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EQALM Symposium 2023

Metrology input for post-market surveillance of IVD tests

Vincent DELATOUR

October 19th, 2023

Regulatory drivers for establishing metrological traceability

EU regulation 2017/746 on in vitro diagnostic medical devices (IVDR)

"Metrological traceability of values assigned to calibrators and/or control materials shall be assured through suitable reference measurement procedures and/or suitable reference materials of a higher metrological order"

ISO 17511:2020 ***"A manufacturer shall document the complete calibration hierarchy and identify the highest metrological reference to which the resulting measured quantity values are traceable"***

ISO 15189:2022 ***Medical laboratories - Requirements for quality & competence***

NMIs mission : help medical labs & IVD industrials meet regulatory requirements regarding metrological traceability

- ✓ **Development of higher order reference methods**
- ✓ **Production of primary Certified Reference Materials (purified compounds)**
- ✓ **Production of secondary Certified Reference Materials (matrix mateched)**
- ✓ **Provision of calibration services to IVD manufacturers & EQA providers : assignment of reference method target values to EQA materials & calibrators**

Post-market surveillance

Different tools are available to evaluate the performance of IVD tests

✓ **IQC materials can help detecting errors but as they are not meant to be commutable, they can't be used to evaluate results trueness**

b. The laboratory shall select IQC material that is fit for its intended purpose. When selecting IQC material, factors to be considered shall include:

1. stability with regard to the properties of interest;
2. the matrix is as close as possible to that of patient samples;
3. the IQC material reacts to the examination method in a manner as close as possible to patient samples;
4. the IQC material provides a clinically relevant challenge to the examination method, has concentration levels at or near clinical decision limits and when possible, covers the measurement range of the examination method.

Post-market surveillance

Different tools are available to evaluate the performance of IVD tests

- ✓ IQC materials can help detecting errors but as they are not meant to be commutable, they can't be used to evaluate results trueness
- ✓ **EQA materials can be used to evaluate results trueness in condition that :**
  - materials commutability has been properly assessed and is adequate
  - target values are assigned with a reference method

e) When selecting EQA programme(s), the laboratory should consider the type of target value offered.

Target values are:

1) independently set by a reference method, or

2) set by overall consensus data, and/or

3) set by method peer group consensus data, or

4) set by a panel of experts.

NOTE 1 When method-independent target values are not available, consensus values can be used to determine whether deviations are laboratory- or method-specific.

NOTE 2 Where lack of commutability of EQA materials can hamper comparison between some methods, it can still be useful for comparisons to be made between methods for which it is commutable, rather than relying only on within-method comparisons.

Different types of External Quality Assessment Schemes

Miller et al. Clin Chem. 2011;57(12):1670-80

Table 3. Evaluation capabilities of PT/EQA related to scheme design.

				Evaluation capability						
				Accuracy					Standardization or harmonization[b]	
				Individual laboratory						
	Sample characteristics				Relative to participant results		Reproducibility		Measurement procedure calibration traceability	
Category	Commutable	Value assigned with RMP[a] or CRM	Replicate samples in survey	Absolute vs RMP or CRM	Overall	Peer group	Individual laboratory intralab CV	Measurement procedure interlab CV	Absolute vs RMP or CRM	Relative to participant results
1	Yes	Yes	Yes	X	X	X	X	X	X	X
2	Yes	Yes	No	X	X	X		X	X	X
3	Yes	No	Yes		X	X	X	X		X
4	Yes	No	No		X	X		X		X
5	No	No	Yes			X	X	X		
6	No	No	No			X		X		

- EQAS relying on non-commutable materials don't make it possible to assess comparability of results between different peer groups
- EQAS relying samples which target values have not been value assigned with a reference method don't make it possible to assess absolute bias

Post-market surveillance

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- ✓ **EQA materials can be used to evaluate results trueness in condition that :**
  - materials commutability has been properly assessed and is adequate
  - target values are assigned with a reference method

f. When an EQA programme is either not available, or not considered suitable, the laboratory shall use alternative methodologies to monitor examination method performance. The laboratory shall justify the rationale for the chosen alternative and provide evidence of its effectiveness.

NOTE : Acceptable alternatives include:

participation in sample exchanges with other laboratories;

interlaboratory comparisons of the results of the examination of identical IQC materials, which evaluates individual laboratory IQC results against pooled results from participants using the same IQC material;

analysis of a different lot number of the manufacturer's end-user calibrator or the manufacturer's trueness control material;

analysis of microbiological organisms using split/ blind testing of the same sample by at least two persons, or on at least two analyzers, or by at least two methods;

analysis of reference materials considered to be commutable with patient samples;

Post-market surveillance

Different tools are available to evaluate the performance of IVD tests

- ✓ IQC materials can help detecting errors but as they are not meant to be commutable, they can’t be used to evaluate results trueness
- ✓ EQA materials can be used to evaluate results trueness in condition that :
  - materials commutability has been properly assessed and is adequate
  - target values are assigned with a reference method
- ✓ **Secondary CRMs can be used as trueness verifiers but commutability assessment is cumbersome, which limits their availability**

Post-market surveillance

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- ✓ EQA materials can be used to evaluate results trueness in condition that :
  - materials commutability has been properly assessed and is adequate
  - target values are assigned with a reference method
- ✓ Secondary CRMs can be used as trueness verifiers but commutability assessment is cumbersome, which limits their availability
- ✓ **Comparison studies : panels of (fresh) patient samples (commutable by definition) are measured with an IVD-MD and a reference method : costly!**

1. **RMPs are not available for many measurands and/or are too costly and/or do not meet adequate analytical performance specification**
2. **Commutability evaluation of EQA materials and of secondary CRMs is cumbersome**

Current issues … and possible solutions

RMPs are not available for many measurands and/or are too costly and/or do not meet adequate analytical performance specifications

- **Possible causes :**
  1. **Lack of primary CRMs to calibrate RMPs**
  2. **Validating RMPs of high accuracy with sufficiently small measurement uncertainty to meet the clinical need can be challenging when it comes to measure large and/or low abundant measurands in complex matrices**
  3. **IDMS-based RMPs usually have low throughput due to high hands-on time**
  4. **There are too many measurands for which RMPs are needed**

Current issues … and possible solutions

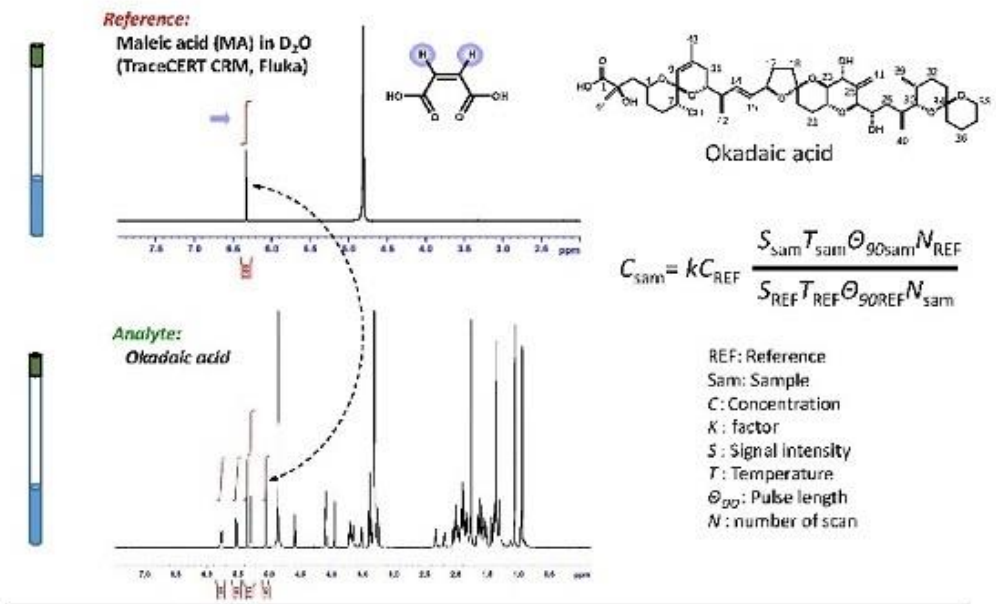
RMPs are not available for many measurands and/or are too costly and/or do not meet adequate analytical performance specifications

- **Possible causes :**
  1. **Lack of primary CRMs to calibrate RMPs**

- **Possible solutions:**
  1. **New purity assessment techniques to identify and quantify impurities faster**

Toxins (Basel). 2016 Oct 13;8(10):294. doi: 10.3390/toxins8100294.

