Standardization of Pre-analytical Procedures for Diagnostics and Clinical Research: SPIDIA4P Project

OECI 2021 ONCOLOGY DAYS

Jun 16th, 2021

Dr. Uwe Oelmueller, SPIDIA4P Coordinator

www.spidia.eu

New Technologies and Standards for Pre-analytical Workflows

SPIDIA – FP7 (2008 – 2013)

- ⇨ 16 Partners
- New technologies for sample collection, stabilization, processing, transport, storage (Blood, Tissues)
- 9 EU CEN Standards

SPIDIA4P – H2020 (2017 – 2021)

- ⇨ 19 Partners
- ⇨ 14 associated consortia & stakeholder organizations
- 13 additional new CEN & ISO Standards
- EQAs
- European and International implementation

www.spidia.eu ⇨ **Subscribe the Newsletter!**

The SPIDIA project has received funding under the Seventh Research Framework Program of the European Union, FP7-HEALTH-2007-1.2.5, under grant agreement no. 222916. The SPIDIA4P project receives funding from the European Union's Horizon 2020 research and innovation programme under grant agreement no. 733112.

Deficiencies in Routine Healthcare and Research demand for Improvements

- Diagnostic errors cause about 10% of all patient deaths and about 17% of adverse events

  Institute of Medicine (IOM) Report Sept. 2015

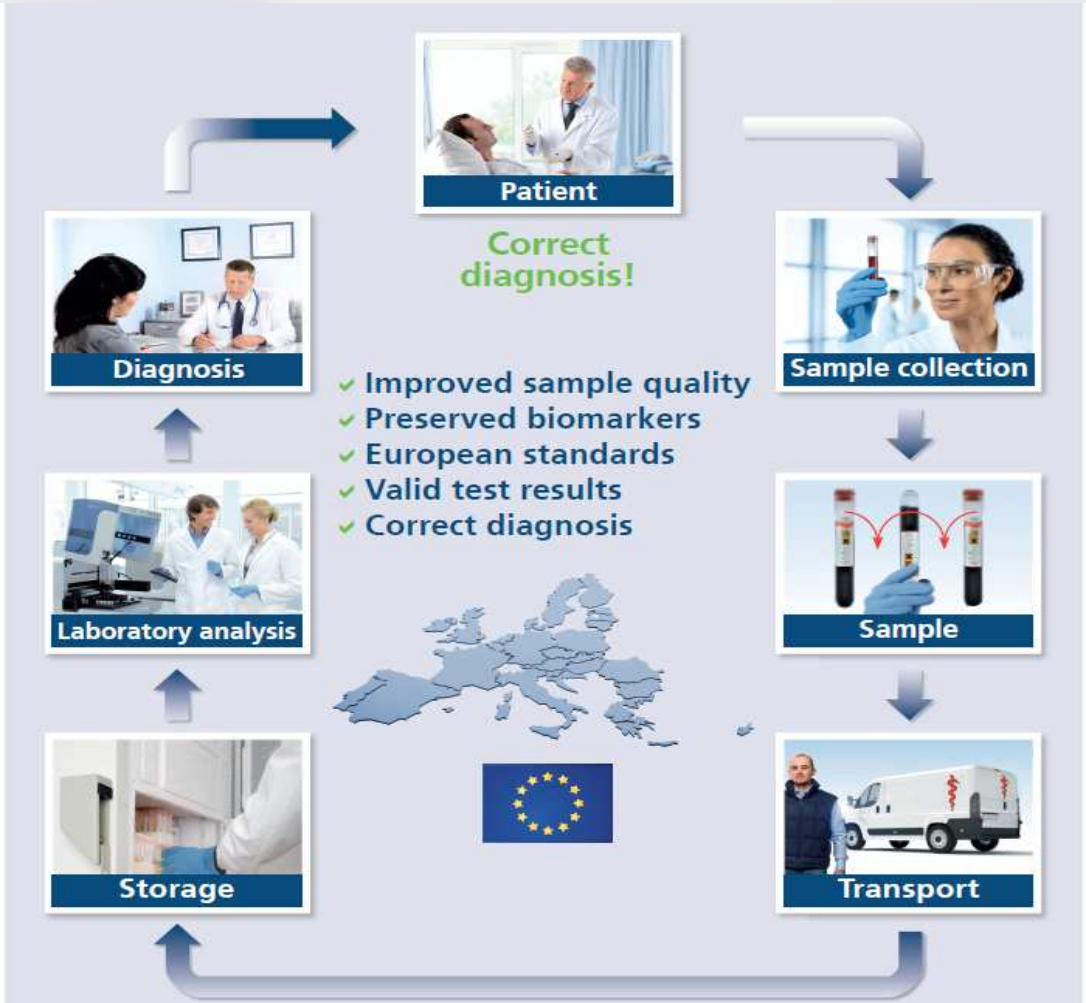
- Pre-analytical phase accounts for 46% to 68% of clinical laboratory errors

