

Traceability in Laboratory Medicine: What Every Laboratory Specialist Should Know

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Outline

- Why we need comparable results
- How to achieve comparable results traceable to a reference system
- Global challenges to traceability
- Traceability resources

Primary reasons for testing

- To identify individuals at increased risk of disease and/or monitor disease management
- To develop epidemiologic data from which to establish public health strategies for disease management on a population level

Good laboratory medicine requires:

- Total error of a measurement result is small enough to reflect a patient's true biological condition
- Test results are traceable (**equivalent**) and independent of
 - ❖ where and when a test was performed
 - ❖ the measurement procedure used

In the context of laboratory medicine,
“traceability” really means

Metrological Traceability

What is **Metrological Traceability**?

- Definition from the International vocabulary of

Referred to as the
Metrological Traceability Chain

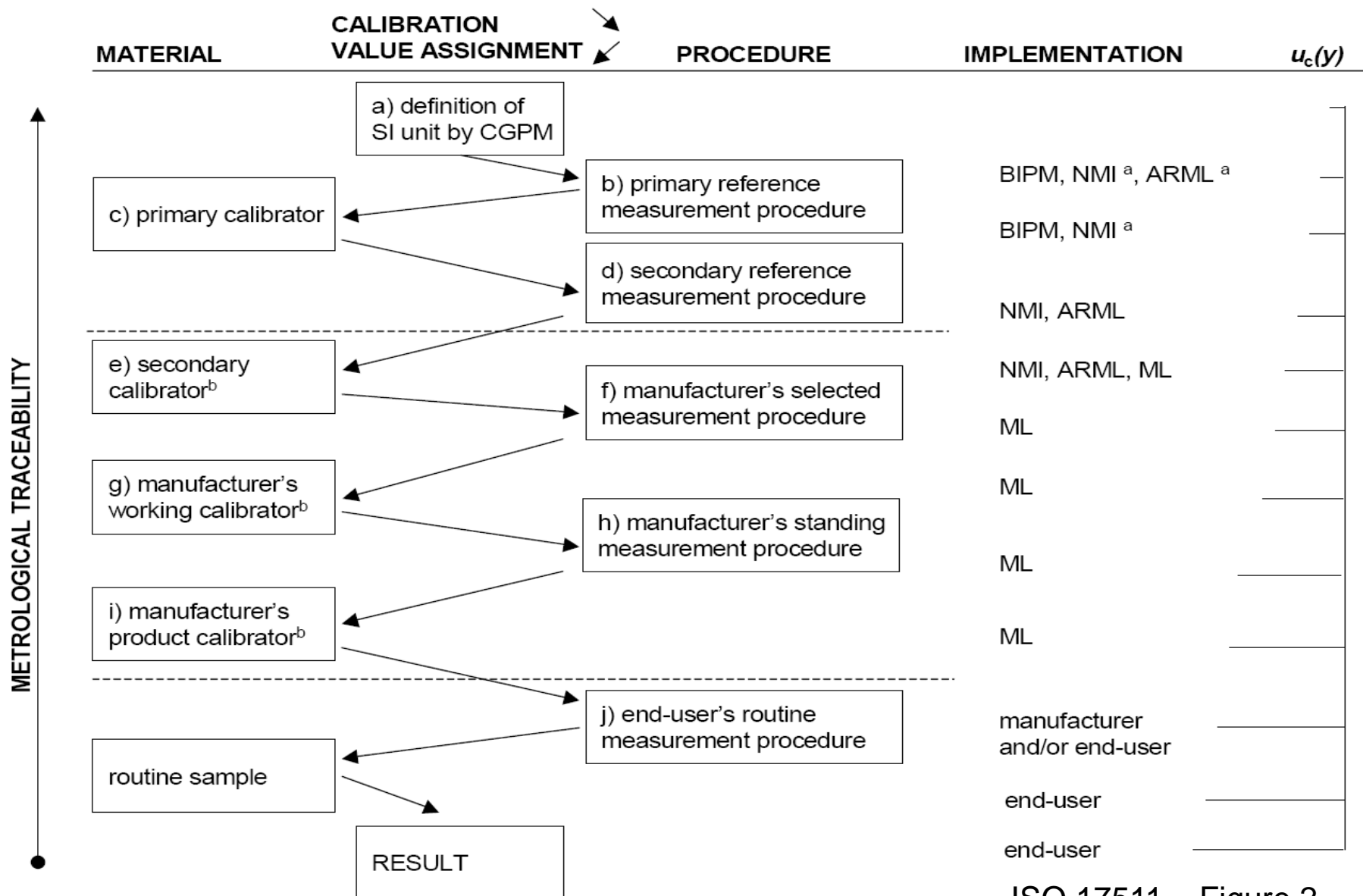
related to reference through a documented
unbroken chain of calibrations, each
contributing to the measurement uncertainty

Traceability of Laboratory Results

The concept of traceability is based on principles described in *ISO Standard 17511*.