PULCON (Pulse-length based Concentration determination)



Current issues … and possible solutions

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  1. **New purity assessment techniques to identify and quantify impurities faster**

Label-free Quantification of Host-Cell Protein Impurity in a Recombinant Hemoglobin Reference Material

André Henrion, Cristian Arsene, Maik Liebl, and Gavin O'Connor*

Current issues … and possible solutions

RMPs are not available for many measurands and/or are too costly and/or do not meet adequate analytical performance specifications

- **Possible causes :**

  2. Validating RMPs of high accuracy with **sufficiently small measurement uncertainty to meet the clinical need** can be challenging when it comes to measure large and/or low abundant measurands in complex matrices

- **Possible solutions:**

  2. Better consider measurement uncertainty at each level of the calibration hierarchy and its impact on the overall quality of laboratory tests.

     → JCTLM Task Force on Reference Measurement Systems Implementation

Current issues … and possible solutions

Clin Chem Lab Med 2021; 59(8): 1362–1368 DE GRUYTER

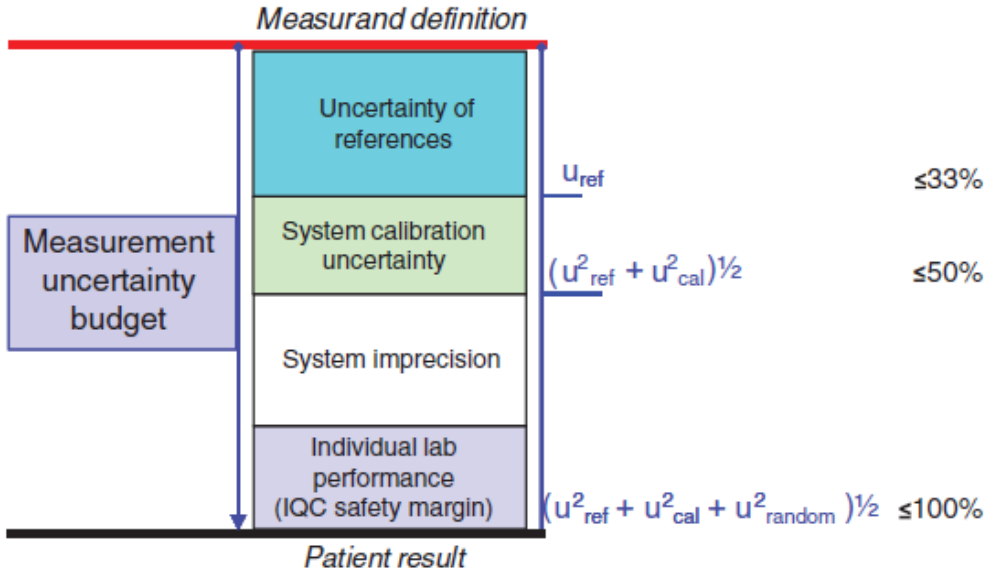
Opinion Paper

Federica Braga* and Mauro Panteghini

Performance specifications for measurement uncertainty of common biochemical measurands according to Milan models

Conclusions

. We recommend that no more than one third of the total uncertainty budget, established by appropriate analytical performance specifications, is consumed by the uncertainty of references and approximately 50% of the total budget consumed by the manufacturer's calibration and value transfer protocol. The remaining 50% should be available for the commercial system imprecision and individual laboratory performance as a safety margin



Current issues … and possible solutions

Clinical Chemistry 67:12
1590–1605 (2021)

Special Report

Optimizing Available Tools for Achieving Result Standardization: Value Added by Joint Committee on Traceability in Laboratory Medicine (JCTLM)

Mauro Panteghini,[a,*] Federica Braga ,[a] Johanna E. Camara,[b] Vincent Delatour,[c] Katleen Van Uytfanghe ,[d] Hubert W. Vesper,[e] and Tianjiao Zhang,[f] for the JCTLM Task Force on Reference Measurement System Implementation

SUMMARY: We produced a synopsis of JCTLM-listed higher-order CRMs and RMPs for the selected measurands, including their main characteristics for implementing traceability and fulfilling (or not) the APS for suitable MU. Results showed that traceability to higher-order references can be established by IVD manufacturers within the defined APS for most of the 13 selected measurands. However, some measurands do not yet have suitable CRMs for use as common calibrators. For these measurands, splitting clinical samples with a laboratory performing the RMP may provide a practical alternative for establishing a calibration hierarchy.

Current issues … and possible solutions

RMPs are not available for many measurands and/or are too costly and/or do not meet adequate analytical performance specifications

- **Possible causes :**
  3. **IDMS-based RMPs usually have low throughput due to high hands-on time**

- **Possible solutions:**
  3. **Develop high throughput RMPs**

     → **Automation can help decreasing hands-on time**

     → **Measuring a panel of measurands simultaneously can also help providing more cost-effective calibration services**

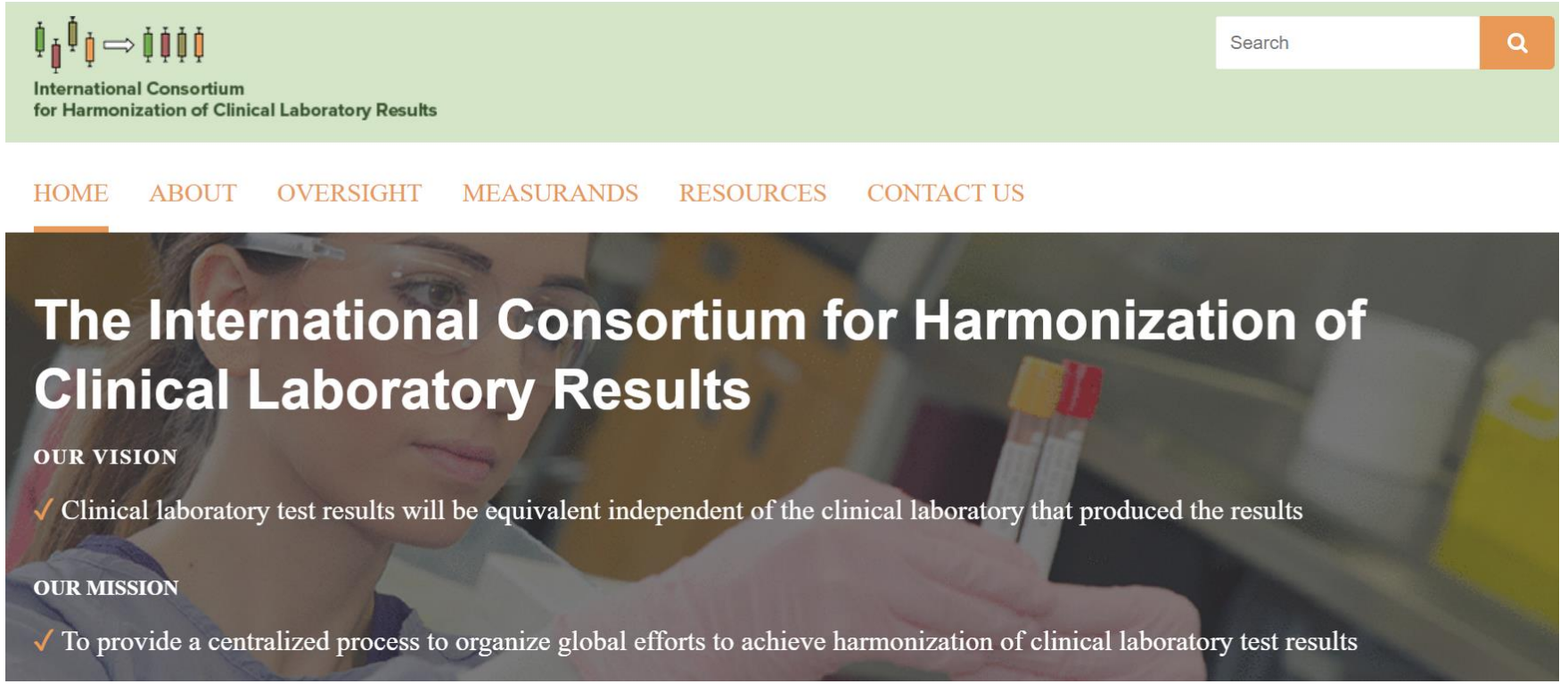
Current issues … and possible solutions

RMPs are not available for many measurands and/or are too costly and/or do not meet adequate analytical performance specifications

- **Possible causes :**
  4. **There are too many measurands for which RMPs are needed**

- **Possible solutions:**
  4. **Better coordinate & prioritize activities of NMIs and reference laboratories**
     - → **Improve collaboration between NMIs and assays providers & EQA providers**
     - → **Focus NMIs activities on measurands in real need for metrology input**

Current issues … and possible solutions



Measurand	Matrix	Medical Impact of Harmonization	Harmonization Status	Resources	Organization
Pregnancy-Associated Plasma Protein A	Plasma		Active		IFCC
Anti-Hepatitis B Surface Antigen (Anti-HBsAg)	Serum, Heparin Plasma	High	Needed	WHO	
Anti-myeloperoxidase (MPO) antibody, IgG	Serum	High	Needed	JCTLM	IFCC
B-type Natriuretic Peptide (BNP)	Serum	High	Needed		

An elephant in the room?

