New CEN and ISO Standards for Improving Diagnostics and Research – How They are Developed

Lecture Course

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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

Two Major Efforts for Improvements

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

The Right View: An Analytical Test Result is a Result of an Entire Workflow

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

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 including BBMRI-ERIC
- ⇨ 14 associated consortia & stakeholders
- 13 additional new CEN & ISO Standards
- EQAs
- European implementation

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

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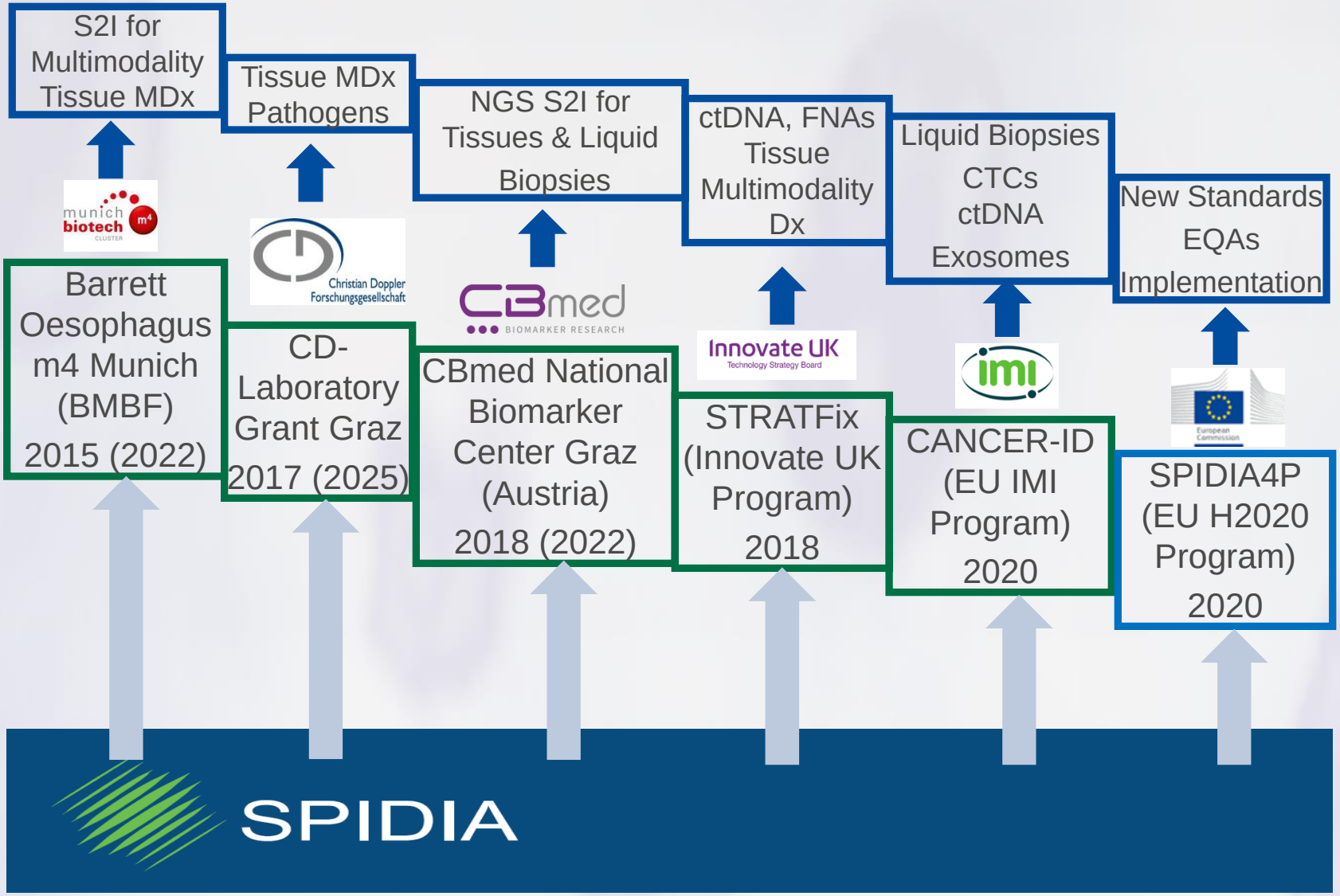
European Grant Consortia Network on Diagnostic Workflow Technologies & Standardization