In vitro diagnostic medical devices -
Measurement of quantities in biological
samples - **Metrological traceability of
values assigned to calibrators and
control materials**

Traceability to Système International



Three Separate Measurement Components that Require Traceability

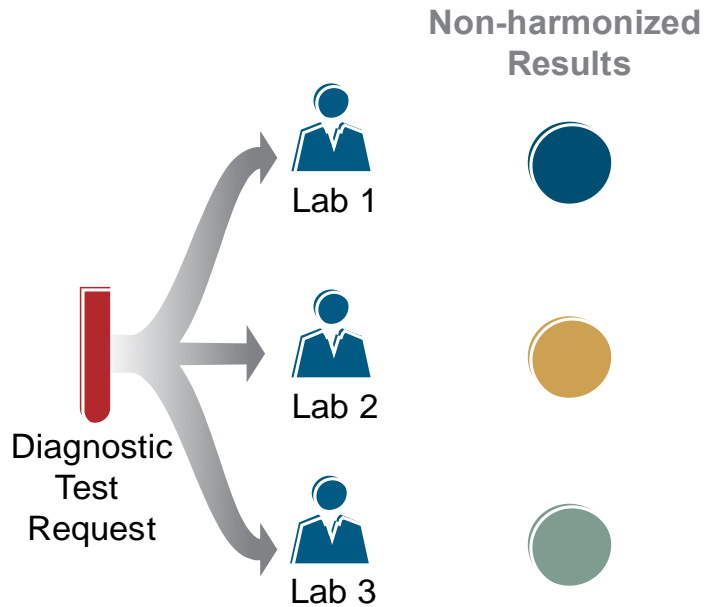
- Research Laboratories that support investigational studies
- Manufacturers that develop and provide routine clinical assays
- Clinical laboratories that provide test results for assessing risk and monitoring therapy

When and Why Is Traceability Most Important?

- To insure the reliability and comparability of research findings across studies
- When patients are seen in a variety of health care settings, each using different clinical labs
- When patient's test results are being compared to clinical guidelines from the medical literature and/or large national or international research studies (e.g., estimated GFR for CKD, HbA1c for diabetes, cholesterol for CVD, etc.).

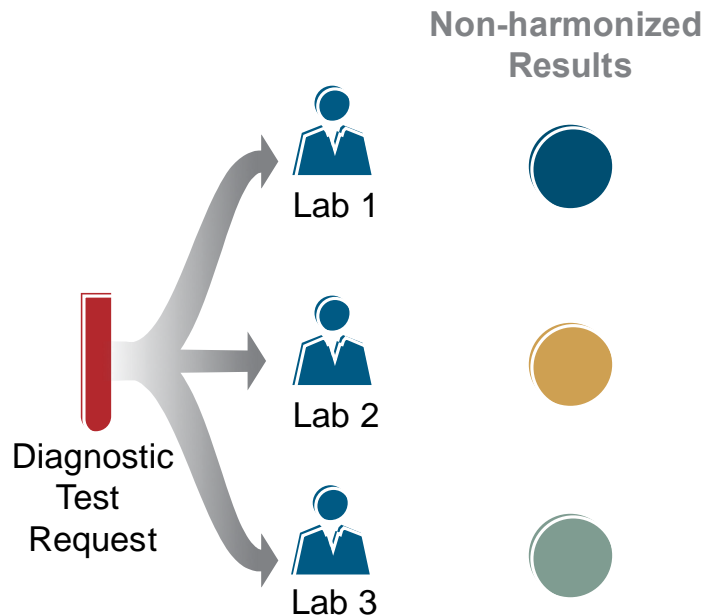
Test results that are not traceable (**equivalent**) are considered non-harmonized

Non-harmonized laboratory testing



Why does it matter?

Non-harmonized laboratory testing

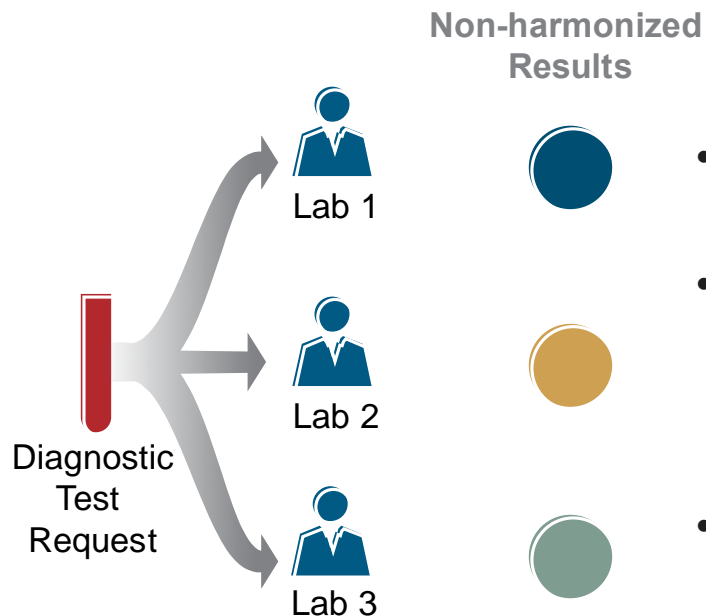


Why does it matter for patients ?

