EU SPIDIA Project - Standardization and Improvement of Generic Preanalytical Tools and Procedures for In Vitro Diagnostics

Swiss Symposium on Lab Automation

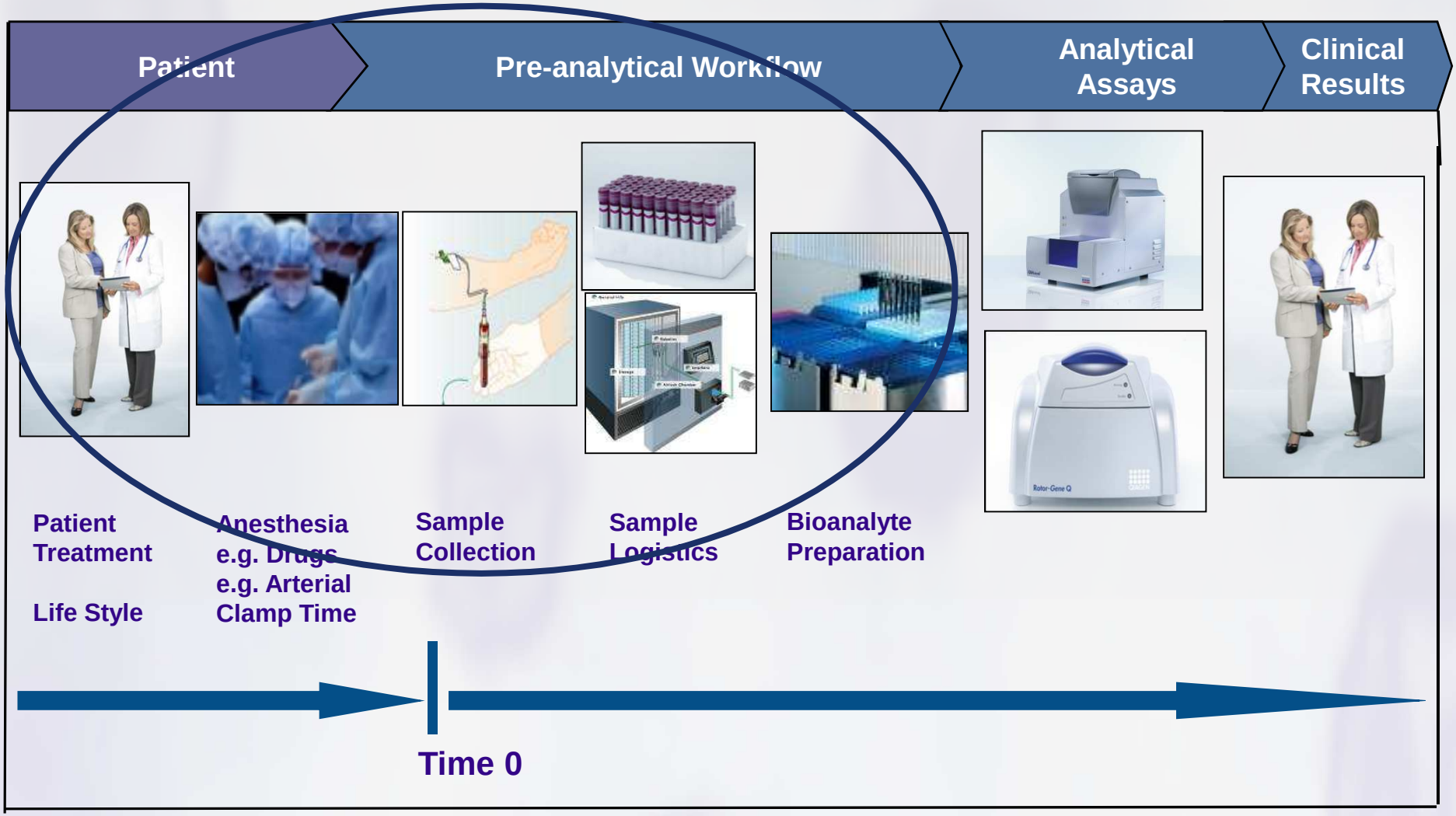
Rapperswil, March 20th 2014

Dr. Uwe Oelmüller
SPIDIA Coordinator
QIAGEN GmbH

Agenda

- **Introduction**
- Pre-analytical Workflow Studies
- New Technologies
- New Standards

