



Medical University of Graz

Reference Materials for Standardization

Kurt Zatloukal

Diagnostic and Research Center for Molecular Biomedicine

Institute of Pathology, Medical University Graz, Austria



Conflict of Interest Statement



Founder and CEO of Zatloukal Innovations GmbH
Research funding Qiagen
Lecture honorarium AstraZenca



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



CHAPTER VI CLINICAL EVIDENCE, PERFORMANCE EVALUATION AND PERFORMANCE STUDIES

Article 56 Performance evaluation and clinical evidence

3. A performance evaluation shall follow a defined and methodologically sound procedure for the demonstration of the following, in accordance with this Article and with Part A of Annex XIII:

- (a) scientific validity;
- (b) analytical performance;
- (c) clinical performance.



IVDR: Definitions

(55) ‘calibrator’ means a measurement reference material used in the calibration of a device;

(56) ‘control material’ means a substance, material or article intended by its manufacturer to be used to verify the performance characteristics of a device;



Annex I:

CHAPTER II REQUIREMENTS REGARDING PERFORMANCE, DESIGN AND MANUFACTURE

9.3. Where the **performance of devices** depends on the use of calibrators and/or control materials, the metrological traceability of values assigned to calibrators and/or control materials shall be assured through suitable reference measurement procedures and/or **suitable reference materials** of a higher metrological order. Where available, **metrological traceability of values assigned to calibrators and control materials shall be assured to certified reference materials or reference measurement procedures.**

(w) analytical performance characteristics, such as analytical sensitivity, analytical specificity, trueness (bias), precision (repeatability and reproducibility), accuracy (resulting from trueness and precision), limits of detection and measurement range, (information needed for the control of known relevant interferences, cross-reactions and limitations of the method), measuring range, linearity and **information about the use of available reference measurement procedures and materials** by the user;

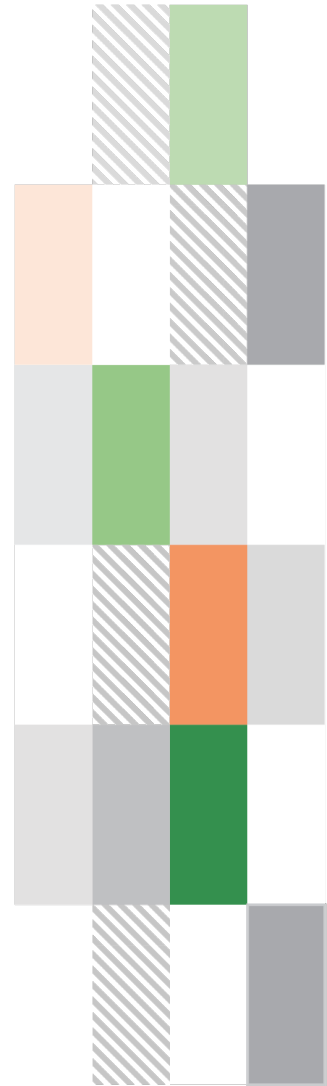


Annex II

(a) **Trueness of measurement** This Section shall provide information on the trueness of the measurement procedure and summarise the data in sufficient detail to allow an assessment of the adequacy of the means selected to establish the trueness. Trueness measures apply to both quantitative and qualitative assays **only when a certified reference material or certified reference method is available.**

Annex XIII

For novel markers or other markers **without available certified reference materials or reference measurement procedures**, it may not be possible to demonstrate trueness. If there are no comparative methods, different approaches may be used if demonstrated to be appropriate, such as comparison to some other well-documented methods or the composite reference standard. **In the absence of such approaches, a clinical performance study comparing performance of the novel device to the current clinical standard practice is required.**



Article 100 :The European Union reference laboratories (for class D devices)

(h) to provide recommendations on suitable reference materials and reference measurement procedures of higher metrological order;

5. The EU reference laboratories shall form a network in order to coordinate and harmonise their working methods as regards testing and assessment. That coordination and harmonisation shall involve: (a) applying coordinated methods, procedures and processes; (b) **agreeing on the use of same reference materials and common test samples** and seroconversion panels;

Annex X. Laboratory tests performed by an EU reference laboratory shall in particular focus on analytical and diagnostic sensitivity **using the best available reference materials.**



