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Pre-analytical requirements for in-vitro diagnostic medical devices

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Impact of Errors in Medical Diagnostics

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- 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

Changes is in Regulatory Requirements for IVDs in Europe (Examples)

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- Broader application

  80% of all diagnostics on market are expected to require additional data

  - Scientific evidence
  - Analytical performance (incl. pre-analytics)
  - Clinical performance
- New risk classification
- Responsible person
- Conformity assessment procedure: 3 possible procedures
- UDI Identification System
- Quality management system: each manufacturer must have a QMS
- Software in scope included
- Post Market Surveillance
- Higher requirements for Notified Bodies

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

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CLINICAL EVIDENCE, PERFORMANCE EVALUATION AND PERFORMANCE STUDIES

Article 56 Performance evaluation and clinical evidence 1.Confirmation of conformity with relevant general safety and performance requirements set out in Annex I, in particular those concerning the performance characteristics referred to in Chapter I and Section 9 of Annex I, under the normal conditions of the intended use of the device, and the evaluation of the interference(s) and cross-reaction(s) and of the acceptability of the benefit-risk ratio referred to in Sections 1 and 8 of Annex I, shall be based on scientific validity, analytical and clinical performance data providing sufficient clinical evidence, including where applicable relevant data as referred to in Annex III.

IVDR *Annex I*
General Safety and Performance Requirements

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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.

Compliance with IVDR is Mandatory for LDT

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(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 II
Technical Documentation

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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

Companion Diagnostics:
A rapidly growing list (FDA 2019)

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DRUG	DISEASE	TARGET	BIOSAMPLE	ASSAY
ado-trastuzumab emtansine	Breast cancer	HER2	DNA/protein from FFPE tissue	IHC/FISH
ado-trastuzumab emtansine	Gastric cancer	HER2	DNA/protein from FFPE tissue	IHC/FISH
afatinib	NSCLC	EGFR	DNA from FFPE tissue	NGS/PCR
alectinib	NSCLC	ALK	DNA from FFPE tissue	NGS
ceritinib	NSCLC	ALK	DNA/Protein from FFPE tissue	NGS/IHC
cetuximab (1)	CRC	EGFR	Protein in FFPE tissue	IHC
cetuximab (2)	mCRC	KRAS	DNA from FFPE tissue	NGS/PCR
cobimetinib+ vemurafenib	Melanoma	BRAF	DNA from FFPE tissue	NGS
crizotinib	NSCLC	ALK	DNA from FFPE tissue	NGS/FISH
crizotinib	NSCLC	ROS1	RNA from FFPE tissue	NGS
crizotinib	NSCLC	ALK	Protein/DNA in FFPE tissue	IHC
dabrafenib	Melanoma	BRAF	DNA from FFPE tissue	NGS/PCR
dabrafenib+trametinib	NSCLC	BRAF	DNA/RNA from FFPE tissue	NGS
deferasirox	Thalassemia	Iron	Liver imaging	MRI
enasidenib	AML	IDH2	DNA from blood or bone marrow	PCR
Erlotinib	NSCLC	EGFR	DNA from FFPE tissue or cfDNA from blood	PCR/NGS
gefitinib	NSCLC	EGFR	DNA from FFPE tissue	PCR/NGS
imatinib mesylate	GIST	c-Kit	Protein in FFPE tissue	IHC
imatinib mesylate	MDS, MPD	PDGFRB	Fresh bone marrow	FISH
imatinib mesylate	ASM	c-Kit	Fresh bone marrow	PCR
midostaurin	AML	FLT3	DNA from blood or bone marrow	PCR
nilotinib	CML	BCR-ABL1	RNA from blood	RT-PCR
olaparib	Breast cancer	BRCA1/2	DNA from blood	PCR, Sanger seq.
osimertinib	NSCLC	EGFR	DNA from FFPE tissue or cfDNA from blood	PCR/NGS
panitumumab (1)	CRC	EGFR	Protein in FFPE tissue	IHC
panitumumab (2)	CRC	KRAS	DNA from FFPE tissue	PCR
panitumumab (3)	mCRC	KRAS/NRAS	DNA from FFPE tissue	NGS
pembrolizumab	NSCLC/gastric or GEJ Adenoca.	PD-L1	FFPE tissue	IHC
pertuzumab	Breast cancer	HER2/NEU	DNA/protein from FFPE tissue	NGS/IHC/FISH
rucaparib	Ovarian cancer	BRCA1/2	DNA from FFPE tissue	NGS
trametinib	Melanoma	BRAF	DNA from FFPE tissue	NGS/PCR
trastuzumab	Breast , Gastric Ca	HER2/NEU	DNA from FFPE tissue	NGS/FISH/IHC/CISH
vemurafenib	Melanoma	BRAF	DNA from FFPE tissue	NGS/PCR
venetoclax	CLL	LSI TP53	blood	FISH

Companion Diagnostics (FDA-listed)