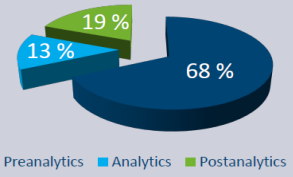


SPIDIA's Road to Standardization

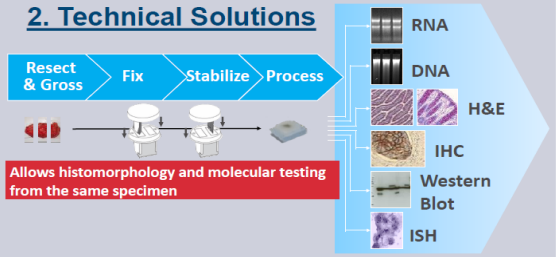
- 2017: Progressing to ISO/FDIS
- 2014: 8 new projects for ISO Standards approved in ISO/TC 212 „*Clinical laboratory testing and in vitro diagnostic test systems*"

- 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.

The Vienna Agreement, signed 1991

The Vienna Agreement was drawn up with the aim of preventing duplication of effort and reducing time when preparing standards.

As a result, new standards projects are jointly planned between CEN and ISO.

Wherever appropriate priority is given to cooperation with ISO provided that international standards meet European legislative and market requirements and that non-European global players also implement these standards.

Source: https://www.cencenelec.eu/intcoop/StandardizationOrg/Pages/default.aspx

CEN - Twofold Role of Standardization

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

Products of European Standardization

European Standard – EN

Goal: Development of normative specifications reflecting the current state of technology

European Technical Specification – CEN/TS

Goal: Specifications which aid market development and growth

European Technical Report – CEN/TR

Goal: Specifications of a recommendatory and explanatory nature

CEN Workshop Agreement – CWA

Goal: Special specifications developed with the rapid consensus of expert stakeholders

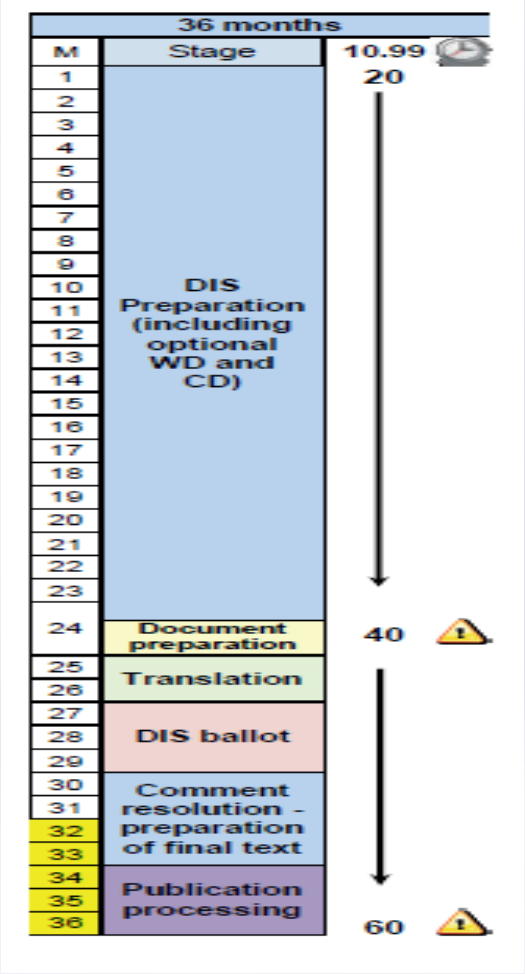
Highly Consensus Driven Process Needed for Developing Standards