  Medical Laboratory Observer, May 2014

- Irreproducible preclinical research exceeds 50%, US $28B / year spent on preclinical research that is not reproducible - in the US

  Freedman LP, Cockburn IM, Simcoe TS (2015) PLoS Biol 13(6): e1002165.doi:10.1371/journal.pbio.1002165

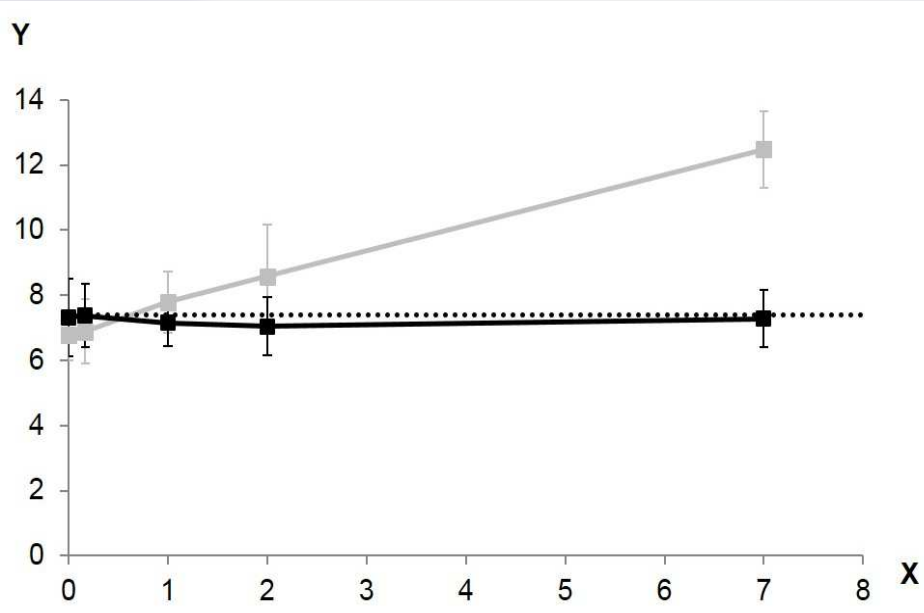
An Analytical Test Result is the Result of an Entire Workflow



Specifying, developing and verifying preanalytical workflows is an essential part of analytical test development

European Conference. Standards: Your Innovation Bridge. Brussels (2014). SPIDIA Booth.

Post Blood Collection ccfDNA Profile Changes - Impact on EGFR Test



X venous whole blood storage duration (in days) before plasma preparation

Y ΔCT = CT (mutant) - CT (wildtype control)

EDTA Blood

Stabilized Blood

···· Threshold (given by the examination provider)

The average of 8 donors is shown

- Spiked restriction enzyme treated EGFR DNA with mutation T790M, equivalent to 200 copies
- ccfDNA tested with the commercially available EGFR Plasma PCR Kit (RUO)

Source:

ISO 20186-3:2019: Molecular in vitro diagnostic examinations — Specifications for pre- examination processes for venous whole blood — Part 3: Isolated circulating cell free DNA from plasma. Annex A.

Major Efforts for Improvements

- **Technologies**
- **ISO & CEN Standards**
- **External Quality Assessment (EQA) Schemes**
- **Implementation** - healthcare, biobanking, research

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SPIDIA's Road to Standardization

under Vienna Agreement (1991)

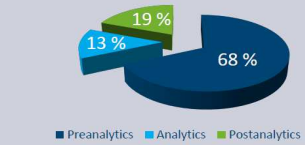
ISO

- 2019: 8 ISO/International Standards
- 2014: 8 new projects for ISO Standards approved in ISO/TC 212 „*Clinical laboratory testing and in vitro diagnostic test systems*"

