SPIDIA4P - Standardisation of generic Pre-analytical Procedures for In-vitro DIAgnostics for Personalized Medicine

COST ACADEMY - TRAINING ON STANDARDIZATION WITH CEN-CENELEC

December 2nd, 2021

Dr. Uwe Oelmueller, SPIDIA4P Coordinator

www.spidia.eu

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

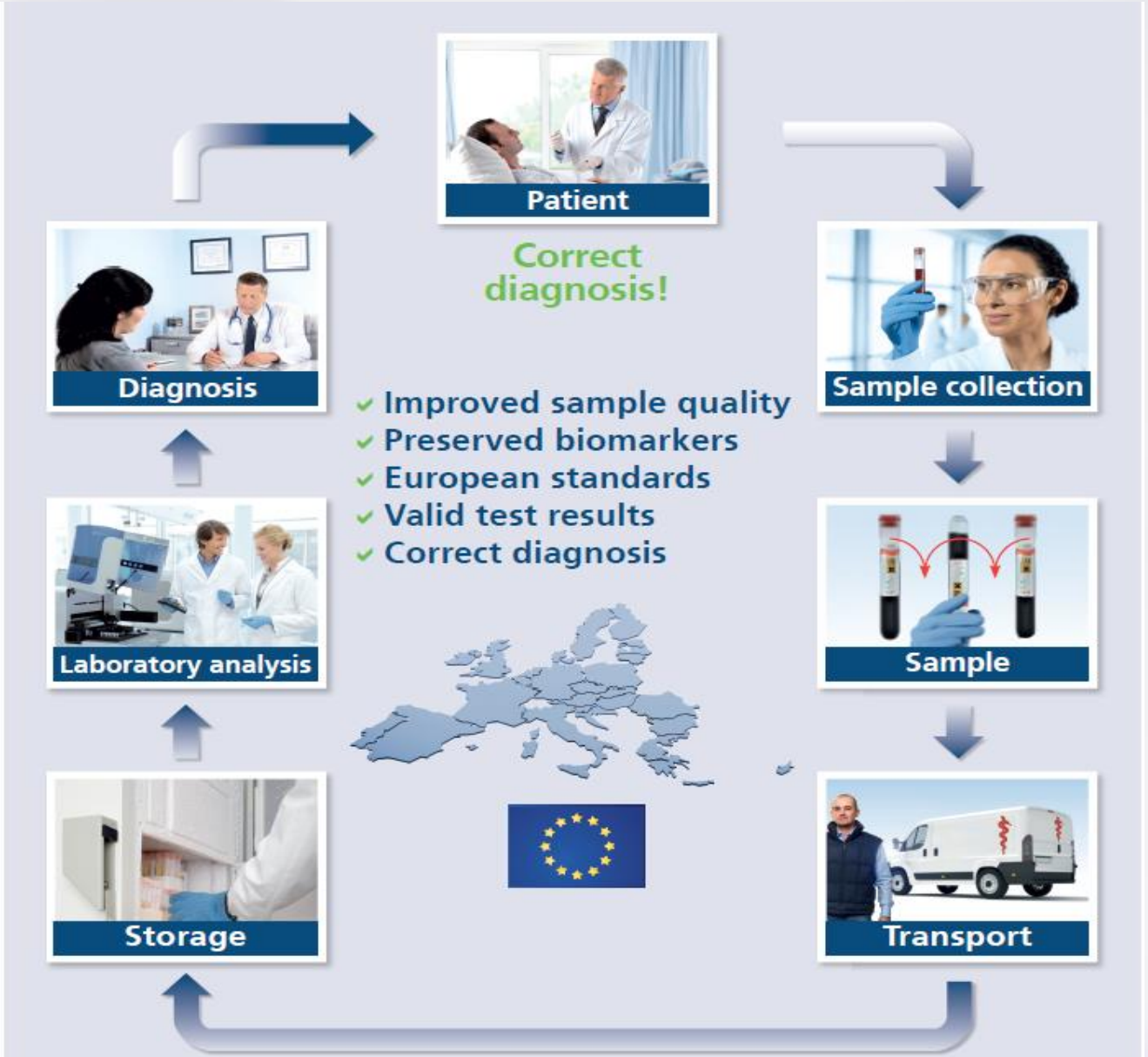
- Pre-analytical phase accounts for 46% to 68% of clinical laboratory errors

  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



- Patient specimen can change drastically during the pre-analytical workflow
  ⇨ causing wrong diagnostic test results

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

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

Major Efforts for Improvements

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

The SPIDIA project has received funding under the Seventh Research Framework Programme 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.

