Does the EU IVDR 2017/746 present a suitable Framework for Safe and Effective Medical Tests?
I. Role of Laboratory Medicine

II. Rationale for the IVDR 2017/746
   - Regulates market access of IVDs
   - Focus on Clinical Evidence requirements

III. Frameworks for Test Evaluation & Clinical Care Pathway mapping

IV. ISO 17511:2020 and the Metrological Traceability Concept
   - Stakeholders involved
   - Critical Appraisal of successes and failures: the IFCC SD and EQA organizer’s perspective

V. Conclusions
I. Role of Laboratory Medicine

THE ROLE OF LABORATORY SPECIALISTS:
• Our goal: to improve patient outcome
• Our tools: safe and effective Medical Tests
• Our mechanism: support medical decisions

• “Medicine is a science of uncertainty and an art of probability” claimed William Osler. History, physical examination, imaging, electrocardiogram, and laboratory investigations are all fraught with uncertainties, frequently prompting further investigations, including laboratory methods, which usually reduce the diagnostic uncertainty.

• However, in extreme cases, numerous investigations may be expensive, painful, and lead nowhere; aptly coined the Ulysses syndrome.

• Medical diagnosis must therefore rest on knowledge and skills in medicine combined with aptitude in the handling of uncertainties.
Establishing maximum allowable MU is key to keep tests fit-for-clinical-purpose!
II. Rationale for the EU IVD Regulation

The purpose of IVDR legislation is to regulate the trade in IVDs in the EU and, and by doing so, to guarantee the safety, suitability and performance as well as safeguard the health and ensure the necessary protection of patients, users and other persons.
The European Commission is attempting to build a strong **European Health Union**, in which all EU countries prepare and respond together to health crises, medical supplies being available, affordable and innovative, but also to improve prevention, treatment and aftercare for diseases such as cancer. The European Health Union will

1. better protect the health of EU citizens;
2. equip the EU and its Member States to better prevent and address future pandemics;
3. improve resilience of Europe’s health systems.

https://eur-lex.europa.eu/content/summaries/summary-29-expanded-content.html
• IVDD regulates commercial IVDs (CE-IVDs)
• IVDR regulates CE-IVDs and In House-IVDs (LDTs)

Since 26 May 2022: from IVDD to IVDR

1998 - 2022
Entry into force: 2017
5 years for Implementation
Date of application: May 26th, 2022
Areas of the EU Regulatory Framework

Pre-market

- Qualification/classification
- Conformity assessment
- Performance evaluation/performance study

Post-market

- Post-market surveillance (manufacturer)
- Market surveillance (competent authorities)
- Vigilance

SKML Congres 2024
Governance of EU-level implementation

MEDICAL DEVICE COORDINATION GROUP (MDCG)

1. Notified Body Oversight (NBO)
2. Standards
3. Clinical Investigation and Evaluation (CIE)
4. Post-Market Surveillance and Vigilance (PMSV)
5. Market Surveillance (MS)
6. Borderline and Classification (B&C)
7. New Technologies (NET)
8. Eudamed
9. Unique Device Identification (UDI)
10. International
11. In Vitro Diagnostic Medical Devices (IVD)
12. Nomenclature
13. Annex XVI

EFLM observers
The EU IVDD has been revised and strengthened in the IVD Regulation

Key changes:

• Risk-based test classification
• **Clinical evidence requirement**
• Notified body assessment
• Expert panel advice & EURL
• EUDAMED database
• UDI
• CE-IVDs versus IH-IVDs (exempted!)
In Vitro Diagnostic MD

- any medical device which is a reagent, reagent product, calibrator, control material, kit, instrument, apparatus, equipment, **software** or system,
- whether used alone or in combination, intended...to be used *in vitro* for the examination of specimens, including blood and tissue donations... from the human body,
- solely or principally for...providing information..

Note that tangible products/ kits are regulated by the IVDR, while the IVDR does not regulate lab medicine services.
... solely or principally for the purpose of providing information on one or more of the following:

(a) Concerning a physiological or pathological process;
(b) Concerning congenital physical or mental impairments;
(c) Concerning the predisposition to a medical condition or a disease;
(d) To determine the safety and compatibility with potential recipients;
(e) To predict treatment response or reactions;
(f) To define or monitor therapeutic measures.