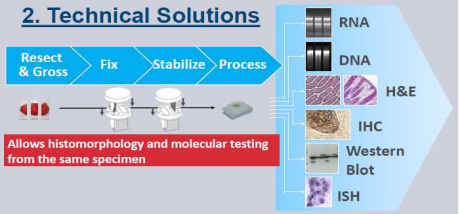
cen

- 2015: 9 CEN Technical Specifications published
- 2013: 9 new projects approved in CEN/TC 140 „*In vitro diagnostic medical devices*"
- 2010: Start of standardization work

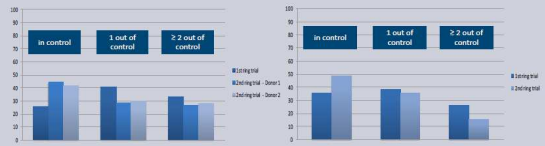
1. Problem - Errors in Diagnostics



2. Technical Solutions



3. Ring-Trials – Blood RNA (l.) and DNA (r.)

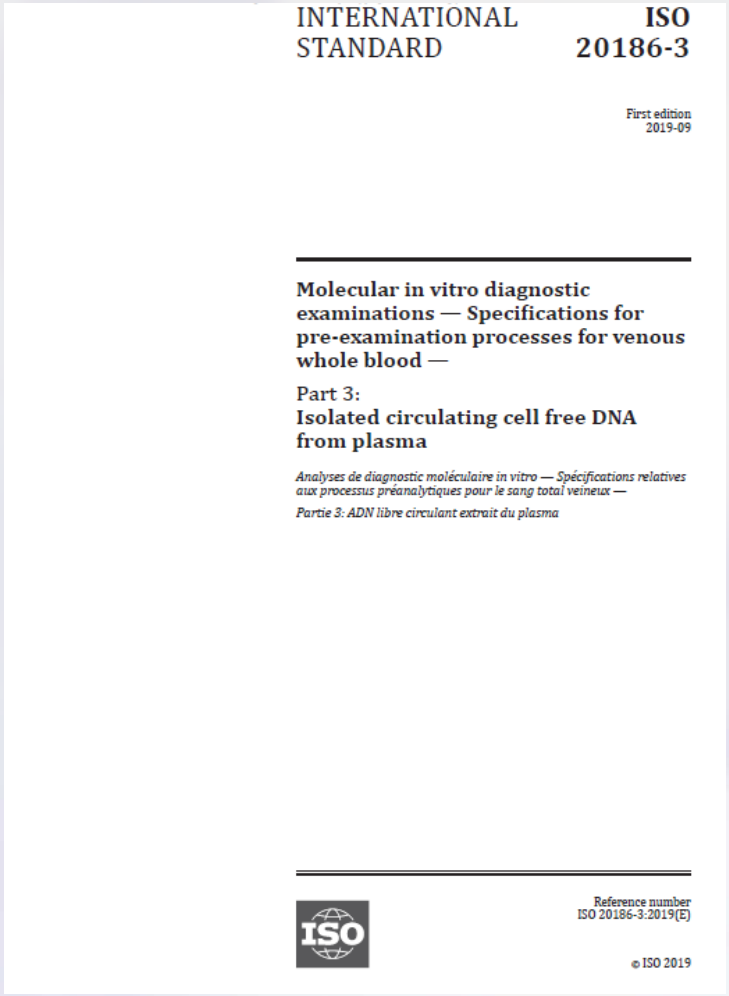


SEVENTH FRAMEWORK PROGRAMME

SPIDIA

European Conference. Standards: Your Innovation Bridge. Brussels (2014). SPIDIA Booth.

22 CEN & ISO Standard Documents and EQAs by 2021



INTERNATIONAL STANDARD **ISO 20186-3**

First edition
2019-09

Molecular in vitro diagnostic examinations — Specifications for pre-examination processes for venous whole blood —

Part 3:
Isolated circulating cell free DNA from plasma

Analyses de diagnostic moléculaire in vitro — Spécifications relatives aux processus préanalytiques pour le sang total veineux —
Partie 3: ADN libre circulant extrait du plasma