New Technologies, Standards, EQAs 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!**

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SPIDIA's Road to Standardization – SPIDIA4P Building on Success

under Vienna Agreement (1991)

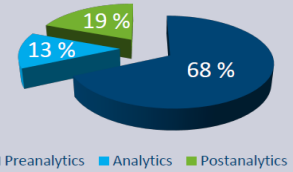
ISO

- 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*"

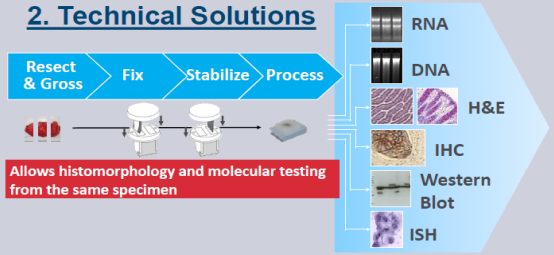
CEN

- 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

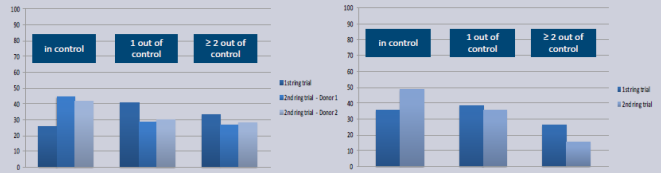
1. Problem - Errors in Diagnostics



2. Technical Solutions



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



SEVENTH FRAMEWORK PROGRAMME

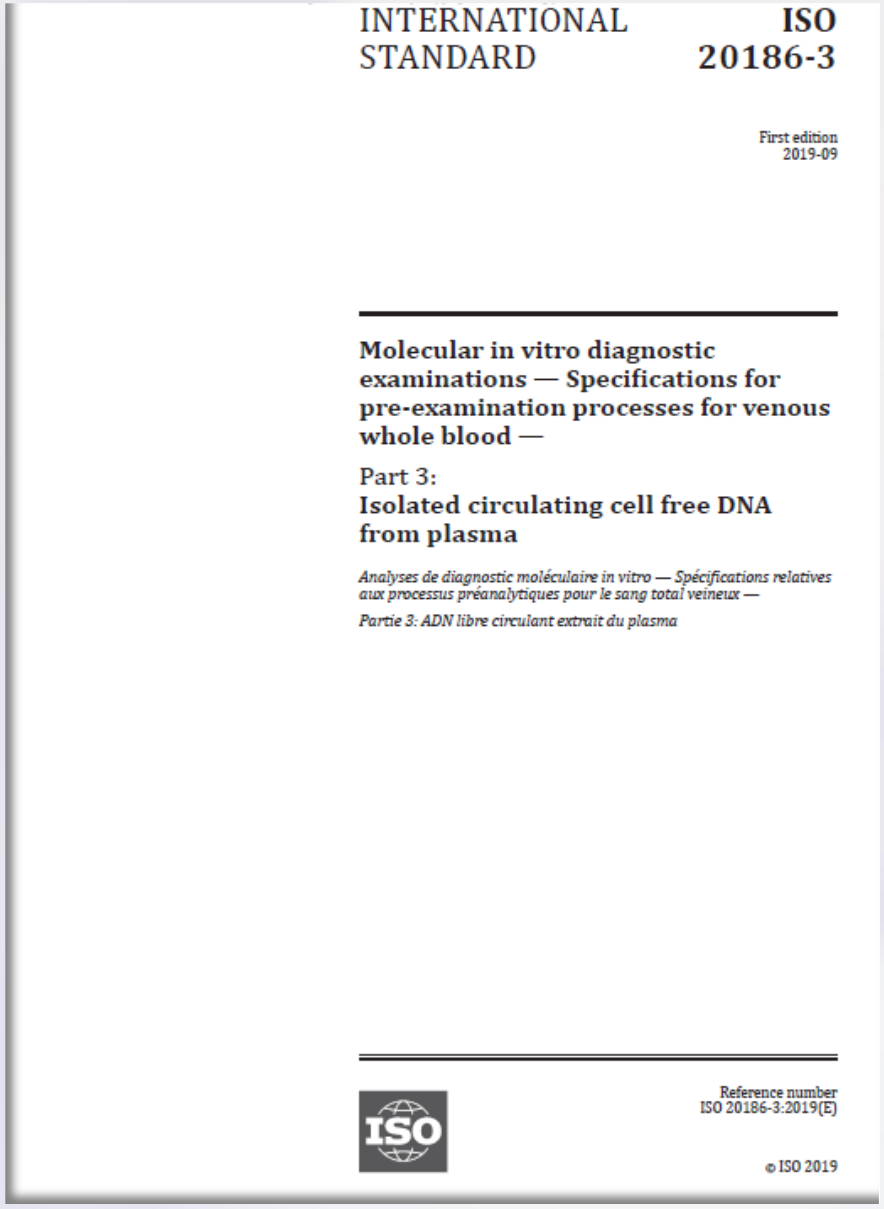
SPIDIA

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

CEN CENELEC

European Commission

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

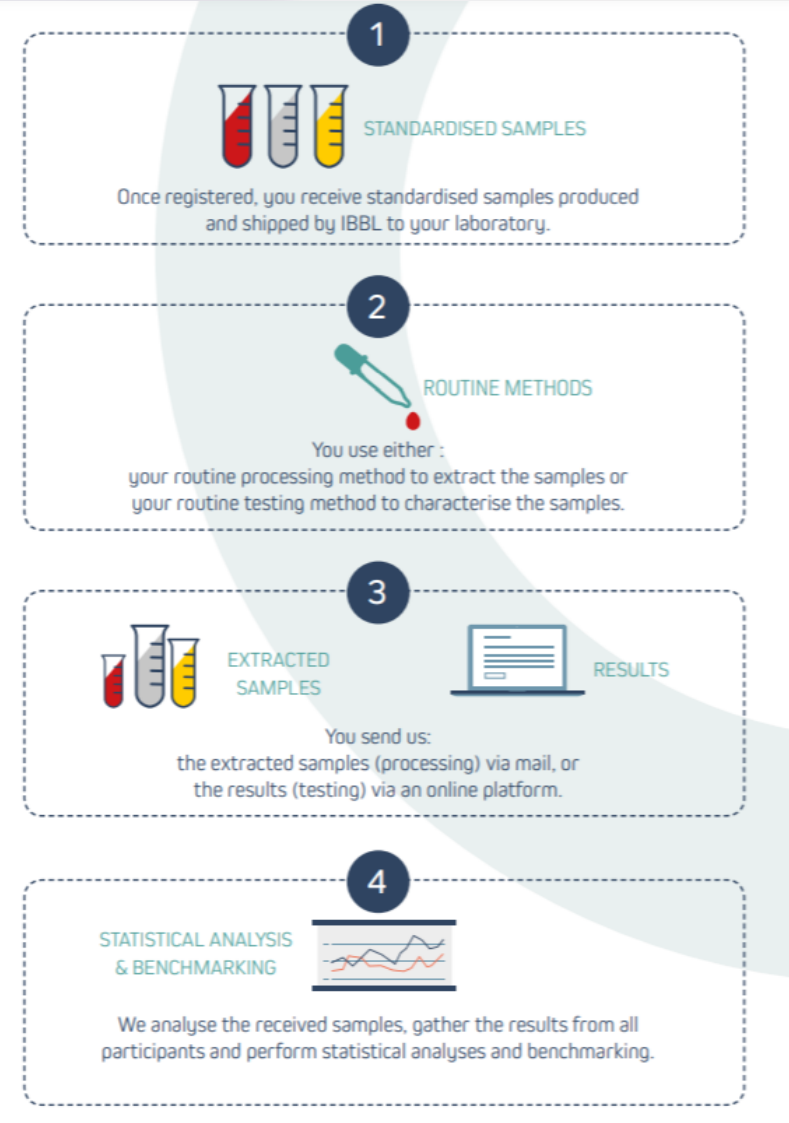
Reference number