- Creates difficulty in comparing results from different providers
- Makes it confusing to investigate the medical implications of test results
- May result in incorrect treatment
- May lead to unnecessary retesting and possible unnecessary visits to healthcare provider

Why does it matter?

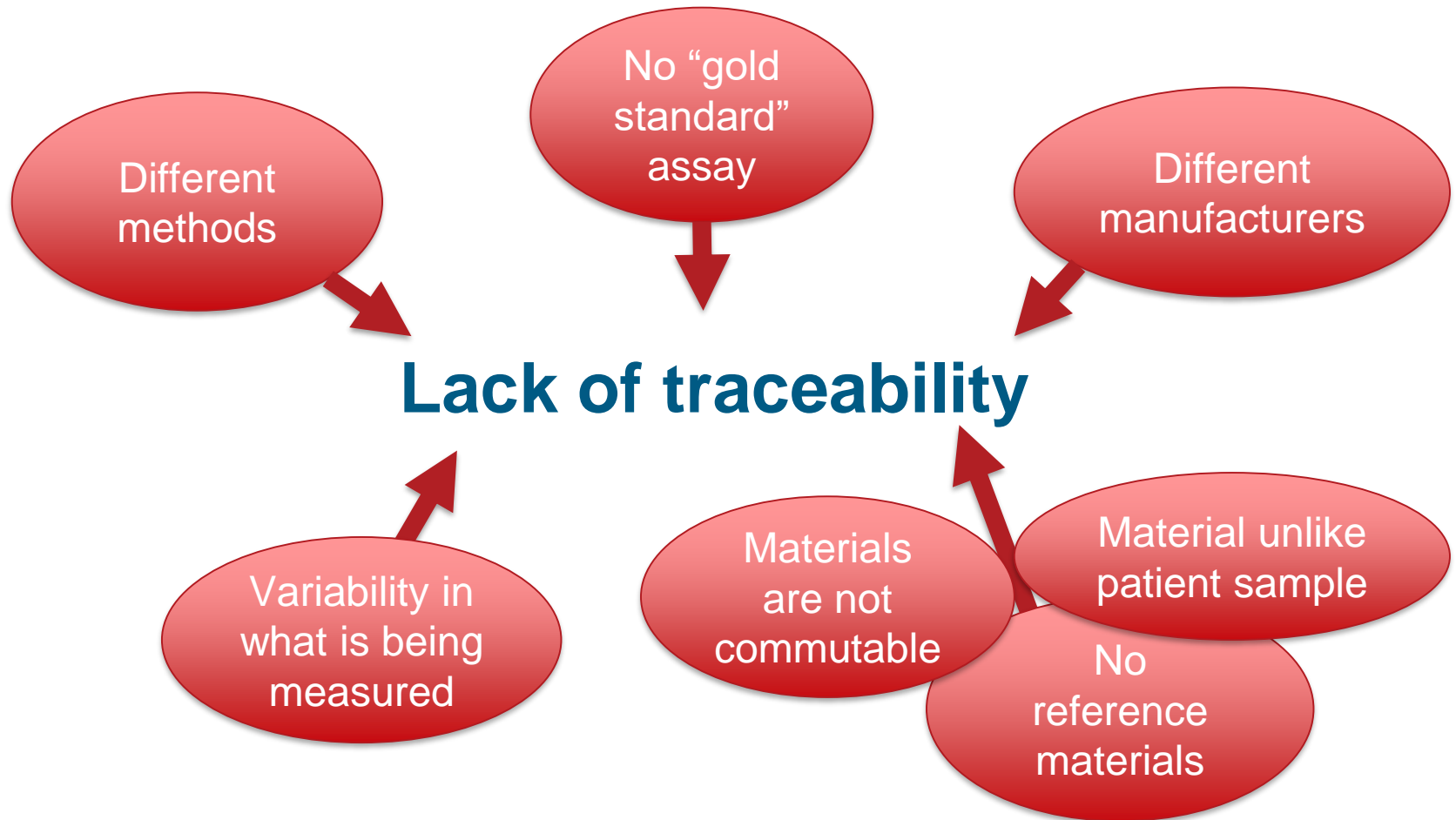
Non-harmonized laboratory testing



Why does it matter for the Healthcare System?