Commutability evaluation of EQA materials and of secondary CRMs is cumbersome

- **Consequences :**

  1. Standardization is compromised and/or a calibration bias is introduced
  → **results are not standardized and/or inaccurate**

Clinical Chemistry 59:9
1322–1329 (2013)

Proteomics and Protein Markers

The Importance of Commutability of Reference Materials Used as Calibrators: The Example of Ceruloplasmin

Ingrid Zegers,[1*] Robert Beetham,[2] Thomas Keller,[3] Joanna Sheldon,[4] David Bullock,[5] Finlay MacKenzie,[5] Stefanie Trapmann,[1] Hendrik Emons,[1] and Heinz Schimmel[1]

BACKGROUND: Different methods for ceruloplasmin tend to give different results in external quality assessment schemes. During the production of the certified reference material ERM-DA470k/IFCC discrepant measurement results were also found for ceruloplasmin measured with different methods, and consequently the protein could not be certified in the material.

CONCLUSIONS: Ceruloplasmin in ERM-DA470 is a fully documented example of a situation in which, due to lack of commutability, the use of a common material for calibration did not lead to harmonization .

Commutability evaluation of EQA materials and of secondary CRMs is cumbersome

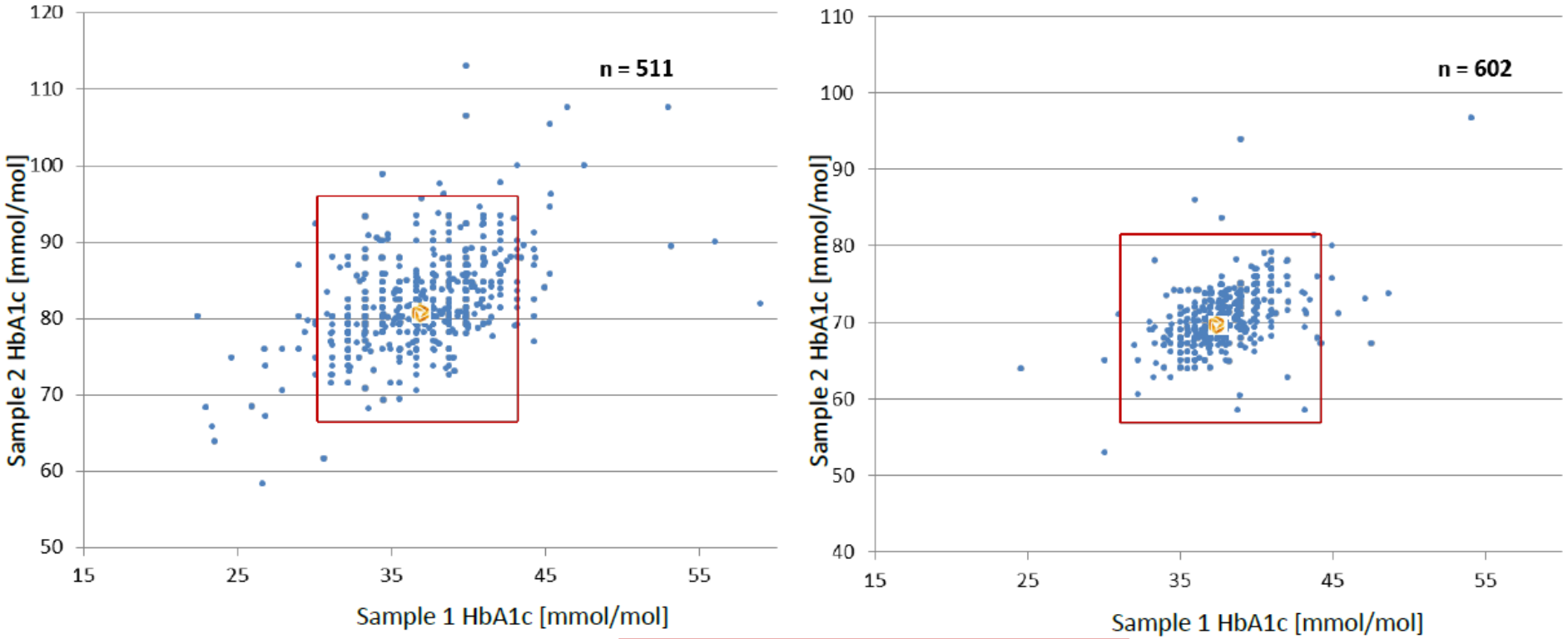
- **Consequences :**
  1. Standardization is compromised and/or a calibration bias is introduced
     → results are not standardized and/or inaccurate

  2a. Results comparability across different platforms cannot be evaluated

  → the effectiveness of standardization programs cannot be monitored

Current issues … and possible solutions

HbA1c EQAS results



acceptability range ± 18 % from target value

January 2009
lyophilized samples

INSTAND

May 2015
fresh blood samples

Commutability evaluation of EQA materials and of secondary CRMs is cumbersome

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  1. Standardization is compromised and/or a calibration bias is introduced
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  2a. Results comparability across different platforms cannot be evaluated

  → the effectiveness of standardization programs cannot be monitored
  → **EQA data cannot be aggregated (cf. HALMA project)**

Commutability evaluation of EQA materials and of secondary CRMs is cumbersome

- **Consequences :**
  1. Standardization is compromised and/or a calibration bias is introduced
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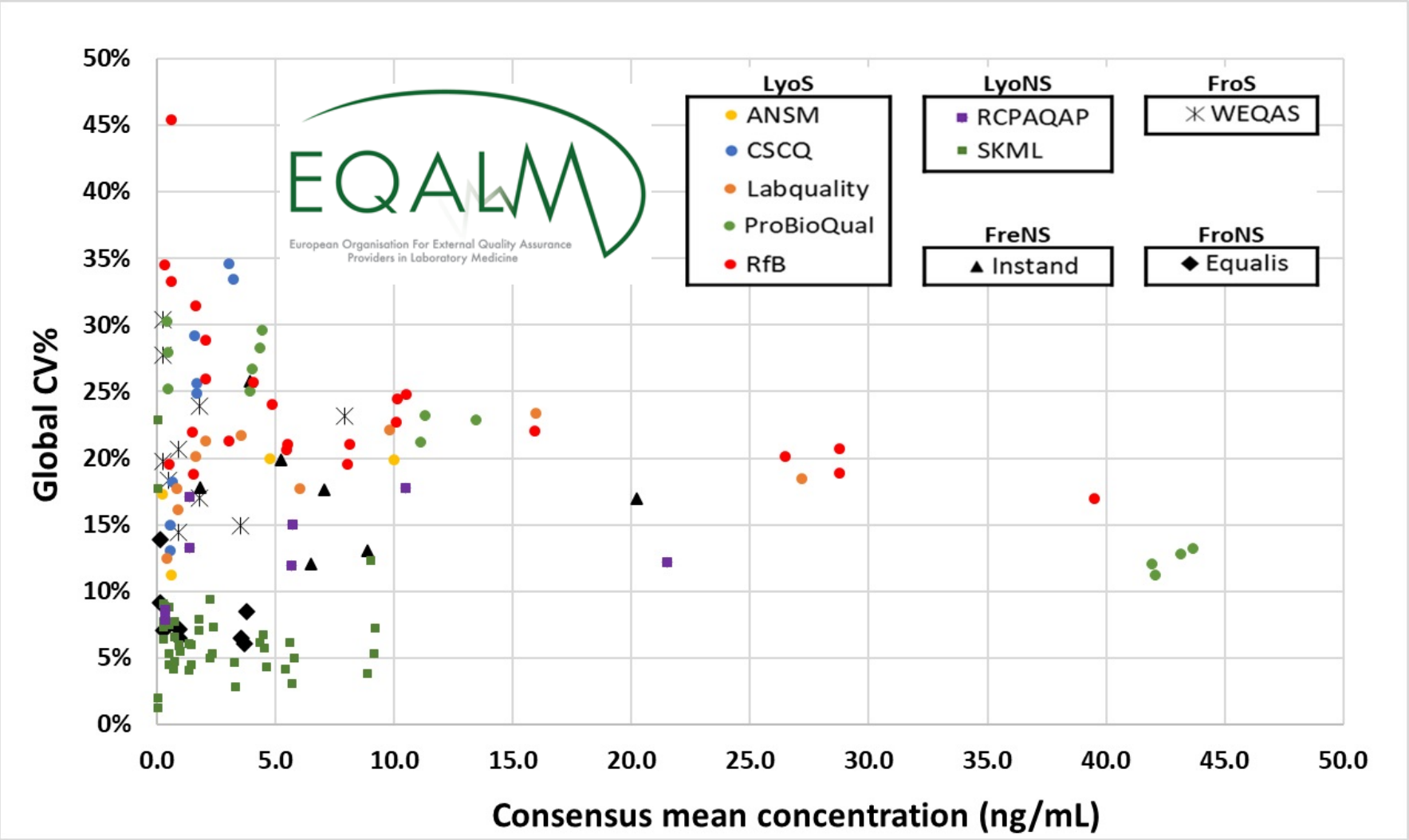
  2a. Results comparability across different platforms cannot be evaluated
     → the effectiveness of standardization programs cannot be monitored
     → EQA data cannot be aggregated (cf. HALMA project)
     → **the suitability of using common reference ranges cannot be evaluated**

