Standardized and Improved Pre-analytical Workflows: Crucial for Reliable Diagnostics, Research and Biobanking

ISBER 2018 Annual Meeting

Dallas, May 24th 2018

Dr. Uwe Oelmüller, SPIDIA4P Coordinator, QIAGEN GmbH

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

- Unnecessary expenditure caused by pre-analytical errors in a typical U.S. hospital (~ 650 beds) of ~ $1.2 million per year

  Green SF. Clin Biochem. 2013

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

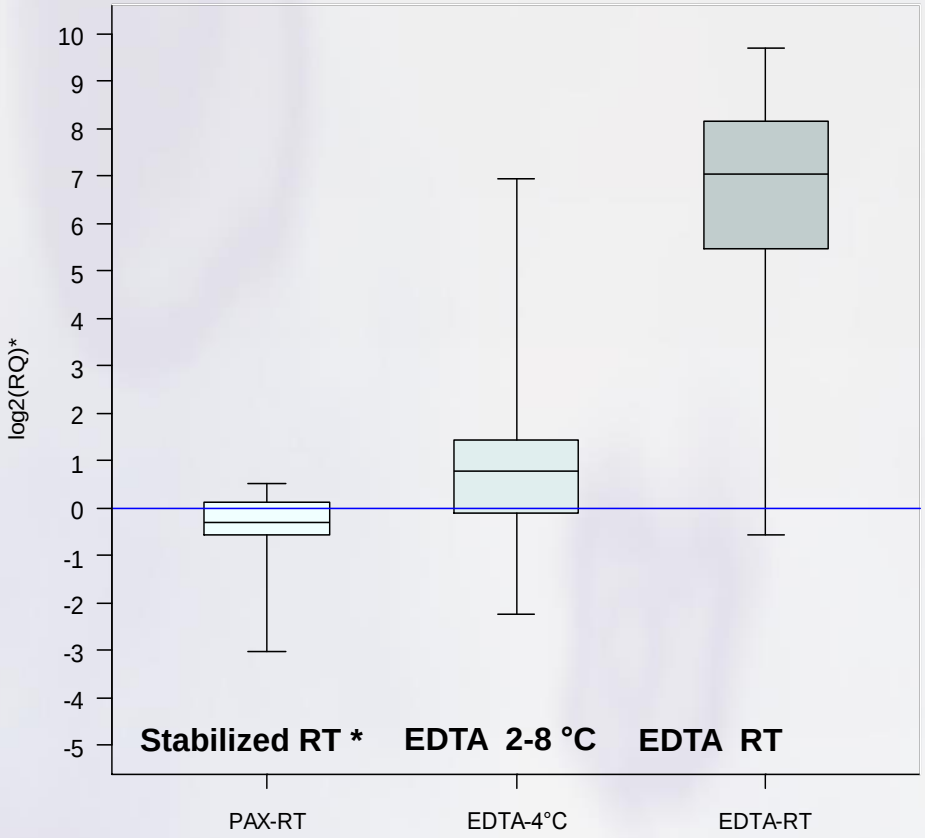
  Freedman LP, Cockburn IM, Simcoe TS (2015) PLoS Biol 13(6): e1002165.doi:10.1371/journal.pbio.1002165