SCOPE ENLARGEMENT
Including high risk “In House” tests

Companion Diagnostics
Genetic testing
Major changes to how IVDs are classified.

Will be a RISK-RULE BASED SYSTEM using Global Harmonisation Task Force (GHTF) classification rules.

Impacts most IVD manufacturers and 80-90% of tests: quantum leap!

Classification depends upon THE INTENDED USE AND THE LEVEL OF RISK TO THE PATIENT AND THE PUBLIC (taking into account the likelihood of harm and the severity of that harm).

Identical devices may be classified differently if they are to be used for different diagnostic purposes. This is why the manufacturer’s intended use of the device is critical to determining the appropriate class.
Risk-based Classification System under the IVDR 2017/746

D  ▪ High public health risk
   ▪ Blood safety / high risk infectious diseases

C  ▪ High risk for individual patients
   ▪ E.g. cancer markers, dangerous infectious diseases, etc.

B  ▪ Medium risk for individual patients
   ▪ E.g. blood chemistry, pregnancy tests, etc.

A  ▪ Low risk for individual patients
   ▪ Instruments, accessories, specimen collection systems etc.

CCLM 2021, Cobbaert et al.
Clinical Evidence

= clinical data and performance evaluation results, pertaining to a device of sufficient amount and quality **to allow a qualified assessment of whether the device achieves the intended clinical benefit and safety, when used as intended by the manufacturer.**
III. Cyclical Framework for the Evaluation of *in vitro* Medical Tests

Key components of the test evaluation process are driven by the clinical need of using a test in the clinical pathway.
The Test Evaluation Cycle

Is there an unmet clinical need and is there an effective intervention?
Clinical pathway mapping:
What is the purpose and role of the test?
Intended Purposes of Medical Tests

- Predisposition
- Risk Stratification
- Screening
- Early Detection
- Diagnosis
- Staging
- Prognosis
- Monitoring (Disease)
- Monitoring (Treatment)
- Surveillance
- Treatment Decisions

Disease
A test is a procedure that makes use of an assay in the context of a particular disease, in a particular population for a particular purpose, followed by action.

Before a new test is fully evaluated, the
- unmet clinical needs,
- intended purpose (screening, diagnosis, monitoring, etc.)
- role (add on, replacement, triage),
- clinical pathway,
- population,
- healthcare setting in which the test is intended to be used,
- condition that is intended to be managed with the use of the test,
- procedures for evaluating these, and
- potential final outcomes of testing
must be clearly defined.
The ability of an assay to correctly detect or measure a particular analyte/measurand.

- preanalytical considerations
- analytical sensitivity/specificity
- limit of detection/quantitation,
- measurement range
- linearity
- metrological traceability,
- imprecision and trueness
Key messages - 2

**Analytical performance specifications (APS)**

- should reflect clinical needs
- can be based on **3 different models**: 1/ outcomes, 2/ biological variation, 3/ state-of-the art;
- should be set at a level that achieves net health benefit for patients at reasonable costs;
- should be tailored to the purpose and role of the test in a well-defined clinical pathway;
- should be commensurate with the impact of the laboratory test on subsequent medical decisions and actions;

Remember...

High quality analytical performance does not guarantee high quality clinical action or patient compliance or that the chosen treatment will be effective.

The opposite is also true; poor analytical performance of a test that plays a small part in a complex clinical pathway may not necessarily lead to adverse or unfavourable outcomes.

Outcome-based APS

- address the influence of analytical performance on clinical outcomes that are relevant to patients and society;
- are only useful where the links between the test, clinical decision-making and clinical outcomes are straightforward and strong;
- are often influenced by the current measurement quality and results may vary according to the actual test method used, the investigated population and healthcare settings.

The Test Evaluation Cycle

- The ability of a biomarker to detect patients with a particular clinical condition or in a physiological state

- How well does it work in practice?
- In what subset of patients?
- Is it really better than the conventional test®?
- How do alternative tests compare?

