Does the EU IVDR 2017/746 present a suitable Framework for Safe and Effective Medical Tests?

4 June 2024
C.M. Cobbaert, Leiden University Medical Centre, Leiden, NL
Chair IFCC Scientific Division EC
Chair EFLM Task Force European Regulatory Affairs

International Federation of Clinical Chemistry and Laboratory Medicine

Advancing excellence in laboratory medicine for better healthcare worldwide

ifcc.org

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I. Role of Laboratory Medicine

THE ROLE OF LABORATORY SPECIALISTS:

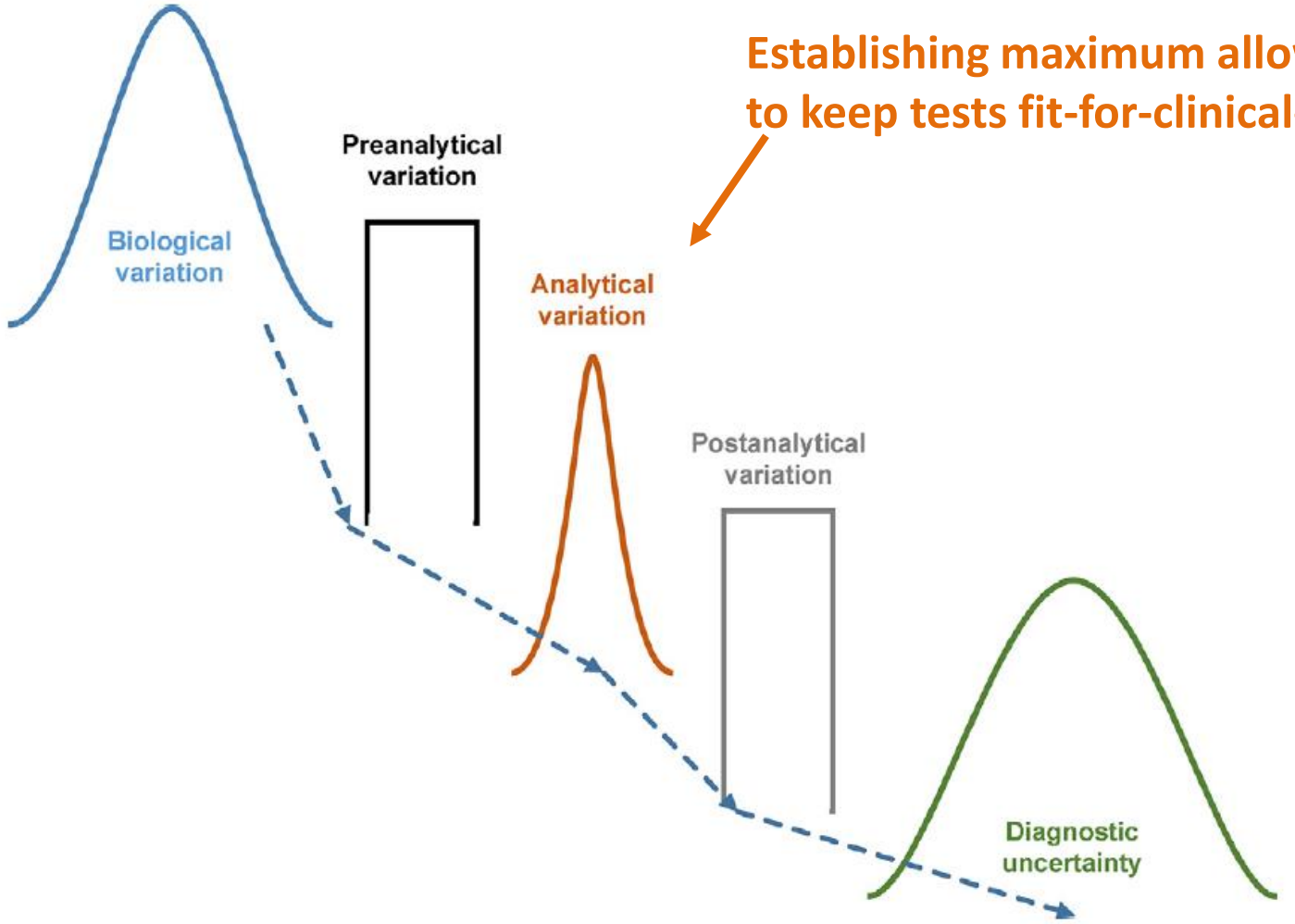
- **Our goal**: to improve patient outcome
- **Our tools**: safe and effective Medical Tests
- **Our mechanism**: support medical decisions

Laboratory specialist
safe & effective patie

- **"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.**

Diagnostic versus Measurement Uncertainty

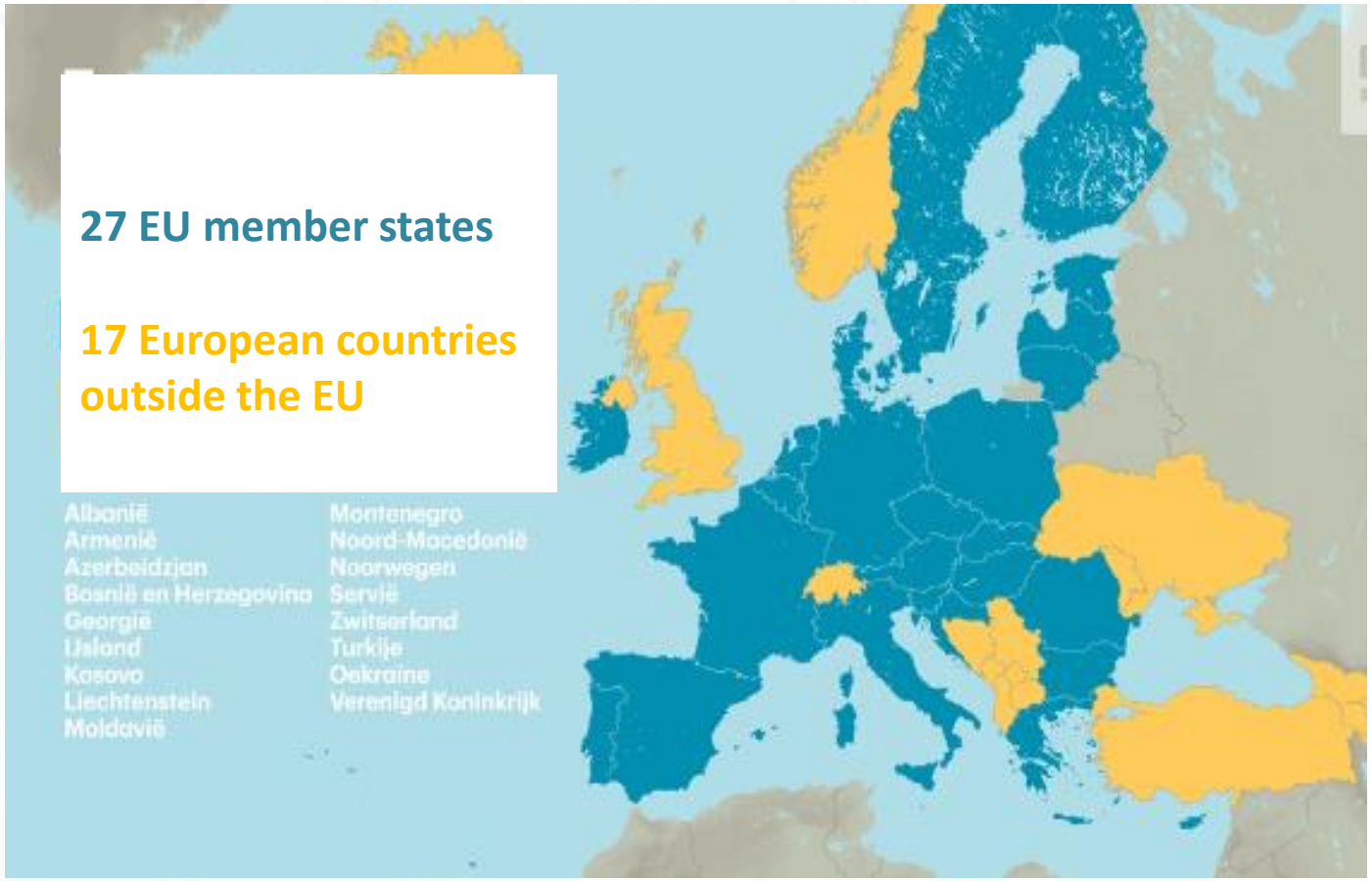
Establishing maximum allowable MU is key to keep tests fit-for-clinical-purpose!



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.

European Health Union



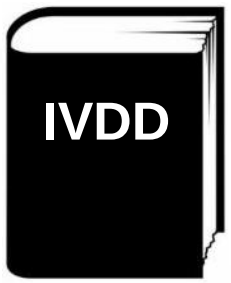
The European Commission is attempting to build a strong **European Health Union**, in which all EU countries prepare and respond together to health crises, medical supplies being available, affordable and innovative, but also to improve prevention, treatment and aftercare for diseases such as cancer. 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.

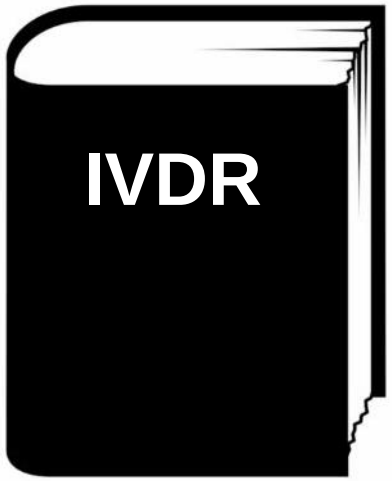
https://eur-lex.europa.eu/content/summaries/summary-29-expanded-content.html

Since 26 May 2022: from IVDD to IVDR

- IVD**D** regulates commercial IVDs (CE-IVDs)
- IVD**R** regulates CE-IVDs and In House-IVDs (LDTs)