IVDR Annex I

General Safety and Performance Requirements

13. Construction of devices and interaction with their environment

13.1. **If the device is intended for use in combination with other devices or equipment, the whole combination,** including the connection system, shall be safe and shall not impair the specified performances of the devices. Any restrictions on use applying to such combinations shall be indicated on the label and/or in the instructions for 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**

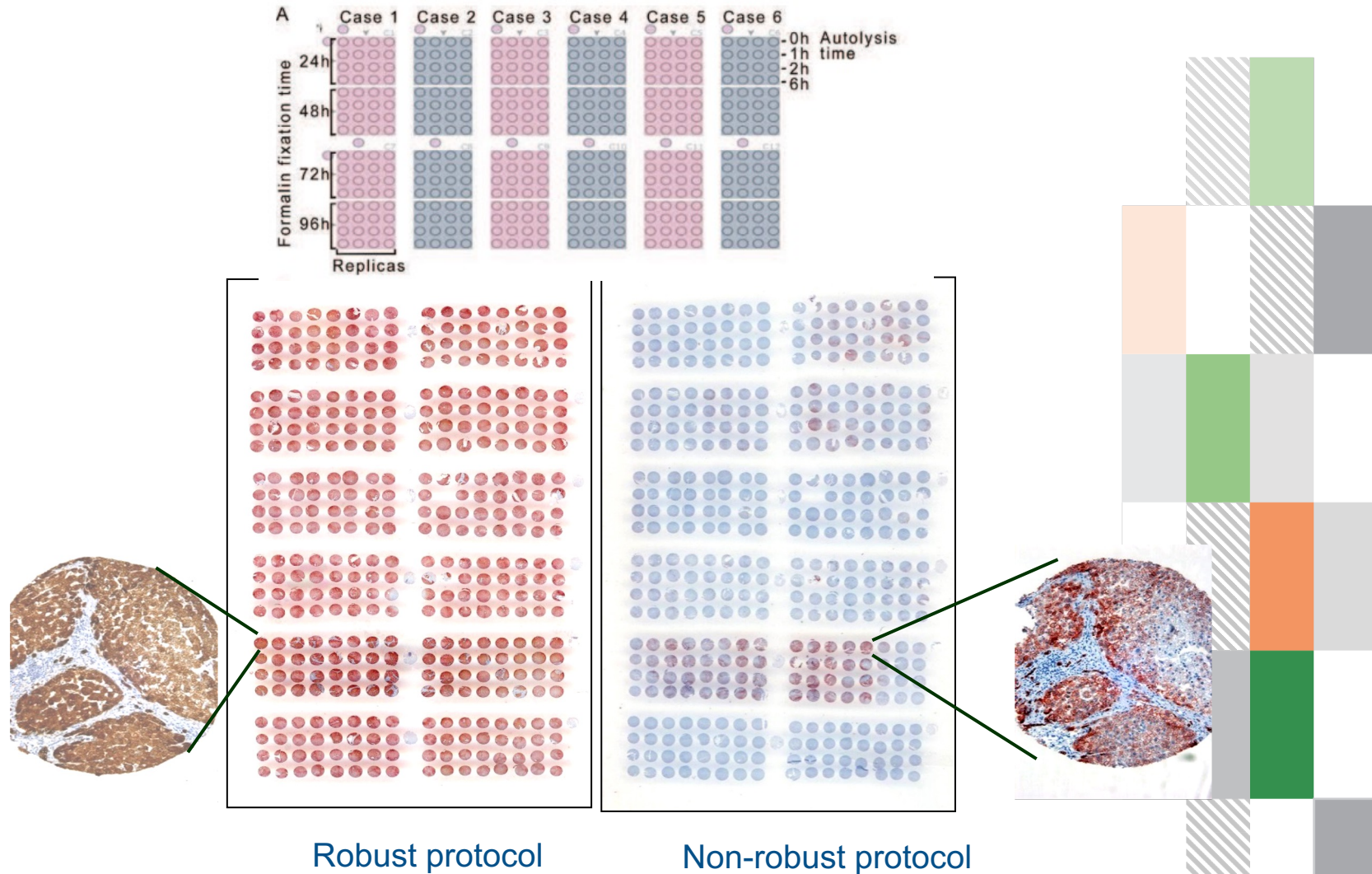
(a) **the analytical performance**, such as, analytical sensitivity, analytical specificity, trueness (bias), precision (repeatability and reproducibility), accuracy (resulting from trueness and precision), limits of detection and quantitation, measuring range, linearity, cut-off, **including determination 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.

