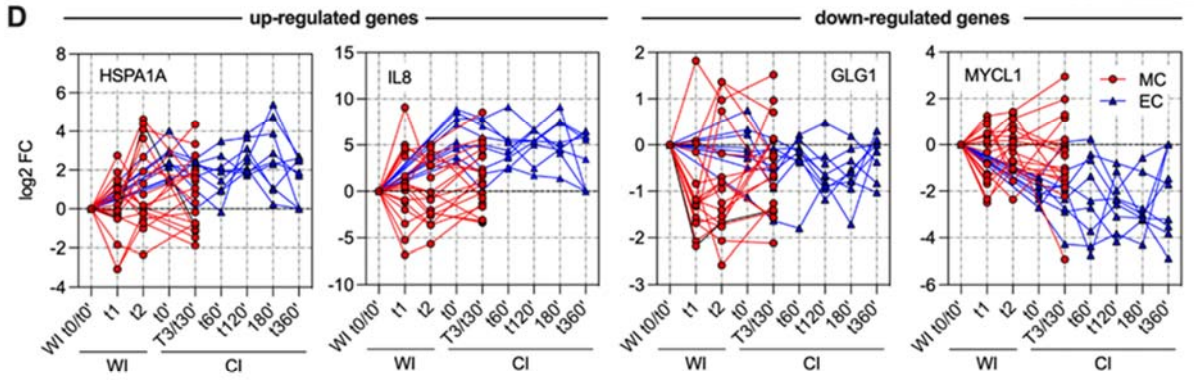

Formalin Fixation and Storage Interferes with qRT-PCR

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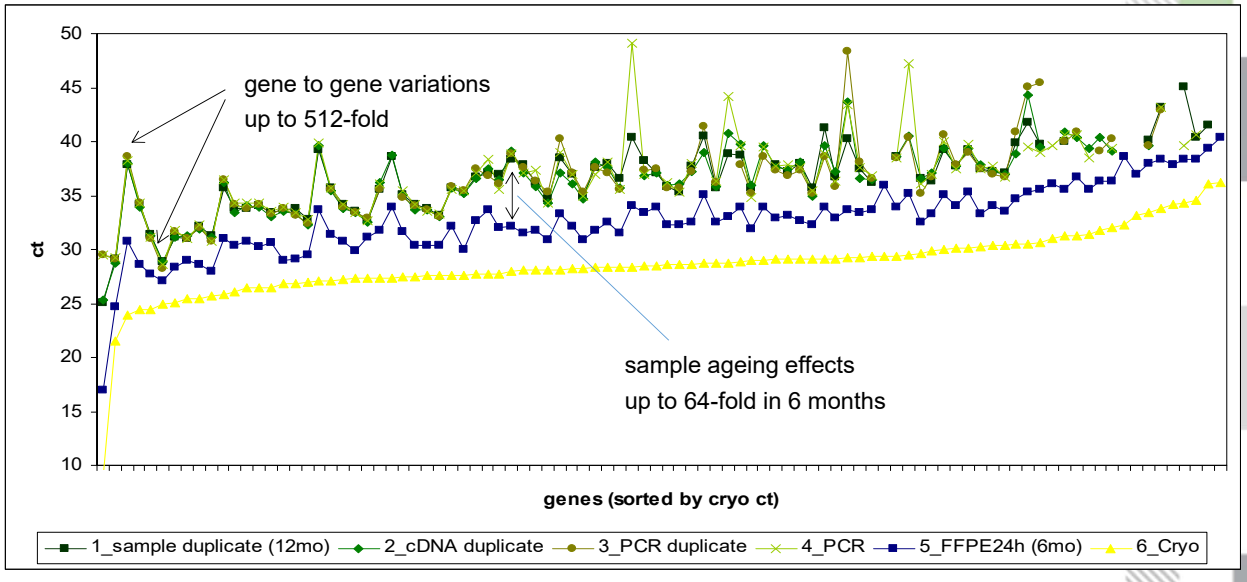
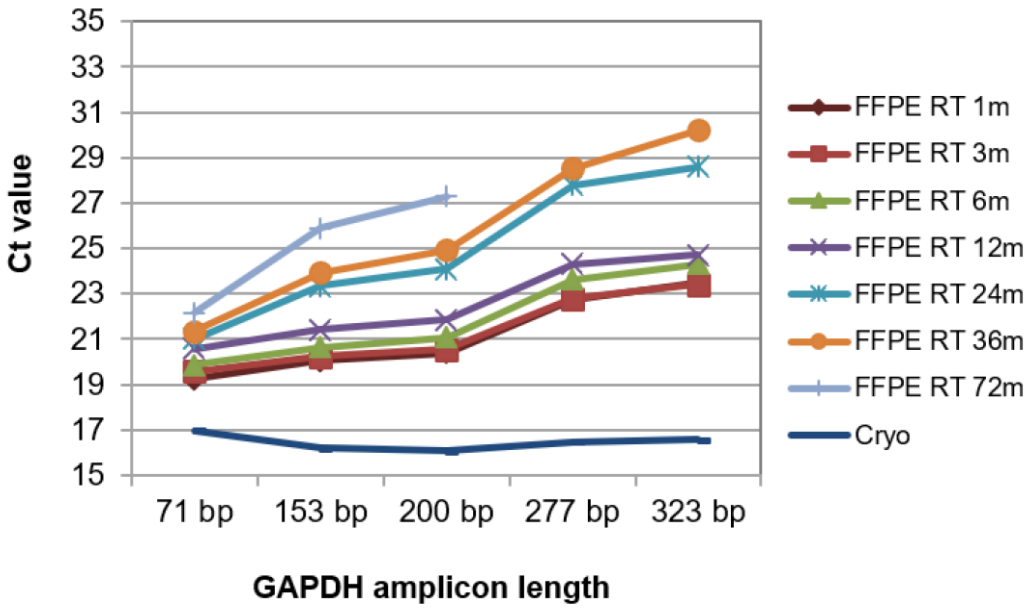