1998 - 2022



Entry into force: 2017

5 years for Implementation

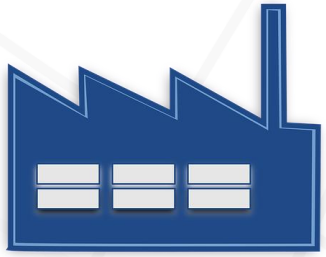
Date of application: May 26th, 2022

CE-IVDs

LDTs

Laboratory-developed tests / In-house devices

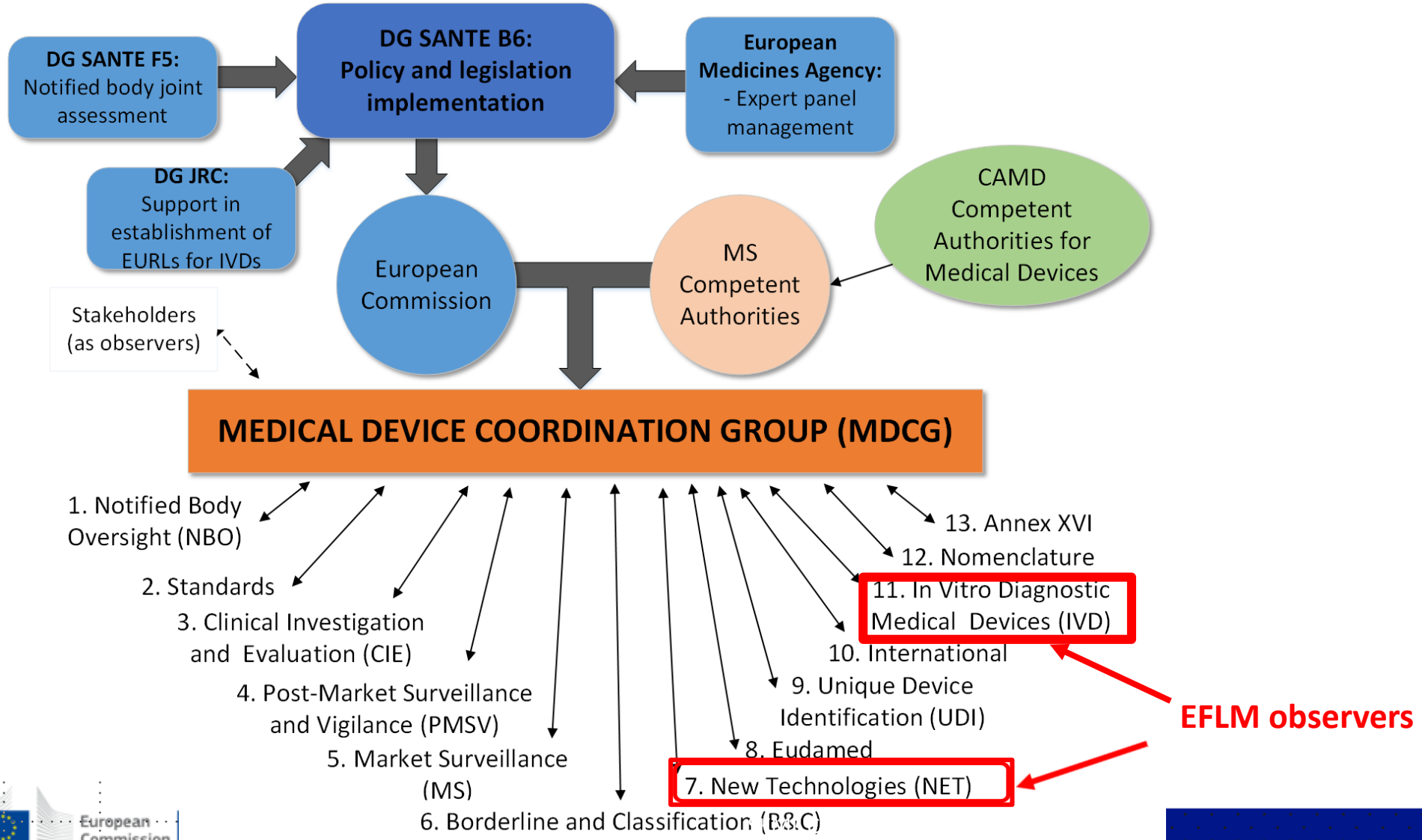
Areas of the EU Regulatory Framework



Pre-market → **Post-market**

Pre-market	Post-market
Qualification/ classification	Post-market surveillance (manufacturer)
Conformity assessment	Market surveillance (competent authorities)
Performance evaluation/ performance study	Vigilance

Governance of EU-level implementation



IVDR KEY CHANGES

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

L 117/176 EN Official Journal of the European Union 5.5.2017

REGULATION (EU) 2017/746 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL

of 5 April 2017

on *in vitro* diagnostic medical devices and repealing Directive 98/79/EC and Commission Decision 2010/227/EU

(Text with EEA relevance)

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!)

Redefinition of an IVD medical device

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.

Scope Enlargement

... solely or principally for the purp[illegible]f providing information on one or more of the following:

SCOPE ENLARGEMENT
Including high risk "In House" tests

(a) Concerning a physiological or pathological p[illegible]
(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 respon[illegible]e or reactions;
(f) To define or monitor therap[illegible]utic measures.

Companion Diagnostics

Genetic testing

Test (Re)Classification

- 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

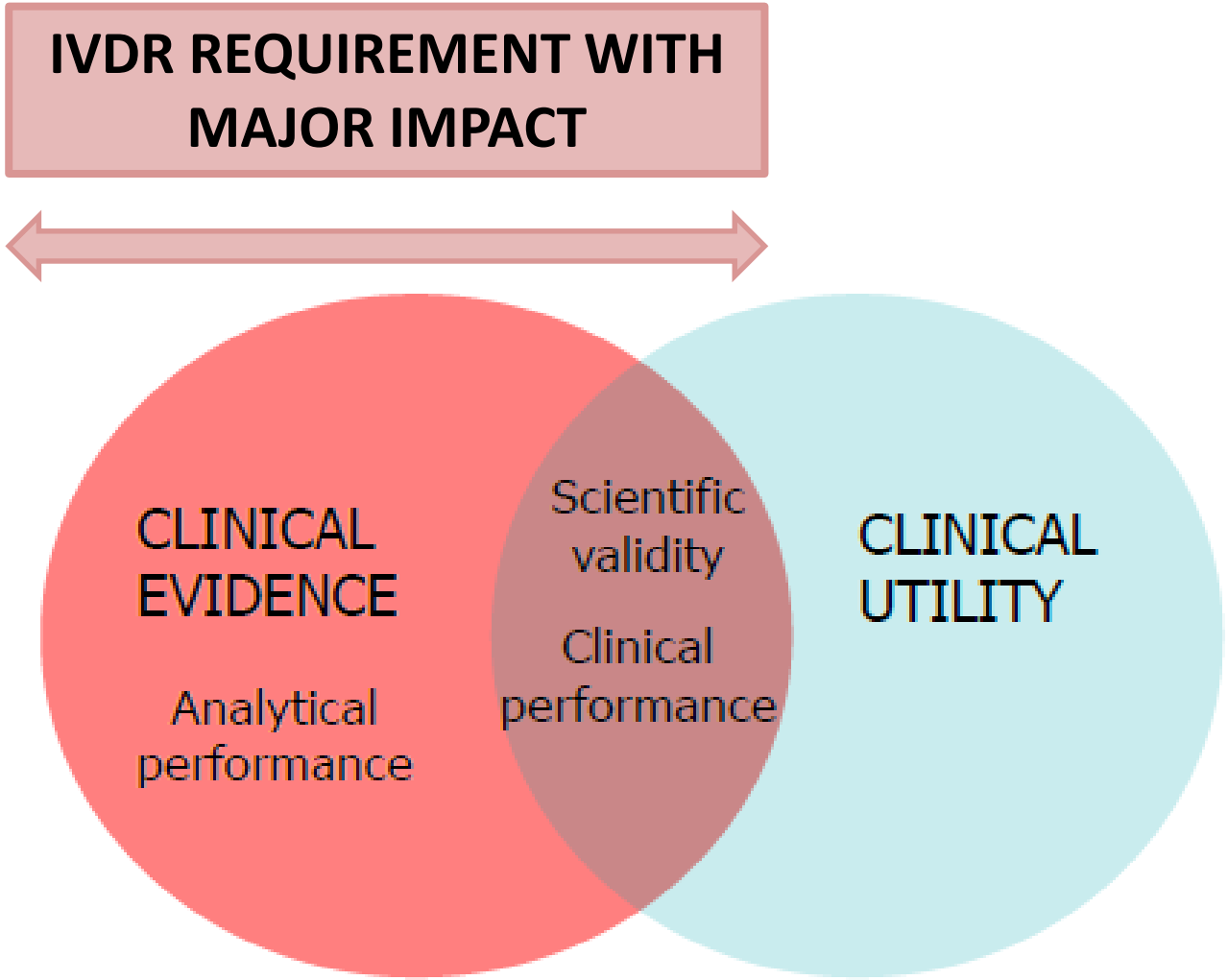
D	▪ High public health risk ▪ Blood safety / high risk infectious diseases
C	▪ High risk for individual patients ▪ E.g. cancer markers, dangerous infectious diseases, etc.
B	▪ Medium risk for individual patients ▪ E.g. blood chemistry, pregnancy tests, etc.
A	▪ Low risk for individual patients ▪ Instruments, accessories, specimen collection systems etc.

CCLM 2021, Cobbaert et al.

Clinical Evidence Requirement

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 M*edical Tests

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

Clinica Chimica Acta 427 (2014) 49–57

Contents lists available at ScienceDirect

Clinica Chimica Acta

journal homepage: www.elsevier.com/locate/clinchim

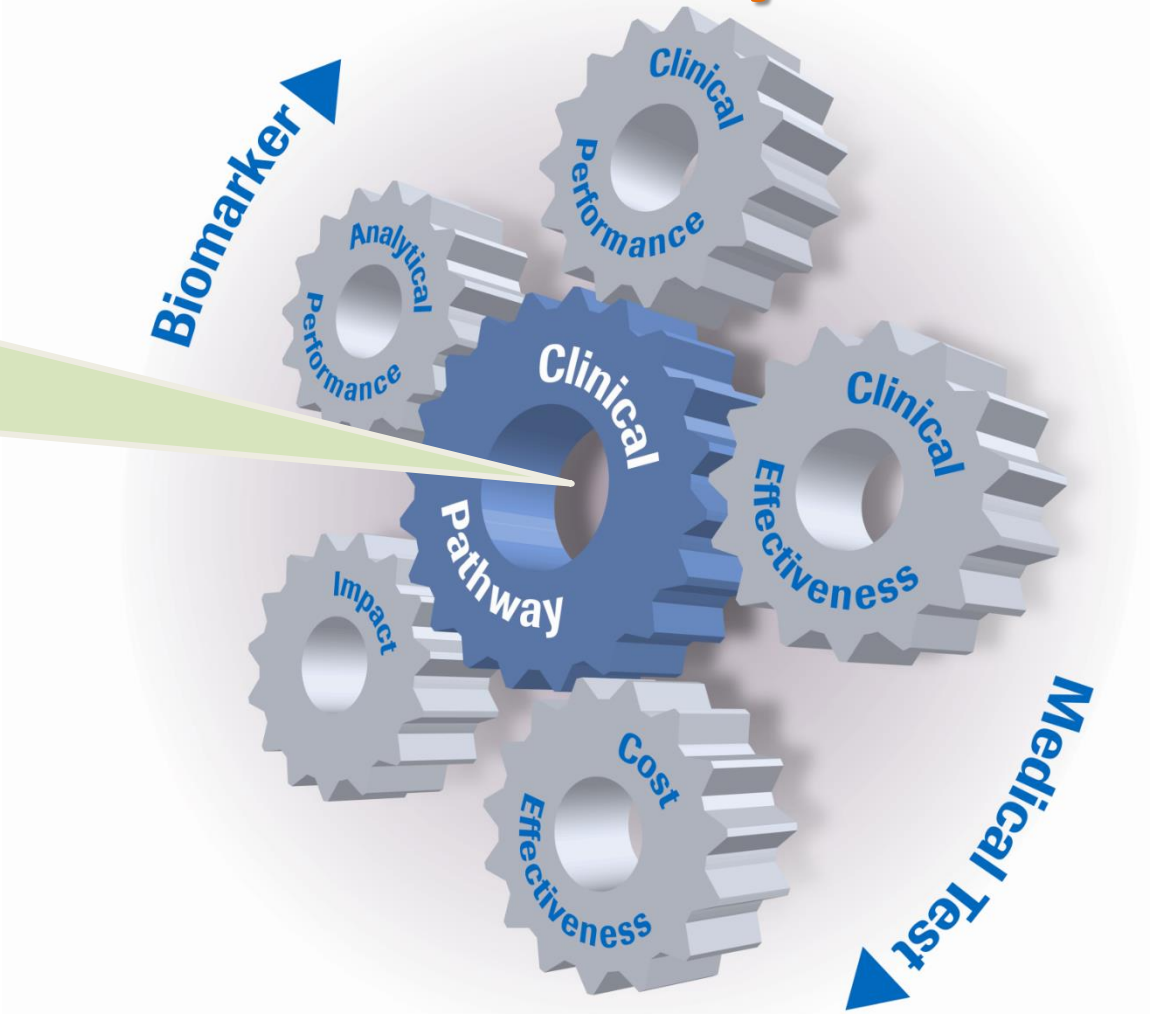
Special report

From biomarkers to medical tests: The changing landscape of test evaluation

Andrea R. Horvath [a,b,*], Sarah J. Lord [b,c,l], Andrew StJohn [d], Sverre Sandberg [e], Christa M. Cobbaert [f], Stefan Lorenz [g], Phillip J. Monaghan [h], Wilma M. Verhagen-Kamerbeek [i], Christoph Ebert [j], Patrick M.M. Bossuyt [k],
For the Test Evaluation Working Group of the European Federation of Clinical Chemistry Laboratory Medicine