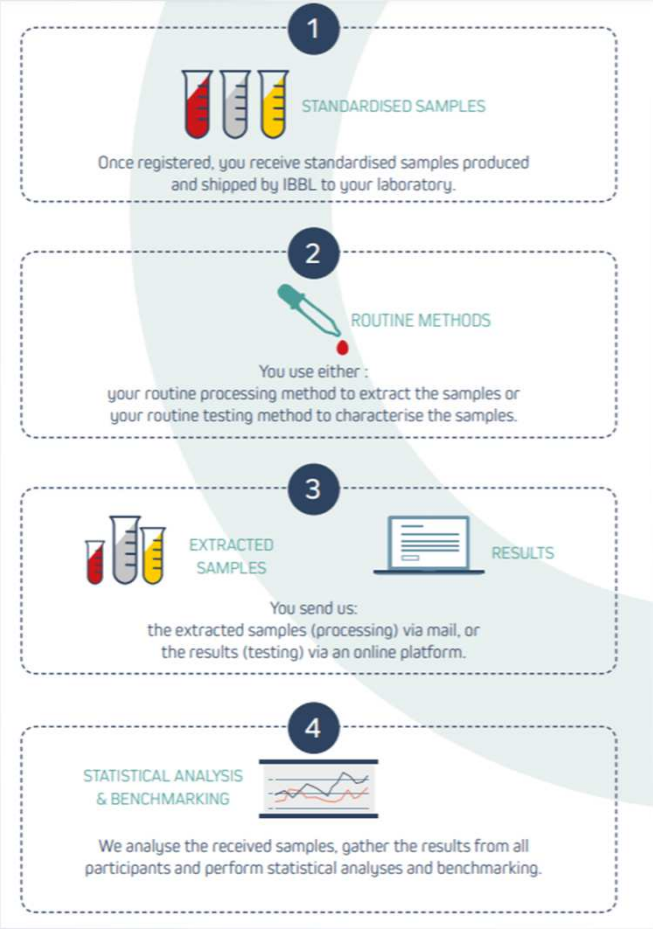
Reference number
ISO 20186-3:2019(E)

© ISO 2019

- Molecular in-vitro diagnostic examinations - Specifications for **pre-examination processes** for
  - **Blood** — Cellular RNA, gDNA, ccfDNA, ccfRNA
  - **Blood** – Exosomes / EVs
  - **Blood Tumor Cells** – DNA, RNA, staining
  - **Tissue** (FFPE) — DNA, RNA, Proteins
  - **Tissue** (Frozen) – DNA, RNA, Proteins
  - **Tissue** (FFPE) – in situe staining
  - **Fine Needle Aspirates** – DNA, RNA, Proteins
  - **Saliva** – DNA
  - **Urine & Body Fluids** – cfDNA
  - **Metabolomics** – Urine, Serum, Plasma
  - **Microbiome** – Stool, Saliva etc.