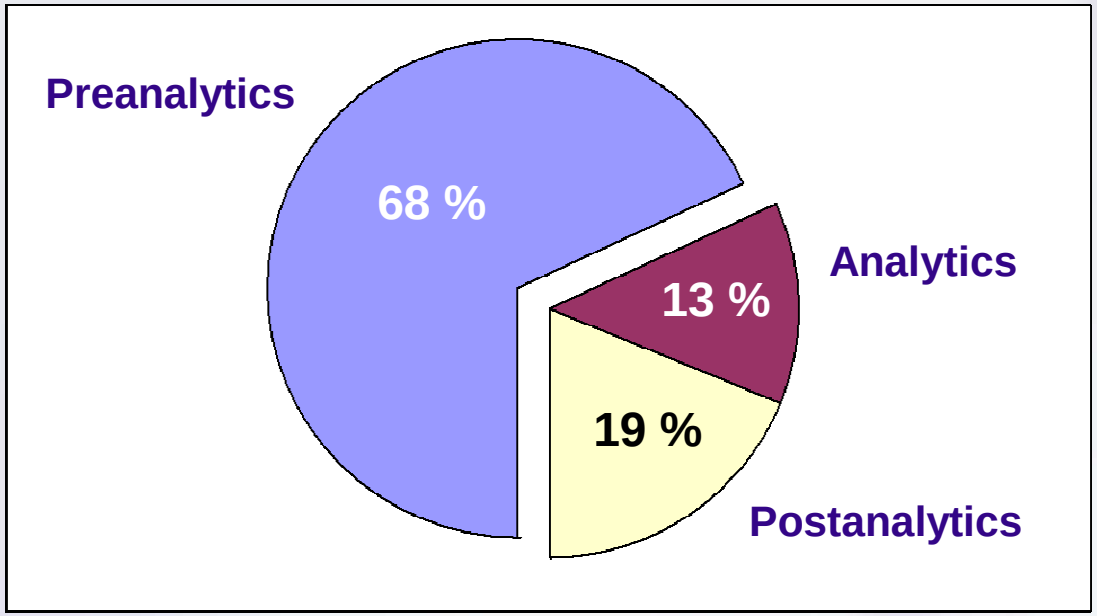
Diagnostic Workflow
From Patients to Clinical Results



Pre-Analytical Errors Impacting Diagnostic Results

"Preanalytical errors still account for nearly 60%-70% of all problems occurring in laboratory diagnostics, most of them attributable to mishandling procedures during collection, handling, preparing or storing the specimens".

Lippi G. *et al.*. Preanalytical quality improvement: from dream to reality. Clin Chem Lab Med. 2011 Jul; 49(7):1113-26. Epub 2011 Apr 25.



Costs of ~ 347,000 € / year in an average German hospital caused by pre-analytical errors

Frost & Sullivan 2011 on behalf of BD

Facts

European Commission FP7-HEALTH

Funding Scheme: Collaborative Research Project (Grant Agreement no: 222916)

- Consortium — 7 public research organizations
8 companies
1 standards organization (CEN)
- Coordinator — QIAGEN GmbH
- Funding Period — 4.5 years (2008 – 2013)
- Budget — 13 Mio € (9 Mio € EC)
- Web page — www.spidia.eu

Project Main Goals

1. **Evidence based Pan-European guidelines**
   - Blood, Tissues, Body Fluids
2. **New tools & technologies**
   - Sample collection, stabilization, transport, processing
3. **Sample quality biomarkers**
4. **Dissemination of results**
5. **Co-work with international initiatives**
   - NCI / BBRB
   - CLSI, BBMRI, EFLM, m^4 Cluster Munich etc.

Agenda

- Introduction
- **Pre-analytical Workflow Studies**
- New Technologies
- New Standards

How Do Pre-analytical Workflows Impact Patients Samples?