Cog wheel structure: interdependence between APS and CPS!
• Average baseline: Top of arrow
• On-treatment LDL-c levels: bottom of arrow
• Dotted lines: recommended LDL-c levels according to ESC/EAS guidelines

Analytical performance goals LDL-c tests

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Goal</th>
</tr>
</thead>
<tbody>
<tr>
<td>CV&lt;sub&gt;a&lt;/sub&gt;</td>
<td>&lt;4%</td>
</tr>
<tr>
<td>Bias</td>
<td>&lt;4%</td>
</tr>
</tbody>
</table>

On-treatment goal 2.6-4.14 mmol/L

Current LDL-c on-treatment goals 1–1.5 mmol/L

Analytical performance goals are not updated since 1995 whereas current treatment goals are 2.5 to 3-fold lower

Packard et al. Heart, 2021
Disconnect LDL-c test Analytical Performance and Clinical Performance

Test evaluation framework

Disconnect between Analytical Performance and required Clinical Performance of LDL-c tests
Dutch SKML EQA:
LDL-c recovery in a normal native sample

Proficiency testing
• Lab monitoring two-weekly
• Native sample
• 107-124 labs
Dutch SKML EQA: LDL-c recovery in native hyperTG samples

Proficiency testing
- Lab monitoring two-weekly
- Native sample
- 107-124 labs

normal TG

2022.4 A
Dutch SKML EQA:
LDL-c recovery in native hyperTG samples

Proficiency testing
- Lab monitoring two-weekly
- Native sample
- 107-124 labs

The problem is non-selectivity of the test, not lack of standardization!
Current Analytical Performance of LDL-c tests ensures measurements are ACCURATE around former Clinical Decision Points

Bias distribution of LDL-c measurements reported by assay and reagent manufacturers as part of their submission for CDC certification (2016-2019)

38 assay and reagent manufacturers

Means of duplicate measurements

N = 1,914

Calibration and non-selectivity bias are mostly sufficient for former LDL-c targets

By courtesy of Dr H. Vesper, CDC, Atlanta, Georgia, USA

mg/dL x 0.0259 = mmol/L
Current Analytical Performance of LDL-c testing demonstrates INSUFFICIENT ACCURACY to support New Clinical Guidelines

Bias distribution of LDL-c measurements reported by assay and reagent manufacturers as part of their submission for CDC certification (2016-2019)

What can we do?

Calibration and non-selectivity bias are mostly sufficient for former LDL-c targets

Calibration and non-selectivity bias are higher at new EAS/ESC and AHA/ACC targets

By courtesy of Dr H. Vesper, CDC, Atlanta, Georgia, USA
Clinically superior Apolipoprotein B test as CVD risk marker

• ApoB shown to be clinically superior to LDL-c in MI prediction

• **Primary prevention**
  - Copenhagen General Population Study
  - UK Biobank

• **Secondary prevention**
  - INTERHEART
  - FOURIER
  - IMPROVE-IT

2019 ESC/EAS Guidelines

**Lipid analyses for CVD risk estimation**

ApoB analysis is recommended for risk assessment, particularly in people with high TG, DM, obesity or metabolic syndrome, or very low LDL-C. It can be used as an alternative to LDL-C, if available, as the primary measurement for screening, diagnosis, and management, and may be preferred over non-HDL-C in people with high TG, DM, obesity, or very low LDL-C.

Marston et al. JAMA Cardiol. 2022
Johannesen et al. J Am Coll Cardiol. 2021

2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. Eur Heart J. 2020
LDL-c recovery in a hyperTG native sample

Imprecision diagnostics

Molecularly defined ApoB does not suffer from non-selectivity

Interlaboratory CVa of 21% for LDL-c

Interlaboratory CVa of 9% for ApoB
Clinical test-treatment pathways for CVD reduction according to current and new practices

Current practice
Target population
Individuals with(out) documented CVD
Individuals at increased CVD risk

Test: Classical lipid profile

Management decision
High LDLc and risk SCORE2
Generic treatment with statins, ACE-inhibitors, etc.
Low LDLc and risk SCORE2
No treatment

Health outcome
Suboptimal due to
Residual risk beyond LDLc reduction
Underdiagnosis of CVD in women
Underdiagnosis of remnant disease

Editorial
Implementing cardiovascular precision diagnostics: laboratory specialists as catalysts?