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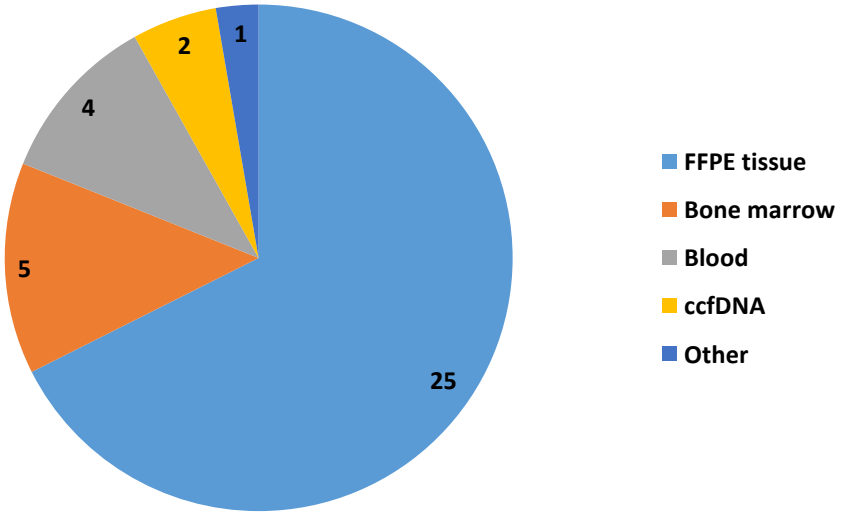
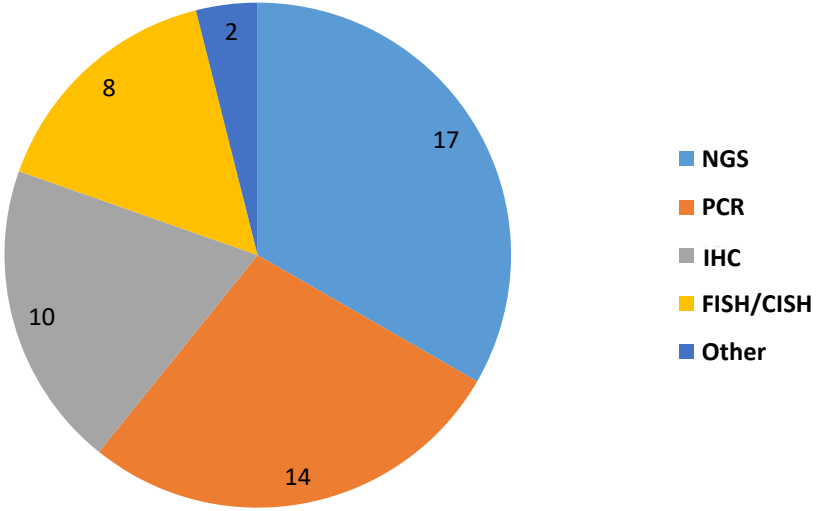
Biosamples



Assays



FFPE tissue is the most common biosample for companion diagnostics

In-situ detection is the most common assay for companion diagnostics

Stumptner et al. in Handbook for Biomarkers in Precision Medicine, 2019

Formalin Fixation and Storage Interferes with qRT-PCR

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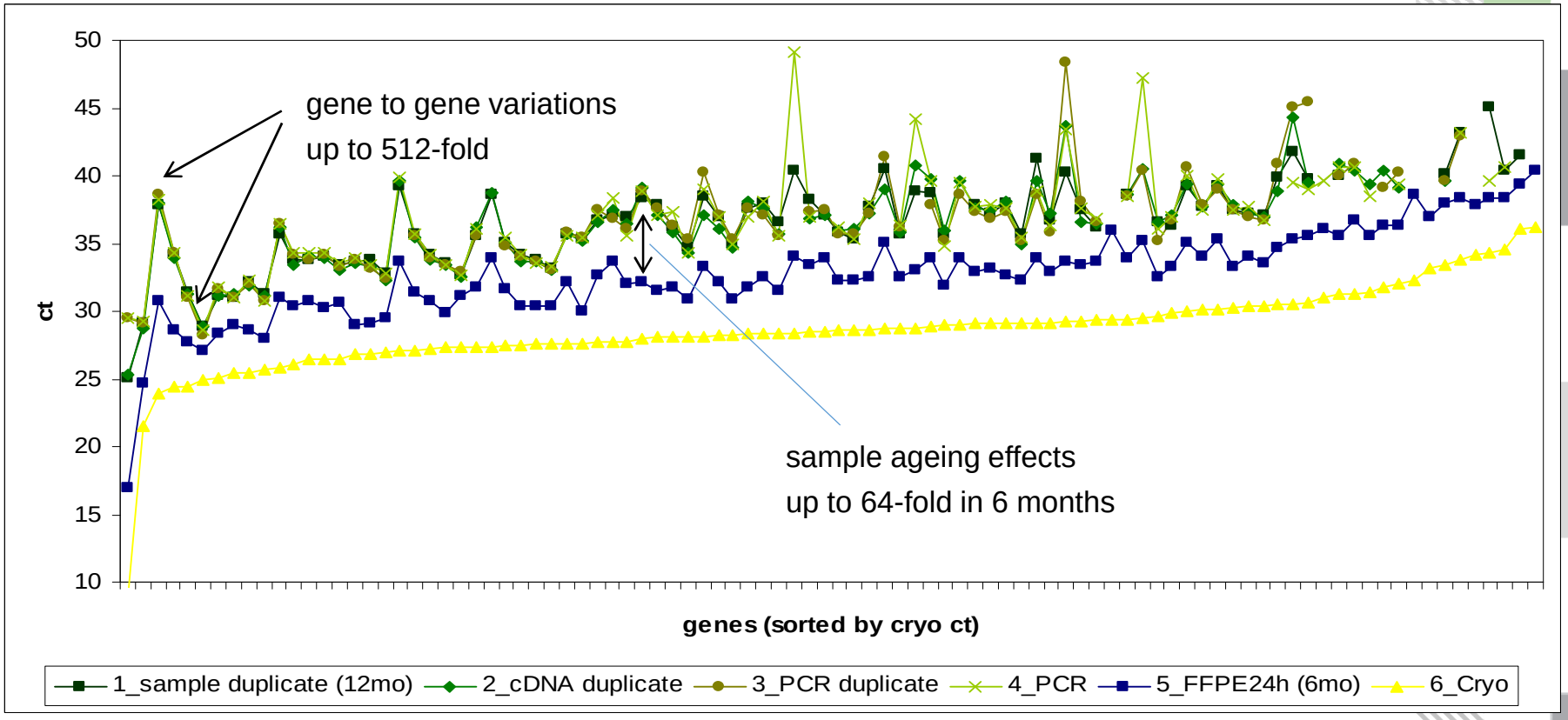