- **Blood, Tissues, Body Fluids**
  - RNA, DNA
  - Proteins & Phosphoproteins
  - Metabolites
  - Tissue Morphology

⇨ Changes during pre-analytical workflows

⇨ Different analytical test technologies

⇨ **SPIDIA internal studies**

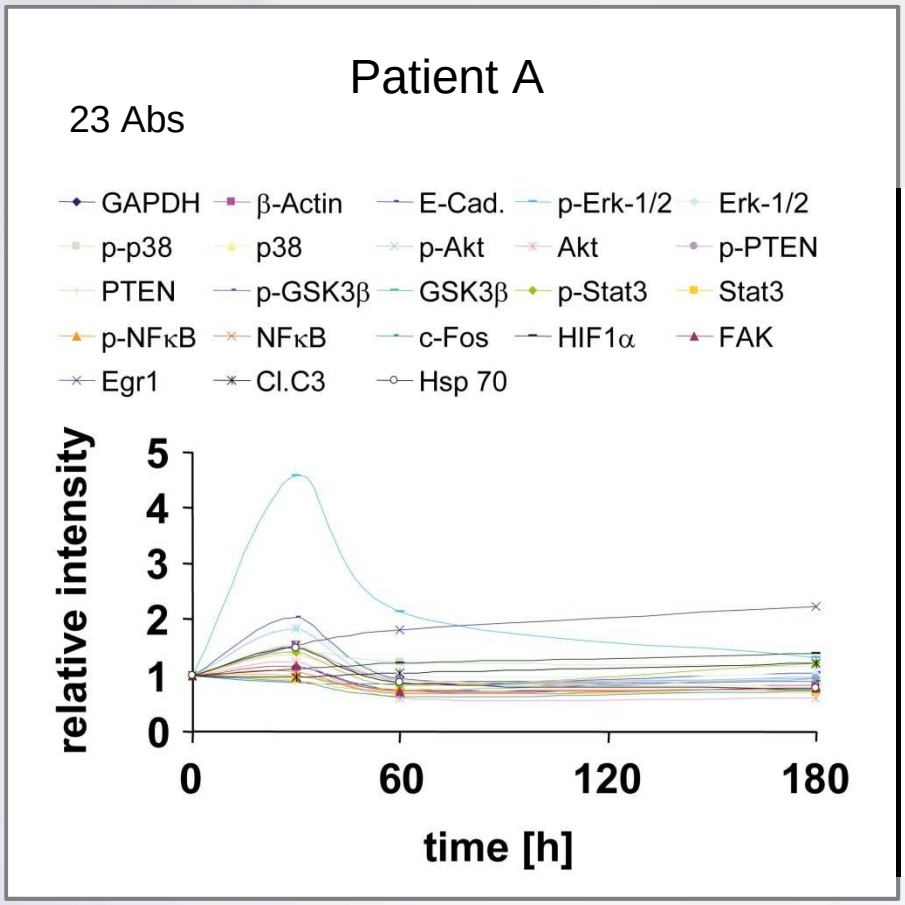
⇨ **SPIDIA Pan-European ring-trials**

⇨ **SPIDIA international ring-trials**