Importance of commutability in EQA schemes

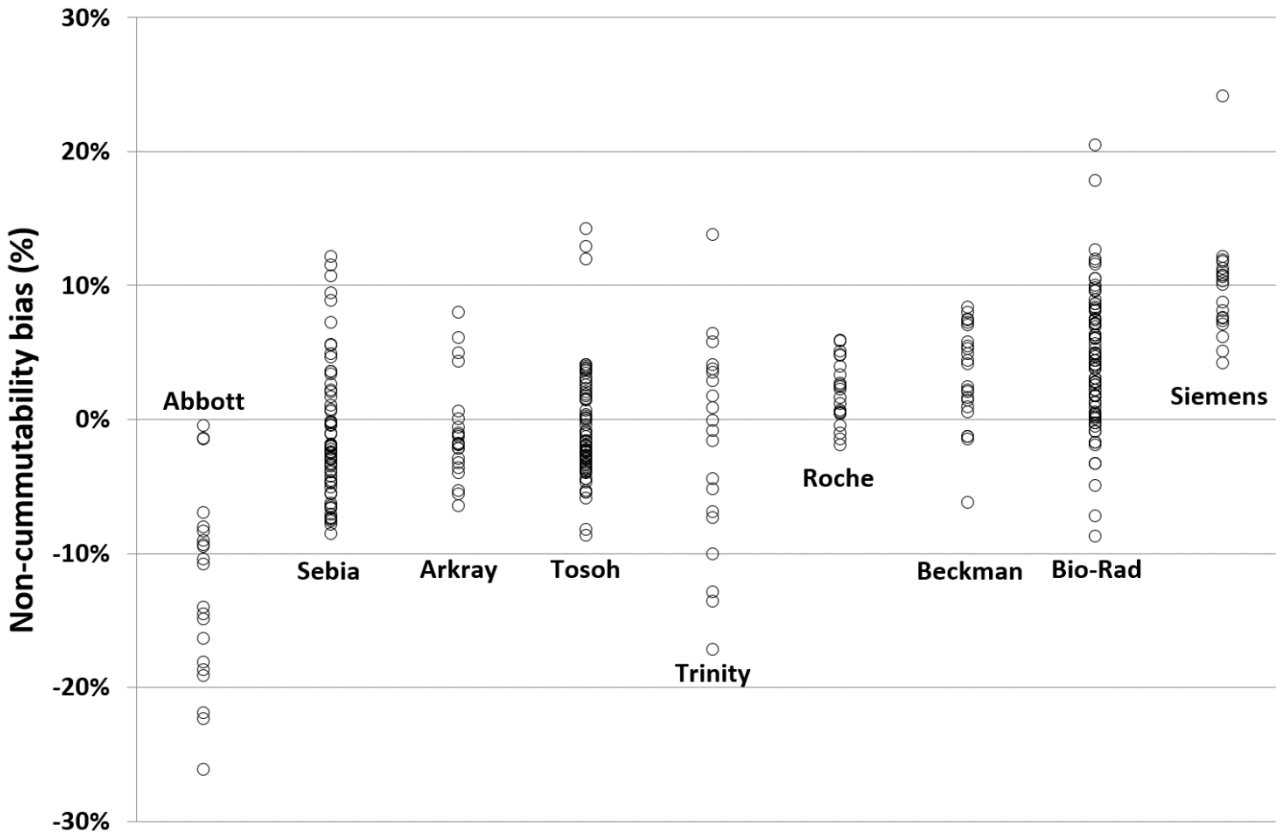


Huynh et al. Clin Chem Lab Med. 2021 Jun 21;59(10):1610-1622

Commutability evaluation of EQA materials and of secondary CRMs is cumbersome

- **Consequences :**
  1. Standardization is compromised and/or a calibration bias is introduced
     → results are not standardized and/or inaccurate
  2a. Results comparability across different platforms cannot be evaluated
     → the effectiveness of standardization programs cannot be monitored
     → EQA data cannot be aggregated (cf. HALMA project)
     → the suitability of using common reference ranges cannot be evaluated
  2b. Target values assigned to EQA materials are consensus means
     → results trueness cannot be evaluated

Current issues … and possible solutions



- An EQA material may be commutable for one method but not for others
- Some methods are more affected than others by matrix effects

Delatour et al. Clin Chem Lab Med. 2019;57(10):1623-1631.

Delatour et al. Clin Chem. 2020;66(2):390-391

Commutability evaluation of EQA materials and of secondary CRMs is cumbersome

- **Consequences :**
  1. Standardization is compromised and/or a calibration bias is introduced
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     → EQA data cannot be aggregated (cf. HALMA project)
     → the suitability of using common reference ranges cannot be evaluated
  2b. Target values assigned to EQA materials are consensus means
     → results trueness cannot be evaluated

- **Possible solutions:**
  1. **New IFCC recommendations on commutability**

IFCC recommendations on commutability

Clinical Chemistry

Clinical Chemistry 64:3
447–454 (2018)

Special Reports

IFCC Working Group Recommendations for Assessing Commutability Part 1: General Experimental Design

W. Greg Miller,[1*] Heinz Schimmel,[2] Robert Rej,[3] Neil Greenberg,[4] Ferruccio Ceriotti,[5] Chris Burns,[6] Jeffrey R. Budd,[7] Cas Weykamp,[8] Vincent Delatour,[9] Göran Nilsson,[10] Finlay MacKenzie,[11] Mauro Panteghini,[12] Thomas Keller,[13] Johanna E. Camara,[14] Ingrid Zegers,[2] and Hubert W. Vesper,[15] for the IFCC Working Group on Commutability

Clinical Chemistry 64:3
455–464 (2018)

Special Reports

IFCC Working Group Recommendations for Assessing Commutability Part 2: Using the Difference in Bias between a Reference Material and Clinical Samples

Göran Nilsson,[1] Jeffrey R. Budd,[2] Neil Greenberg,[3] Vincent Delatour,[4] Robert Rej,[5] Mauro Panteghini,[6] Ferruccio Ceriotti,[7] Heinz Schimmel,[8] Cas Weykamp,[9] Thomas Keller,[10] Johanna E. Camara,[11] Chris Burns,[12] Hubert W. Vesper,[13] Finlay MacKenzie,[14] and W. Greg Miller,[15*] for the IFCC Working Group on Commutability

Clinical Chemistry 64:3
465–474 (2018)

Special Reports

IFCC Working Group Recommendations for Assessing Commutability Part 3: Using the Calibration Effectiveness of a Reference Material

Jeffrey R. Budd,[1] Cas Weykamp,[2] Robert Rej,[3] Finlay MacKenzie,[4] Ferruccio Ceriotti,[5] Neil Greenberg,[6] Johanna E. Camara,[7] Heinz Schimmel,[8] Hubert W. Vesper,[9] Thomas Keller,[10] Vincent Delatour,[11] Mauro Panteghini,[12] Chris Burns,[13] and W. Greg Miller,[14*] for the IFCC Working Group on Commutability

Clinical Chemistry 0:0
1–10 (2020)

Special Reports

IFCC Working Group Recommendations for Correction of Bias Caused by Noncommutability of a Certified Reference Material Used in the Calibration Hierarchy of an End-User Measurement Procedure

W. Greg Miller,[a,*] Jeffrey Budd,[b] Neil Greenberg,[c] Cas Weykamp,[d] Harald Althaus,[e] Heinz Schimmel,[f] Mauro Panteghini,[g] Vincent Delatour,[h] Ferruccio Ceriotti,[i] Thomas Keller,[j] Douglas Hawkins,[k] Chris Burns,[l] Robert Rej,[m] Johanna E. Camara,[n] Finlay MacKenzie,[o] Eline van der Hagen,[d] Hubert Vesper,[p] for the IFCC Working Group on Commutability