Sample-to-Insight Diagnostic Workflows

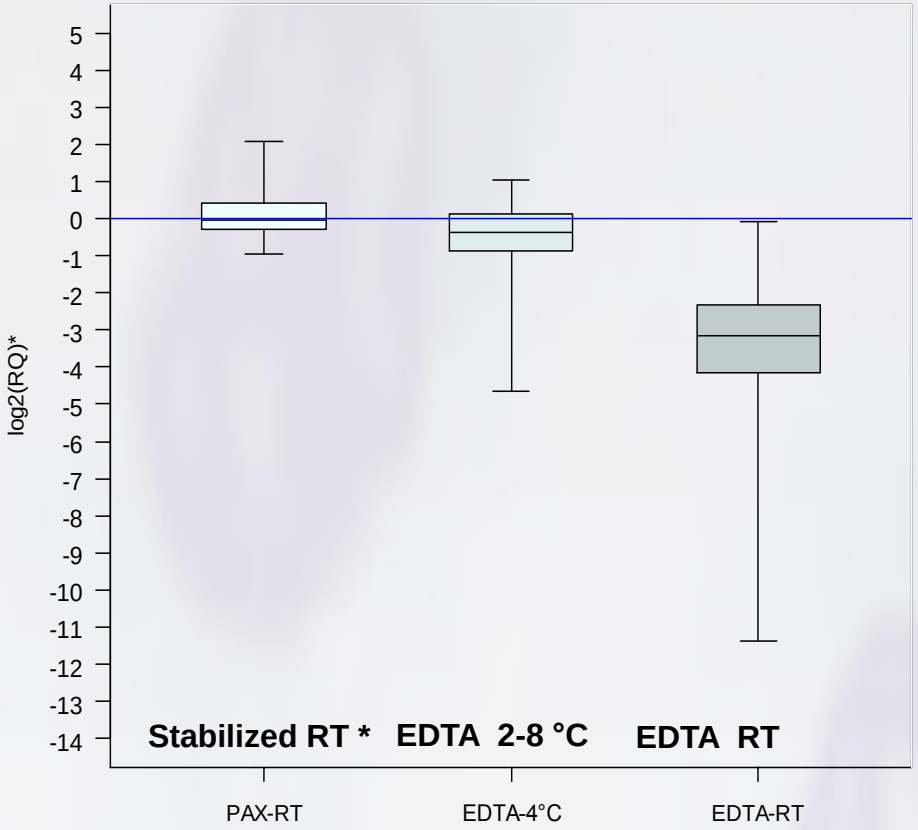
European Conference. Standards: Your Innovation Bridge. Brussels (2014). SPIDIA Booth.