The Test Evaluation Cycle

Is there an unmet clinical need and is there an effective intervention?



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Clinical pathway mapping:

What is the purpose and role of the test?

CVRM pathway

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

Subtoptimal due to
Residual risk beyond LDLc reduction
Underdiagnosis of CVD in women
Underdiagnosis of remnant disease

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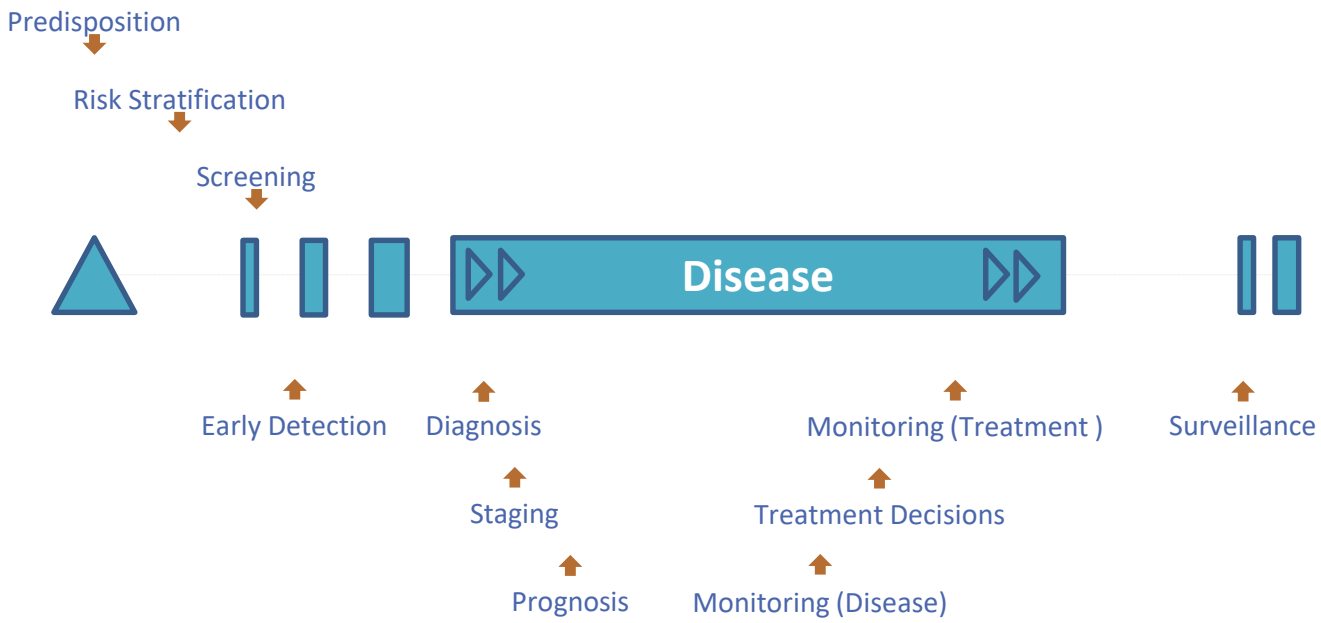
Intended Purposes of Medical Tests



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Key messages - 1

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 Test Evaluation Cycle

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;

Clin Chem Lab Med 2015; 53(6): 841–848

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.

Clin Chem Lab Med 2015; 53(6): 841–848

Key messages - 3

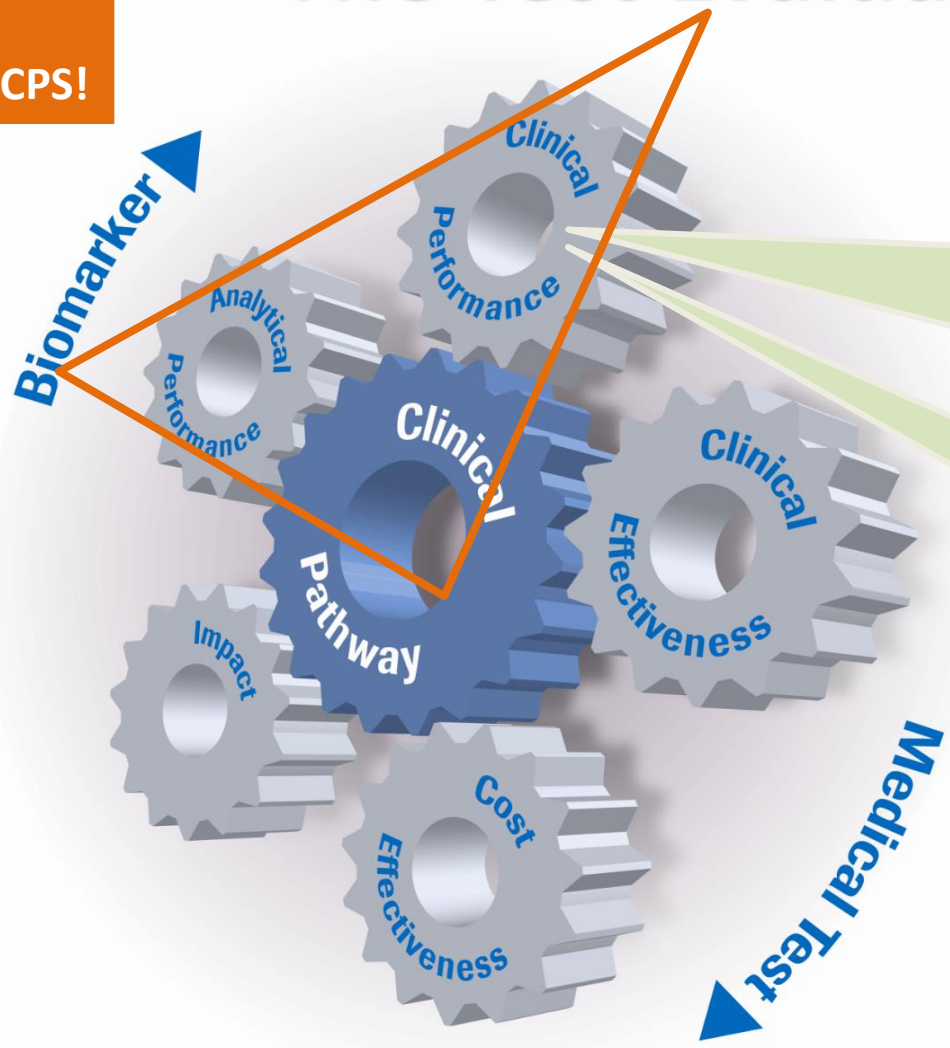
Outcome-based APS

- 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.

Clin Chem Lab Med 2015; 53(6): 841–848

The Test Evaluation Cycle

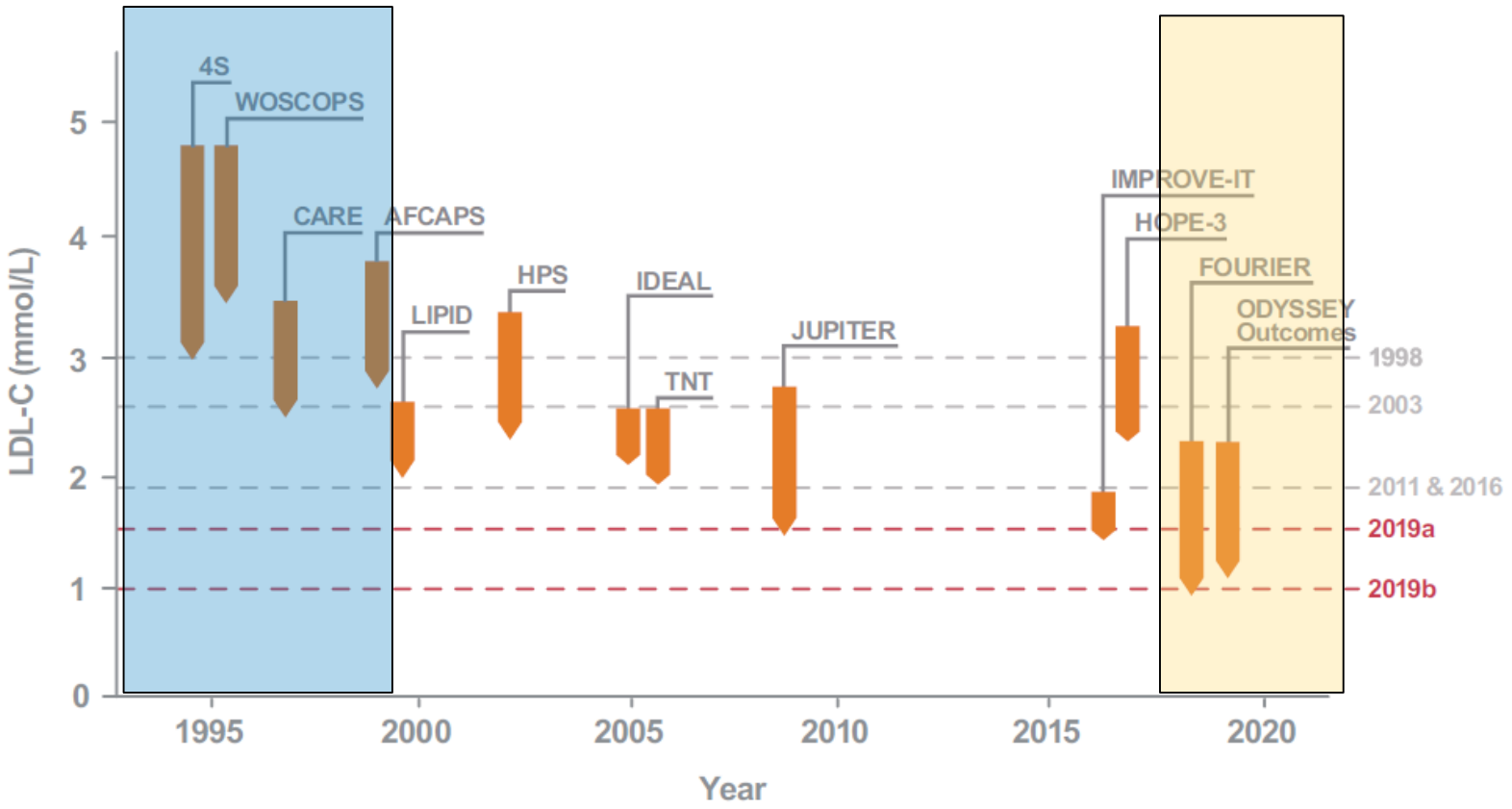
Cog wheel structure: interdependence between APS and CPS!