Kashofer K, et al. PLoS ONE 8(7): e70714.

Ageing Effects on RNA Quality in FFPE Tissues

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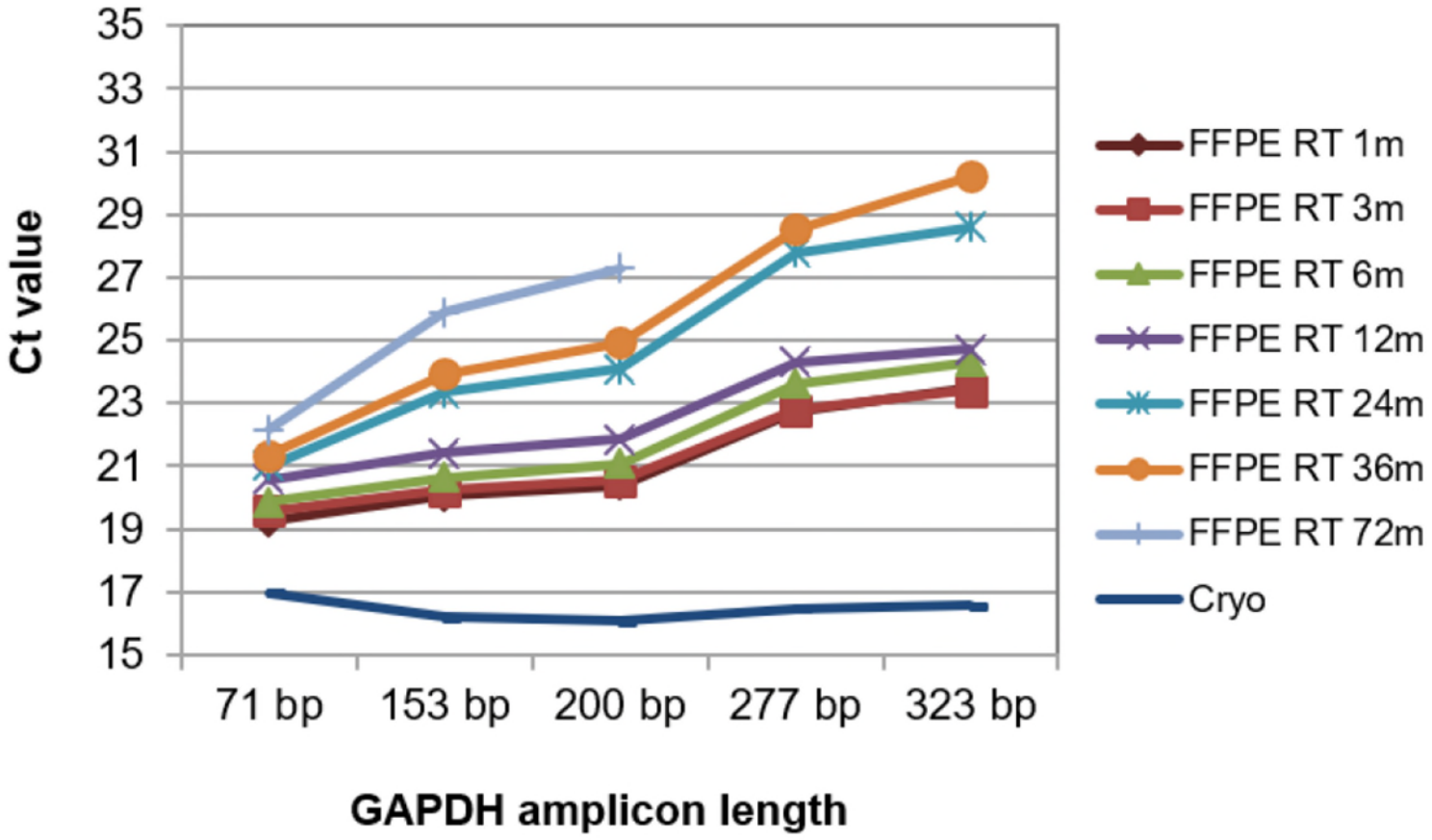
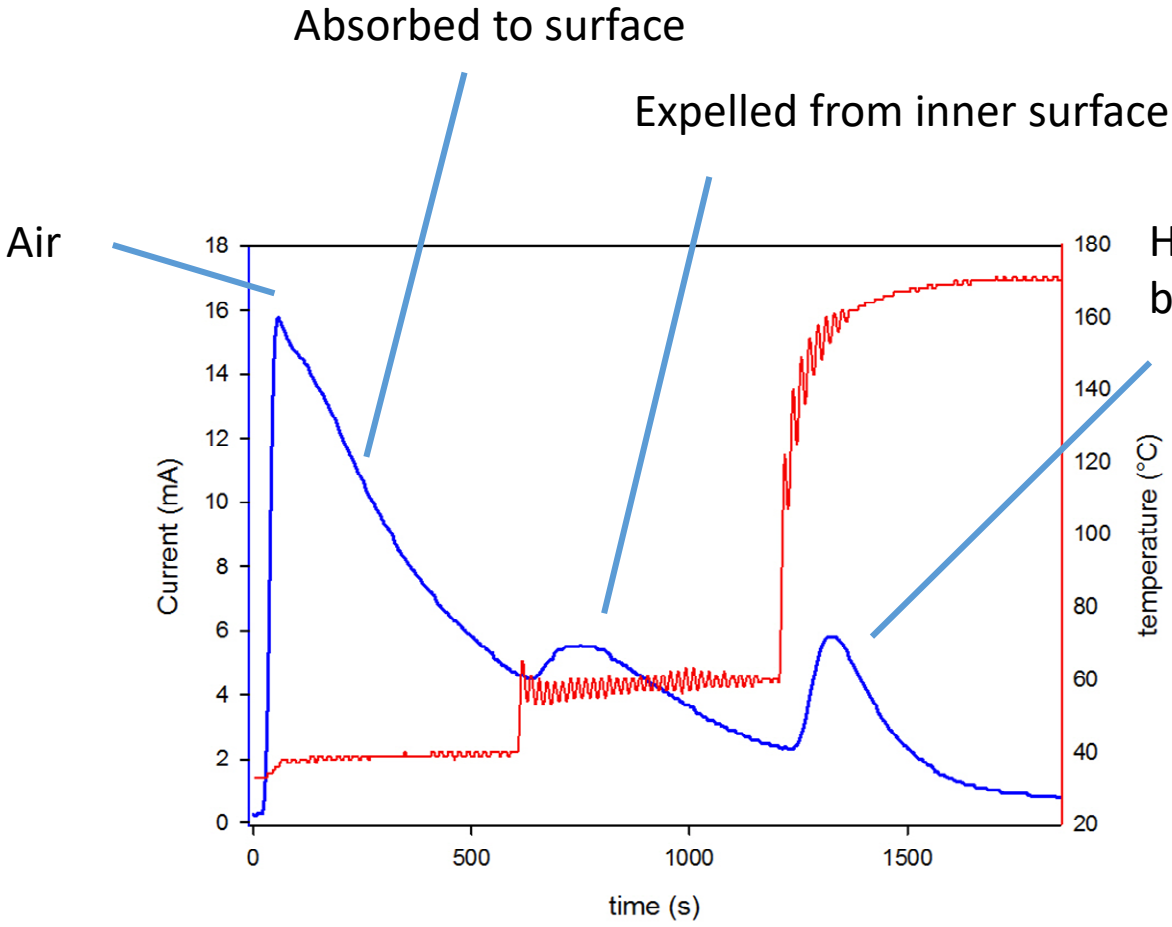