- Problems for the portable medical record
- Outcomes-based reimbursement
 - If we can't compare lab values, how can we tell who is doing a good job with their patients?
- Makes it more difficult to assess health trends
- Complicates longitudinal testing
- Inhibits the development of accurate national/international guidelines for treating patients

Challenges for achieving traceability

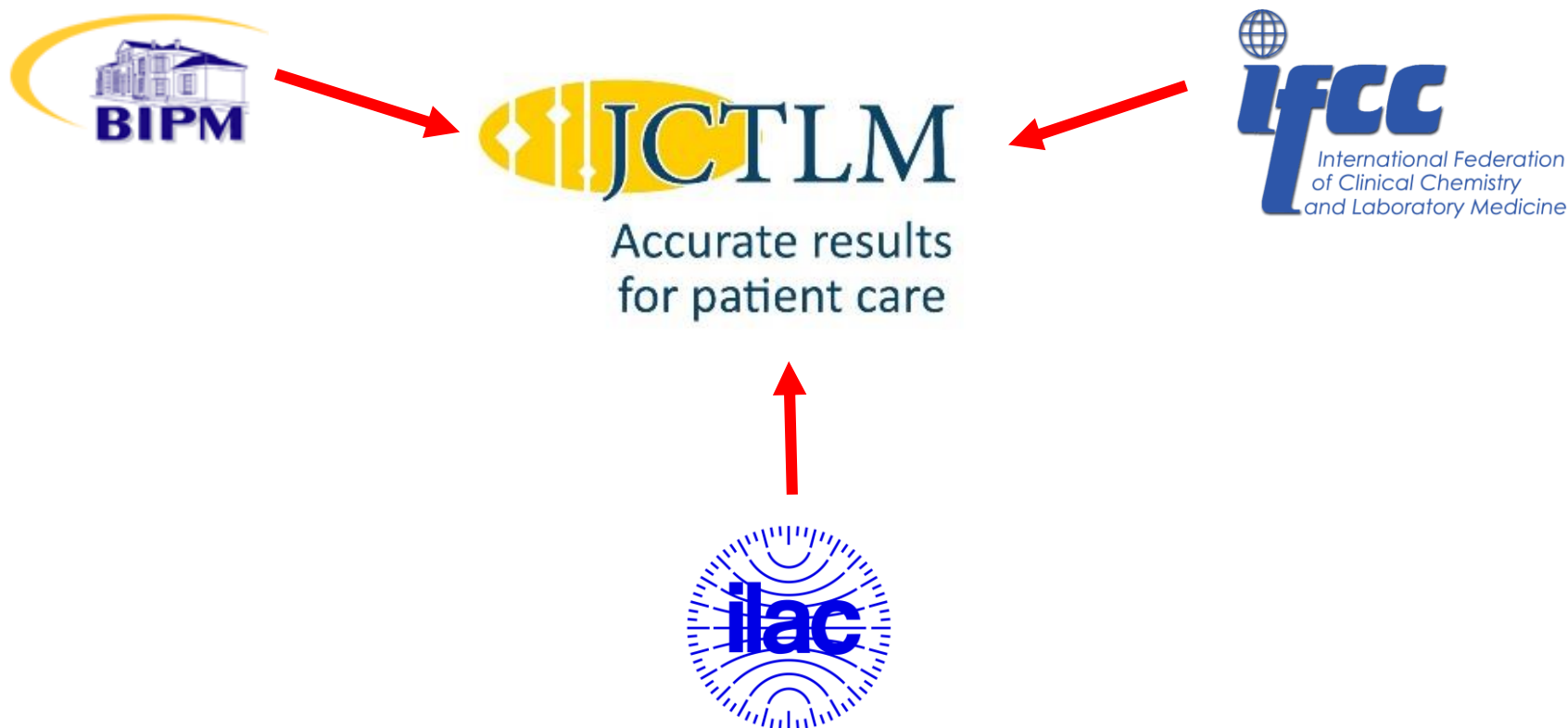


Tools Needed for Traceability

- Reference measurement procedure(s)
 - Gold Standard
- Reference materials (commutable)
- Reference MP laboratories

JCTLM Formation

The JCTLM was formed in 2002 bringing together the sciences of metrology, laboratory medicine and laboratory quality management to promote global traceability



JCTLM Database

- **JCTLM** through **BIPM** maintains a database of **Reference Measurement Systems** <http://www.bipm.org/jctlm/>
- **JCTLM database** was developed to help the **IVD industry** meet metrological traceability requirements of the **EU IVD Directive**
- **JCTLM** coordinates the nomination and review process for database entries

JCTLM Review for compliance with ISO standards

ISO 17511 In vitro diagnostic medical devices - Measurement of quantities in biological samples - Metrological traceability of values assigned to calibrators and control materials (under revision)

ISO 15193:2009 Requirements for content and presentation of reference measurement procedures

ISO 15194:2009 Requirements for certified reference materials and the content of supporting documentation

ISO 18153 Metrological traceability of values for catalytic concentration of enzymes assigned to calibrators and control materials

ISO 15195: 2003 Reference Measurement Laboratories

JCTLM Database : www.bipm.org/jctlm/



Bureau International des Poids et Mesures

Database of higher-order reference materials,
measurement methods/procedures and services



JCTLM Database
Laboratory medicine and *in vitro* diagnostics

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JCTLM database: Laboratory medicine and *in vitro* diagnostics

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➤ Analyte keyword search for reference materials, measurement methods/procedures and services

Type an analyte name in part or full, e.g. cholesterol

Refine search by analyte category

All

Refine search by matrix category

All

Please select your requirement :

- ☒ Higher-order reference materials
- ☐ Reference measurement methods/procedures
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Search



Results of the search for higher-order reference materials

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➔ **Your search criteria:** Higher-order reference materials; Analyte: cholesterol; Analyte category: -; Matrix category: -

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Your search criteria produced 9 summary results.