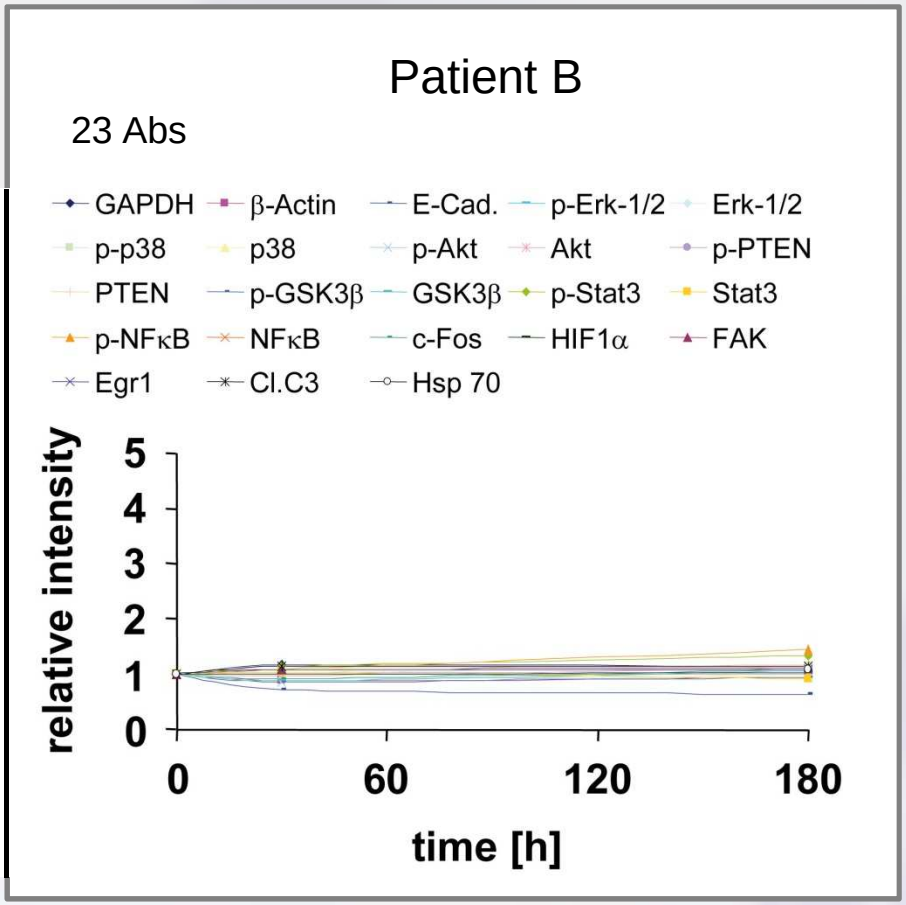
Inter-Patient Samples Variability

Impact of ischemia time on protein expression of intestine

Revers Phase Protein Array Analysis



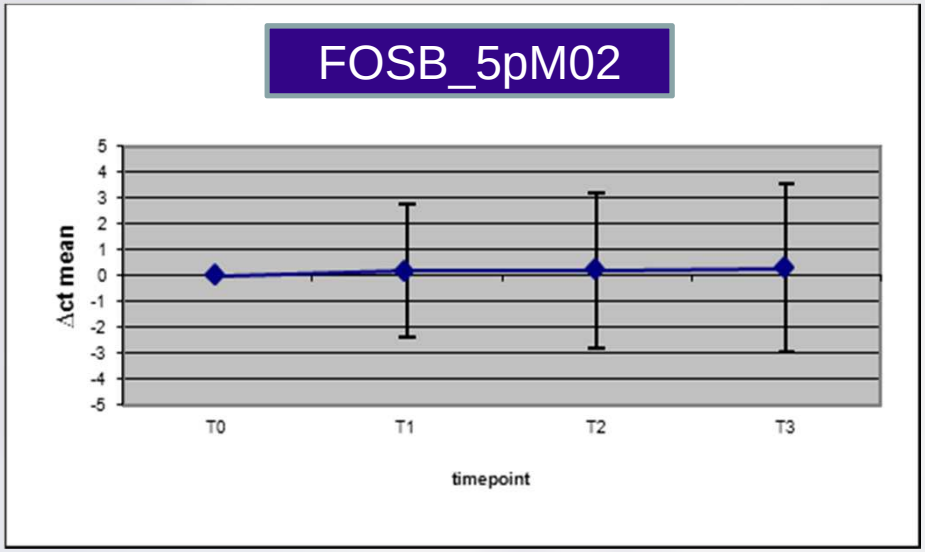
WI: 45 min, CI: 35 min, t_0: arrival at pathol. Lab.

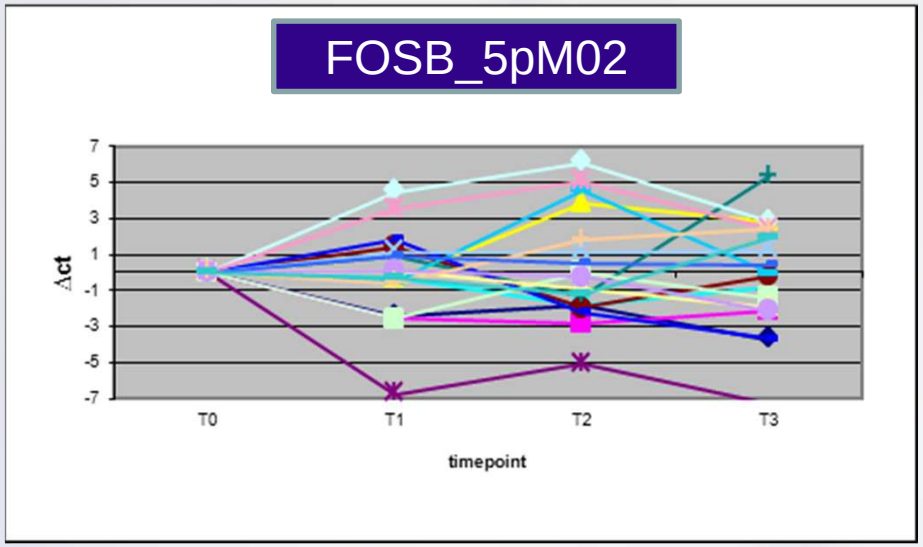


WI: 25 min, CI: 45 min, t_0: arrival at pathol. Lab.