D. Groelz et al., PLOS one 2018

Water Content of FFPE Tissue



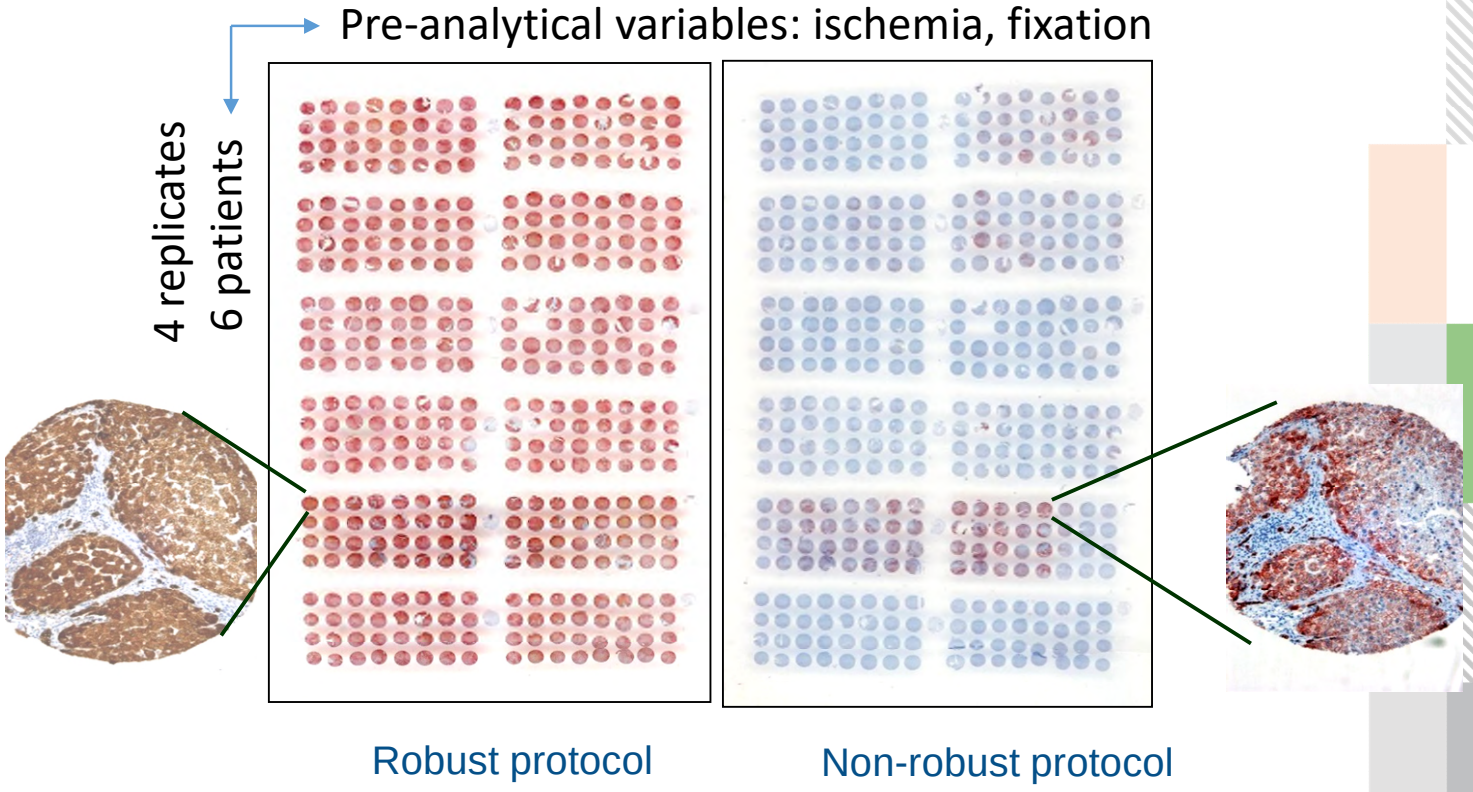
Phosphorous pentoxide – based water analysis

Sources of residual water:

- Fixation
- Tissue processing
- Storage

P Abuja et al., unpublished

Analytical Performance: Differences in Pre-analytical Robustness



Stumptner et al., Methods Enzymol. 2015

Differences:
Analytical and Clinical Performance

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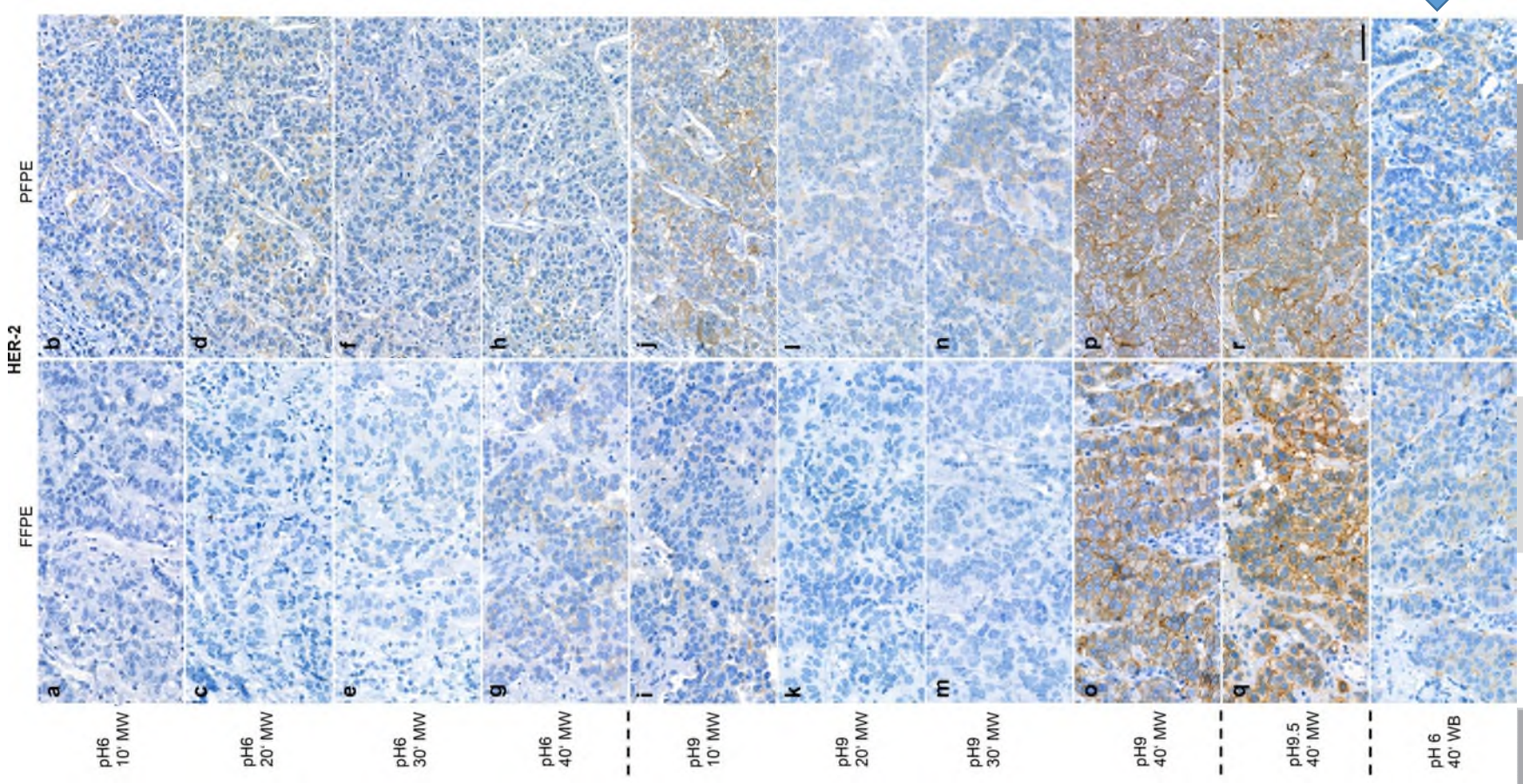
IVD

Breast cancer HER-2 IHC



K. Zatloukal, LISAvienna Regulatory Konferenz 2021

Stumptner at al., N Biotech 2019

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

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ISO 20916
Clinical performance study

EN 13612
IVD performance testing
Study design & performace

ISO 14971:2019
Risk assessment

EN ISO 20166 series
EN ISO 20186 series
EN ISO 20184 series
Pre-examination processes

ISO 15189
Quality management
& competencies
Diagnostic laboratories

ISO 13485
Quality management
For medical device life cycle

ISO 17025
Quality management
& competencies
Testing & Calibration laboratories

ISO 9001
General quality management

ISO Standards and CEN/TS for Pre-examination Processes

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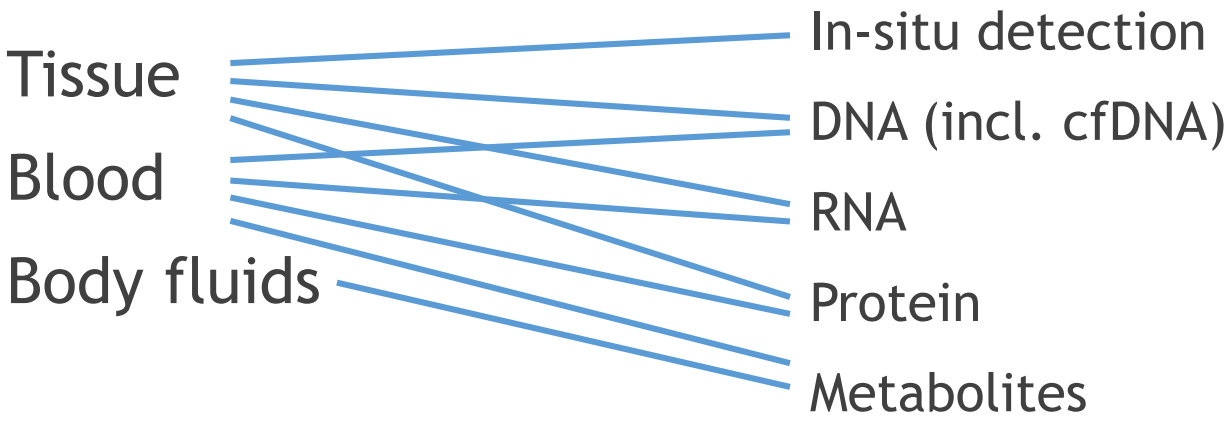

In addition: FNA, CTCs, exosomes, saliva, microbiome

⇨ Standards as enabler of innovation

SPIDIA SPIDIA4P

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ISO Standards and CEN/TS for Pre-examination Processes