Select one or several higher-order reference material summary descriptions amongst the following list and click on 'View' to access more information.

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Sort by : ☒ Analyte ☐ Matrix/Material ☐ Organization

Select	Analyte	Analyte category	Matrix/Material	Organization
<input type="checkbox"/>	cholesterol	metabolites and substrates	cholesterol crystalline material	NIM
<input type="checkbox"/>	cholesterol	metabolites and substrates	cholesterol crystalline material	NIST
<input type="checkbox"/>	cholesterol	metabolites and substrates	human serum	NIST
<input type="checkbox"/>	cholesterol	metabolites and substrates	human serum	ReCCS
<input type="checkbox"/>	cholesterol	metabolites and substrates	cholesterol crystalline material	NMIJ
<input type="checkbox"/>	HDL cholesterol	metabolites and substrates	frozen human serum	LNE
<input type="checkbox"/>	LDL cholesterol	metabolites and substrates	frozen human serum	LNE
<input type="checkbox"/>	total cholesterol	metabolites and substrates	frozen human serum	HSA
<input type="checkbox"/>	total cholesterol	metabolites and substrates	frozen human serum	LNE

➤ [Deselect all items from the list](#)

View





Result of the search: list of higher-order reference materials

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➔ **Your search criteria:** Higher-order reference materials; Analyte: cholesterol; Analyte category: -; Matrix category: -

➔ [Save as PDF](#)

➔ [Modify your selection](#)

➤ Results of the search

total cholesterol in frozen human serum

Health Sciences Authority (HSA), Singapore

Phone: +65 6775 1605 ext 104

Email: HSA_CML@hsa.gov.sg

Fax: +65 6775 1398

Web: <http://www.hsa.gov.sg>

Name of the reference material	HRM-3002A, Creatinine, Glucose, Total Cholesterol, Urea, and Uric Acid in Frozen Human Serum
Quantity	Amount-of-substance concentration
Analyte certified/assigned value	3.45 mmol/l to 5.92 mmol/l
Expanded uncertainty (level of confidence 95 %)	0.07 mmol/l to 0.11 mmol/l
Reference(s) on commutability	See Certificate of Analysis for HRM-3002A
Traceability	SI
CRM listing	List I

JCTLM Database : www.bipm.org/jctlm/



Bureau International des Poids et Mesures

Database of higher-order reference materials,
measurement methods/procedures and services



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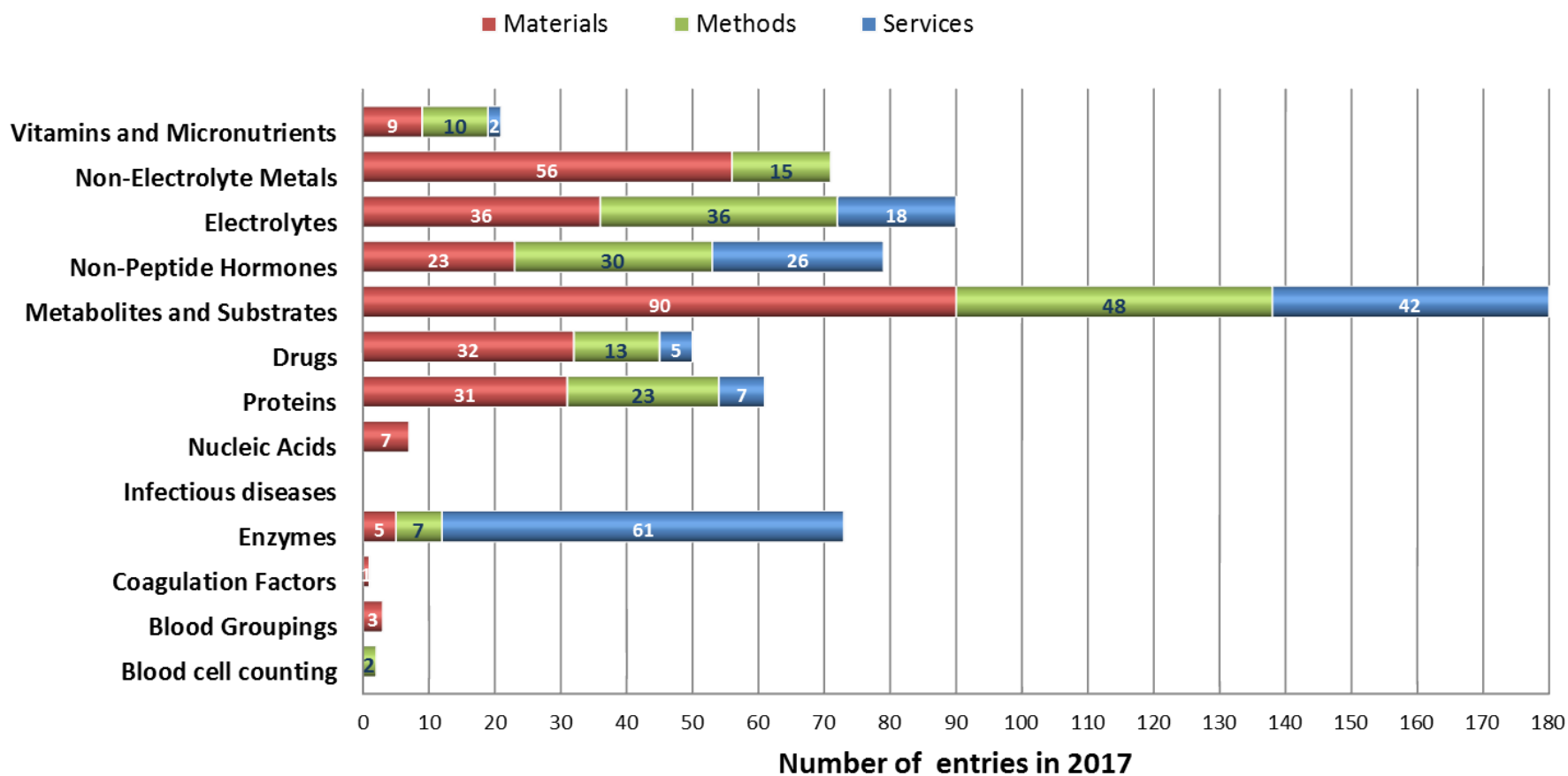
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JCTLM Database: Entries as of March 2017