Changes of Blood Cellular RNA Profile: 48 Hours After Collection

Up-regulated FOSB mRNA level



Down-regulated TNFRS mRNA level

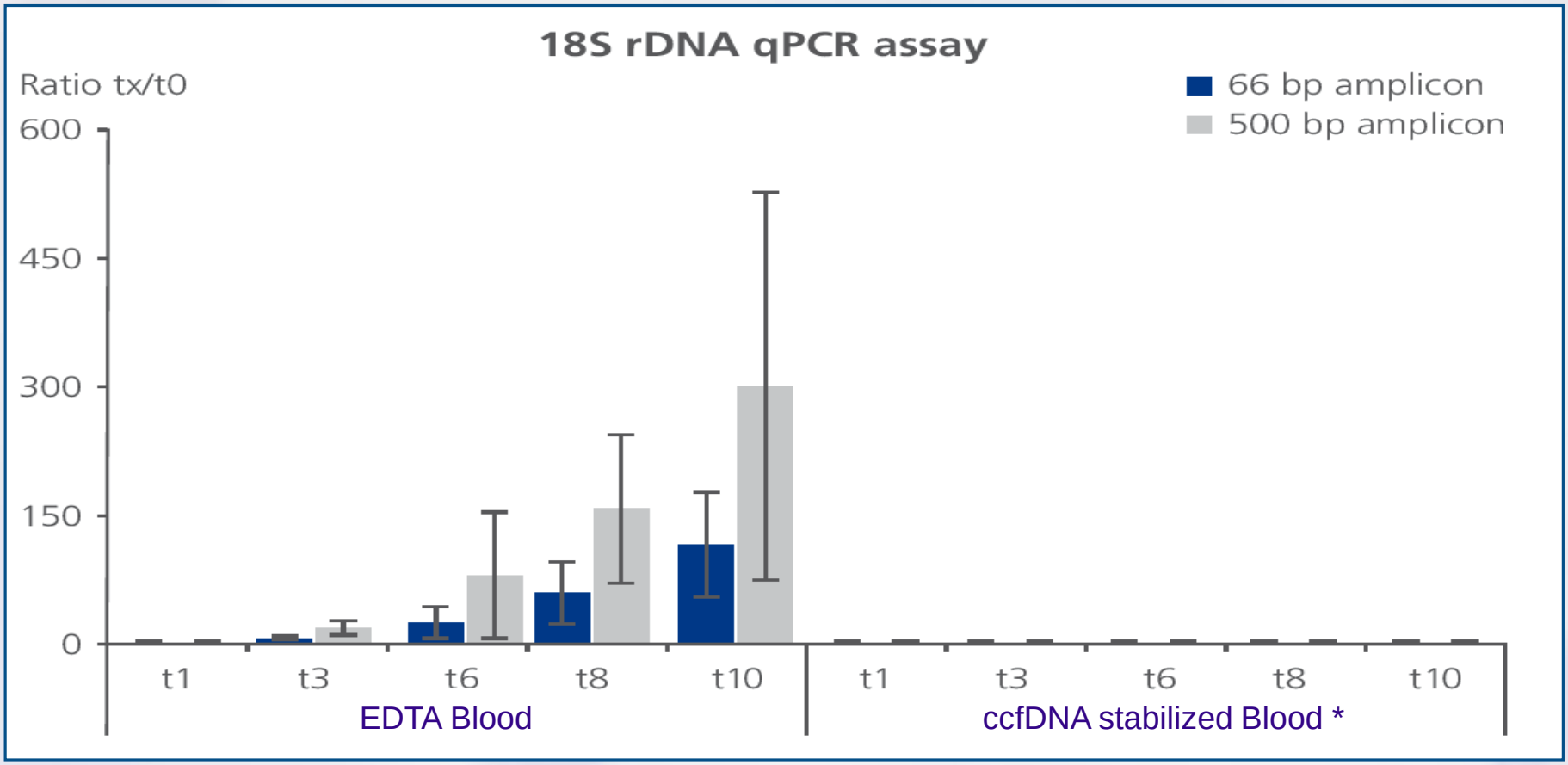


* PAXgene Blood RNA

Malentacchi F et al. (2014). SPIDIA-RNA: Second External Quality Assessment for the Pre-Analytical Phase of Blood Samples Used for RNA Based Analyses. PLoS ONE 9(11): e112293.

Zhan H et al. (2014). Biomarkers for Monitoring Pre-Analytical Quality Variation of mRNA in Blood Samples. . PLoS ONE 9(11): e111644.

Pre-analytical Impacts on Blood ccfDNA Profiles



* PAXgene Blood ccfDNA Tube

Andrea Ullius[1,2], Joachim Bonnet[3], Wera Hofmann[3], Markus Stumm[4], Nadine Dettmann[1,2], Katharina Pfaff[1,2], Franziska Heese[1,2] and Daniel Grölz[1,2]. [1]QIAGEN GmbH, Hilden, Germany; [2] PreAnalytiX GmbH, Hombrechtikon, Switzerland; [3]LifeCodexx AG, Konstanz, Germany; [4] Centre for Prenatal Diagnostics and Human Genetics, Berlin, Germany

ESBB Congress London, 2015

Two Major Efforts for Improvements

- **Technologies** for securing high quality samples
- **International Standards** for pre-analytical workflows

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 – 2020)

- ⇨ 19 Partners
- ⇨ 14 associated consortia & stakeholders
- 13 additional new CEN & ISO Standards
- EQAs
- European implementation

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

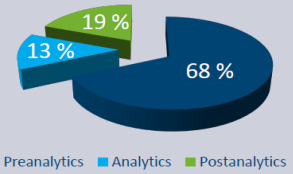
The SPIDIA project has received funding under the Seventh Research Framework Program of the European Union, FP7-HEALTH-2007-1.2.5, under grant agreement no. 222916. The SPIDIA4P project receives funding from the European Union's Horizon 2020 research and innovation programme under grant agreement no.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

SPIDIA's Road to Standardization

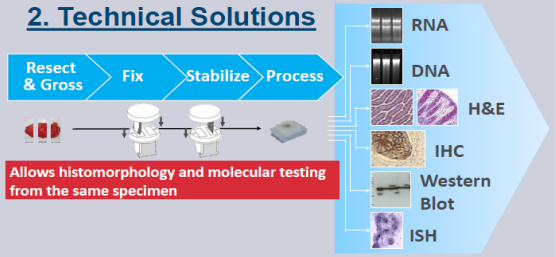
- 2017: Progressing to ISO/FDIS
- 2014: 8 new projects for ISO Standards approved in ISO/TC 212 „*Clinical laboratory testing and in vitro diagnostic test systems*"

- 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

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

Twofold Role of ISO & CEN Standards

Traditional Role of Standards

- Source of technical know-how
- Trade facilitation and opening of markets
- Providing a scientific basis for legislation in the health, safety and environment sectors