Gündisch et al., J. Proteome Res. 2012

Human Liver - Transcript Level Changes during Warm and Cold Ischemia





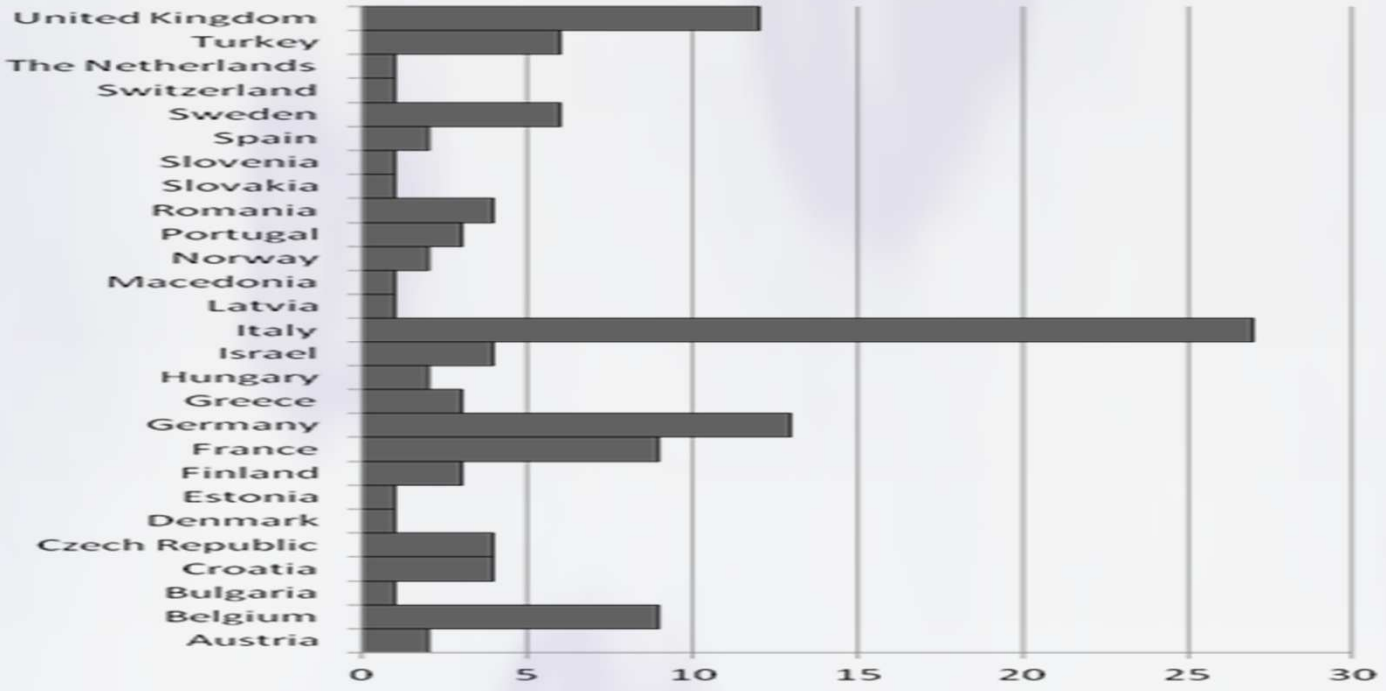
qRT-PCR:

- **dCT mean** seems stable over all time points
- STD and **individual patient** results reveal high interpatient variability

SPIDIA partners Medical University of Graz & Erasmus Medical Center Rotterdam – publication in preparation