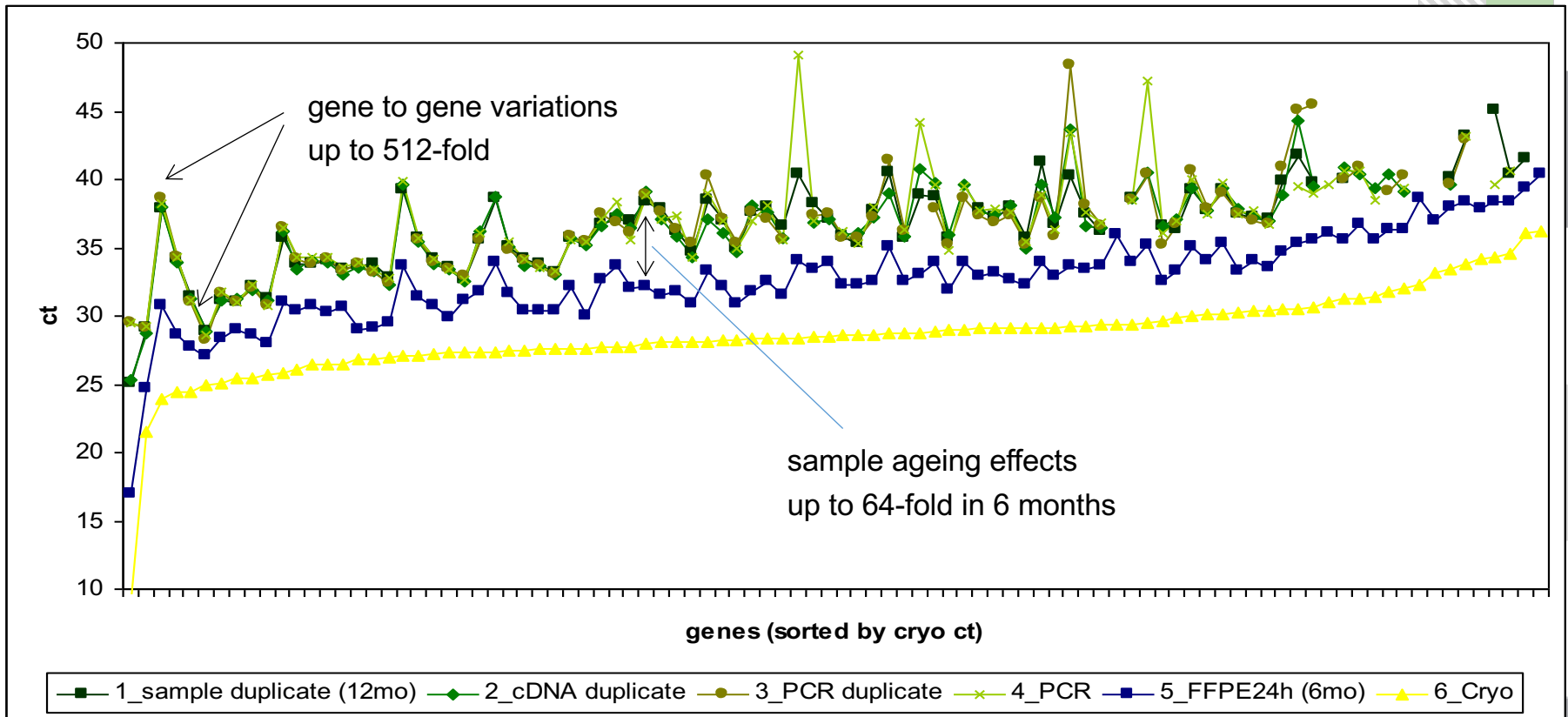
Challenges in Applying IVDR Requirements in Pathology

- Tissues cannot be produced in constant quality and sufficient quantity to be used as certified reference material
- Tissues are not stable
- Cells are no proper surrogate for tissues, particularly with respect to pre-analytical effects
- Spike-in biomolecules may behave differently than natural biomolecules (e.g., isolated DNA is different than fcDNA)
- What is a proper reference material for digital pathology and an AI algorithm?