293 Certified Reference Materials

184 RMPs that represent 80 different analytes in 9 categories

161 reference measurement services delivered by 17 reference labs

A photograph of a large, jagged iceberg floating in the ocean under a blue sky with wispy clouds. The iceberg has several sharp peaks and is partially submerged.

Challenges for traceability

Measurands for which
reference procedures
exist or can be developed

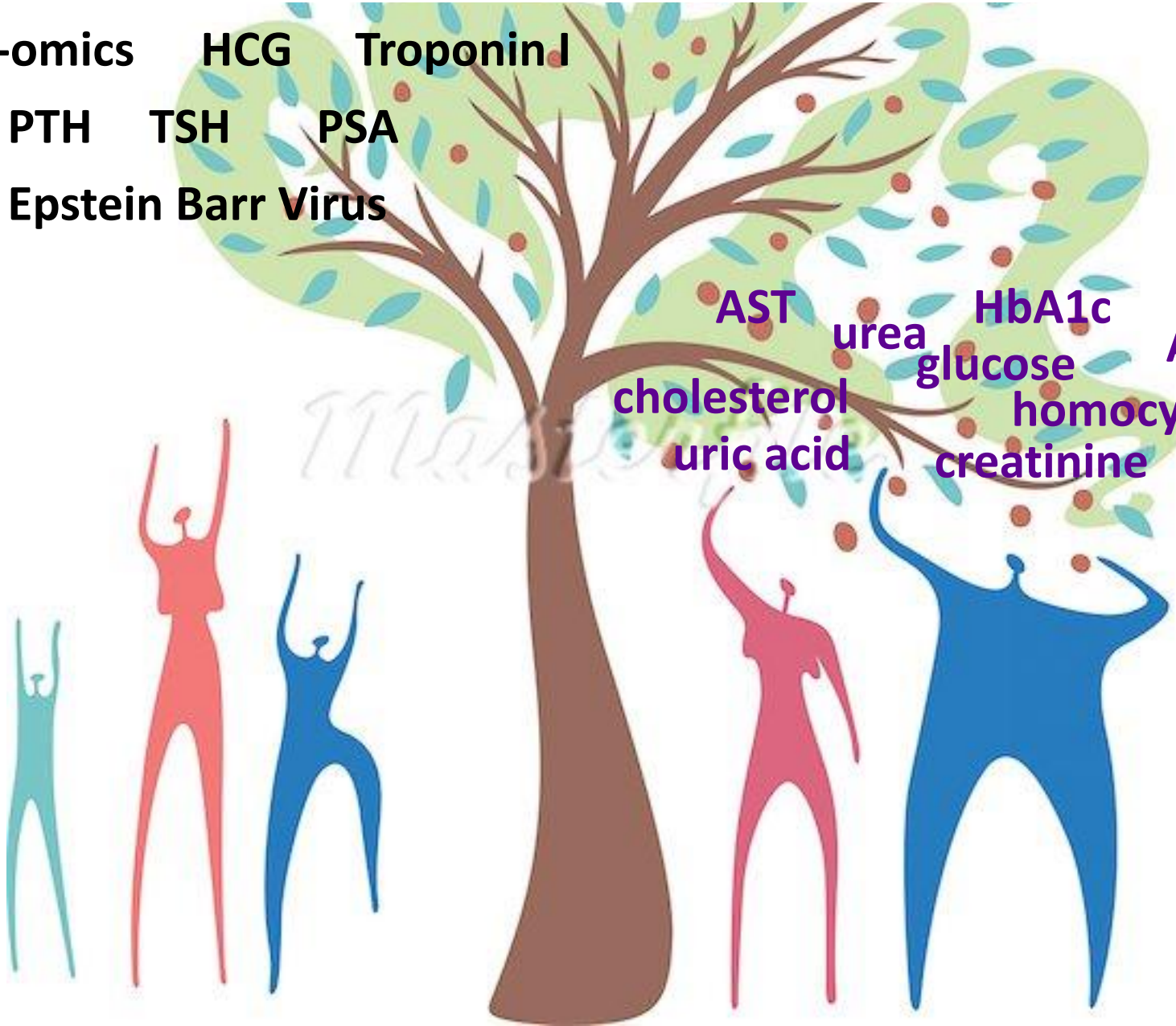
Picking the low-hanging fruit !