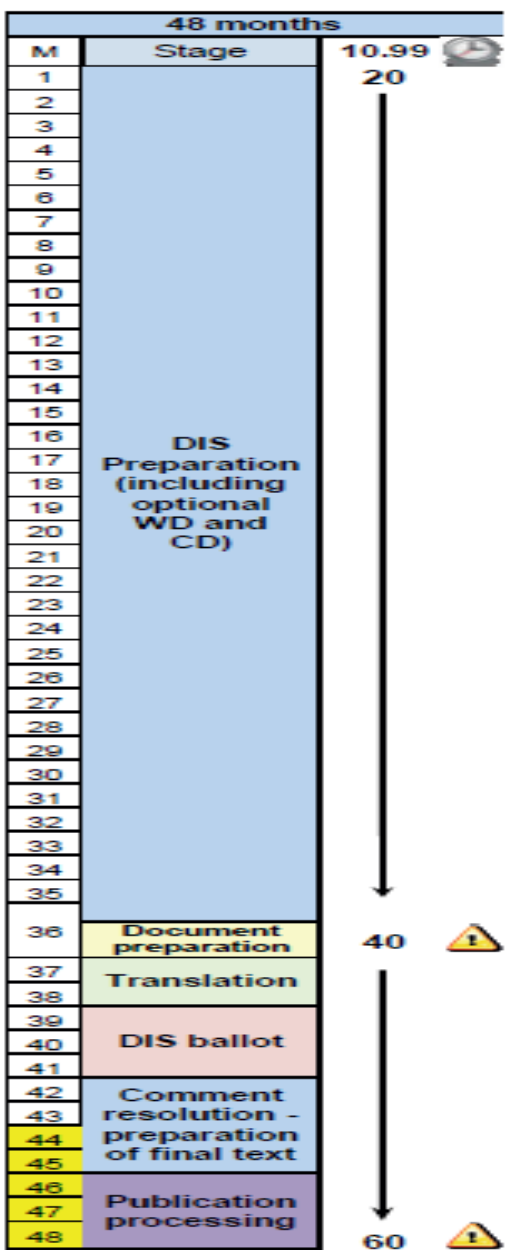
- **CEN**
  - Recognized by the EU and the European Free Trade Association (EFTA) as being **responsible for developing standards at European level**
  - Development of a European Standard (EN) or International Standard (ISO) is governed by the principles of **consensus, openness, transparency, national commitment** and **technical coherence**
  - One European Standard replaces 34 national standards

- **CEN/TC 140** (Committee for in vitro diagnostic medical devices)
  - **out of 34 EU countries National Standards Bodies (NSB), 24 active in CEN/Technical Committe TC 140 and 16 in responsible working group CEN/TC 140/WG 3**
  - **Stakeholders in liaison & cooperations**
    - **European Commission** (EC), **ESP** (European Society of Pathology), **EFLM** (European Federation of Laboratory Medicine), **IFCC** (Int. Federation of Clinical Chemistry and Laboratory Medicine), **JISC** (Japanese Industrial Standards Committee), **MedTech** (Alliance of European medical technology industry associations, founded by **EDMA**), **EPBS** (European Association for Professions in Biomedical Science), **BBMRI-ERIC** (Biobanking and BioMolecular resources Research Infrastructure - European Research Infrastructure Consortium), in progress, **ISO/TC 212** (Clinical laboratory testing and in vitro diagnostic test systems), **ISO/TC 276** Biotechnology

ISO/IS Development – Usually a 36 to 48 Months Period

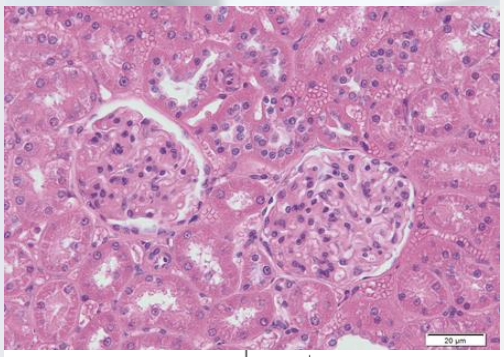
ISO/TC 212
(Technical Committee for Clinical laboratory testing and in vitro diagnostic test systems)

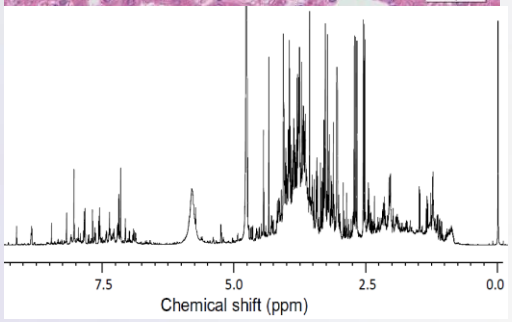




Source:
https://www.iso.org/files/live/sites/isoorg/files/developing_standards/docs/en/Target_date_planner_4_ISO_standards_development_tracks_2017.pdf