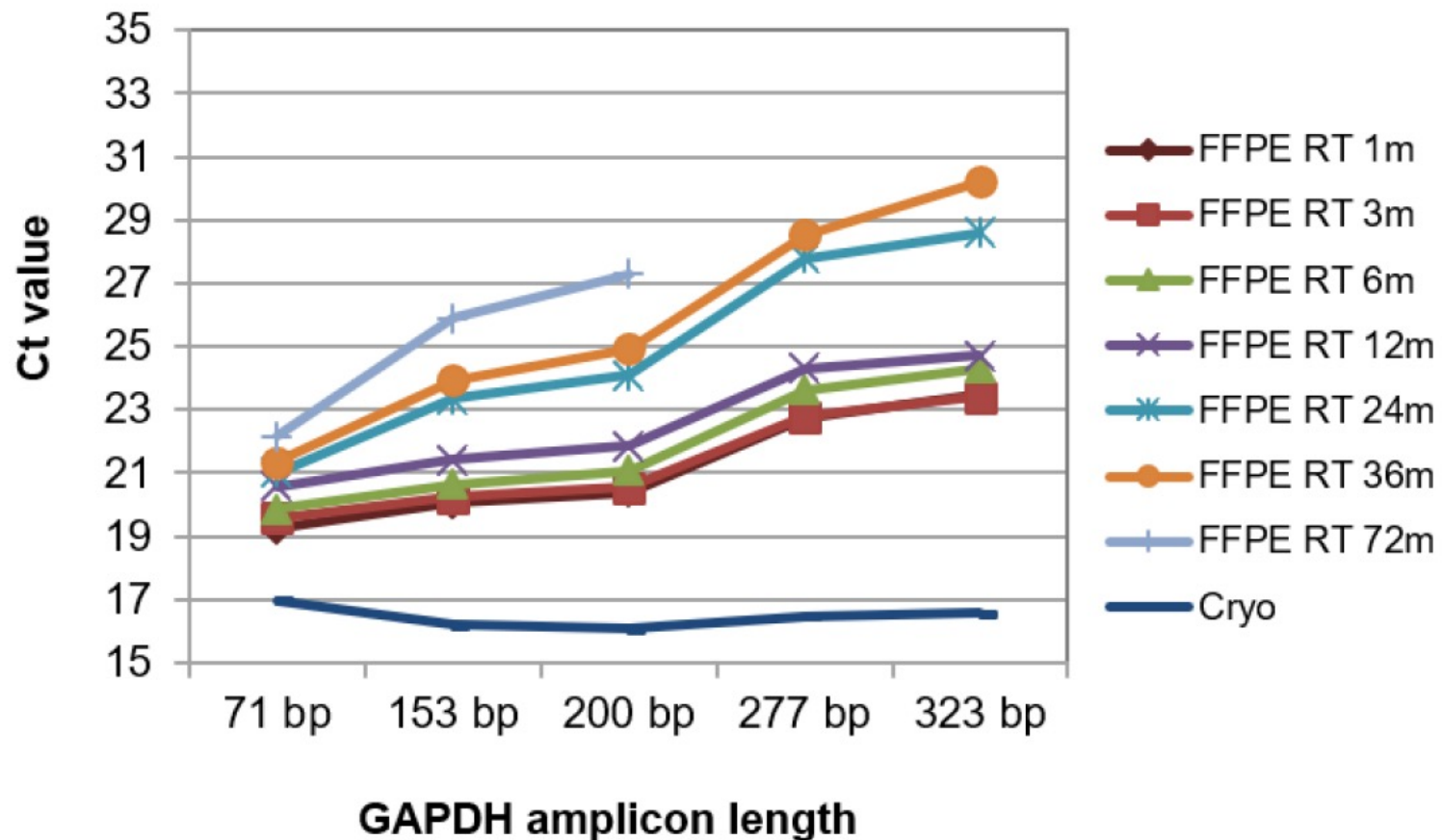
Analytical Performance: Differences in Pre-analytical Robustness