published CEN published ISO in development

The External Quality Assurance (EQA) Program in SPIDIA4P

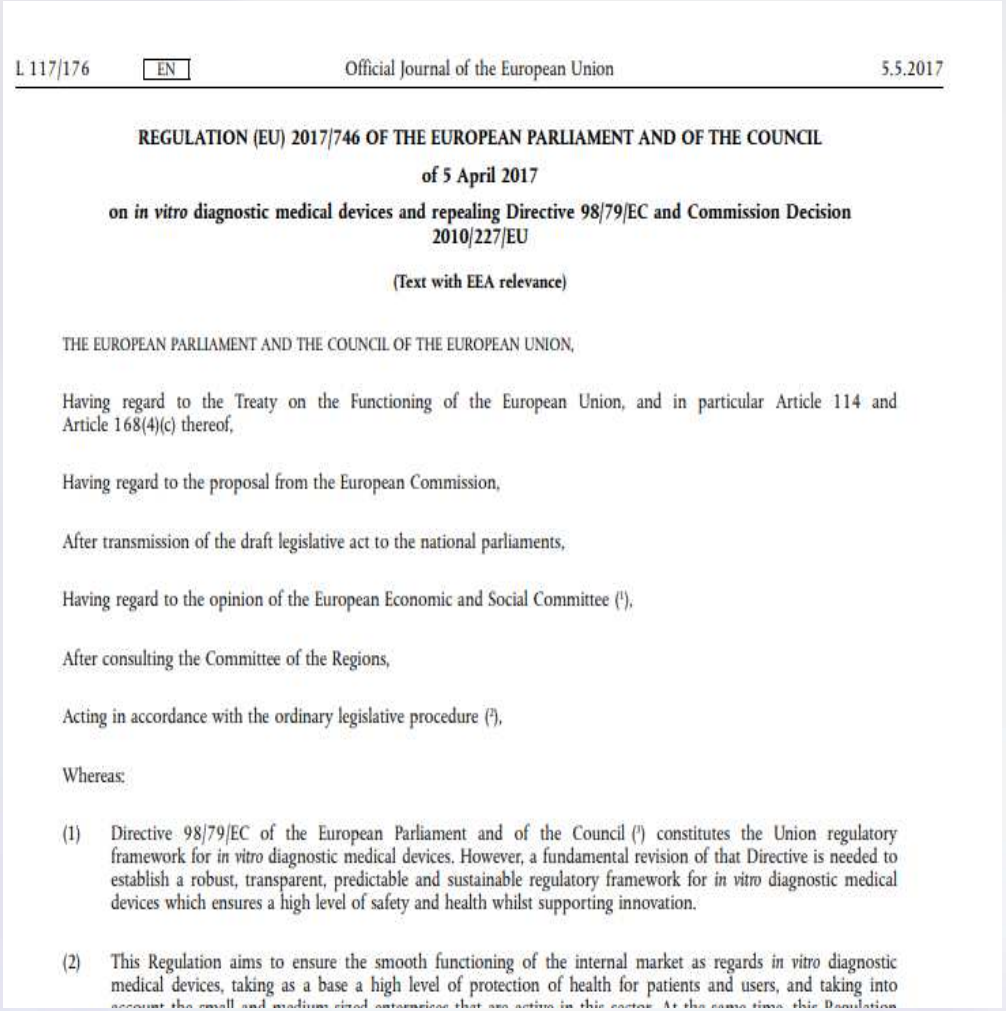


Implemented by Integrated Biobank of Luxembourg (IBBL) in annual PT Program

- DNA extraction from whole blood
- RNA extraction from whole blood
- DNA extraction from FFPE material
- RNA extraction from FFPE material
- Microbial DNA extraction from saliva
- Microbial DNA extraction from stool
- DNA extraction from frozen tissue
- Total RNA extraction from frozen tissue
- Cell-free DNA (cfDNA) extraction from whole blood
- Cell-free RNA (cfRNA) extraction from plasma
- Dual DNA/RNA Extraction from Frozen Tissue
- Circulating Tumor Cells (CTC) Detection and Isolation
- Viable PBMC isolation

Source: https://www.ibbl.lu/ibbl-bioservices/biospecimen-proficiency-testing

New EU In Vitro Diagnostic Medical Device Regulation (IVDR)



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

(Text with EEA relevance)

THE EUROPEAN PARLIAMENT AND THE COUNCIL OF THE EUROPEAN UNION,

Having regard to the Treaty on the Functioning of the European Union, and in particular Article 114 and Article 168(4)(c) thereof,

Having regard to the proposal from the European Commission,

After transmission of the draft legislative act to the national parliaments,

Having regard to the opinion of the European Economic and Social Committee [1],

After consulting the Committee of the Regions,

Acting in accordance with the ordinary legislative procedure [2],

Whereas:

(1) Directive 98/79/EC of the European Parliament and of the Council [3] constitutes the Union regulatory framework for *in vitro* diagnostic medical devices. However, a fundamental revision of that Directive is needed to establish a robust, transparent, predictable and sustainable regulatory framework for *in vitro* diagnostic medical devices which ensures a high level of safety and health whilst supporting innovation.

(2) This Regulation aims to ensure the smooth functioning of the internal market as regards *in vitro* diagnostic medical devices, taking as a base a high level of protection of health for patients and users, and taking into account the small and medium sized enterprises that are active in this sector. At the same time, this Regulation

- entered into force on 26 May 2017
- will replace the EU's current Directive on in vitro diagnostic medical devices (98/79/EC)
- transition period until 26 May 2022

New In Vitro Diagnostic Regulations 2017 (IVDR)

- **Pre-analytical workflow parameters** in several sections

  - 6. PRODUCT VERIFICATION AND VALIDATION (Annex II)

  - 6.1. Information on analytical performance of the device
  - 6.1.1. Specimen type