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?**

CVRM & History of LDL-c Lowering Trials



- 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	
CV_a	<4%
Bias	<4%
On-treatment goal	**2.6-4.14 mmol/L**

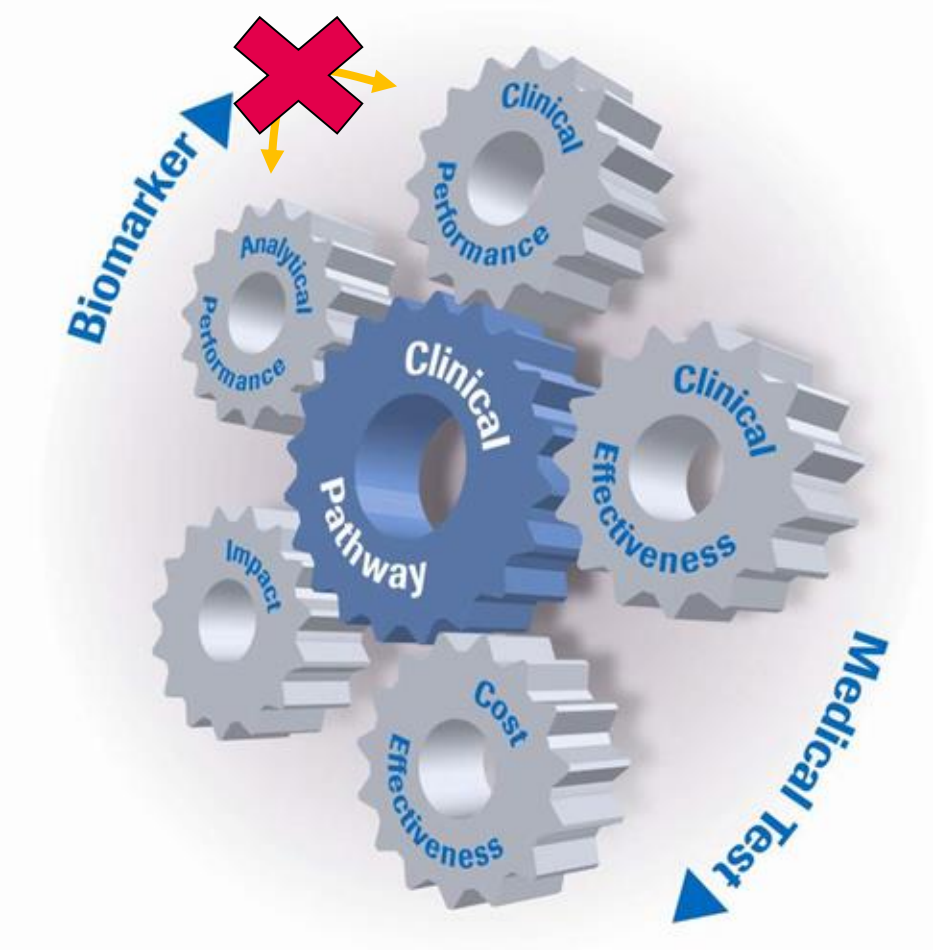
Current LDL-c on-treatment goals	**1–1.5 mmol/L**

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

Cobbaert, Ann. Clin. Biochem., 2023
Packard et al. Heart, 2021

Disconnect LDL-c test Analytical Performance and Clinical Performance

Test evaluation framework

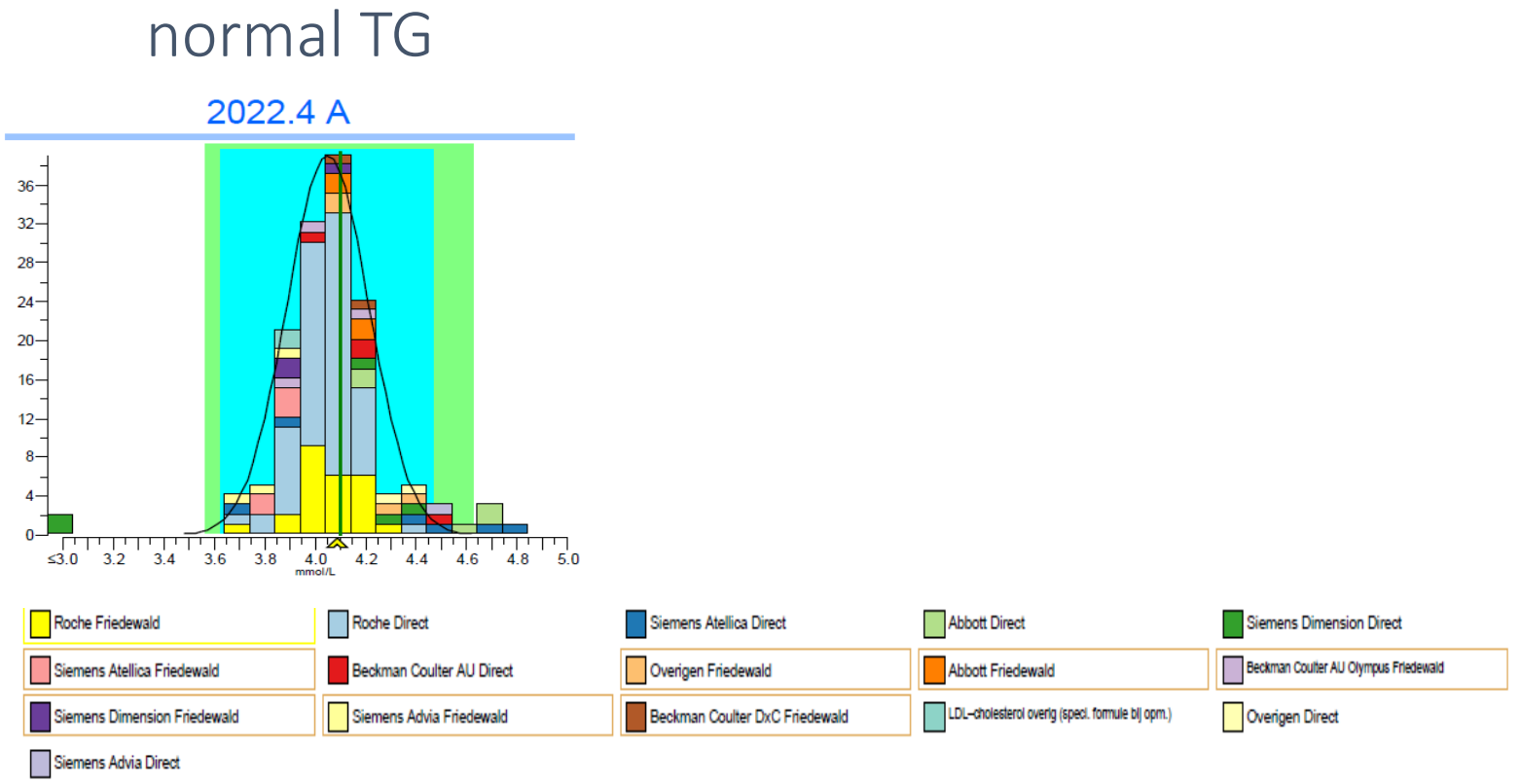


Disconnect between
Analytical Performance and
required Clinical Performance
of LDL-c tests