ISO 20186-3:2019(E)

© 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 final stage

External Quality Assurances (EQAs) developed 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 In Vitro Diagnostic Regulations 2017 (IVDR)

- **Pre-analytical workflow parameters** in several sections, e.g. Annex II:

  - 6. PRODUCT VERIFICATION AND VALIDATION (Annex II)

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

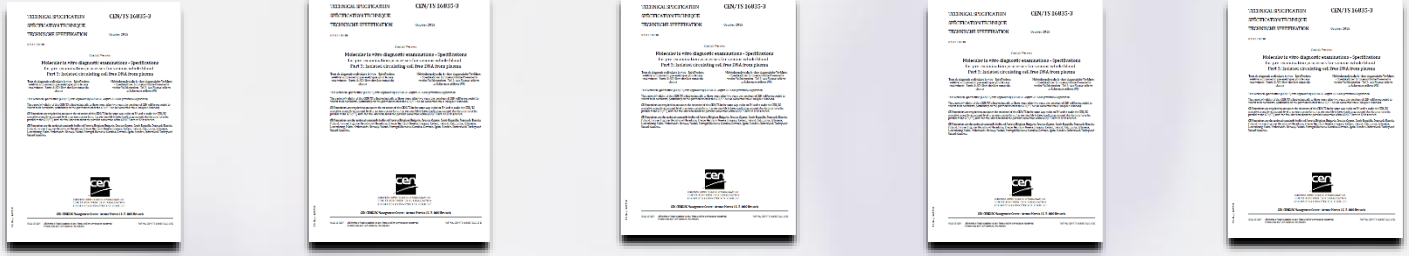
    This Section shall describe the different specimen types that can be analysed, including their stability such as storage, where applicable specimen transport conditions and, with a view to time-critical analysis methods, information on the timeframe between taking the specimen and its analysis and storage 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 New Pre-analytical Standards to support Legislation