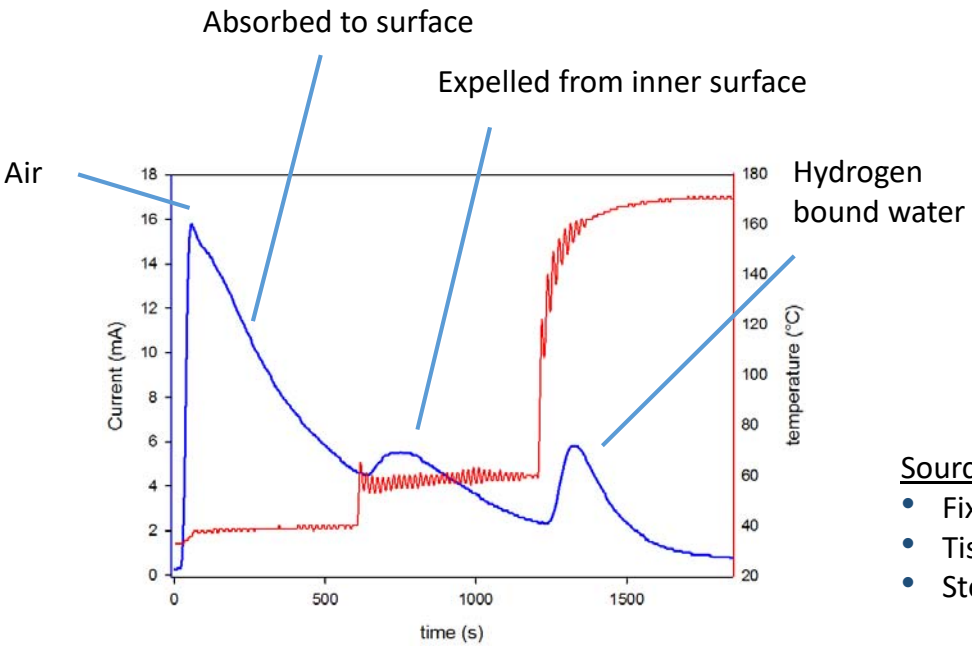
Kashofer K, et al. PLoS ONE 8(7): e70714.