Valued-added role for research and innovation

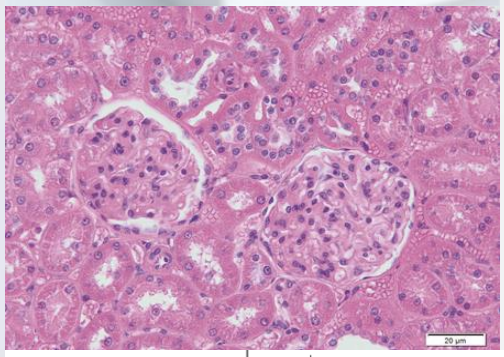
- Speeding up innovation by providing the requisite knowledge base

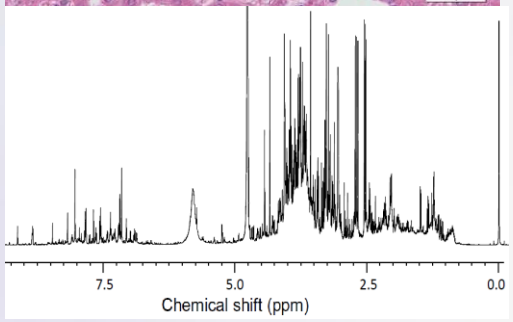
  (technology transfer)

➢ New ideas, technologies and products benefit from standardization to get into the marketplace and to be successful

Source: Gindele 2013
http://www.iso.org/iso/home/about/conformity-assessment.htm

9 CEN Technical Specifications released in Europe in 2015 / 16





- Molecular in-vitro diagnostic examinations - Specifications for pre-examination processes for
  - blood — Cellular RNA
  - blood — Genomic DNA
  - blood — Circulating cell free DNA
  - FFPE tissue — DNA
  - FFPE tissue — RNA
  - FFPE tissue — Proteins
  - frozen tissue — RNA
  - frozen tissue — Proteins
  - metabolomics in urine, serum and plasma

⇨ Professional societies and organizations play a central role in implementation (e.g. BBMRI-ERIC, ESP, EFLM, MedTech etc.)

CEN/TS 16835-3 - Pre-examination Process for Blood ccfDNA

TECHNICAL SPECIFICATION

SPÉCIFICATION TECHNIQUE

TECHNISCHE SPEZIFIKATION

CEN/TS 16835-3

October 2015

ICS 11.100.30

English Version

Molecular in vitro diagnostic examinations - Specifications for pre-examination processes for venous whole blood - Part 3: Isolated circulating cell free DNA from plasma

Tests de diagnostic moléculaire in vitro - Spécifications relatives aux processus pré-analytiques pour le sang total veineux - Partie 3: ADN libre circulant extrait du plasma

Molekularanalytische in-vitro-diagnostische Verfahren - Spezifikationen für präanalytische Prozesse für venöse Vollblutproben - Teil 3: Aus Plasma isolierte zirkulierende zellfreie DNS

This Technical Specification (CEN/TS) was approved by CEN on 31 August 2015 for provisional application.

The period of validity of this CEN/TS is limited initially to three years. After two years the members of CEN will be requested to submit their comments, particularly on the question whether the CEN/TS can be converted into a European Standard.

CEN members are required to announce the existence of this CEN/TS in the same way as for an EN and to make the CEN/TS available promptly at national level in an appropriate form. It is permissible to keep conflicting national standards in force (in parallel to the CEN/TS) until the final decision about the possible conversion of the CEN/TS into an EN is reached.

CEN members are the national standards bodies of Austria, Belgium, Bulgaria, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, Former Yugoslav Republic of Macedonia, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, Netherlands, Norway, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden, Switzerland, Turkey and United Kingdom.