New EU IVDR – in-vitro Diagnostic Device Regulation 2017

Pre-analytical workflow parameters



EN ISO & CEN Standards

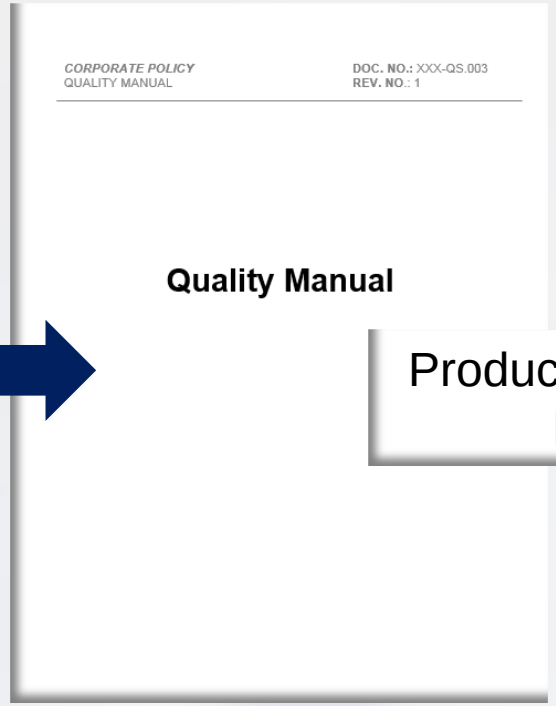
SOPs

Technologies & Products

Training Programs & Implementation of Preanalytical Standards

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

Certification according to ISO 13485

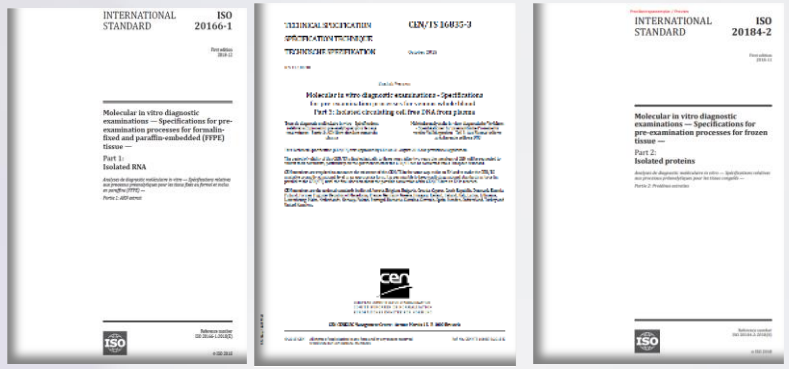

CORPORATE POLICY
QUALITY MANUAL
DOC. NO.: XXX-QS.003
REV. NO.: 1

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

TECHNICAL SPECIFICATION CEN/TS 16835-3

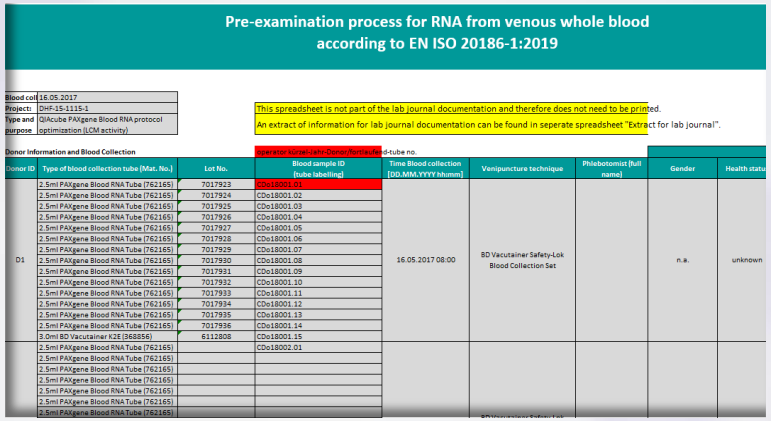
Molecular in vitro diagnostic examinations - Specifications for pre-examination processes for blood plasma

Part 3: Isolated circulating cell-free DNA from plasma

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

This spreadsheet is not part of the lab journal documentation and therefore does not need to be printed.
An extract of information for lab journal documentation can be found in seperate spreadsheet "Extract for lab journal".

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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