Ageing Effects on RNA Quality in FFPE Tissues



D. Groelz et al., PLOS one 2018

Water Content of FFPE Tissue



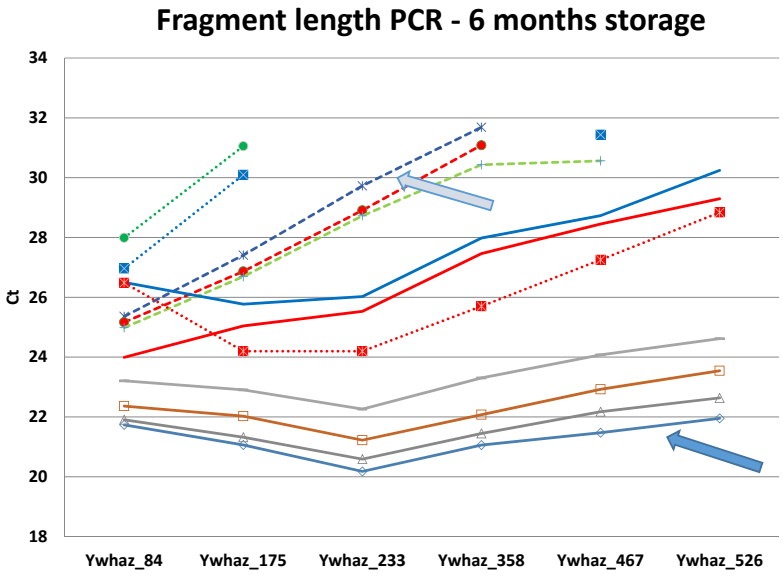
Phosphorous pentoxide – based water analysis

Sources of residual water:

- Fixation
- Tissue processing
- Storage

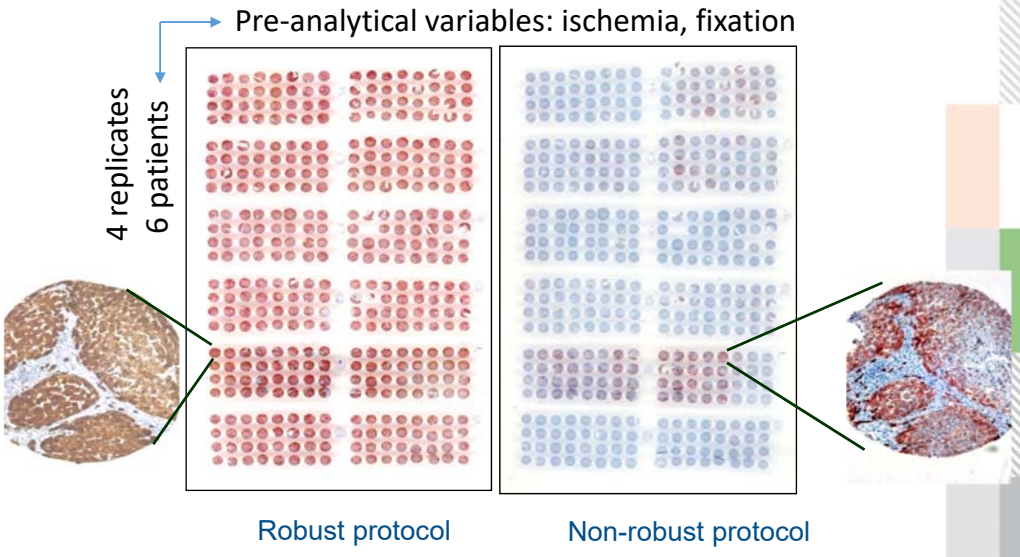
P Abuja et al., unpublished

Tissue Humdity and Fragment-length RT-PCR



P Abuja et al., unpublished

Analytical Performance: Differences in Pre-analytical Robustness

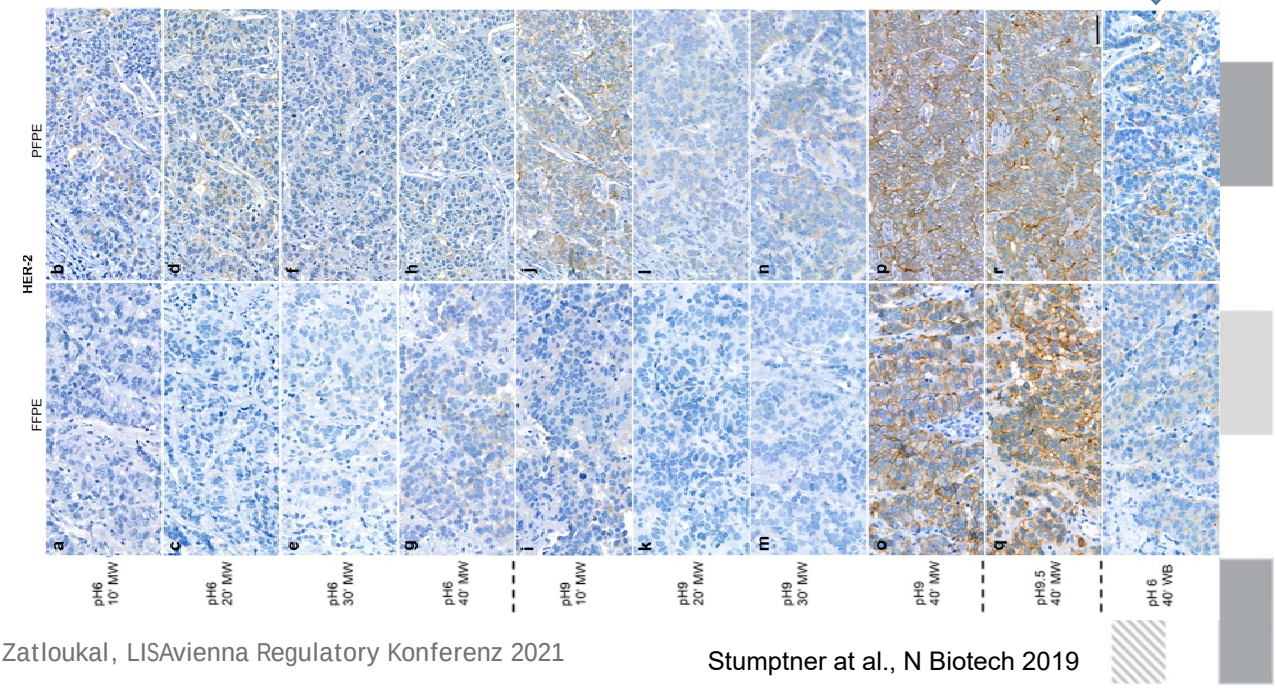


Stumptner et al., Methods Enzymol. 2015

Differences:
Analytical and Clinical Performance

IVD

Breast cancer HER-2 IHC



K. Zatloukal, LISAvienna Regulatory Konferenz 2021

Stumptner at al., N Biotech 2019

Regulatory Requirements for IVD in EU

L 117/176 EN Official Journal of the European Union 5.5.2017

REGULATION (EU) 2017/746 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL

of 5 April 2017

on *in vitro* diagnostic medical devices and repealing Directive 98/79/EC and Commission Decision 2010/227/EU

In force since May 26th 2017

To be applied to all diagnostics on the market and put into service (by manufacturer and lab-developed tests) from May 26th 2022