-omics HCG Troponin I

PTH TSH PSA

Epstein Barr Virus

AST urea HbA1c ALT
cholesterol glucose homocysteine
uric acid creatinine



Challenges for Traceability

- A national database in Finland suggests there are ~4000 clinically relevant analytes measured across the scope of laboratory medicine (P Laitinen, Finland)
- The Joint Committee for Traceability in Laboratory Medicine (JCTLM) database holds 293 certified reference materials; 184 reference measurement procedures covering 80 measurands
www.bipm.org/jctlm/



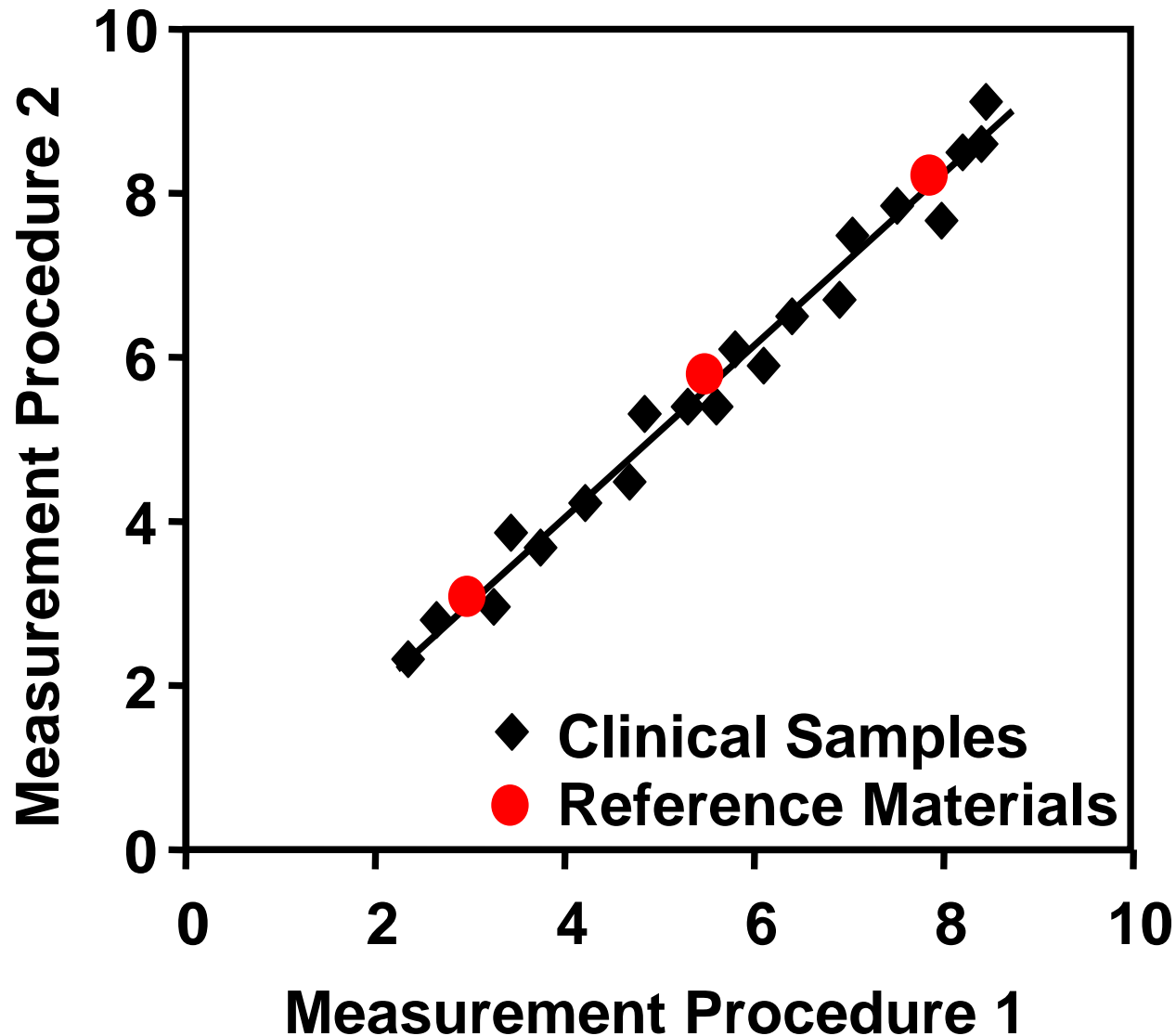
- The World Health Organisation (WHO) catalogue of blood products and related biological standards contains ~300 entries
<http://www.who.int/bloodproducts/catalogue/en/>