Blood – Pan European Ring Trials
Blood DNA & RNA, Plasma fcDNA

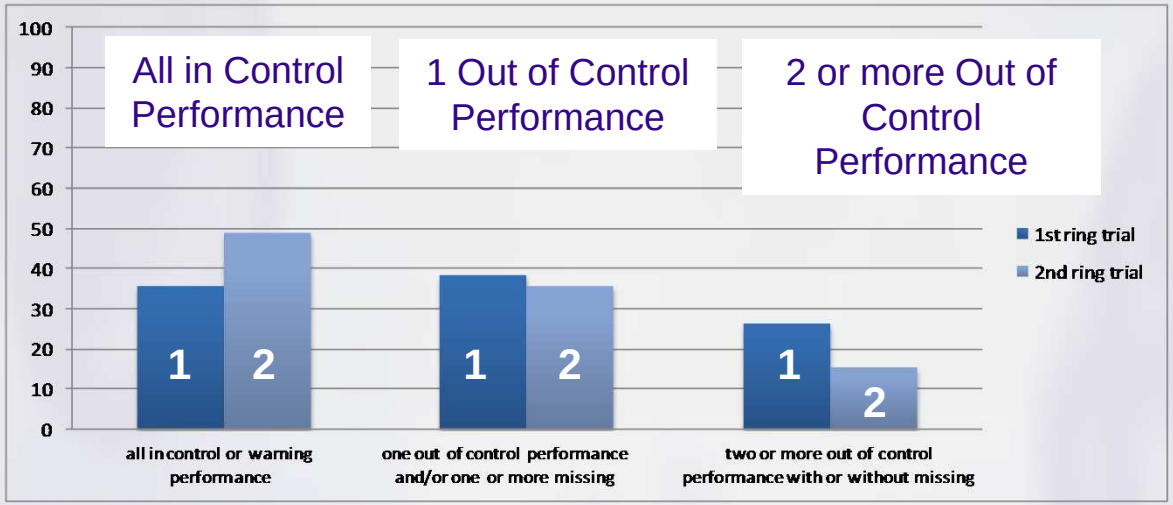
- Supported by the EFCC
- Phase 1 Trials - Laboratories used their workflows & tools
- Phase 2 Trials - Laboratories will use SPIDIA's optimized workflows
- Isolated bioanalyties sent back to SPIDIA's laboratories – intensive downstream testing



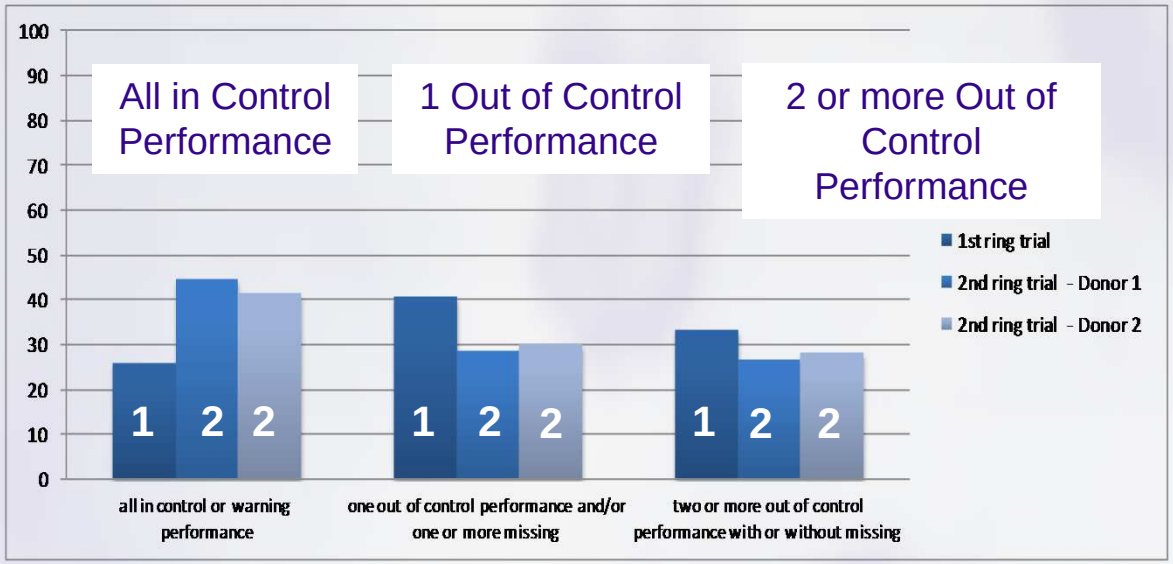
Pazzagli et al.
Unpublished data

Optimized Workflows can Improve Test Results

1st vs 2nd SPIDIA Blood Ring Trials



Blood DNA Ring Trials 1 & 2



Blood RNA Ring Trials 1 & 2

SPIDIA partners IRCCS & University of Florence – publication in preparation

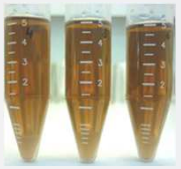
Agenda

- Introduction
- Pre-analytical Workflow Studies
- **New Technologies**
- New Standards