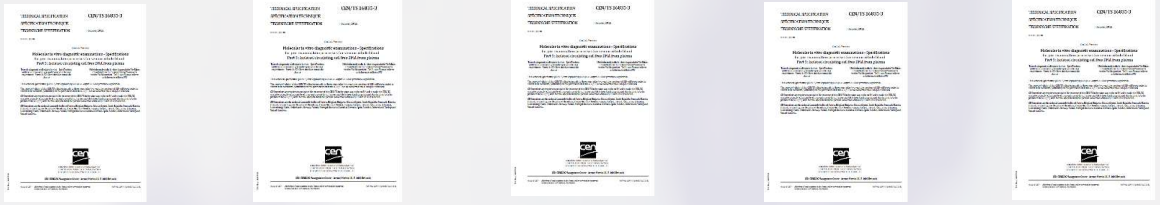
    This Section shall describe the different specimen types that can be analysed, including their stability such as storage, where applicable specimen transport conditions and, with a view to time-critical analysis methods, information on the timeframe between taking the specimen and its analysis and storage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

- **State-of-the-Art** required for device developments in various articles and annexes

Role of Standards and Technologies

New EU IVDR – in-vitro Diagnostic Device Regulation 2017

Pre-analytical workflow parameters



EN ISO & CEN Standards

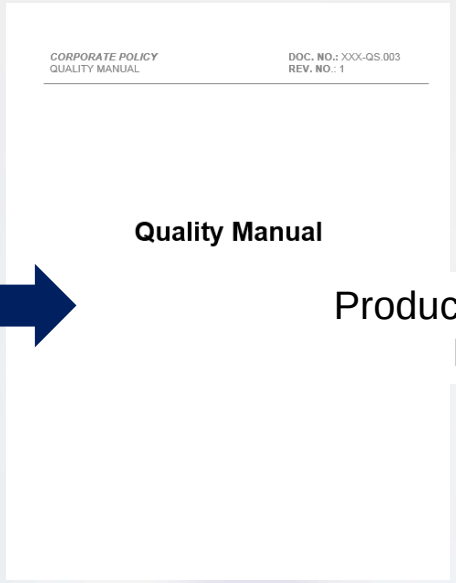
SOPs

Technologies & Products

Trainings & Implementation of Preanalytical Standards

Example: SPIDIA4P industry partner PreAnalytiX – ISO 20186 series in CE-IVD and FDA projects

Certification according to ISO 13485

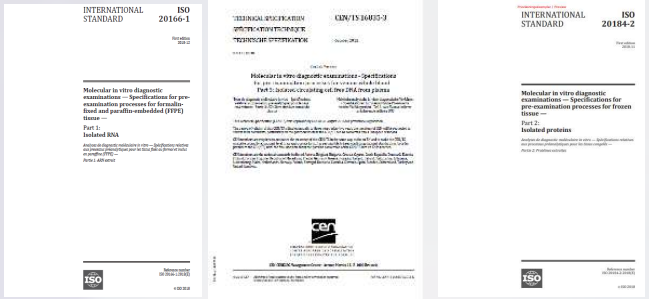

CORPORATE POLICY
QUALITY MANUAL
DOC. NO.: XXX-QS.003
REV. NO.: 1

Quality Manual

Company Quality Manual: Process Landscape

Product Development Process

Global Process SOPs incl. legal requirements


INTERNATIONAL STANDARD ISO 20166-1

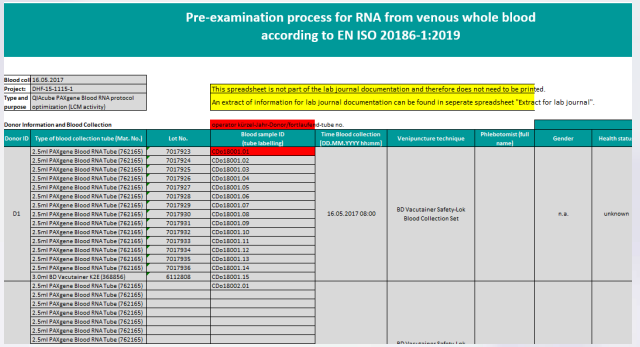
Molecular in vitro diagnostic examinations — Specifications for pre-examination processes for formalin-fixed and paraffin-embedded (FFPE) tissue —

Part 1: Isolated RNA

INTERNATIONAL STANDARD ISO 20184-2

Molecular in vitro diagnostic examinations — Specifications for pre-examination processes for frozen tissue —

Part 2: Isolated proteins


Pre-examination process for RNA from venous whole blood according to EN ISO 20186-1:2019

Technical SOPs for pre-analytical workflows based on ISO & CEN standards

A big Thank You goes to . . .

. . . to the SPIDIA & SPIDIA4P Consortium Members, CEN/TC 140, ISO/TC 212 and all European and International Partners!

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