Christa M Cobbaert
Calibration hierarchy — Full metrological traceability to SI

**Metrological Traceability in the IVDR:**
- 7 times mentioned
- Values should be assigned through suitable RMPs and RMs of a higher metrological order!
- Where available: to certified RMs or RMPs
- Test fitness for the intended use is key!
- Traceability starts with defining the measurand!
Stakeholders Involved
Committee based mode

Governments

Regulators/Notified Bodies

IFCC, International bodies

National Metrology Institutes

Calibration Laboratories

IVD Manufacturers

EQA providers

Accrediting Bodies

Clinical Laboratories

Clinicians

Patients

CE marking under the IVDD → IVDR

ISO 15193, 15194, 15195
ISO 17025
ISO 17511

SKML Congres 2024

Adapted - by courtesy of Dr J. Middle, AQMLM
Many assays have been standardized (or harmonized) over the last decades

- Simple parameters: glucose, creatinine, cholesterol
- Enzymes
- Peptides, hormones, proteins
  - TSH (IFCC-C)
  - FT4 (IFCC-C)
  - CDT (IFCC-WG)

….. but this represents only a small percentage of performed laboratory tests (<15%)

Many questions are pending:

- **Identical needs of standardization/harmonization** for
  - all tests (established, new)?
  - clinicians and laboratory medicine specialists?
  - patients, health professionals and manufacturers?
- **Which priorities?**
HbA$_{1c}$ : an example of (long but) successful standardization

- **A rationale in public health:**
  - Diabetes mellitus: an underdiagnosed "non infectious epidemic disease" with severe long-term complications
  - HbA$_{1c}$: the "gold standard" marker of glycemic balance

- **A clear strategy of standardization with a common approach of IFCC and manufacturers** (IFCC-WG on HbA$_{1c}$ standardization)

- **A sustainable standardization system** (reference measurement procedure maintained by an IFCC network of reference laboratories) in the 2000s

- **A successful* implementation** in routine laboratory medicine and clinical practice, involving all partners, allowing **new intended uses of the test** (diagnosis vs follow-up)

* but relatively long : all stakeholders were not associated from the beginning (clinicians: concerns with proposed change of values: % $\Rightarrow$ mmol/mol)
Status of Hemoglobin A1c Measurement and Goals for Improvement:
From Chaos to Order for Improving Diabetes Care

Randie R. Little,¹ Curt L. Rohlfing,¹ and David B. Sacks²,³ for the National Glycohemoglobin Standardization Program (NGSP) Steering Committee

Measurement of Hemoglobin A1c
A new twist on the path to harmony

David B. Sacks, MS, CHL, FRCPath

2674 Diabetes Care, Volume 35, December 2012
care.diabetesjournals.org

Clinica Chimica Acta 418 (2015) 63–71

Invited critical review
The long and winding road to optimal HbA1c measurement

Randie R. Little*, Curt L. Rohlfing

Department of Pathology and Anatomical Sciences, University of Missouri School of Medicine, One Hospital Dr, Columbia, MO, United States
Carbohydrate-deficient transferrin (CDT): another example of success

- CDT: validated marker of alcohol abuse
- Establishment of an HPLC-based reference method by the IFCC-WG on CDT standardization (WG-CDT)
- Determination of \( \text{IFCC}_{\text{CDT}} \) values
- Implementation of \( \text{IFCC}_{\text{CDT}} \) values by (several) manufacturers

... method is also JCTLM listed

All aspects, including metrological requirements, must be considered (cooperation with JCTLM and metrology partners)
Thyroid tests: another example of relative success

- Thyroid tests: among the most widely prescribed lab tests by GPs and specialists
- IFCC Committee on standardization of thyroid tests (C-STFT)
  - Standardization of FT4 values
  - Harmonization of TSH values
  - Network of IFCC reference laboratories

Excellent outcome of the analytical phase

- Valid and sustainable anchor for manufacturers/laboratories
- Recognized need of standardization

… but concerns with changes in reference intervals (manufacturers, regulators eg FDA…)
  - Incomplete involvement of clinicians

All aspects, including clinical context, manufacturers’ needs and regulatory aspects, must be considered
Autoimmune tests: an example of (relative) failure

IFCC C-HAT (Committee on Harmonization of Autoimmune Tests)

👉 Outstanding activity and productivity

- Excellent cooperation with JRC for preparation of reference materials
  - IgG anti-MPO (ERM DA478) and IgG anti-proteinase 3 (ERM DA483): achieved
  - β2 GP1 and GBM antisera: being prepared