- Frozen tissue — Part 1: Isolated RNA; EN ISO 20184-1:2018
- Frozen tissue — Part 2: Isolated proteins; EN ISO 20184-2:2018
- Frozen tissue - Part 3: Isolated DNA; EN ISO 20184-3: 2021
- FFPE tissue — Part 2: Isolated RNA; EN ISO 20166-1:2018
- FFPE tissue — Part 3: Isolated proteins; EN ISO 20166-2:2018
- FFPE tissue — Part 1: Isolated DNA; EN ISO 20166-3:2018
- FFPE tissue — Part 4: In situ detection techniques; EN ISO 20166-4:2021
- Venous whole blood — Part 1: Isolated cellular RNA; EN ISO 20186-1: 2019
- Venous whole blood — Part 2: Isolated genomic DNA; EN ISO 20186-2: 2019
- Venous whole blood — Part 3: Isolated circulating cell free DNA from plasma; EN ISO 20186-3: 2019
- Metabolomics in urine, venous blood serum and plasma; EN ISO 23118:2021
- Saliva – Isolated human DNA; CEN/TS 17305:2019
- Human specimens – Isolated microbiome DNA; CEN TS 17626:2021
- Circulating tumor cells (CTCS) – Part 1: Isolated RNA; CEN/TS 17390-1:2020
- Circulating tumor cells (CTCS) – Part 2: Isolated DNA; CEN/TS 17390-2:2020
- Circulating tumor cells (CTCS) – Part 3: Preparation for analytical CTC staining; CEN/TS 17390-3:2020

More To Come ……

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Biobanking and BioMolecular resources Research Infrastructure Austria

SPIDIA4P

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- 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

Topics Addressed by the ISO Standards Example: FFPE tissue — Part 1: Isolated DNA; EN ISO 20166-3:2018

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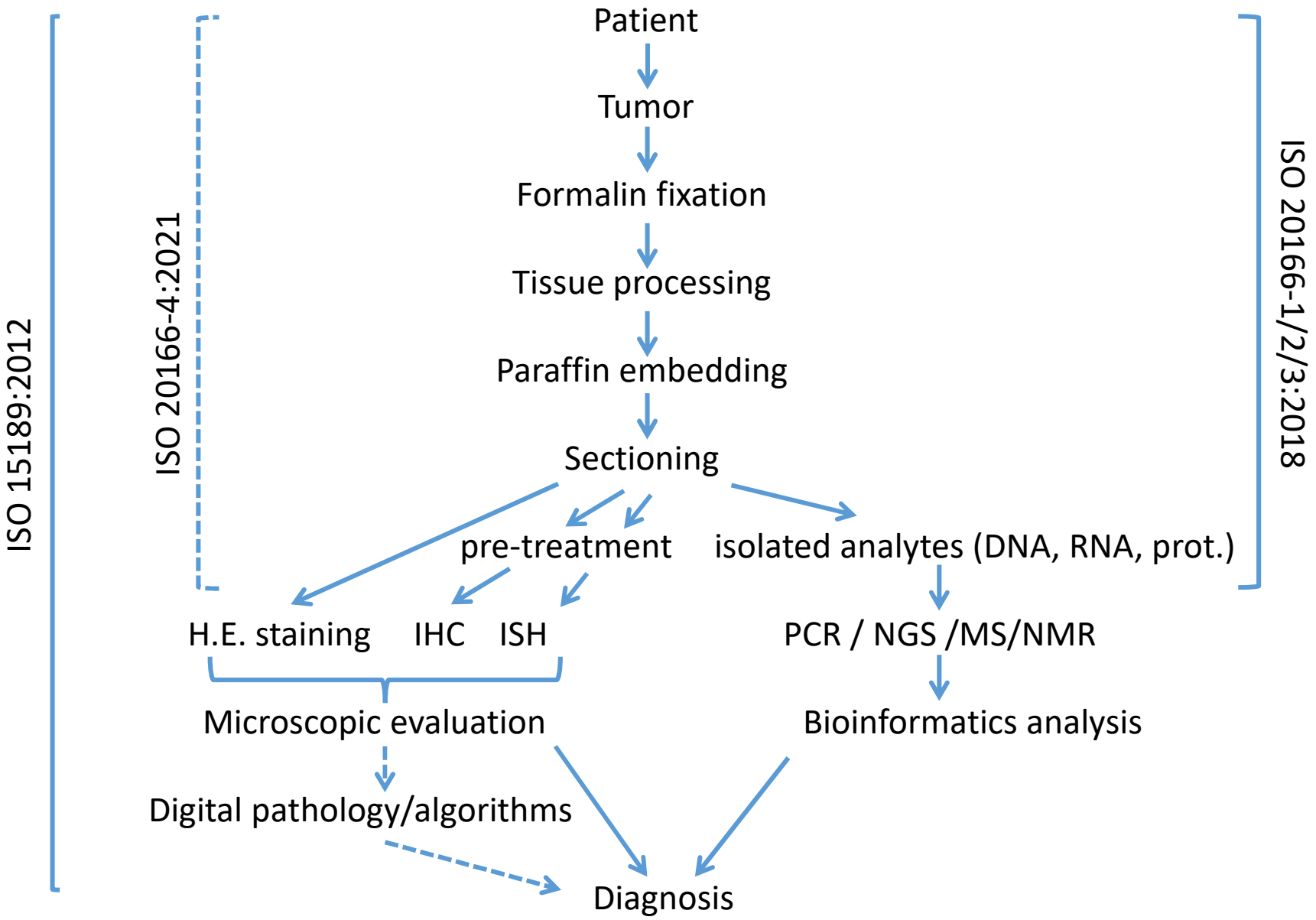
Introduction
1 Scope
2 Normative reference
3 Terms and definitions
4 General considerations