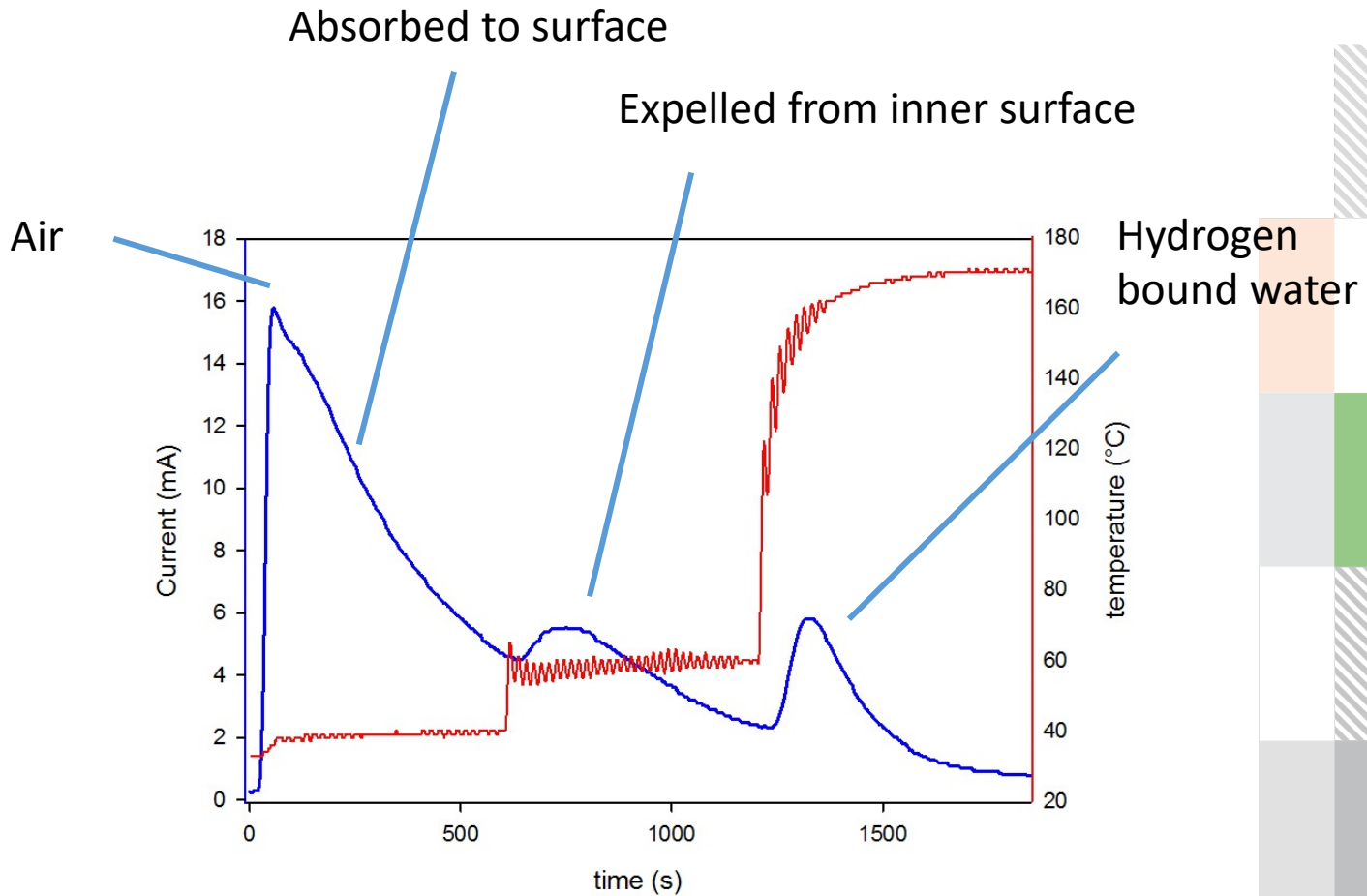
Formalin Fixation Interferes with qRT-PCR