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
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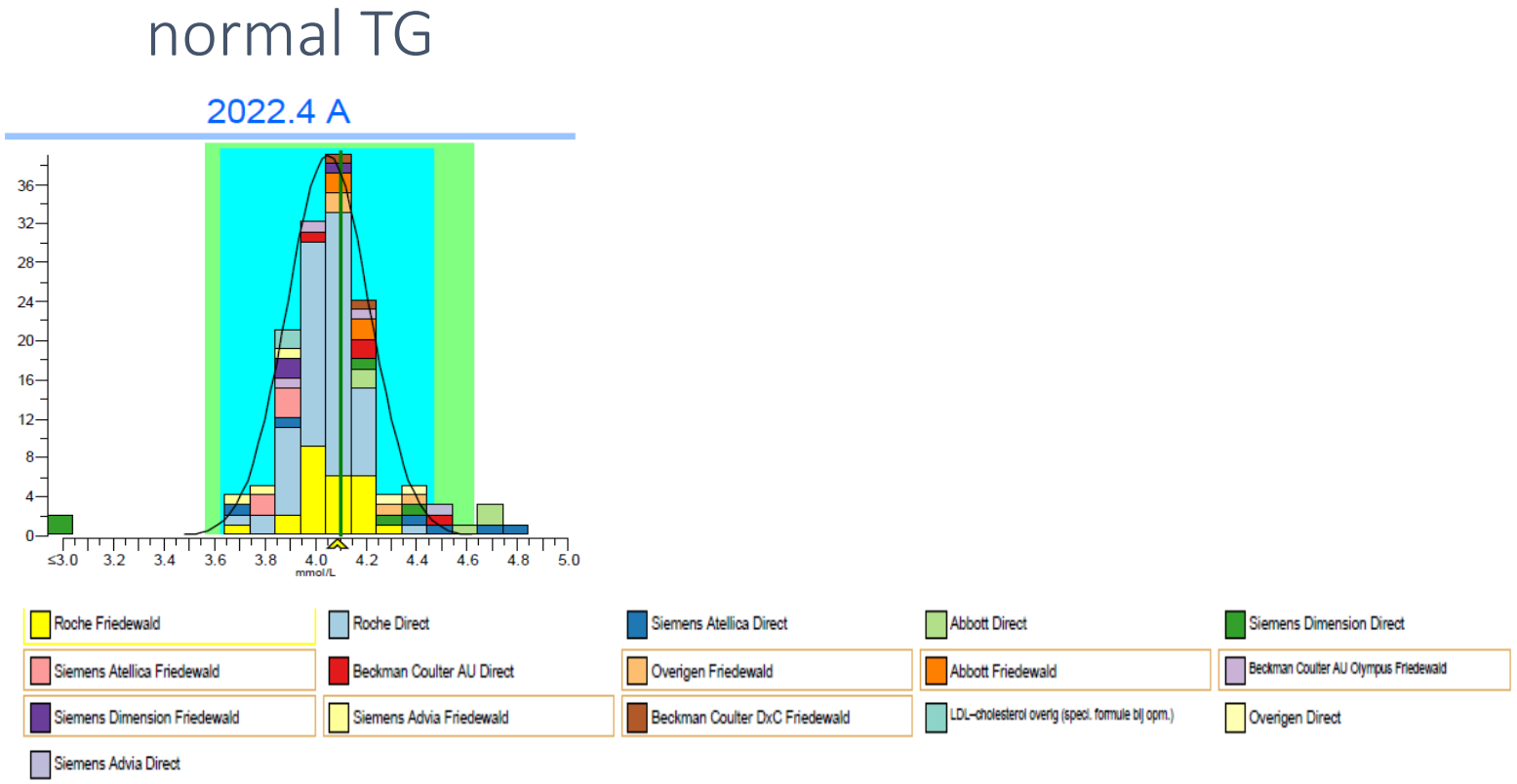
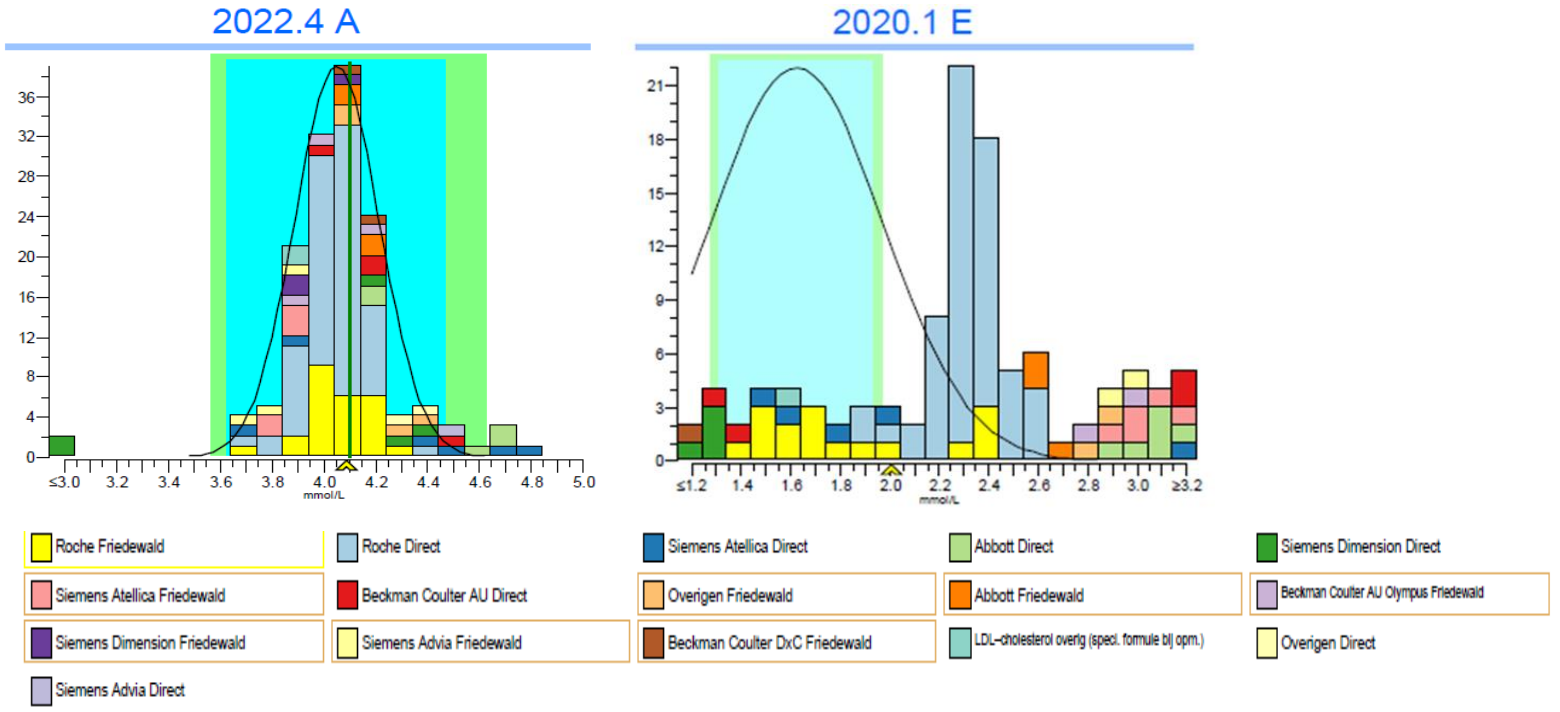


Dutch SKML EQA: LDL-c recovery in native hyperTG samples

Proficiency testing

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

Trimodal curve!
normal TG tests at low end: not fit for purpose!



The problem is non-selectivity of the test, not lack of standardization!

SUFFICIENTLY Current Analytical Performance of LDL-c tests ensures measurements are ACCURATE around former Clinical Decision Points

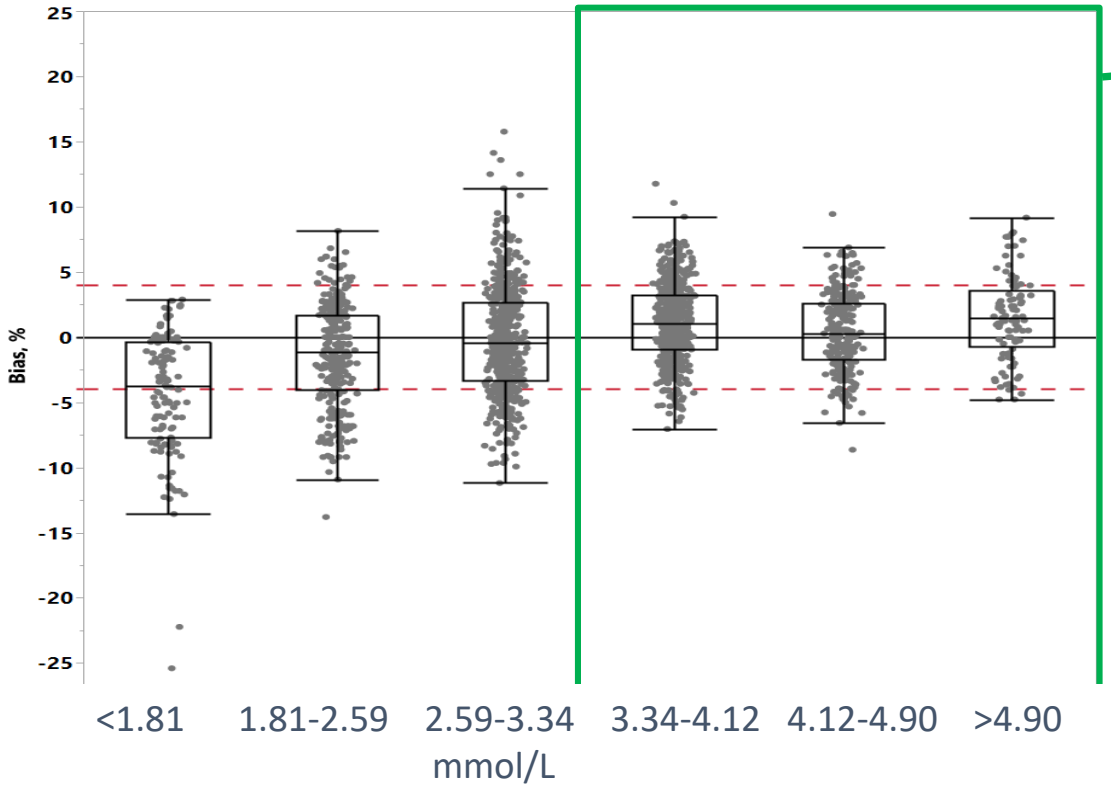
Bias distribution of LDL-c measurements reported by assay and reagent manufacturers as part of their submission for CDC certification (2016-2019)

38 assay and reagent manufacturers

Means of duplicate measurements

N = 1,914

mg/dL x 0.0259 = mmol/L

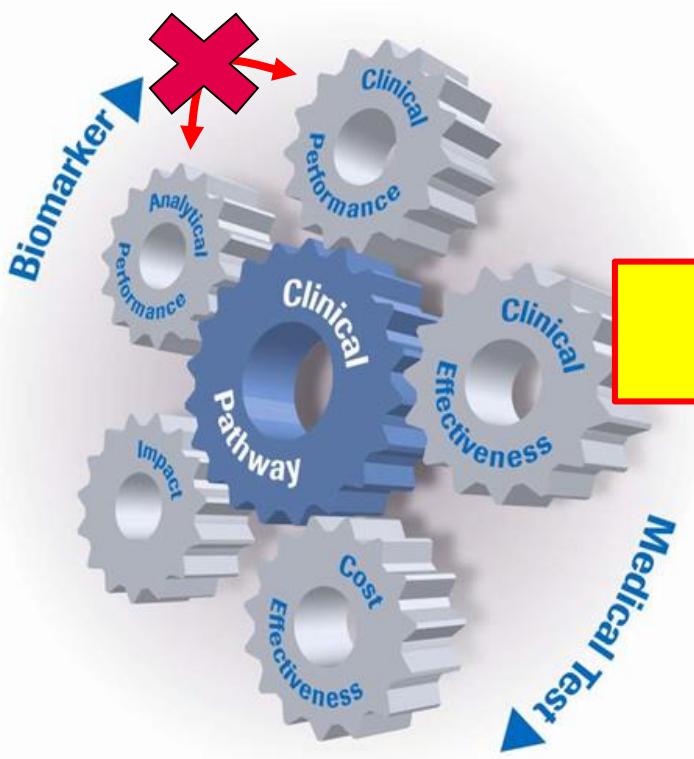


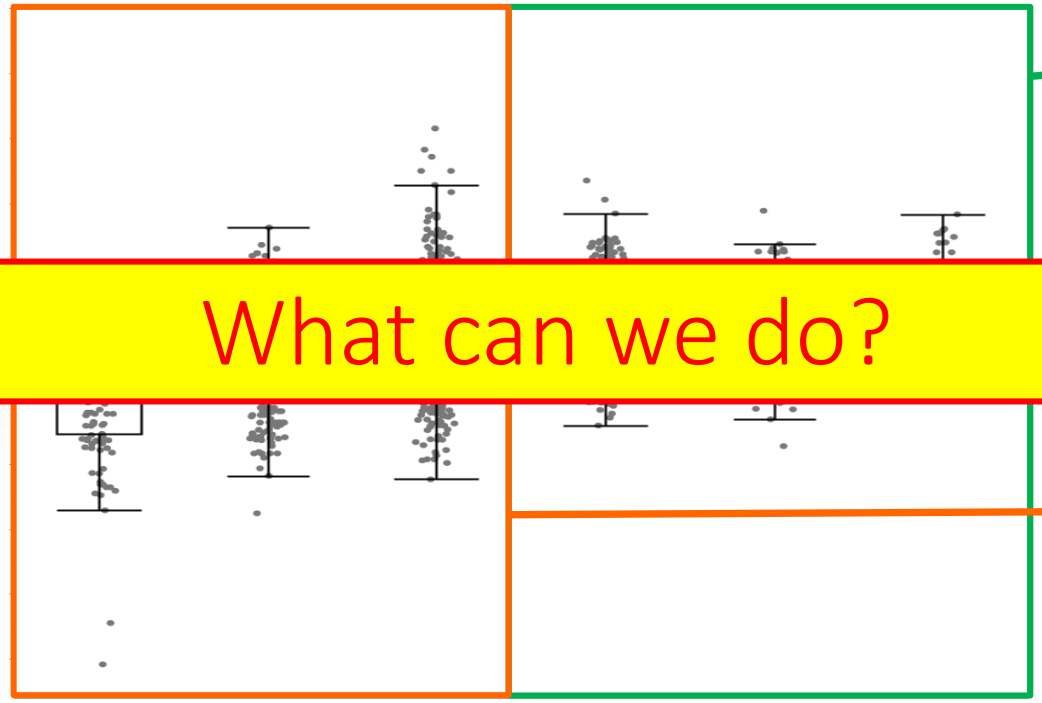
Calibration and non-selectivity bias are mostly sufficient for former LDL-c targets

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

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
- <u>Primary prevention</u>
  - Copenhagen General Population Study
  - UK Biobank
- <u>Secondary prevention</u>
  - INTERHEART
  - FOURIER
  - IMPROVE-IT
  - ….