EUROPEAN COMMITTEE FOR STANDARDIZATION
COMITÉ EUROPÉEN DE NORMALISATION
EUROPÄISCHES KOMITEE FÜR NORMUNG

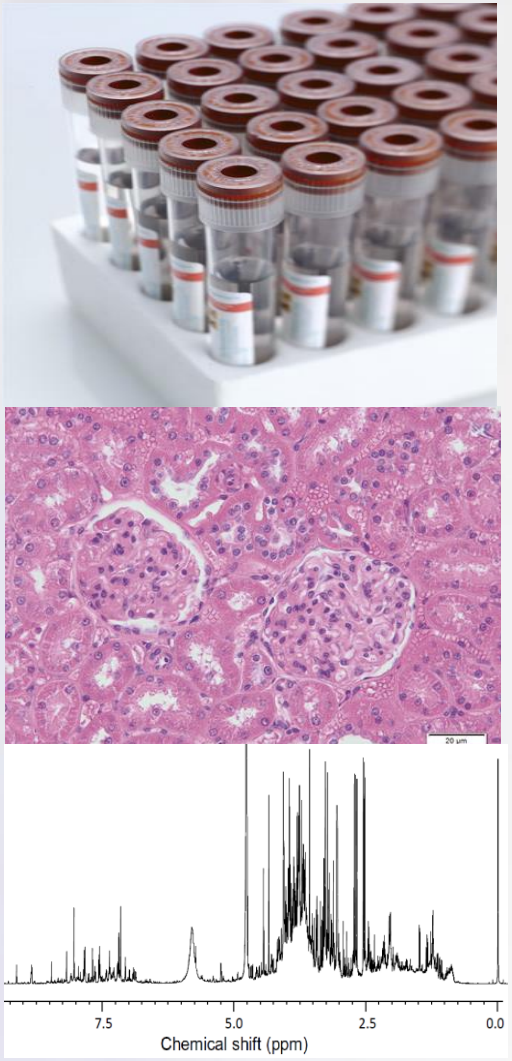
CEN-CENELEC Management Centre: Avenue Marnix 17, B-1000 Brussels

Ref. No. CEN/TS 16835-3:2015 E

ISO/IS Standard expected for early 2019

CEN/TS 16835-3 - Pre-examination Process for Blood ccfDNA

SPIDIA4P - More Standards, EQAs and Support Tools to come



. . . . pre-examination processes for

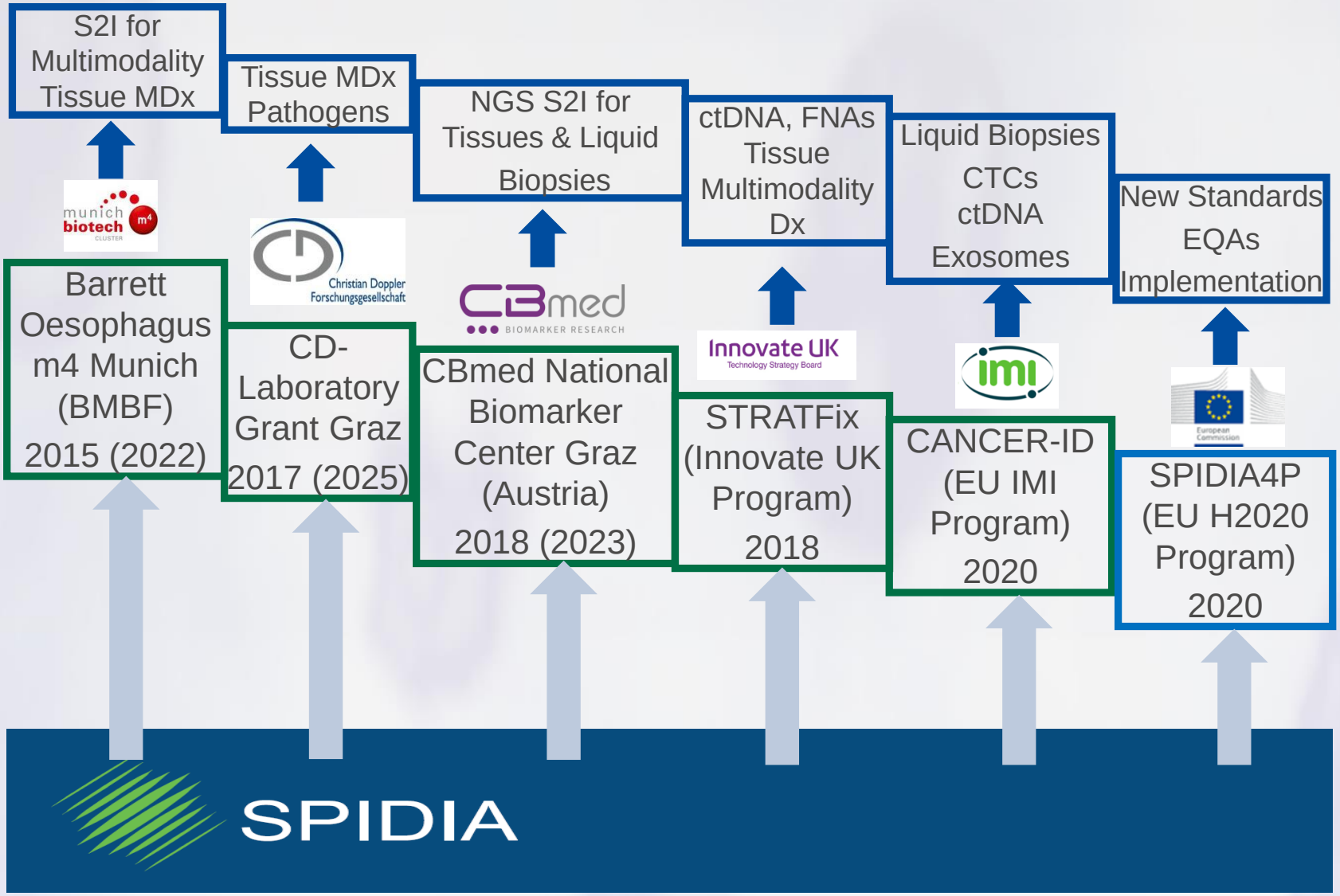
- Venous whole blood — CTCs: DNA, RNA, stains & proteins
- Venous whole blood – Exosomes: nucleic acids; ccfRNA
- Urine & other body fluids – cfDNA
- Saliva – Human DNA
- Saliva and stool – Microbiome DNA
- Frozen Tissue – DNA
- Fine Needle Aspirates (FNAs) – DNA, RNA, proteins
- FFPE Tissue – in situ stainings incl. IHC
- Metabolomics of body fluids: ISO Standard