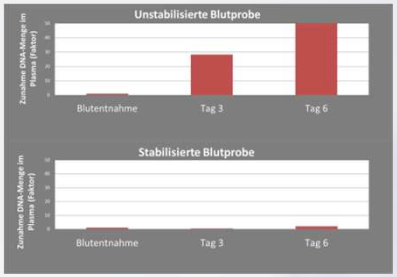
New Technologies & Tools Improving Pre-analytical Workflows & Samples Qualities

- **Tissues ⇨ PAXgene Tissue**
  - Collection & Stabilization of morphology, antigenicity, DNA, RNA, proteome, phospho-proteome

- **Fine Needle Aspirates**
  - Stabilization of morphology, antigenicity, DNA, RNA, proteome



- **Blood / Plasma**
  - Stabilization of Circulating Cell-Free DNA Profiles

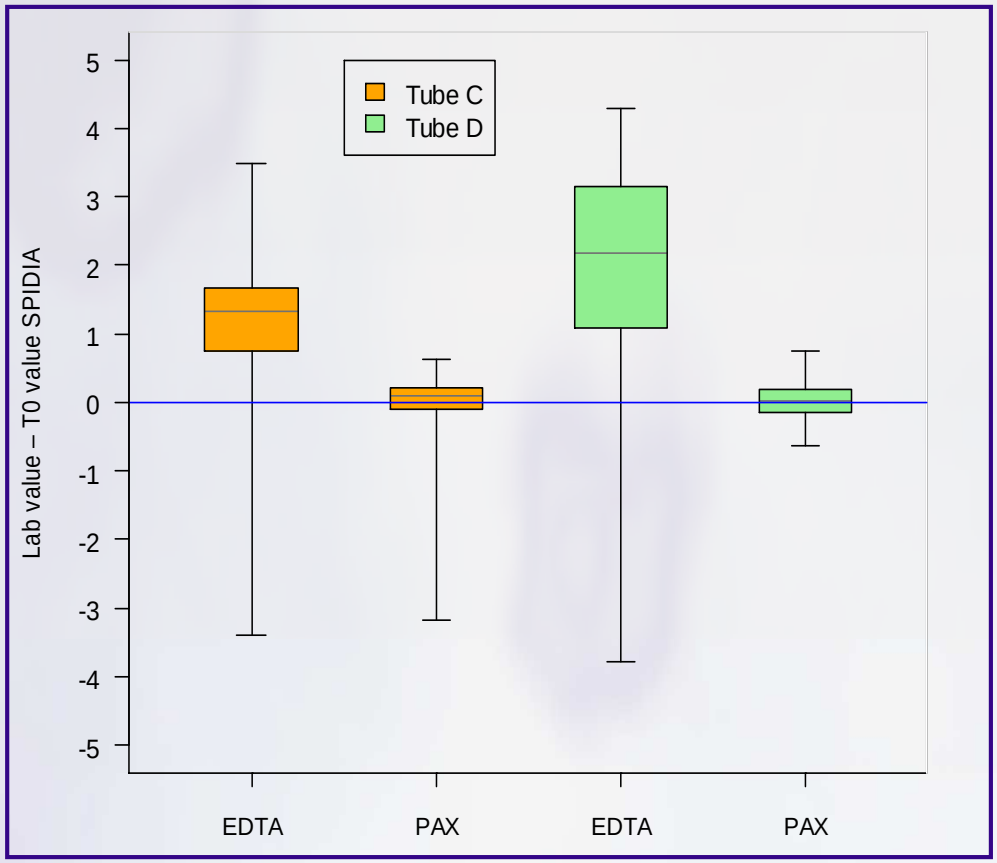


- **Whole Blood**
  - New stabilization technologies

- **Swabs**
  - Stabilization and improved processing for molecular analysis

IL-8 mRNA Level Changes during Transport to Laboratory and Storage at Laboratory

Ring Trial: EDTA Blood vs. PAXgene Blood RNA Stabilization (room temp.)