2019 ESC/EAS Guidelines

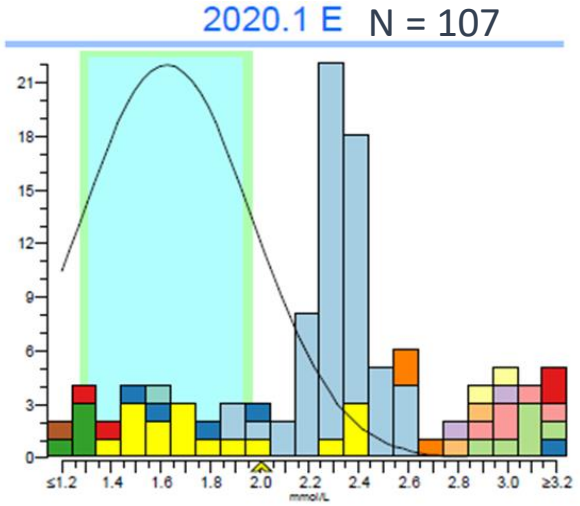
Lipid analyses for CVD risk estimation
ApoB analysis is recommended for risk assessment, particularly in people with high TG, DM, obesity or metabolic syndrome, or very low LDL-C. It can be used as an alternative to LDL-C, if available, as the primary measurement for screening, diagnosis, and management,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

SKML EQA:
LDL-c recovery in a hyperTG native sample

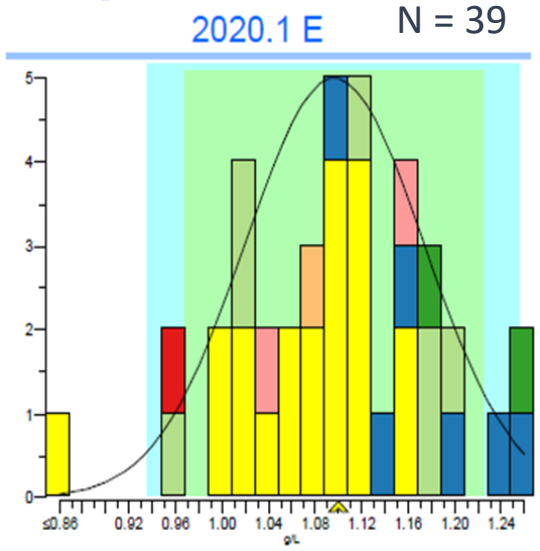
LDL-c

Interlaboratory CV_a of 21%

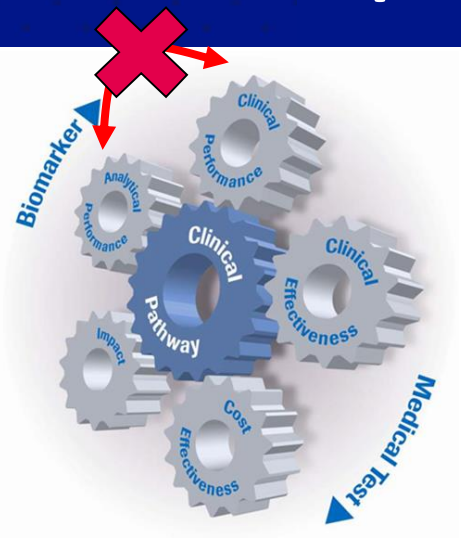


ApoB

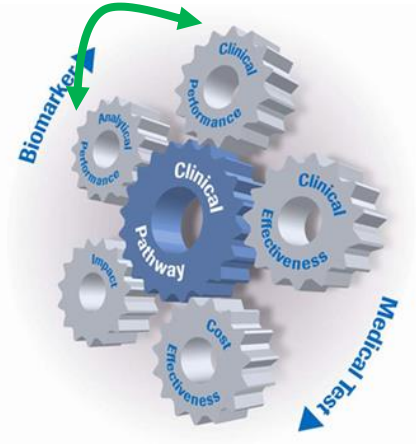
Interlaboratory CV_a of 9%



Imprecision diagnostics



Precision diagnostics



Molecularly defined ApoB does not suffer from non-selectivity

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

Subtoptimal due to
- Residual risk beyond LDLc reduction
- Underdiagnosis of CVD in women
- Underdiagnosis of remnant disease

Modified from Ruhaak, van der Laarse, Cobbaert, Ann Clin Biochem, 2019

Annals of Clinical Biochemistry
Volume 60, Issue 3, May 2023, Pages 151-154

https://doi.org/10.1177/00045632231166855

SAGE journals

Editorial

Implementing cardiovascular precision diagnostics: laboratory specialists as catalysts?

Christa M Cobbaert

IV. ISO 17511:2020
& the Metrological Traceability Concept

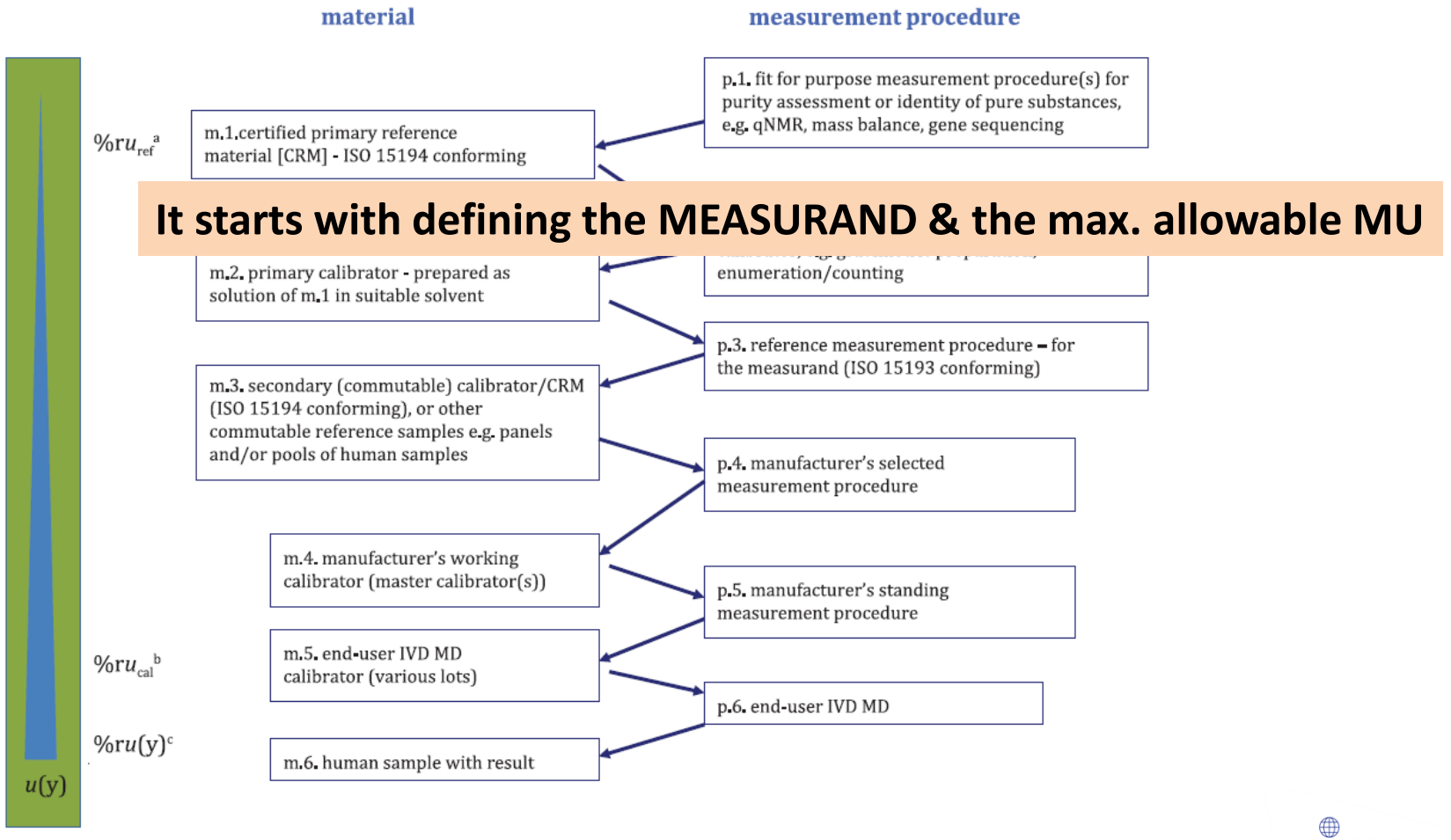
INTERNATIONAL STANDARD **ISO 17511**

Second edition
2020-04

Harmonized with the IVDR!