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

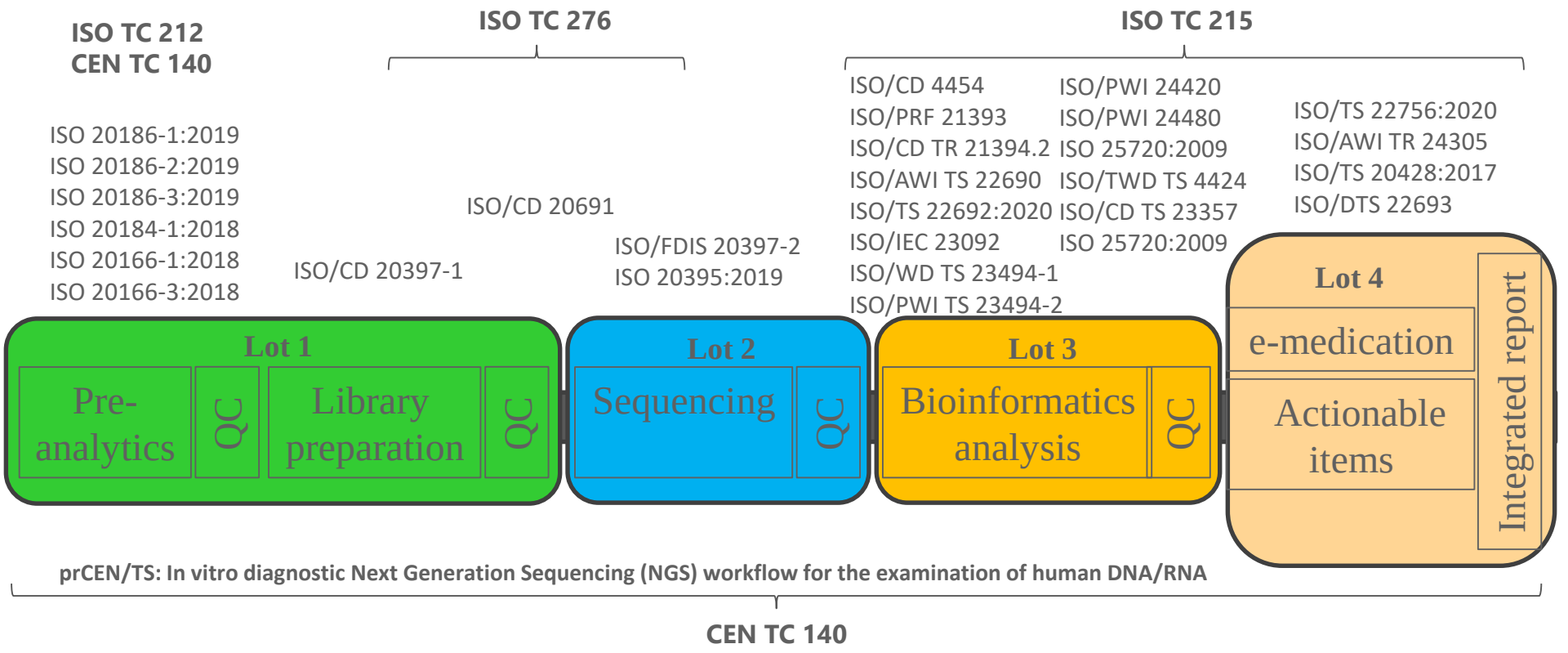
6 Inside the laboratory
6.1 Information about the reception of the specimen
6.2 Formalin fixation of the specimen or sample
6.3 Evaluation of the pathology of specimen and selection of sample(s)
6.4 Post-fixation of frozen samples
6.5 Decalcification
6.6 Processing and paraffin embedding
6.7 Storage 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

Standards for Pre-examination and Medical Diagnostics



Relevant Standard Landscape for Next Generation Sequencing



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Sample Quality Requirements for Performance Testing

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EN Official Journal of the European Union

REGULATION (EU) 2017/746 OF THE EUROPEAN PARLIAM

of 5 April 2017

on *in vitro* diagnostic medical devices and repealing Directive 98 sion 2010/227/EU

Needs biosamples with defined pre-analytical quality

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 is all about Patient Safety

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…but a long way to go

- Lack of awareness and knowledge in health systems and SMEs
- Implementation of quality management is a long and expensive process
- Transition period 2017- 2022: missed opportunity for most actors
- Lack of capacities (academia, health system, SMEs, regulators)
- Rapidly developing field (e.g., NGS, AI-based decision support)

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gateway for health
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BBMRI – Large Prospective Cohorts

NGS for Personalized Therapy

ESGI

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EASI Genomics

QIAGEN

Bridging the gap ... CORBEL

JPI a healthy diet for a healthy life

Christian Doppler Forschungsgesellschaft

ID Information und Dokumentation im Gesundheitswesen

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Thank You for Your Attention!