9 CEN Technical Specifications released in Europe in 2015 / 16

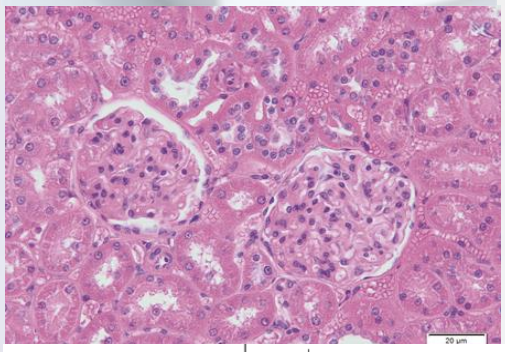


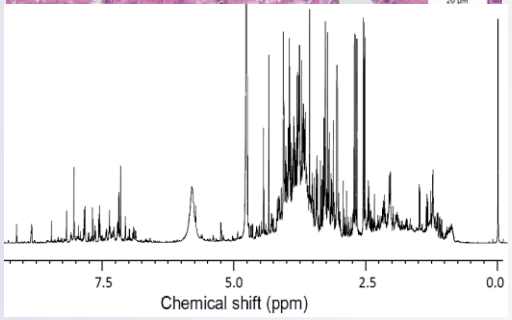


- Molecular in-vitro diagnostic examinations - Specifications for pre-examination processes for
  - blood — Cellular RNA
  - blood — Genomic DNA
  - blood — Circulating cell free DNA
  - FFPE tissue — DNA
  - FFPE tissue — RNA
  - FFPE tissue — Proteins
  - frozen tissue — RNA
  - frozen tissue — Proteins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

- 8 under late stage development to ISO Standards (FDIS next step)

. . . more Standards to come





- 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
- Metabolomics of body fluids: International ISO Standard
- FFPE Tissue – in situ stainings incl. IHC

➢ . . . plus implementation tools

➢ . . . plus control tools (External Quality Assessment)

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

Pre-analytical Workflow - Same Standards for all Segments

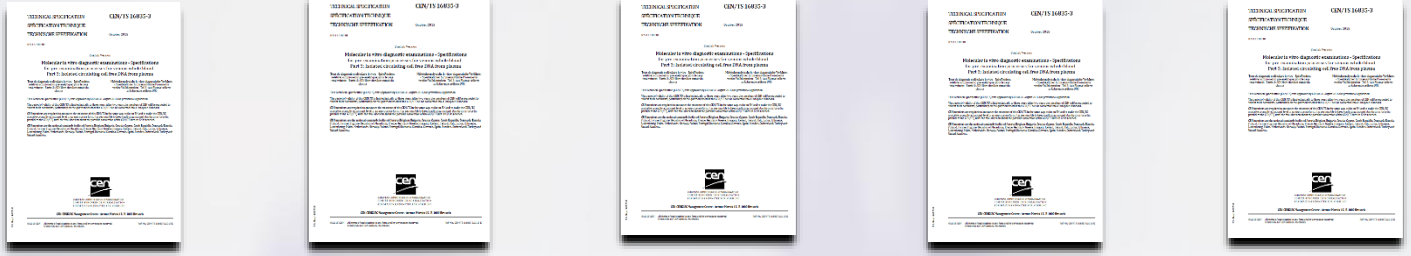
- **Biobanks**
  - Source for high quality samples
  - ⇨ BBMRI-ERIC plays a central role
- **Biomedical & Translational Research**
  - Academia
  - Pharma industry
  - Diagnostic Industry
- **Diagnostics**
  - High sample quality is the safe way
  - Analytical assay might tolerate lower quality or not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

SPIDIA4P

Role of Standards and Technologies

EU IVDR – In-vitro-Diagnostic Device Regulation

Pre-analytical workflow parameters



EN ISO & CEN Standards

SOPs

Technologies & Products

SPIDIA4P

A big Thank You goes to . . .

. . . to the SPIDIA & SPIDIA4P Consortium Members and all European and International Partners!

Thank you!

Questions ?