In vitro diagnostic medical devices — Requirements for establishing metrological traceability of values assigned to calibrators, trueness control materials and human samples

Calibration hierarchy — Full metrological traceability to SI

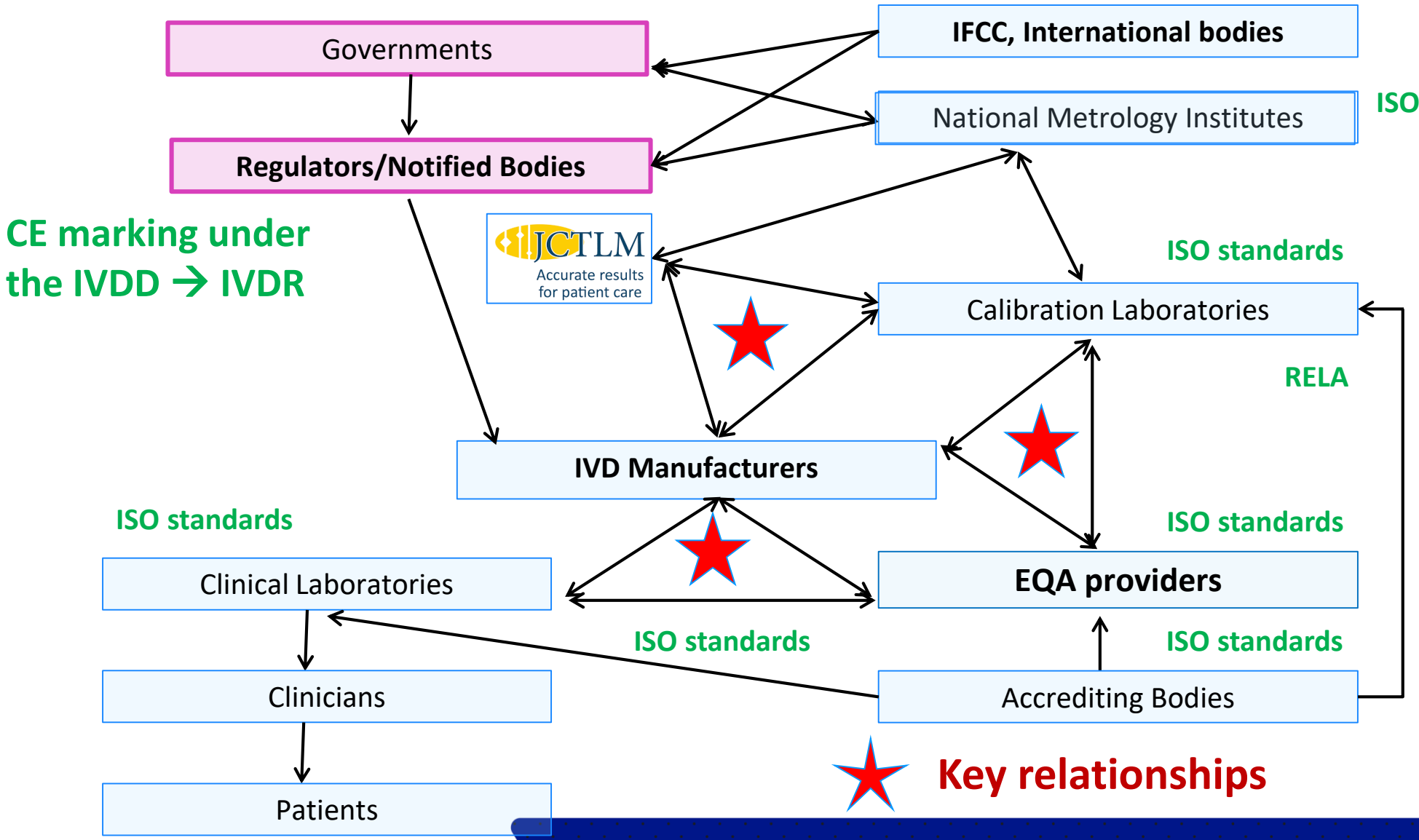


Metrological Traceability in the IVDR:

- 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



Standardization/harmonization in Laboratory Medicine: current status

- **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 2000 s
- **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: % ⇨ mmol/mol)

Clinical Chemistry 57:2
205–214 (2011)

Status of Hemoglobin A_{1c} Measurement and Goals for Improvement: From Chaos to Order for Improving Diabetes Care

Randie R. Little,[1*] Curt L. Rohlfing,[1] and David B. Sacks[2,3*] for the National Glycohemoglobin Standardization Program (NGSP) Steering Committee

REVIEW ARTICLE

Measurement of Hemoglobin A_{1c}

A new twist on the path to harmony

DAVID B. SACKS, MB, CHB, FRCPATH

Clinica Chimica Acta 418 (2013) 63–71

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journal homepage: www.elsevier.com/locate/clinchim

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 $_{IFCC}$CDT values
- Implementation of $_{IFCC}$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 : amont 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** :

Clin Chem Lab Med 2023; 61(1): 48–54 DE GRUYTER

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/cclm-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 ß2-microglobulin Reference Material

ß2-microglobulin Reference Material: Summary View

1 Results

EXPORT PDF EXPORT XLS SUMMARY VIEW →Select all results

beta-2-microglobulin in processed human serum

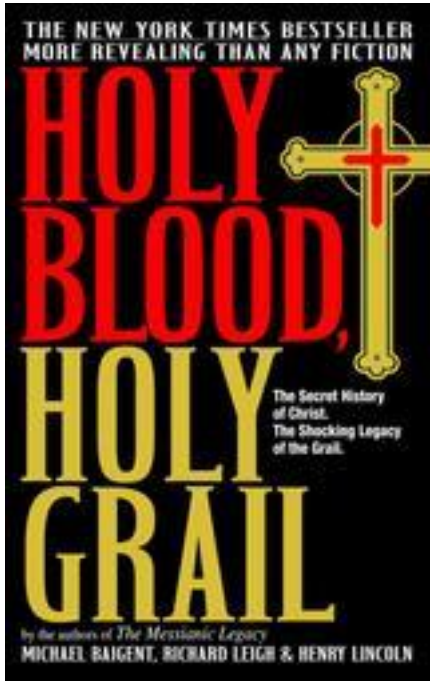
European Commission - Joint Research Centre →(EU - JRC) - Belgium
Phone +32 (0) 14 571 705

ERM-DA470k/IFCC, human serum

Quantity	Mass concentration
Analyte certified / assigned value	2.17 mg/L
Expanded uncertainty (level of confidence 95 %)	0.07 mg/L
Reference(s) of commutability	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)	Development and preparation of a new serum protein reference material: feasibility studies and processing, I. Zegers et al., *Clin. Chem. Lab. Med.*, 2010, 48(6), 805-13
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 ß2-microglobulin RM was verified in Accuracy Based EQA Scheme in NL

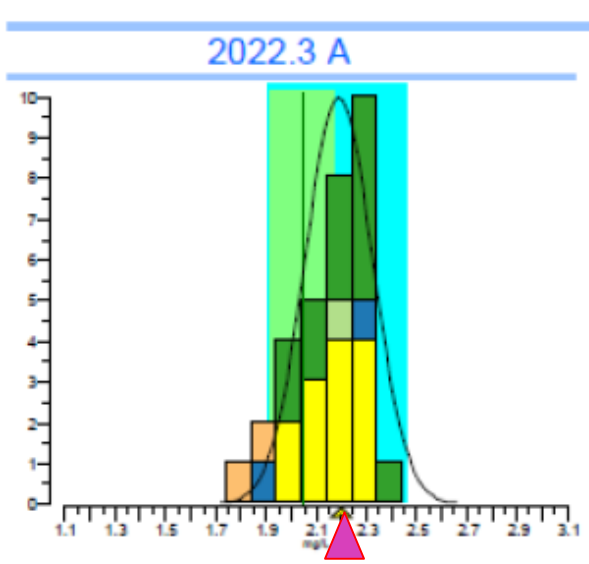


3 pillars for accuracy based EQA scheme:

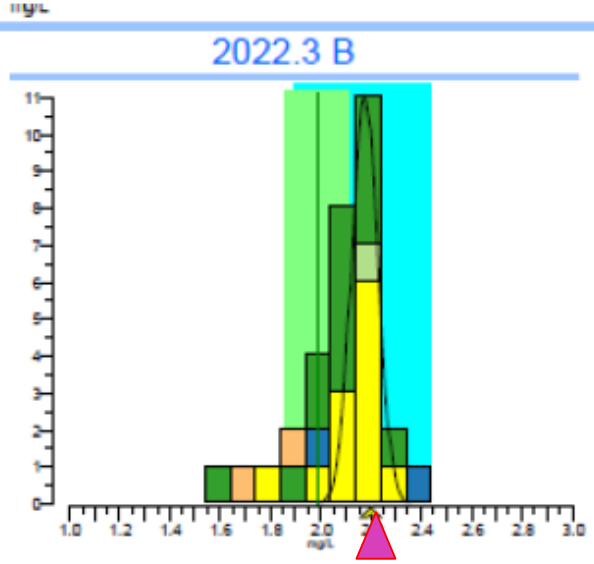
1. Commutable EQA materials (CLSI C37A)
2. Value assigned with ERM-DA470k for trueness verification
3. Scoring system based on biological variation and clinical relevance (TE_a).

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

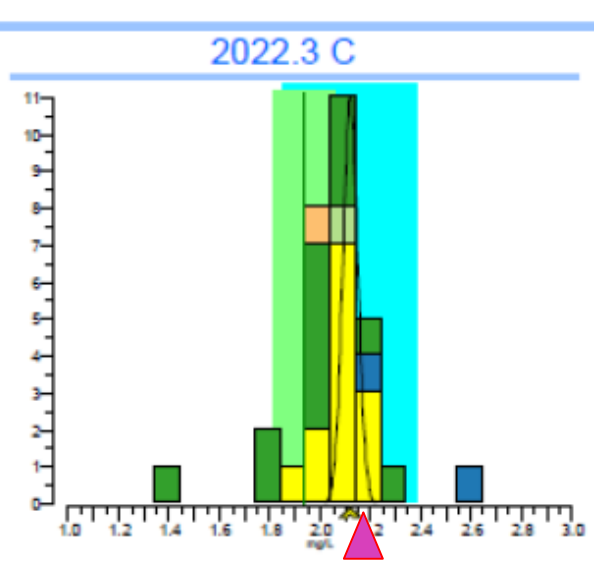
Collateral damage: Dutch EQA-data for ß2-microglobulin



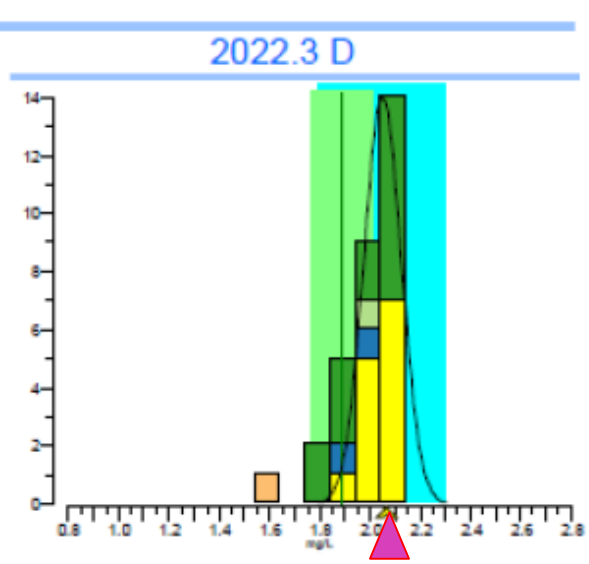
	cons.	meth.	ref.	lab
gem.	2.19	2.19	2.05	2.2
SD	0.13	0.13		
n	13	13		
nu	0	0		
rec.	100%	100%	107%	



	cons.	meth.	ref.	lab
gem.	2.18	2.18	1.99	2.2
SD	0.05	0.05		
n	12	12		
nu	1	1		
rec.	101%	101%	111%	



	cons.	meth.	ref.	lab
gem.	2.12	2.12	1.94	2.12
SD	0.03	0.03		
n	13	13		
nu	3	3		
rec.	100%	100%	109%	



	cons.	meth.	ref.	lab
gem.	2.05	2.05	1.89	2.07
SD	0.07	0.07		
n	13	13		
nu	0	0		
rec.	101%	101%	110%	