28.1.2022 EN Official Journal of the European Union L 19/3

REGULATION (EU) 2022/112 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL

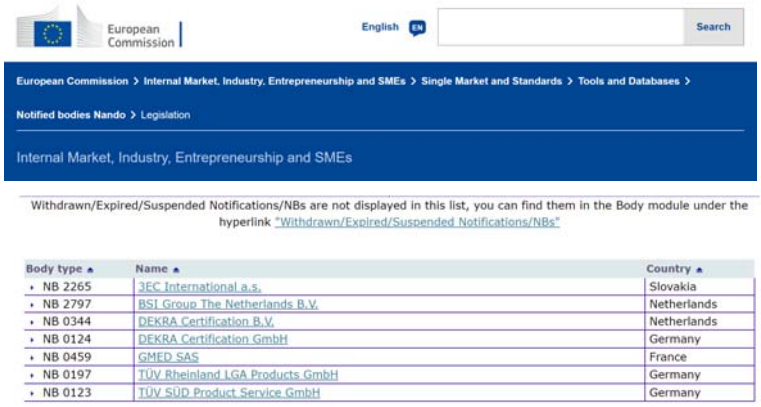
of 25 January 2022

amending Regulation (EU) 2017/746 as regards transitional provisions for certain *in vitro* diagnostic medical devices and the deferred application of conditions for in-house devices

New transition period for class C devices on the market May 26th 2026

Who is Responsible?

- European Commission
- Competent Authority (Ministry of Health)
- Notified Body
- EMA (Companion diagnostics)



Body type	Name	Country
NB 2265	JEC International a.s.	Slovakia
NB 2797	BSI Group The Netherlands B.V.	Netherlands
NB 0344	DEKRA Certification B.V.	Netherlands
NB 0124	DEKRA Certification GmbH	Germany
NB 0459	GMED SAS	France
NB 0197	TÜV Rheinland LGA Products GmbH	Germany
NB 0123	TÜV SÜD Product Service GmbH	Germany

Compliance with IVDR is Mandatory for LDT

(28) To ensure the highest level of health protection, the rules governing *in vitro* diagnostic medical devices, manufactured and used within a single health institution only, should be clarified and strengthened.

Article 5.

With the exception of the relevant **general safety and performance requirements set out in Annex I**, the requirements of this Regulation shall not apply to devices manufactured and used only within health institutions established in the Union, provided that all of the following conditions are met:

(a) the devices are **not transferred to another legal entity**;
(b) manufacture and use of the devices occur under appropriate quality management systems;
(c) the laboratory of the health institution is **Compliant with standard EN ISO 15189** or where applicable national provisions, including national provisions regarding accreditation;
(d) the health institution justifies in its documentation that the target patient group's specific needs cannot be met, or cannot be met at the appropriate level of performance by an **equivalent device available on the market**;
(e) the health institution **provides information upon request** on the use of such devices to its competent authority, which shall include a justification of their manufacturing, modification and use;

IVDR *Annex I*
General Safety and Performance Requirements

GENERAL REQUIREMENTS

3. Manufacturers shall establish, implement, document and maintain a risk management system (for each device)

REQUIREMENTS REGARDING PERFORMANCE, DESIGN AND MANUFACTURE

9. Performance characteristics

9.1. Devices shall be designed and manufactured in such a way that they are **suitable for the purposes**

(a) **the analytical performance**, such as, analytical sensitivity, analytical specificity, trueness (bias), precision (repeatability and reproducibility), accuracy (resulting from trueness and precision), limits of detection and quantitation, measuring range, linearity, cut-off, including determination of appropriate criteria for specimen collection and handling and control of known relevant endogenous and exogenous interference, cross-reactions; and

(b) **the clinical performance**, such as diagnostic sensitivity, diagnostic specificity, positive predictive value, negative predictive value, likelihood ratio, expected values in normal and affected populations.