👉 But reluctance/resistance of major manufacturers to implement use of new reference materials in their procedures (costs of recalibration/regulatory rules)

Typical example of defective implementation ⇒ need for a strategy of implementation from the beginning

All aspects, including manufacturers' needs and regulatory aspects, must be considered
Challenges related to Regulatory Frameworks

Facts

- Complexity of regulatory frameworks within and between countries and regions
- National regulations sometimes supported by national, non-standardized reference measurement procedures/reference materials
- Cost of new applications for market distribution (e.g. in case of change of units/reference values.decision limits)

2021 international workshop:
Guidelines and Recommendations

W. Greg Miller*, Gary Myers, Christa M. Cobbaert, Ian S. Young, Elvar Theodorsson, Robert I. Wielgosz, Steven Westwood, Stephanie Maniguet and Philippe Gillery

Overcoming challenges regarding reference materials and regulations that influence global standardization of medical laboratory testing results

https://doi.org/10.1515/ccm-2022-0943
Received September 21, 2022; accepted September 22, 2022; published online October 17, 2022

Abstract

Background: Standardized results for laboratory tests are particularly important when their interpretation depends on fixed medical practice guidelines or common reference intervals. The medical laboratory community has developed a roadmap for an infrastructure to achieve standardized test results described in the International Organization for Standardization standard 17511:2020 In vitro diagnostic medical devices – Requirements for establishing metrological traceability of values assigned to calibrators, trueness control materials and human samples. Among the challenges to implementing metrological traceability are the availability of fit-for-purpose matrix-based certified reference materials (CRMs) and requirements for regulatory review that differ among countries. A workshop in December 2021 focused on these two challenges and developed recommendations for improved practices.
But also, slow adoption of Available RMs/RMPs - the β2-microglobulin Reference Material
1 Results

beta-2-microglobulin in processed human serum

European Commission - Joint Research Centre (EU - JRC) - Belgium
Phone: +32 (0) 14 571 705

ERM-DA470k/IFCC, human serum

<table>
<thead>
<tr>
<th>Quantity</th>
<th>Mass concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Analyte certified / assigned value</td>
<td>2.17 mg/L</td>
</tr>
<tr>
<td>Expanded uncertainty (level of confidence 95 %)</td>
<td>0.07 mg/L</td>
</tr>
</tbody>
</table>

Information available in the Certification Report of the certification of the mass concentration of beta-2-microglobulin in human serum: ERM-DA470k/IFCC

Traceability

traceable to SI

CRM listing

List I


Relevant publication(s)

Comment(s)

Each sample consists of at least 1 mL processed human serum. It contains the following additives: (4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid (HEPES), sodium azide, bezamidine chloride and aprotinin). The material is kept under nitrogen gas in glass vials.

This Certified Reference Material has been reviewed for compliance with ISO 15194:2009
Adoption of latest β2-microglobulin RM was verified in Accuracy Based EQA Scheme in NL

3 pillars for accuracy based EQA scheme:

1. Commutable EQA materials (CLSI C37A)

2. Value assigned with ERM-DA470k for trueness verification

3. Scoring system based on biological variation and clinical relevance ($TE_a$).

Introduced in the Netherlands since 2005 for general clinical chemistry and lipids/apos, and more recently for immunochemistry.
SKML Congres 2024

Collateral damage: Dutch EQA-data for β2-microglobulin

SKML notes 10% bias compared to the Reference Value assigned with ERM-DA470k/IFCC. NONE of the participating labs recovered the assigned value within allowable Total Error. ALL participating Dutch labs got a ZERO SCORE in the EQA!

Source: SKML letter dd 22 February 2023, section HIM, Inez-Anne Haagen
Yet, manufacturers’ traceability in IFU is still to the first WHO standard from 1987! No proven commutability!? 

Manufacturer stated:
- WHO material depleted,
- WHO not able to provide timeline for successor
- Impact to assignment process, use material within traceability chain
ERM-DA474/IFCC

Declaration of Conformity and Origin

To whom It May Concern:

The material for the certified reference material ERM-DA474/IFCC was produced by Siemens Healthcare Diagnostics Products GmbH, Marburg (DE).
Interference by macroprolactin in assays for prolactin: will the In Vitro Diagnostics Regulation lead to a solution at last?
The Macroprolactin Problem

- Immunoassays for serum prolactin are widely used in the investigation of infertility and the diagnosis of prolactinomas – a prolactin secreting pituitary adenoma characterised by hyperprolactinaemia. Assays are also utilised for monitoring the response to both medical or surgical treatment.