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

JCTLM listed Reference Material ERM-DA470k/IFCC

European Commission

ERM European Reference Materials

JOINT RESEARCH CENTRE
Institute for Reference Materials and Measurements

CERTIFICATE OF ANALYSIS

ERM® - DA470k/IFCC

HUMAN SERUM

Proteins in the reconstituted material [1]	Mass concentration	
	Certified value [2] [g/L]	Uncertainty [3] [g/L]
α_2 macroglobulin (A2M)	1.43 [4]	0.06
α_1 acid glycoprotein (AAG)	0.617 [5]	0.013
α_1 antitrypsin (AAT)	1.12 [5]	0.03
albumin (ALB)	37.2 [4]	1.2
β-2-microglobulin (B2M)	0.00217 [6]	0.00007
complement 3c (C3c)	1.00 [4]	0.04
complement 4 (C4)	0.162 [4]	0.007
haptoglobin (HPT)	0.889 [4]	0.021
immunoglobulin A (IgA)	1.80 [4]	0.05
immunoglobulin G (IgG)	9.17 [4]	0.18
immunoglobulin M (IgM)	0.723 [4]	0.027
transferrin (TRF)	2.36 [5]	0.08
transthyretin (TTR)	0.220 [5]	0.018

1) When the material is reconstituted according to the specified procedure (see page 3).
2) The certified values are the unweighted means of 6-14 accepted mean values, independently obtained by 5-14 laboratories, using ERM-DA470 as calibrant (Baudner et al., EUR reports 15423 and 16882 European Communities, Luxembourg (1993)) or a pure protein preparation.
3) Expanded uncertainty with a coverage factor $k = 2$ corresponding to a level of confidence of about 95 % estimated in accordance with the Guide to the Expression of Uncertainty in Measurement (GUM), ISO, 1995.
4) This certified mass concentration is traceable to the stated value of the mass concentration in USNRP 12-0575C (Reimer et al., Am. J. Clin. Pathol. 77 (1982) 12-19) used as calibrant for assigning values to ERM-DA470, applying the procedures described for the certification of ERM-DA470 and in the report for ERM-DA470k/IFCC.
5) The certified value in the calibrant ERM-DA470 was obtained by calibration with a pure protein preparation (Blirup-Jensen, Clin. Chem. Lab. Med. 39 (2001) 1090-1097). Consequently, the certified value in ERM-DA470k/IFCC is traceable to the International System of Units (SI) via ERM-DA470, applying the procedures described in the certification report of ERM-DA470 (see point 2) and in the certification report for ERM-DA470k/IFCC.
6) The certified value in the pure protein preparation was obtained by amino-acid analysis (A. Muñoz, et al., Anal. Biochem. 408 (1) (2011), 124-131) and confirmed by dry mass determination (S. Blirup-Jensen, Clin. Chem. Lab. Med. 39 (2001) 1090-1097). Consequently, the certified value in ERM-DA470k/IFCC is traceable to the International System of Units (SI) through the pure protein preparation

This certificate is valid for one year after purchase.
Sales date:

Commutable recommended RM for ß2-Microglobulin is available and JCTLM-listed.

https://crm.jrc.ec.europa.eu/p/q/erm-da470k_ifcc+/ERM-DA470k-IFCC-HUMAN-SERUM-proteins/ERM-DA470k_IFCC

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

JRC website: origin of ERM-DA474/IFCC

EUROPEAN COMMISSION
JOINT RESEARCH CENTRE

Institute for Reference Materials and Measurements
Reference Materials Unit

Geel, 11 October 2011

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).

Long lasting Suboptimal Performance of CE-IVD approved prolactin tests

DE GRUYTER

Clin Chem Lab Med 2022; aop

Opinion Paper

Michael N. Fahie-Wilson*, Christa M. Cobbaert, Andrea R. Horvath and Thomas P. Smith

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!

Clin Chem Lab Med 2018; 56(10): 1598–1602 DE GRUYTER

Opinion Paper

Christa Cobbaert*, Nico Smit 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/10.1515/cclm-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)

Clinica Chimica Acta 522 (2021) 184–186

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journal homepage: www.elsevier.com/locate/cca

Editorial

IFCC Scientific Division: A conductor of standardization in laboratory medicine

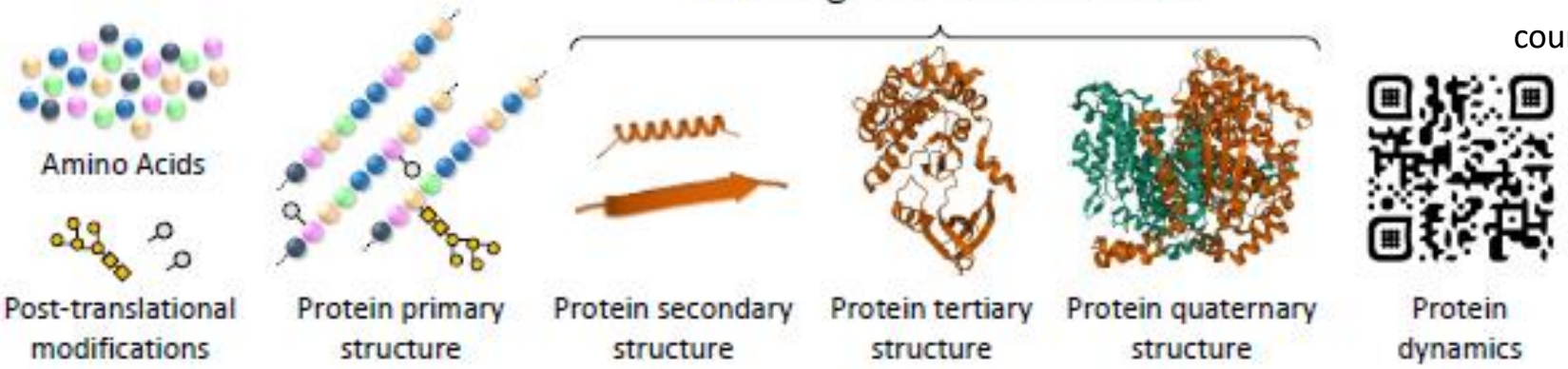
New Kids on the Block: Proteoforms

ProMET

JRP f11 Fundamental protein metrology to support the definition of measurands, analytical targets, and their associated measurement uncertainty

HOS: higher-order structure

courtesy of A. Boeuf, LNE



Proteoforms:

Adatped from Kruijt M, Treep MM, Cobbaert CM and Ruhaak LR. Res Pract Thromb Haemost. 2023;7(2):100079. doi: 10.1016/j.rpth.2023.100079

✓ **Traceability to mol or kg** for unmodified entities

✗ **No references, No metrology frameworks**
No traceability (e.g. mol, kg, s, m)

Precision Diagnostics demands (R)Evolution in Protein Measurement Technologies

Kruijt et al. RPTH 2023

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

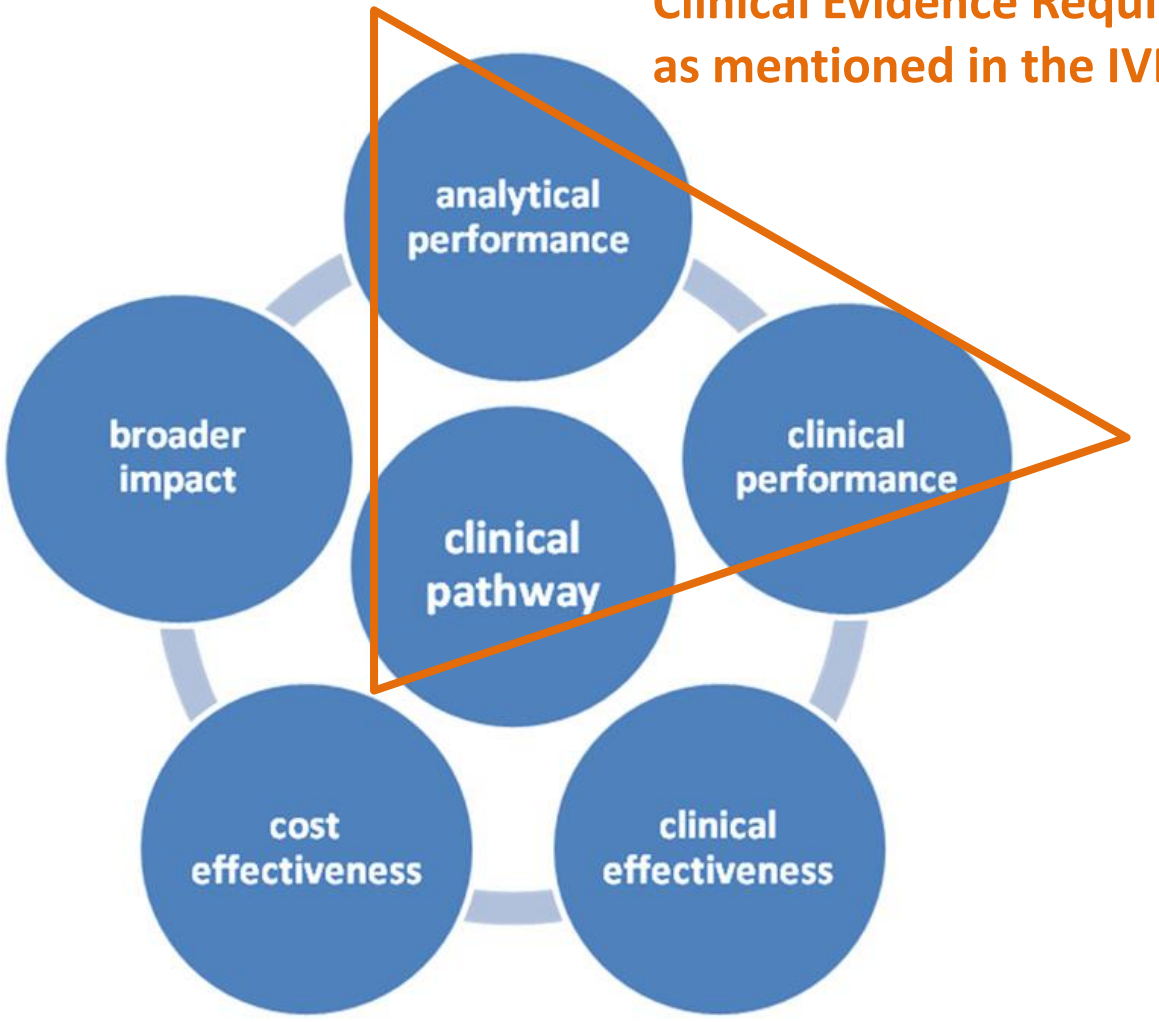
Precision diagnostics reveals the true picture.

How to uncover the true picture?

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

VI. Conclusions

Clinical Evidence Requirement as mentioned in the IVDR Framework



IVDR regulatory framework assesses COMPLIANCE of medical tests FOR EU MARKET ACCESS according to the intended use, risk class and performance claims presented in the IFU and technical dossier.

RATIONAL USE of medical tests in clinical care pathways is the responsibility of lab specialists!

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**

- Regulators

- Manufacturers
- EQA providers

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?**

B. A changing landscape for EQA-organizers & End-Users

- **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 transparancy!
  - 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!

DE GRUYTER Clin Chem Lab Med 2022; 60(1): 33–43

Opinion Paper

Christa Cobbaert*, Ettore D. Capoluongo, Florent J.L.A. Vanstapel, Patrick M.M. Bossuyt, Harjit Pal Bhattoa, 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!

Thanks for your attention.

Questions?

For further information, visit
www.ifcc.org | eacademy.ifcc.org

eAcademy

International Federation of Clinical Chemistry and Laboratory Medicine