IVDR Annex II
Technical Documentation

6. PRODUCT VERIFICATION AND VALIDATION

6.1. Information on analytical performance of the device

6.1.1. Specimen type

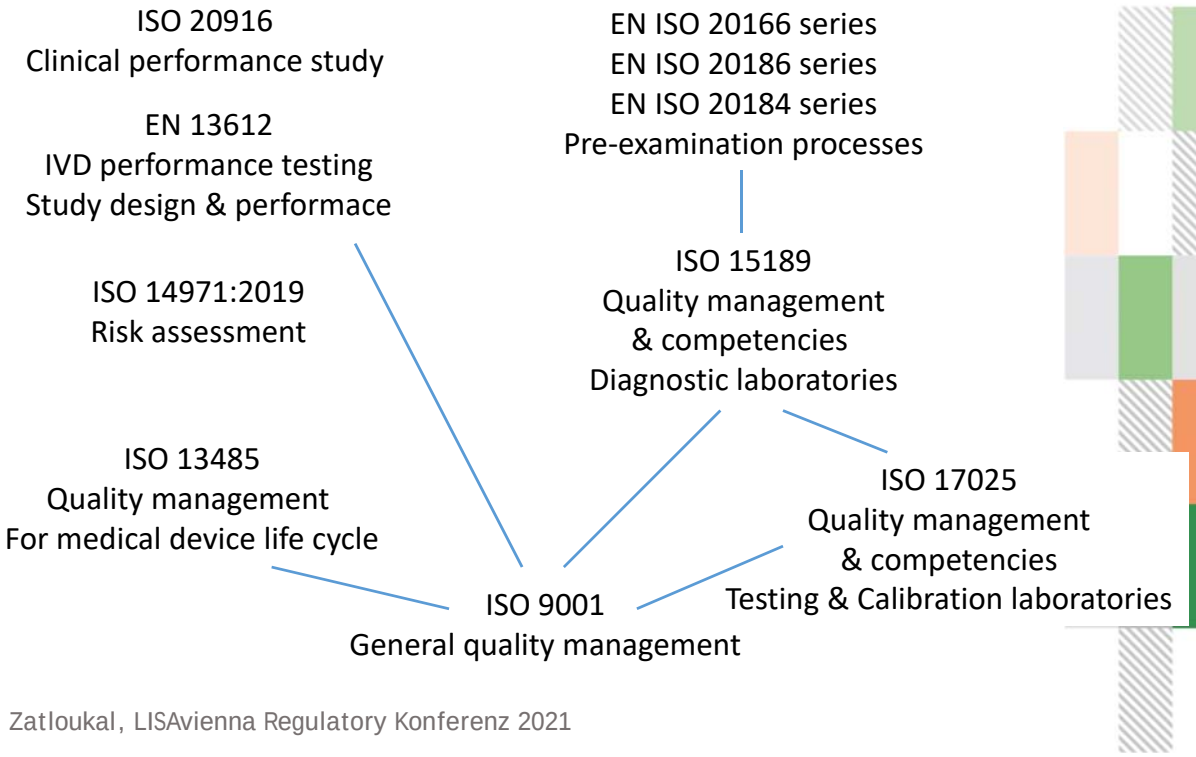
This Section shall describe the different specimen types that can be analysed, including their stability such as storage, where applicable specimen transport conditions and, with a view to time-critical analysis methods, information on the timeframe between taking the specimen and its analysis and storage conditions such *as* duration, temperature limits and freeze/thaw cycles.