Ageing Effects on RNA Quality in FFPE Tissues



Water Content of FFPE Tissue

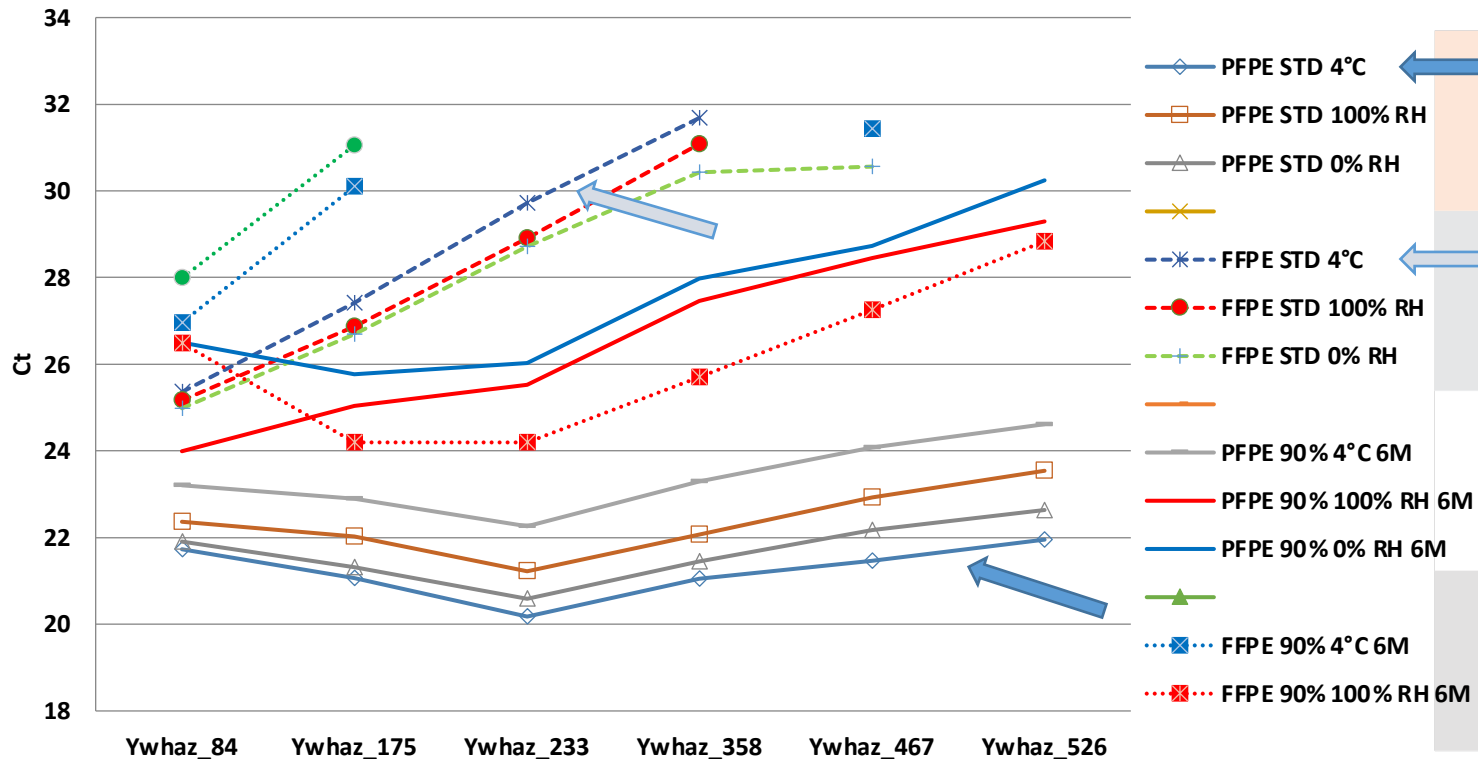


Phosphorous pentoxide – based water analysis



Tissue Humidity and Fragment-length RT-PCR

Fragment length PCR - 6 months storage



IVDR Annex I

General Safety and Performance Requirements

16. Electronic programmable systems — devices that incorporate electronic programmable systems and software that are devices in themselves

16.1. Devices that incorporate electronic programmable systems, including software, or software that are devices in themselves, shall be designed to ensure repeatability, reliability and performance in line with their intended use. In the event of a single fault condition, appropriate means shall be adopted to eliminate or reduce as far as possible consequent risks or impairment of performance.

16.2. For devices that incorporate software or for software that are devices in themselves, the software shall be developed and manufactured in accordance with the state of the art taking into account the principles of development life cycle, risk management, including information security, verification and validation.