- The symptoms related to hyperprolactinaemia are common and non-specific – serum prolactin is used as a screening tool to identify subjects with hyperprolactinaemia who may merit further investigation and treatment.

- Immunoassays for prolactin are almost entirely performed on automated multichannel analysers. All immunoassays for prolactin detect the two main forms of prolactin present in sera;
  1. **Monomeric prolactin**, secreted by the pituitary which is bioactive in vivo.
  2. **Macroprolactin**, a complex of monomeric prolactin with an IgG antibody which is not bioactive in vivo and has no pathological significance.

- Macroprolactin has a longer half-life than monomeric prolactin and accumulates in the circulation leading to apparent hyperprolactinaemia - Macroprolactinaemia.

- Macroprolactinaemia is common and occurs by chance in patients presenting with the non-specific symptoms of hyperprolactinaemia such that 5 - 25% of all cases of hyperprolactinaemia are due to macroprolactinaemia. This widespread form of interference by macroprolactin in commercial assays for prolactin has been recognised for 25 years.

- If macroprolactinaemia is not identified by the laboratory as the cause of the apparent hyperprolactinaemia it can lead to misdiagnosis, unnecessary further investigations, inappropriate treatment, concern for clinician and patient and waste of healthcare resources.

- **True hyperprolactinaemia** (due to elevated levels of bioactive, monomeric prolactin) cannot be distinguished from macroprolactinaemia on clinical grounds alone hence there is a need to identify this condition correctly by the laboratory.
The Macroprolactin Problem

- Macroprolactin can easily be removed from serum by precipitation with polyethylene glycol (PEG) and residual bioactive, monomeric prolactin can then be measured in the supernatant. A technique involving magnetic separation of the precipitate may allow automation of the process.
- PEG precipitation is widely, but not universally, used by clinical laboratories to detect macroprolactinaemia. Best practice guidelines have been proposed but policies and procedures for testing vary considerably.
- Best practice for manufacturers of prolactin assays has also been proposed (2013):
  - Modify prolactin assay to minimise reactivity with macroprolactin.
  - Advise users that macroprolactin interferes in their prolactin assay.
  - Publish a validated method which users can employ to detect macroprolactinaemia in their prolactin assay.
- With only one exception assay manufacturers have not attempted to modify their prolactin assays to minimise interference by macroprolactin.
- Currently, most manufacturers make no mention of interference by macroprolactin in their assay Instructions For Use (IFU). Where manufacturers do give information, it is minimal, inadequate, outdated and, in some cases, incorrect.
- Compliance with the In Vitro Diagnostic Directive 98/79/EC (IVDD) became mandatory in December 2003. With respect to immunoassays for prolactin and interference from macroprolactin there is no evidence that manufacturers in general have complied with those aspects of the IVDD regulations which are now also included in Annex I in the IVDR.
Also, Molecular Tests to Evaluate and Standardize (or to harmonize)

- New challenges:
  - New concepts = MOLECULAR DEFINITION OF HEALTH & DISEASE (PRECISION Dx!)
  - More focus on clinical needs; evolution in science, technology & regulations!

**Opinion Paper**

Christa Cobbaert*, Nico Snit and Philippe Gillery

Metrological traceability and harmonization of medical tests: a quantum leap forward is needed to keep pace with globalization and stringent IVD-regulations in the 21st century!

https://doi.org/10.1519/crm-2018-0343
Received April 4, 2018; accepted April 5, 2018; previously published online May 7, 2018

- **IFCC = Scientific expertise**
  - « Catalist »
  - « Conductor » (P. Gillery, CCA 2021)
New Kids on the Block: Proteoforms

Fundamental protein metrology to support the definition of measurands, analytical targets, and their associated measurement uncertainty

HOS: higher-order structure

Proteoforms:
- Traceability to mol or kg for unmodified entities
- No references, No metrology frameworks
- No traceability (e.g. mol, kg, s, m)


courtesy of A. Boeuf, LNE
Precision Diagnostics demands (R)Evolution in Protein Measurement Technologies

Activity tests provide results without detail.