6.1.2. Analytical performance characteristics

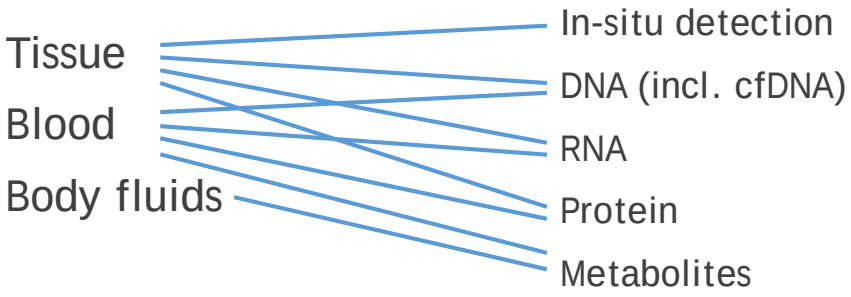
IVDR Guidance

- Harmonized standards
- Common Specifications
- Medical Device Coordination Group endorsed guidance documents
- Other CEN/ISO Standards define state-of-the-art

In vitro Diagnostics Standard Landscape



ISO Standards and CEN/TS for Pre-examination Processes



In addition: FNA, CTCs, exosomes, saliva, microbiome

⇨ Standards as enabler of innovation

SPIDIA SPIDIA4P

More To Come .....

SPIDIA4P

- CEN TS 17626:2021: Specifications for pre-examination processes for human specimen – Isolated **microbiome DNA**
- FprCEN TS 17688-1: Specifications for pre-examination processes for **Fine Needle Aspirates (FNA)** — Part 1: Isolated **cellular RNA**
- FprCEN TS 17688-2: Specifications for pre-examination processes for **Fine Needle Aspirates (FNA)** — Part 2: Isolated **proteins**
- FprCEN TS 17688-3 Specifications for pre-examination processes for **Fine Needle Aspirates (FNA)** — Part 3: Isolated **genomic DNA**
- FprCEN TS 17811 Specifications for pre-examination processes for **urine and other body fluids** — **Isolated cell free DNA**
- FprCEN TS 17747 Specifications for pre-examination processes for **exosomes** and other extracellular vesicles in venous whole blood — **Isolated RNA, DNA and proteins**
- FprCEN TS 17742 Specifications for Pre-examination processes for venous whole blood **- Isolated cell free RNA from plasma**
- WI00140151, In vitro diagnostic **Next Generation Sequencing (NGS) workflows** for the examination of human DNA/RNA.

Instand NGS for Personalized Therapy

ISO Standards Principles

Processes have to verified for fit-for-purpose (fulfillment of performance criteria and intended use) by manufacturer or user

Standardized procedures

Documentation of compliance

Few explicit requirments on reagents or methods exept for formalin

Standards refer to ISO 15189

Topics Addressed by the ISO Standard

Introduction
1 Scope
2 Normative reference
3 Terms and definitions
4 General considerations

5 Outside the laboratory
5.1 Specimen collection
5.1.1 General
5.1.2 Information about the specimen donor/patient
5.1.3 Information about the specimen
5.1.4. Specimen processing
5.2 Transport requirements

6 Inside the laboratory
6.1 Information about the reception of the specimen
6.2 Formalin fixation of the specimen or sample
6.3 Evaluation of the pathology of specimen and selection of sample(s)
6.4 Post-fixation of frozen samples
6.5 Decalcification
6.6 Processing and paraffin embedding
6.7 Storage requirements
6.8 Isolation of DNA
6.8.1 General
6.8.2 General information for DNA isolation procedures
6.8.3 Using commercial kits
6.8.4 Using laboratories' own protocols
6.9 Quality and quality assessment of isolated DNA
6.10 Storage of isolated DNA

Annex A: Impact of the storage temperature on DNA integrity in FFPE blocks of tissue
Bibliography

IVDs Manufactured by Industry and within Health Institutions

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Implications of manufacture and use of devices within the same health institution ('in-house devices') "lab developed tests"

4. Devices that are manufactured and used within health institutions, with the exception of devices for performance studies, shall be considered as having been put into service.