16.3. Software referred to in this Section that is intended to be used in combination with mobile computing platforms shall be designed and manufactured taking into account the specific features of the mobile platform (e.g. size and contrast ratio of the screen) and the external factors related to their use (varying environment as regards level of light or noise).

16.4. Manufacturers shall set out minimum requirements concerning hardware, IT networks characteristics and IT security measures, including protection against unauthorised access, necessary to run the software as intended.

IVDR Annex I General Safety and Performance Requirements



What does this mean for digital pathology and AI?
Specimen ~ slide for scanner
Specimen is ~ data for AI

- (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.



Calibration and EQA



Training of Algorithms has to Include a Broad Spectrum of Data Variables

Report of UN Secretary-general's high-level Panel on Digital Cooperation:

"Gaps in the data on which algorithms are trained can likewise automate existing patterns of discrimination, as machine learning systems are only as good as the data that is fed to them."



Training data should include:

- Various disease types and comorbidities
- Various pre-analytical variables and artefacts
- Data from different populations

ISO 17034:2016(en)

General requirements for the competence of reference material producers

Certified reference material

reference material characterized by a metrologically valid procedure for one or more specified properties, accompanied by a reference material certificate that provides the value of the specified property, its associated uncertainty, and a statement of metrological traceability

Reference material

material, sufficiently homogeneous and stable with respect to one or more specified properties, which has been established to be fit for its intended use in a measurement process



Interaction Platform

Goal:

To provide an interaction platform between the scientific experts, regulatory and health authorities for clinical whole slide images and AI.

Involvement of

- Scientists
- Manufacturers
- Authorities and regulators
- Users
- Patient advocacy groups



The Team



Project Management

Penelope Kungl
Daniela Schaar
Cornelia Stumptner

Scientists

Peter M. Abuja
Esther Förderl-Höbenreich
Silvia Grois
Melina Hardt
Eva Kicker
Martina Loibner
Farah Nader
Stella Wolfgruber

PhD Students

Michael Haider
Birgit Pohn
Meghana Somlapura

Senior Members

Helmut Denk

Medical Bioanalytics, Technician

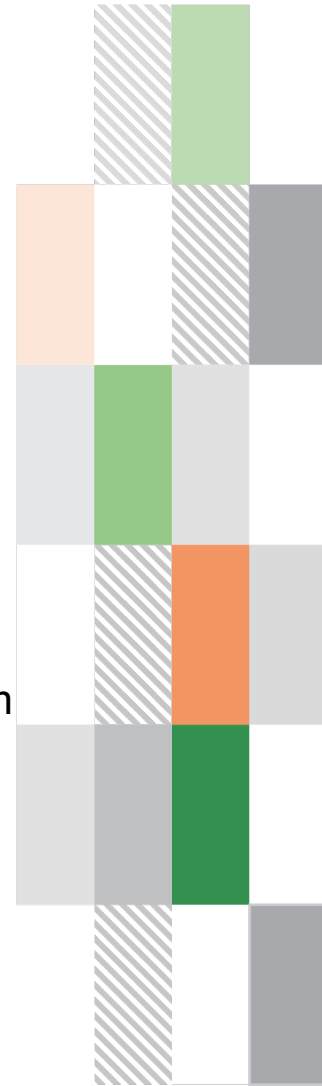
Ulrike Fackelmann
Stephanie Freydl
Daniela Pabst

Data Scientists

Robert Reihs
Markus Plass

Collaborations

H. Müller, Pathology, MUG
A. Holzinger, IMI, MUG
BBMRI-ERIC consortium
BBMRI.at consortium
HRSM Digital Pathology Consortium
SPIDIA consortium
Biobank Graz
Student scanning team



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BBMRI-ERIC
 Biobanking and BioMolecular Resources Research Infrastructure



BBMRI.AT
 Biobanking and BioMolecular Resources Research Infrastructure Austria

ADOPT BBMRI-ERIC gateway for health



European Research Infrastructure on Highly Pathogenic Agents



Project number: 676550



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 BBMRI - Large Prospective Cohorts



Cell-based regenerative medicine: new challenges for EU legislation and governance



BBMRI GA Nr. 212111 1.2.2008-30.04.2010



Thank You for Your Attention!