- Activity tests report a single number (% activity)
- Antithrombin exists in >350 proteoforms
- Multiple reports on specific mutations causing a cryptic clinical phenotype. (arterial and obstetric complications)

Perceived diagnosis painted by clinician.

- Discrepancy between antithrombin activity methods
  - Ungerstedt et al., 2002, Blood

Discordant diagnoses
- Feddersen et al., 2014, Clinical Biochemistry

A challenging diagnosis
- Orlando et al., 2015, Thrombosis Research

Severe thrombophilia not detected by functional assays
- de la Morena-Barrio et al., 2015, Thrombosis Research

How to uncover the true picture?

Precision diagnostics reveals the true picture.

Proteoform detection and quantification has to be considered in Lab Medicine to improve clinical care pathways and ensure future sustainable healthcare.

SKML Congres 2024
Medical tests should be fit-for-clinical-purpose THROUGH THEIR ENTIRE LIFE CYCLE (PEP and PMPF)!

Performance Evaluation Plan (PEP) – Recital (61)
Post-market Performance Follow-up (PMPF) – Recital (63)
Multiple stakeholders involved in Test Evaluation and Implementation in Clinical Care

- Clinicians
- Scientific societies

- Patients

- Academic laboratories
- Clinical laboratories
- NMIs
- IFCC

- Manufacturers
- EQA providers

- Regulators
A. Major outcomes for Regulators regarding APS and fitness for purpose of Tests

- EU CALL applications on Clinical Evidence Generation for Regulators are currently processed.
- Adoption/implementation of commutable matrix-based CRMs for getting accurate results in case of **DISEASE DEFINING TESTS** should become mandatory in order not to harm patients/confuse MDs.
- Country/region specific regulations are far too burdensome for manufacturers, especially in the case of (mathematical) recalibration of tests. Less bureaucracy for **GLOBAL** test restandardization should be considered by regulatory bodies in all areas.

- **For IVDs more uniform regulatory requirements internationally** (especially in case of recalibration) **are needed! Not only at the EU-level!**
- **IVDR should be evaluated regarding its effectiveness!** What are its (un)intended effects on patient management, IVD-sector and EU-healthcare!? **How to move to IVDR 2.0?**
A major goal: how to improve suboptimal test performance & adoption effectiveness of (re)standardization projects?

• Successful adoption/implementation of new/improved tests demands **effective governance in tight network organizations / consortia** with clearly defined roles of **all stakeholders**, including clinical societies.
• Quest for **one shared vision** with unique activities, alignment and transparency!
• The entire testing process in labs should be considered in EQAS.

**Always (re)consider the focus of balancing Analytical and Clinical Performance Specifications in specific clinical care pathways in your institution**

• Classical tests (**continuation** after reevaluation of needs)
• **New areas of laboratory medicine** (proteomics, personalized medicine)
• Necessary priority assessment of **clinical needs**
The Obvious Concluding Message regarding IVDR in general & Clinical Evidence

IVDR not yet a suitable framework! It reveals necessity of a GLOBAL VISION: REGULATORY REQUIREMENTS should be HARMONIZED ACROSS THE GLOBE!

Opinion Paper

Christa Cobbaert*, Ettore D. Capoluongo, Florent J.L.A. Vansiapel, Patrick M.M. Bossuyt, Harjit Pal Bhattoo, Peter Henrik Nissen, Matthias Orth, Thomas Streichert, Ian S. Young, Elizabeth Macintyre, Alan G. Fraser and Michael Neumaier

Implementation of the new EU IVD regulation – urgent initiatives are needed to avert impending crisis

SKML as supervisor of balanced Analytical and Clinical performance goals

... but

All stakeholders have responsibility in balancing Analytical & Clinical Performances of Tests!

Stakeholders involved in Test Evaluation and Standardization

- Clinicians
- Scientific societies
- Patients
- Academic laboratories
- Clinical laboratories
- NMI
- IFCC
- Regulators
- Manufacturers
- EQA providers
Thanks for your attention.

Questions?

For further information, visit

www.ifcc.org | eacademy.ifcc.org