Final responsibility for IVDR compliance of the whole diagnostic workflow is with the user that makes the diagnosis

The Team

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SPIDIA consortium
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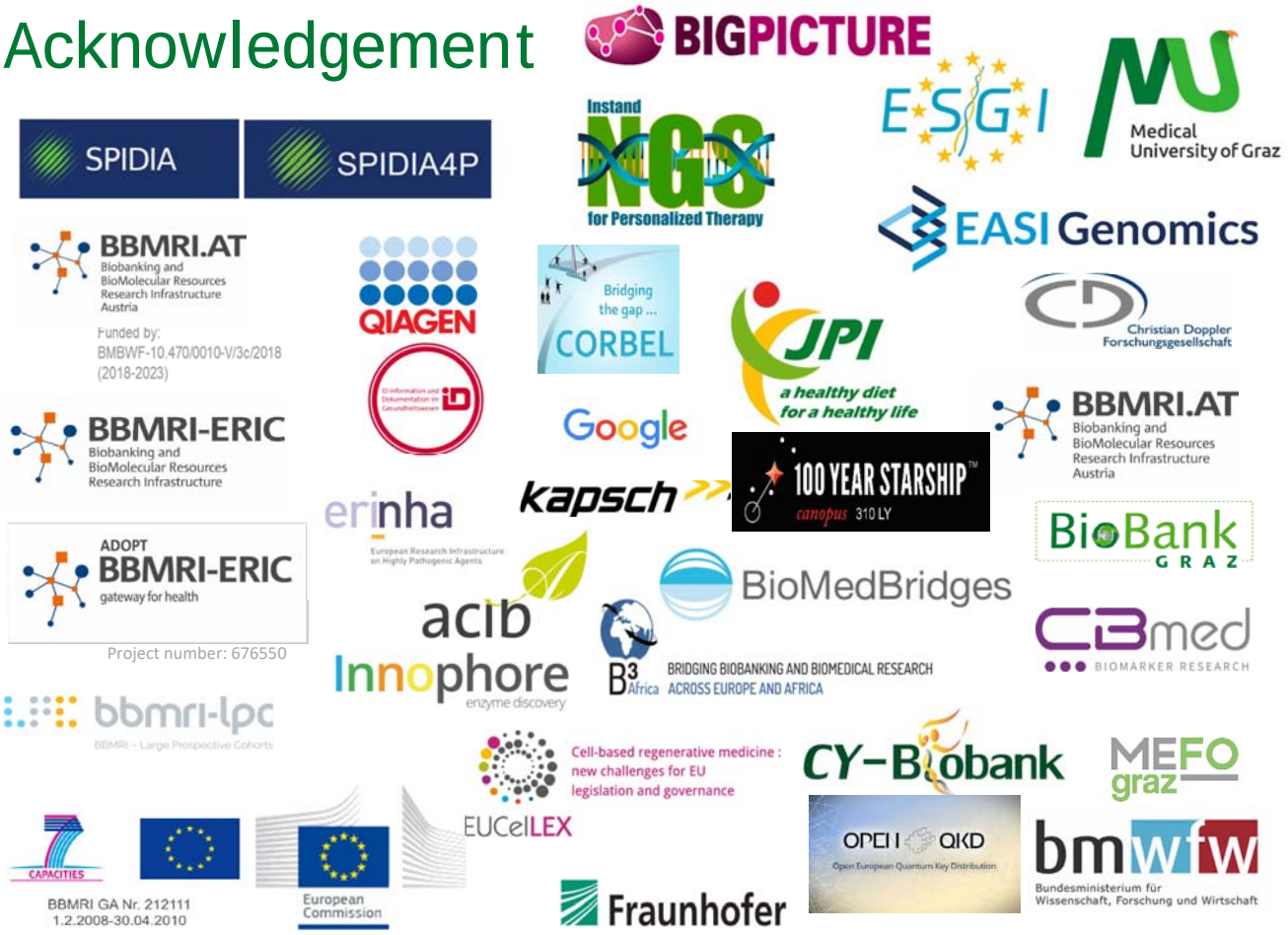

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Thank You for Your Attention!