2nd SPIDIA Blood RNA Ring Trial

- Tube C: Day of Arrival
- Tube D: 24 h after Arrival

SPIDIA partners IRCCS & University of Florence – publication in preparation

Conclusions

- **Pre-analytical workflow steps can have critical influences on analytical test results**
  - ⇨ Quantative analyte profile changes
  - ⇨ Chemical analyte changes
- **High inter-donor / inter-patient variability**
- **Standardization & new technologies can lead to significant improvements**

➢ **Education on pre-analytical workflows and biospecimen science is needed**

Agenda

- Introduction
- Pre-analytical Workflow Studies
- New Technologies
- **New Standards**

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

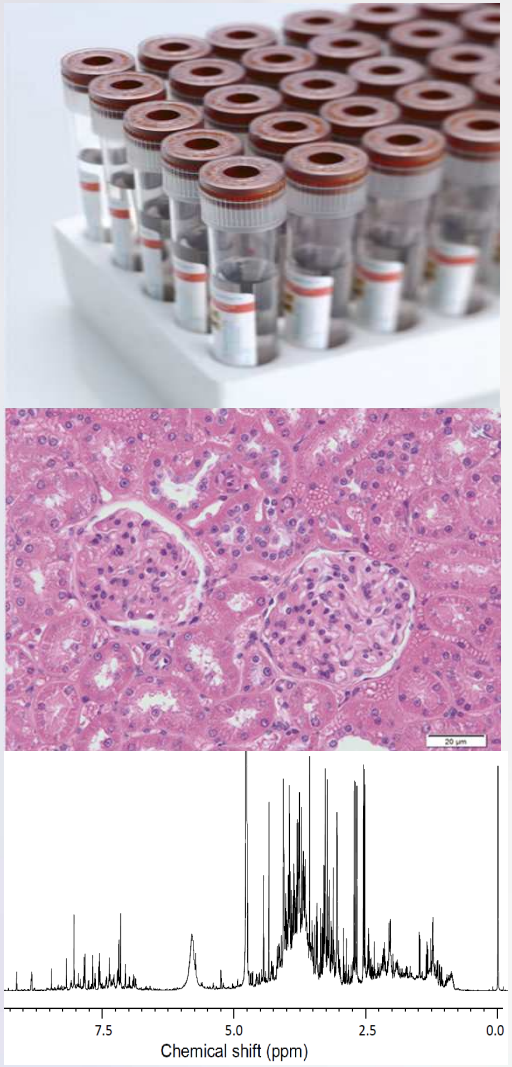
Goal: Specifications of a recommendatory and explanatory nature

CEN Workshop Agreement – CWA

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

First 9 CEN Technical Specifications

CEN/TC 140: *in-vitro* Diagnostic Medical Devices



- Pre-analytical phase: covers all steps from the clinicians requests to the beginning of the analytical examination

- 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

Acknowledgement
SPIDIA Consortium Members

- QIAGEN GmbH - Coordinator
- Medical University of Graz *(Prof. K. Zatloukal)*
- University of Florence *(Prof. M. Pazzagli)*
- CIRMMP Florence, CERM *(Prof. C. Lucinat)*
- TATAA Biocenter
- PreAnalytiX GmbH
- DIAGENIC ASA
- Aros Applied Biotechnology
- Dako Denmark
- ACIES
- Biotechnology Inst. of Czech Academy of Science *(Prof. M. Kubista)*
- European Committee for Standardization (CEN)
- ImmunID Technologies
- Erasmus Medical Center Rotterdam *(Prof. P. Riegman)*
- Technical University Munich *(Prof. H. Hoefler, Prof. K. Becker)*
- Fondazione IRCCS Istituto Nazionale dei Tumori *(Dr. P. Verderio)*

Scientific Advisory Board

- *Prof. François Rousseau* (Univ. Laval, Quebec. Canada)
- *Dr. Roberta M. Madej* (CLSI)

Project Ethics Committee

- *Dr. Anne Cambon-Thomsen* (CNRS, INSERM, France)
- *Dr. Ruth Chadwick* (ESRC Centre, Cardiff University, UK)

SPIDIA Consortium