IFCC recommendations on commutability

Clinical Chemistry 00:0
1–10 (2023)

Special Report

Recommendations for Setting a Criterion for Assessing Commutability of Secondary Calibrator Certified Reference Materials

W. Greg Miller,[a,*] Thomas Keller,[b] Jeffrey Budd,[c] Jesper V. Johansen,[d] Mauro Panteghini,[e] Neil Greenberg,[f] Vincent Delatour,[g] Ferruccio Ceriotti,[h] Liesbet Deprez,[i] Robert Rej,[j] Johanna E. Camara,[k] Finlay MacKenzie,[l] Alicia N. Lyle,[m] Eline van der Hagen,[n] Chris Burns,[o] Pernille Fauskanger,[p] and Sverre Sandberg,[p,q,r] for the IFCC Working Group on Commutability in Metrological Traceability

Clinical Chemistry 00:0
1–11 (2023)

Special Report

Recommendations for Setting a Criterion and Assessing Commutability of Sample Materials Used in External Quality Assessment/Proficiency Testing Schemes

Sverre Sandberg,[a,b,c,*] Pernille Fauskanger,[a] Jesper V. Johansen,[d] Thomas Keller,[e] Jeffrey Budd,[f] Neil Greenberg,[g] Robert Rej,[h] Mauro Panteghini,[i] Vincent Delatour,[j] Ferruccio Ceriotti,[k] Liesbet Deprez,[l] Johanna E. Camara,[m] Finlay MacKenzie,[n] Alicia N. Lyle,[o] Eline van der Hagen,[p] Chris Burns,[q] and W. Greg Miller;[r] for the IFCC Working Group on Commutability in Metrological Traceability

Importance of commutability in EQA schemes

DE GRUYTER

Clin Chem Lab Med 2022; aop

Opinion Paper

Graham R. D. Jones*, Vincent Delatour and Tony Badrick

Metrological traceability and clinical traceability of laboratory results – the role of commutability in External Quality Assurance

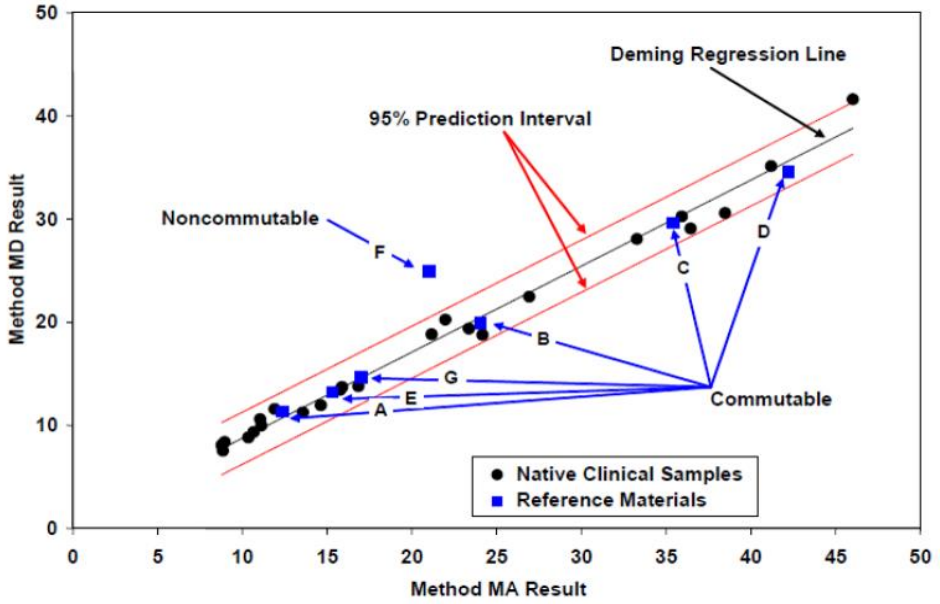
Clinical Chemistry 00:0
1–7 (2022)

Q&A

Interpreting EQA–Understanding Why Commutability of Materials Matters

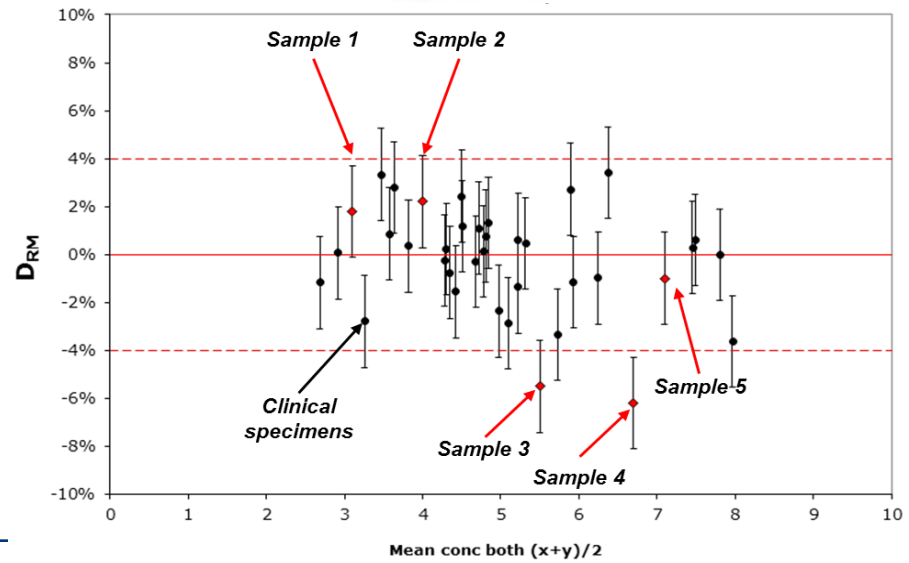
Moderator: Tony Badrick[i,*]
Experts: W. Greg Miller,[a] Mauro Panteghini,[b,c,d] Vincent Delatour,[e] Heidi Berghall,[f] Finlay MacKenzie,[g] and Graham Jones[h]

IFCC recommendations on commutability



Conventional approaches (CLSI C53A & EP14)

- Linear regressions
- 95% prediction intervals
- Uncertainties are neglected : the hypothesis of non-commutability is tested on the 50% level of significance!
- Acceptance criteria don't take the intended use into account



The difference in bias approach (IFCC WG-CMT)

- Difference plots
- Uncertainties are considered : some assessments will be inconclusive
- Acceptance criteria defined as function the intended use :

IQC < EQA < Trueness verifier < CRMs

Commutability evaluation of EQA materials and of secondary CRMs is cumbersome

- **Develop new approaches for making commutability evaluation easier**
  1. **simplified commutability studies involving a reduced number of patient samples and/or a comparison with a material whose commutability was successfully proven in a previous commutability study;**

Commutability in Metrological Traceability (WG-CMT)

ifcc International Federation of Clinical Chemistry and Laboratory Medicine

Current Projects

- How to specify acceptance criteria for commutability assessment.
- How to verify commutability for a new batch of a reference material.

Commutability evaluation of EQA materials and of secondary CRMs is cumbersome

- **Develop new approaches for making commutability evaluation easier**
  1. simplified commutability studies involving a reduced number of patient samples and/or a comparison with a material whose commutability was successfully proven in a previous commutability study;
  2. **multiparameter commutability studies in which commutability of a large number of CRMs and EQA materials will be evaluated simultaneously for a panel of measurands;**

LABAC
Réseau de Laboratoires de Biologie Médicale Accrédités

Multiparameter commutability studies

Glucose	CRM 1	CRM 2	CRM 3	CRM 4	CRM 5	CRM 6	CRM 7	CRM 8	EQA F1	EQA F2	EQA F3	EQA F4	EQA F5	EQA F6	EQA L1	EQA L2	EQA L3	EQA L4	EQA L5	EQA L6	EQA L7	EQA L8	EQA L9	EQA L10	EQA L11	EQA L12	EQA L13	EQA L14	EQA L15	EQA L16
Siemens Vista	C	C	C	C	C	C	C	C	C	C	NC	C	C	C	C	NC	C	NC	NC	I	I	I	NC	C	I	C	NC	C	C	C
Roche Cobas	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C
Beckman DxC	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	I	I	C	C	C	C	C	C	C	C	C
Ortho CD Vitros	I	I	C	I	NC	I	NC	NC	C	C	C	NC	NC	NC	C	NC	C	NC	NC	NC	NC	I	NC	NC	NC	NC	C	C	C	C
Abbott Architect	C	C	NC	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C
Siemens Advia	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	I	C	C	C	C	C	C	C	C	C
Beckman AU	C	C	C	C	C	C	C	C	NA	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C
Siemens EXL	C	C	C	C	C	C	C	C	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA

Creatinine	CRM 1	CRM 2	CRM 3	CRM 4	CRM 5	CRM 6	CRM 7	CRM 8	EQA F1	EQA F2	EQA F3	EQA F4	EQA F5	EQA F6	EQA L1	EQA L2	EQA L3	EQA L4	EQA L5	EQA L6	EQA L7	EQA L8	EQA L9	EQA L10	EQA L11	EQA L12	EQA L13	EQA L14	EQA L15	EQA L16
Siemens Vista	C	C	C	I	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	NC	C	C	C	C	C	C	C	C	I	I
Roche Cobas	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	NC	C	C	C	C	C	C	C	C	C	C
Beckman DxC	C	I	I	C	C	C	C	C	I	C	C	I	C	I	NC	C	C	C	C	NC	I	C	C	C	I	NC	NC	C	C	C
Ortho CD Vitros	C	I	C	C	I	C	NC	I	C	NC	C	NC	C	I	C	C	NC	C	C	NC	NC	C	NC	NC	NC	NC	NC	C	C	C
Abbott Architect	C	C	NC	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	NC	C	C	C	C	C	C	C	C	C	C
Siemens Advia	C	C	C	C	C	C	C	C	C	I	C	C	C	C	C	C	C	C	C	NC	C	C	C	C	C	NC	C	C	C	C
Beckman AU	C	C	NC	C	C	C	C	C	NA	C	C	I	C	C	C	C	C	C	C	NC	C	C	C	C	C	C	C	C	C	C
Siemens EXL	C	C	C	C	C	C	C	C	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA

Uric acid	CRM 1	CRM 2	CRM 3	CRM 4	CRM 5	CRM 6	CRM 7	CRM 8	EQA F1	EQA F2	EQA F3	EQA F4	EQA F5	EQA F6	EQA L1	EQA L2	EQA L3	EQA L4	EQA L5	EQA L6	EQA L7	EQA L8	EQA L9	EQA L10	EQA L11	EQA L12	EQA L13	EQA L14	EQA L15	EQA L16
Siemens Vista	C	C	C	NC	I	C	NC	NC	C	NC	NC	NC	I	NC	C	NC	NC	NC	NC	NC	NC	NC	NC	NC	NC	NC	NC	NC	NC	NC
Roche Cobas	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	NC	C	C	C	C	C	C	C	C	C	C
Beckman DxC	C	NA	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	NC	C	NC	C	I	C	C	NC	NC	NC	C	C	I
Ortho CD Vitros	C	C	C	C	C	C	C	C	C	C	C	NC	C	C	C	C	C	C	C	NC	I	C	NC	C	NC	I	C	C	C	C
Abbott Architect	C	C	NC	I	C	C	C	C	C	C	C	C	C	C	NC	C	C	C	C	NC	C	C	C	C	C	C	C	C	C	C
Siemens Advia	C	C	I	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	NC	C	C	C	C	C	C	C	C	C	C
Beckman AU	C	C	C	C	C	C	C	C	NA	C	C	NC	I	C	C	C	C	C	C	NA	I	C	C	C	C	C	C	C	C	C
Siemens EXL	C	C	C	NC	C	C	I	I	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA

Urea	CRM 1	CRM 2	CRM 3	CRM 4	CRM 5	CRM 6	CRM 7	CRM 8	EQA F1	EQA F2	EQA F3	EQA F4	EQA F5	EQA F6	EQA L1	EQA L2	EQA L3	EQA L4	EQA L5	EQA L6	EQA L7	EQA L8	EQA L9	EQA L10	EQA L11	EQA L12	EQA L13	EQA L14	EQA L15	EQA L16
Siemens Vista	I	C	C	C	I	C	C	I	C	C	C	C	C	C	C	C	C	C	C	NC	C	C	C	C	C	C	C	C	C	C
Roche Cobas	C	C	C	C	I	C	C	C	C	C	C	C	C	C	C	C	C	C	C	NC	C	C	C	C	C	C	C	C	C	C
Beckman DxC	C	C	C	C	I	C	C	C	C	C	C	I	I	I	I	NC	I	C	C	NC	C	C	NC	C	C	C	C	C	I	C
Ortho CD Vitros	I	C	C	I	C	I	I	I	C	NC	NC	C	NC	NC	NC	NC	NC	NC	NC	NA	C	C	NC	NC	NC	NC	NC	NC	NC	NC
Abbott Architect	C	C	I	C	C	C	C	C	C	NC	C	C	C	C	C	C	I	C	C	NC	C	C	C	C	C	C	C	C	C	C
Siemens Advia	C	I	C	I	C	I	I	I	C	C	C	C	C	C	C	C	C	C	I	NC	C	C	C	C	C	C	I	I	C	I
Beckman AU	C	C	C	C	I	C	C	C	C	C	C	C	C	C	C	C	C	C	C	NC	C	C	C	C	C	C	C	C	C	C
Siemens EXL	C	C	C	C	C	C	C	C	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA

Multiparameter commutability studies

Total Cholesterol	CRM 1	CRM 2	CRM 3	CRM 4	CRM 5	CRM 6	CRM 7	CRM 8	EQA F1	EQA F2	EQA F3	EQA F4	EQA F5	EQA F6	EQA L1	EQA L2	EQA L3	EQA L4	EQA L5	EQA L6	EQA L7	EQA L8	EQA L9	EQA L10	EQA L11	EQA L12	EQA L13	EQA L14	EQA L15	EQA L16
Siemens Vista	C	C	C	C	C	C	C	C	C	C	C	C	C	C	I	I	I	NC	C	NC	NC	I	C	NC	NC	NC	NC	C	NC	NC
Roche Cobas	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C
Beckman DxC	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	I	C	C	C	C	I	C	C	NC	NC	C	NC	C	NC	NC
Ortho CD Vitros	C	C	C	C	C	NC	I	C	C	NA	C	C	C	C	C	C	NC	NC	C	NA	I	C	I	NC	C	C	NC	C	C	C
Abbott Architect	C	C	NC	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C
Siemens Advia	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	NC	C	C	C	C
Beckman AU	C	C	C	C	C	C	C	C	NA	C	C	C	C	C	C	C	C	C	C	NC	C	C	C	C	C	C	C	C	C	C
Siemens EXL	C	C	I	C	C	C	C	C	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA

Triglycerides	CRM 1	CRM 2	CRM 3	CRM 4	CRM 5	CRM 6	CRM 7	CRM 8	EQA F1	EQA F2	EQA F3	EQA F4	EQA F5	EQA F6	EQA L1	EQA L2	EQA L3	EQA L4	EQA L5	EQA L6	EQA L7	EQA L8	EQA L9	EQA L10	EQA L11	EQA L12	EQA L13	EQA L14	EQA L15	EQA L16
Siemens Vista	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C
Roche Cobas	C	C	C	C	C	C	C	C	NC	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C
Beckman DxC	I	I	C	C	C	C	NC	I	C	C	C	C	NA	NA	NA	NA	NA	C	C	I	NC	NC	C	C	I	I	I	C	NC	NC
Ortho CD Vitros	C	C	C	C	I	C	C	C	NC	NC	C	NC	C	NC	I	C	NC	NC	C	NC	NC	C	NC	NC	C	C	NC	NC	NC	NC
Abbott Architect	C	C	NC	C	C	C	C	C	C	C	C	C	C	C	C	C	I	C	C	C	C	C	C	C	C	C	C	C	C	C
Siemens Advia	C	C	C	I	C	C	C	I	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C
Beckman AU	C	C	C	C	C	C	C	C	NA	C	C	C	C	C	I	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C
Siemens EXL	C	C	I	I	C	I	I	C	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA

LDLc	CRM 1	CRM 2	CRM 3	CRM 4	CRM 5	CRM 6	CRM 7	CRM 8	EQA F1	EQA F2	EQA F3	EQA F4	EQA F5	EQA F6	EQA L1	EQA L2	EQA L3	EQA L4	EQA L5	EQA L6	EQA L7	EQA L8	EQA L9	EQA L10	EQA L11	EQA L12	EQA L13	EQA L14	EQA L15	EQA L16
Siemens Vista	C	C	C	C	C	C	C	C	C	C	C	C	I	C	NC	C	NC	NC	NC	C	C	C	C	C	I	C	C	I	C	C
Roche Cobas	C	C	C	C	C	C	C	C	I	C	I	I	NC	C	NC	NC	NC	NC	NC	C	I	I	I	I	I	I	C	I	C	C
Beckman DxC	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Ortho CD Vitros	C	C	C	C	C	C	C	C	I	C	C	C	NC	C	NA	C	NC	NC	NC	NC	C	C	C	C	I	C	C	I	C	C
Abbott Architect	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Siemens Advia	C	C	C	C	C	C	C	C	C	C	C	C	I	C	NC	C	NC	NC	NC	NC	C	C	C	C	I	C	C	I	C	C
Beckman AU	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Siemens EXL	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA

HDLc	CRM 1	CRM 2	CRM 3	CRM 4	CRM 5	CRM 6	CRM 7	CRM 8	EQA F1	EQA F2	EQA F3	EQA F4	EQA F5	EQA F6	EQA L1	EQA L2	EQA L3	EQA L4	EQA L5	EQA L6	EQA L7	EQA L8	EQA L9	EQA L10	EQA L11	EQA L12	EQA L13	EQA L14	EQA L15	EQA L16
Siemens Vista	C	I	NC	C	C	C	C	NC	C	NC	NC	NC	I	NC	C	I	NC	I	NC	NC	I	NC	NC	C	NC	C	NC	NC	NC	NC
Roche Cobas	C	C	C	C	C	C	C	C	NC	NC	NC	NC	NC	NC	C	NC	NC	NC	NC	NC	I	NC	NC	C	NC	C	NC	NC	NC	NC
Beckman DxC	C	C	NC	NC	C	C	C	I	I	NC	NC	NC	NC	NC	C	NC	NC	C	I	NC	NC	NC	NC	I	NC	C	NC	NC	NC	NC
Ortho CD Vitros	C	C	I	C	NC	C	NC	NC	NC	C	NC	NC	I	NC	C	I	NC	I	NC	NC	I	NC	NC	C	NC	C	NC	NC	NC	NC
Abbott Architect	C	C	C	NC	C	C	I	NC	I	NC	NC	NC	NC	NC	C	NC	NC	C	NC	NC	NC	NC	NC	NC	NC	NC	NC	NC	NC	NC
Siemens Advia	C	C	C	I	C	C	NC	C	I	I	NC	NC	I	NC	NC	I	NC	NC	NC	NC	I	NC	NC	NC	NC	NC	NC	NC	NC	NC
Beckman AU	C	C	C	I	C	C	C	C	NA	I	NC	NC	I	NC	C	I	NC	C	I	NC	NC	NC	NC	C	NC	C	NC	NC	NC	NC
Siemens EXL	C	C	C	C	C	C	C	C	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA

Multiparameter commutability studies

Na	CRM 1	CRM 2	CRM 3	CRM 4	CRM 5	CRM 6	CRM 7	CRM 8	EQA F1	EQA F2	EQA F3	EQA F4	EQA F5	EQA F6	EQA L1	EQA L2	EQA L3	EQA L4	EQA L5	EQA L6	EQA L7	EQA L8	EQA L9	EQA L10	EQA L11	EQA L12	EQA L13	EQA L14	EQA L15	EQA L16
Siemens Vista	C	C	C	C	NC	C	NC	C	C	NC	C	C	I	C	C	C	C	C	I	NC	C	C	C	C	C	C	C	C	I	C
Roche Cobas	C	C	C	C	I	C	I	C	C	C	C	C	I	C	C	C	C	C	I	NC	C	C	C	C	C	C	C	C	C	C
Beckman DxC	I	C	C	C	I	C	I	C	C	C	C	C	C	C	C	C	C	C	I	NC	C	C	C	C	C	C	C	C	C	C
Ortho CD Vitros	C	I	NC	I	NC	C	NC	I	C	NC	C	I	C	NC	C	C	I	NC	I	NC	NC	I	NC	I	C	NC	I	I	I	I
Abbott Architect	C	C	C	C	I	C	C	C	C	C	C	I	C	C	C	C	C	C	I	NC	I	C	C	C	C	C	C	C	C	C
Siemens Advia	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	NC	C	C	C	C	C	C	C	C	C	C
Beckman AU	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	NC	C	C	C	C	C	C	C	C	C	C
Siemens EXL	NA	NA	C	C	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA

Cl	CRM 1	CRM 2	CRM 3	CRM 4	CRM 5	CRM 6	CRM 7	CRM 8	EQA F1	EQA F2	EQA F3	EQA F4	EQA F5	EQA F6	EQA L1	EQA L2	EQA L3	EQA L4	EQA L5	EQA L6	EQA L7	EQA L8	EQA L9	EQA L10	EQA L11	EQA L12	EQA L13	EQA L14	EQA L15	EQA L16
Siemens Vista	C	C	C	C	C	C	C	C	C	C	C	C	C	NC	C	C	C	C	C	NC	C	C	C	C	C	C	C	C	C	C
Roche Cobas	C	C	C	C	C	C	C	C	C	C	I	C	C	C	C	C	C	C	C	NC	I	I	I	C	C	C	C	I	I	C
Beckman DxC	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	I	C	C	NC	C	C	C	C	C	C	C	C	C	C
Ortho CD Vitros	I	I	NC	NC	NC	NC	NC	I	C	C	C	NC	I	I	C	I	NC	NC	NC	NC	I	I	NC	NC	C	C	C	C	C	C
Abbott Architect	C	C	C	C	I	C	C	C	C	C	C	C	C	C	C	C	C	C	C	NC	C	C	C	C	C	C	I	I	C	C
Siemens Advia	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	NC	C	C	C	C	C	C	I	NC	NC	NC
Beckman AU	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	NC	C	C	C	C	C	C	C	C	C	C
Siemens EXL	NA	NA	C	C	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA

K	CRM 1	CRM 2	CRM 3	CRM 4	CRM 5	CRM 6	CRM 7	CRM 8	EQA F1	EQA F2	EQA F3	EQA F4	EQA F5	EQA F6	EQA L1	EQA L2	EQA L3	EQA L4	EQA L5	EQA L6	EQA L7	EQA L8	EQA L9	EQA L10	EQA L11	EQA L12	EQA L13	EQA L14	EQA L15	EQA L16
Siemens Vista	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	NC	NC	C	C	C	C	C	C	C	C	C
Roche Cobas	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	NC	C	C	C	C	C	C	C	C	C	C
Beckman DxC	C	C	C	C	C	C	C	C	NC	C	C	C	C	C	C	C	NC	C	C	NC	NC	C	NC	C	C	C	C	C	C	C
Ortho CD Vitros	C	I	I	I	I	I	NC	I	C	C	C	NC	C	C	C	C	C	NC	C	NC	NC	NC	NC	NC	C	NC	NC	I	C	C
Abbott Architect	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	NC	C	C	C	C	C	C	C	C	C	C
Siemens Advia	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	NC	I	C	C	C	C	C	C	C	C	C
Beckman AU	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	NC	I	C	C	C	C	C	C	C	C	C
Siemens EXL	NA	NA	C	C	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA

Ca	CRM 1	CRM 2	CRM 3	CRM 4	CRM 5	CRM 6	CRM 7	CRM 8	EQA F1	EQA F2	EQA F3	EQA F4	EQA F5	EQA F6	EQA L1	EQA L2	EQA L3	EQA L4	EQA L5	EQA L6	EQA L7	EQA L8	EQA L9	EQA L10	EQA L11	EQA L12	EQA L13	EQA L14	EQA L15	EQA L16
Siemens Vista	C	C	I	C	C	C	C	C	C	C	C	C	C	I	I	I	I	C	I	I	C	C	C	C	C	C	C	C	NC	I
Roche Cobas	C	C	C	C	C	I	C	C	C	I	C	C	C	C	I	I	C	C	I	I	C	C	C	C	C	C	I	I	I	C
Beckman DxC	I	C	NC	I	I	C	I	I	C	I	C	C	I	C	C	I	I	C	I	I	C	C	C	C	C	C	I	C	C	C
Ortho CD Vitros	C	NC	NC	NC	NC	NC	NC	NC	C	NC	NC	NC	I	I	NC	NC	NC	NC	NC	NC	C	NC	NC	NC	I	NC	NC	C	C	C
Abbott Architect	C	C	C	C	C	C	C	C	C	I	C	C	C	C	C	C	C	C	I	I	C	C	C	C	C	C	C	C	C	C
Siemens Advia	C	C	C	C	C	I	C	I	I	I	C	C	C	C	C	I	I	I	I	I	C	C	C	I	I	C	C	C	C	C
Beckman AU	C	C	C	C	C	C	C	C	C	C	C	I	C	C	C	C	C	I	NC	NC	C	I	C	C	C	C	C	I	C	C
Siemens EXL	NA	NA	C	C	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA

Commutability evaluation of EQA materials and of secondary CRMs is cumbersome

- **Develop new approaches for making commutability evaluation easier**
  1. simplified commutability studies involving a reduced number of patient samples and/or a comparison with a material whose commutability was successfully proven in a previous commutability study;
  2. multiparameter commutability studies in which commutability of a large number of CRMs and EQA materials are evaluated simultaneously for a panel of measurands;
  3. **use of commutability panels consisting of frozen pools which commutability was qualified against a panel of fresh clinical specimens in a first study;**

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  4. **Use of high-throughput RMPs;**

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  3. use of commutability panels consisting of frozen pools which commutability was qualified against a panel of fresh clinical specimens in a first study;
  4. Use of high-throughput RMPs;
  5. **Automated data analysis**

Commutability evaluation of EQA materials and of secondary CRMs is cumbersome

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  2. multiparameter commutability studies in which commutability of a large number of CRMs and EQA materials will be evaluated simultaneously for a panel of measurands;
  3. use of commutability panels consisting of frozen pools which commutability was qualified against a panel of fresh clinical specimens in a first study;
  4. Use of high-throughput RMPs;
  5. Development of automated data analysis
  6. **Invite EQA providers join commutability studies organized by RM producers**

Commutability evaluation of EQA materials and of secondary CRMs is cumbersome

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  1. simplified commutability studies involving a reduced number of patient samples and/or a comparison with a material whose commutability was successfully proven in a previous commutability study;
  2. multiparameter commutability studies in which commutability of a large number of CRMs and EQA materials will be evaluated simultaneously for a panel of measurands;
  3. use of commutability panels consisting of frozen pools which commutability was qualified against a panel of fresh clinical specimens in a first study;
  4. Use of high-throughput RMPs;
  5. Development of automated data analysis
  6. Invite EQA providers join commutability studies organized by RM producers
  7. **Mutualize the resources and capabilities of a coordinated network of reference laboratories that will share the work to jointly assign reference method target values to all study materials;**

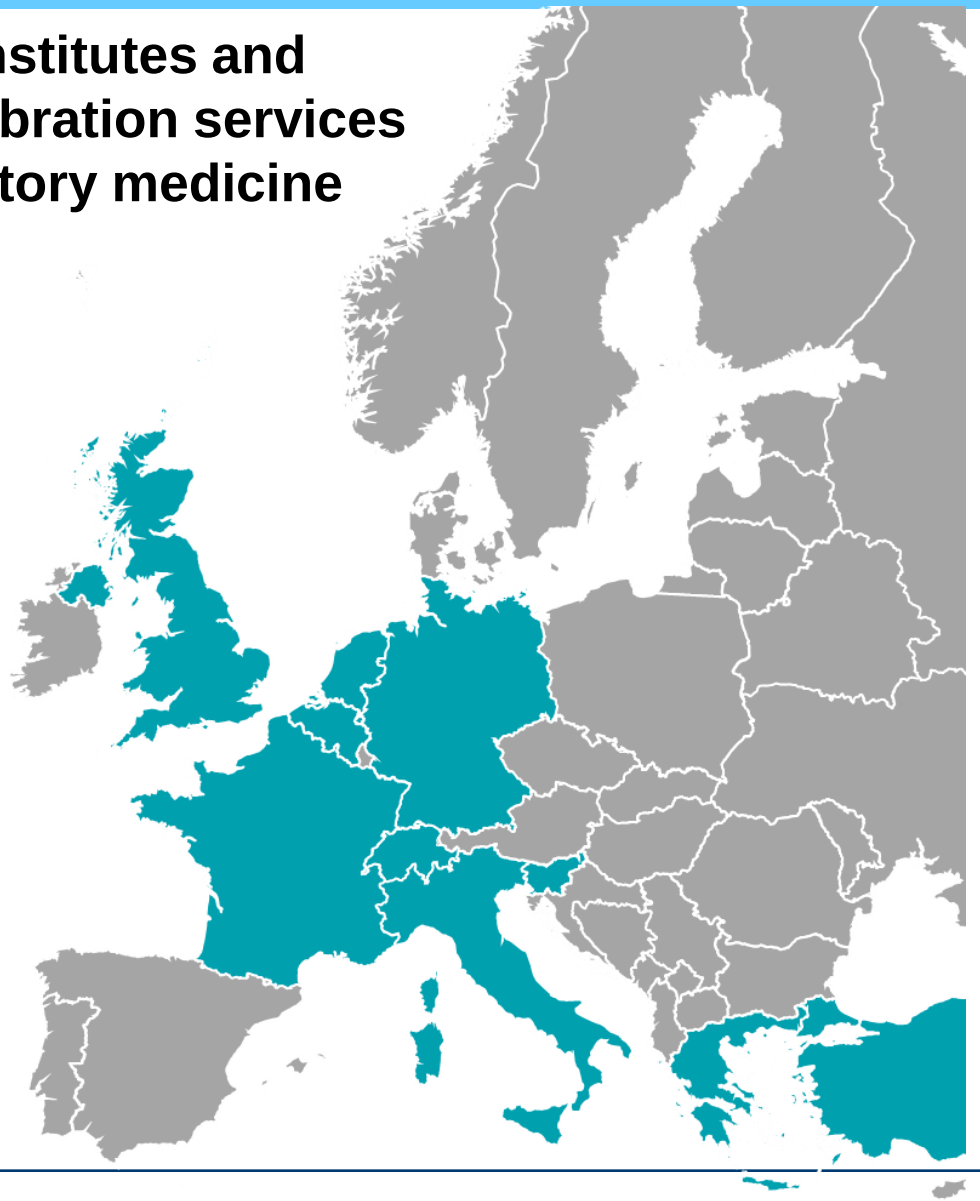
European Metrology Network TraceLabMed

Network of National Metrology Institutes and reference laboratories providing calibration services and reference standards in laboratory medicine

TRACE LAB MED

In 2023:

13 NMIs/DIs &
4 Partners from
10 Countries



European Metrology Network TraceLabMed

✓ A stakeholder consultation is being conducted to establish a priority list of biomarkers for which reference methods and materials are needed

... and design R&D roadmaps of NMIs to avoid duplication of efforts

→ consultation of :
- Standardization organizations : IFCC, ICHCLR, etc...
- Assay manufacturers
- Health authorities,
- Clinicians, biologists, medical associations
- EQA providers

TRACE LAB MED

✓ Online Survey "*Metrological Traceability in EQA schemes*" distributed to all EQALM members : 29 / 39 answered

✓ Results will be presented in a workshop to be held by end 2023

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When to evaluate commutability?

Should commutability of all quality control materials always be evaluated?

- Too costly
- Too labor intensive
- Not always needed

❖ **Commutability of EQA materials matters only if the goal is to assess:**

- Results accuracy against a reference method **(assays trueness)**
- How the different assays agree with each other **(results comparability)**

If commutability of an EQA material is unknown or insufficient, results of a given laboratory can only be compared with results from other laboratories from the same peer group

❖ **Evaluating commutability of IQC materials may be of interest :**

- in the case of **externalized IQC** where results from different peer groups are compared (which is somehow equivalent to an EQAS)
- when IQCs are used to evaluate assays **precison** and non-commutability affects results precision

IFCC International Federation of Clinical Chemistry and Laboratory Medicine

JCTLM Accurate results for patient care

International Consortium for Harmonization of Clinical Laboratory Results

Barriers to global standardization of clinical laboratory testing: reference materials and regulations

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

Barriers to global standardization of clinical laboratory testing: reference materials and regulations

- **NMIs should develop Reference Measurement Systems for measurands for which there is an actual need for standardization**

- New biomarkers do not always lead to a clinically usable product
- IVD producers generally develop internal standardization as part of the initial product development. They then need to deal with the challenge of “retrofitting” existing calibration hierarchies to subsequently developed higher-order RMS.
- IVD manufacturers are often reluctant to recalibrate their assays because of the need to fully justify the time and cost of submitting for new regulatory review

→ NMIs should identify needs at early stages of new IVD-MD development
→ Need for NMIs to gain in efficiency, e.g. through better coordination

How to improve the contribution of metrology institutes to medical laboratory standardization ?

- **Focus on measurands in (real) need for standardization :**
  → improve interactions with the IVD industry to identify needs, ideally at the early stages of the development of new products
  → consult the ICHCLR, IFCC, JCTLM
- **Collaborate with clinicians and IVD manufacturers to properly define the measurand to decide what impurities should be quantified**
- **Improve measurement capabilities to identify and accurately quantify all relevant impurities with appropriate measurement uncertainty**
- **Develop CRMs & RMPs with appropriate APS to meet the medical need**
- **Improve the level of coordination and cooperation between NMIs so as to share the work and prevent duplication of efforts : work in networks!**