➢ . . . plus control tools (EQA schemes)

➢ . . . plus implementation tools

➢ . . . plus proof of commercial success (SMEs, e.g. Inivata Ltd.)

International Grant Consortia Network on Diagnostic Workflow Technologies & Standardization



New In Vitro Diagnostic Regulations 2017

- New European In Vitro Diagnostic Regulation in force since May 2017

- Also pre-analytical workflow parameters become mandatory (IVDR)
  - 6. PRODUCT VERIFICATION AND VALIDATION (Annex II)
  - 6.1. Information on analytical performance of the device
  - 6.1.1. Specimen type

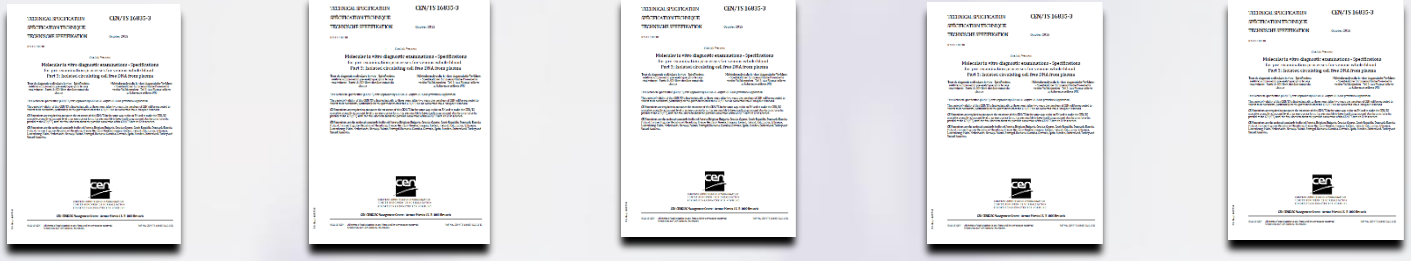
    This Section shall describe the different specimen types that can be analysed, including their stability such as storage, where applicable specimen transport conditions and, with a view to time-critical analysis methods, information on the timeframe between taking the specimen and its analysis and storage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

SPIDIA4P

Role of Standards and Technologies

EU IVDR – In-vitro-Diagnostic Device Regulation

Pre-analytical workflow parameters



EN ISO & CEN Standards

SOPs

Technologies & Products

Pre-analytical Workflow - Same Standards for all Segments

- **Biobanks**
  - Source for high quality samples
  - ⇨ BBMRI-ERIC plays a central role
- **Biomedical & Translational Research**
  - Academia
  - Pharma industry
  - Diagnostic Industry
- **Diagnostics**
  - High sample quality is the safe way
  - Analytical assay might tolerate lower quality or not ⇨ Validation studies

A big Thank You goes to . . .

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

Thank you!

Questions ?