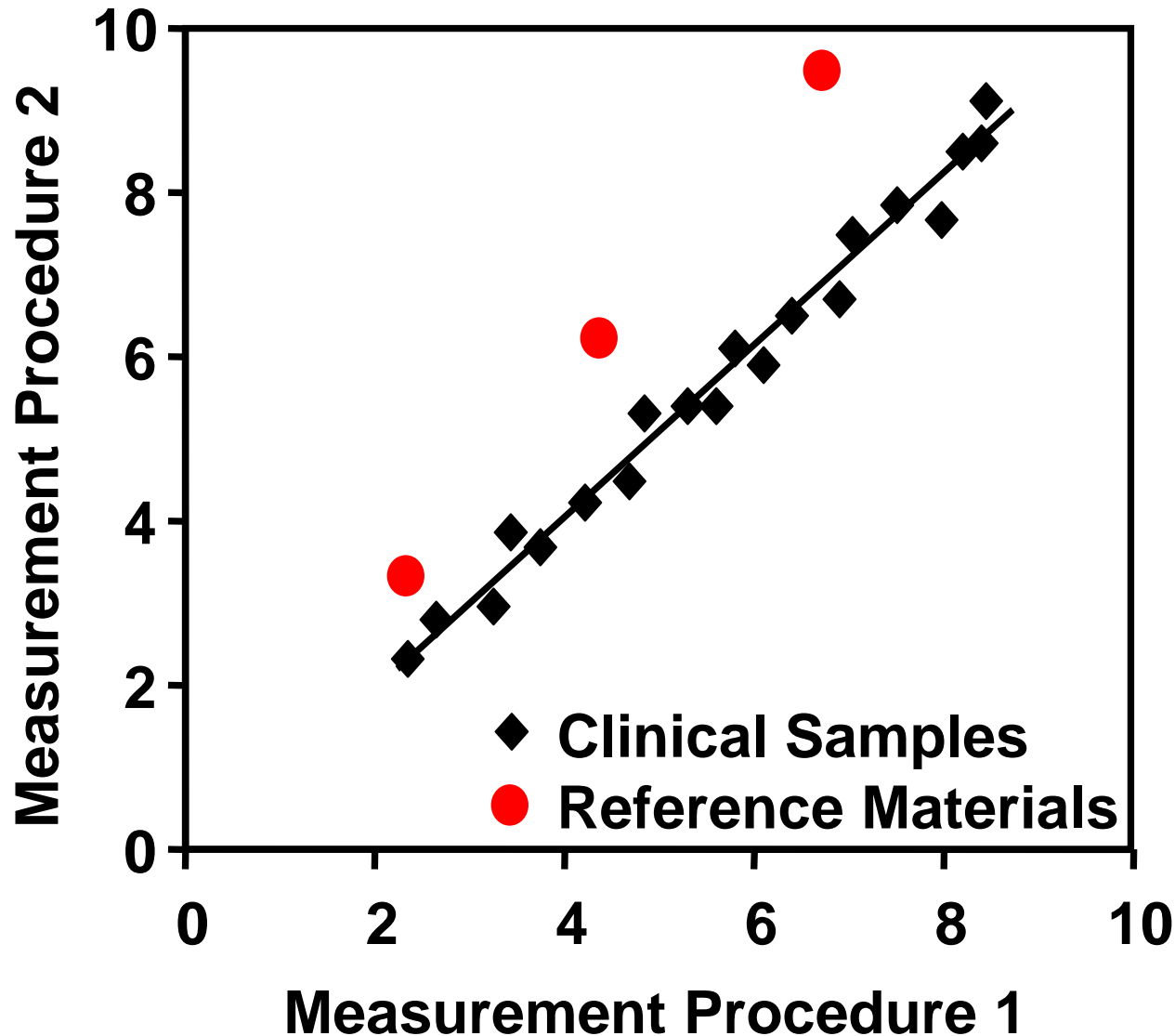
Challenges for Traceability

- **Commutability** is key to establishing traceability in laboratory medicine
- Materials may be labeled as “reference materials”, but have not been validated to be commutable for the intended measurement procedures

Commutable: same relationship for clinical samples and reference materials



Non-commutable: different relationship for clinical samples and reference materials



Metrological Traceability Chain

Materials

Pure Substance
Reference
Material

Procedures

A non-commutable calibrator breaks the traceability chain

Secondary
Reference
Material
(matrix)

Key Step in Calibration

Assign value

Calibrate

Manufacturer's
Product
Calibrator

Assign value

Calibrate

Patient's
Sample

Assign value

Manufacturer's
Internal
Procedure

Clinical
Laboratory
Method

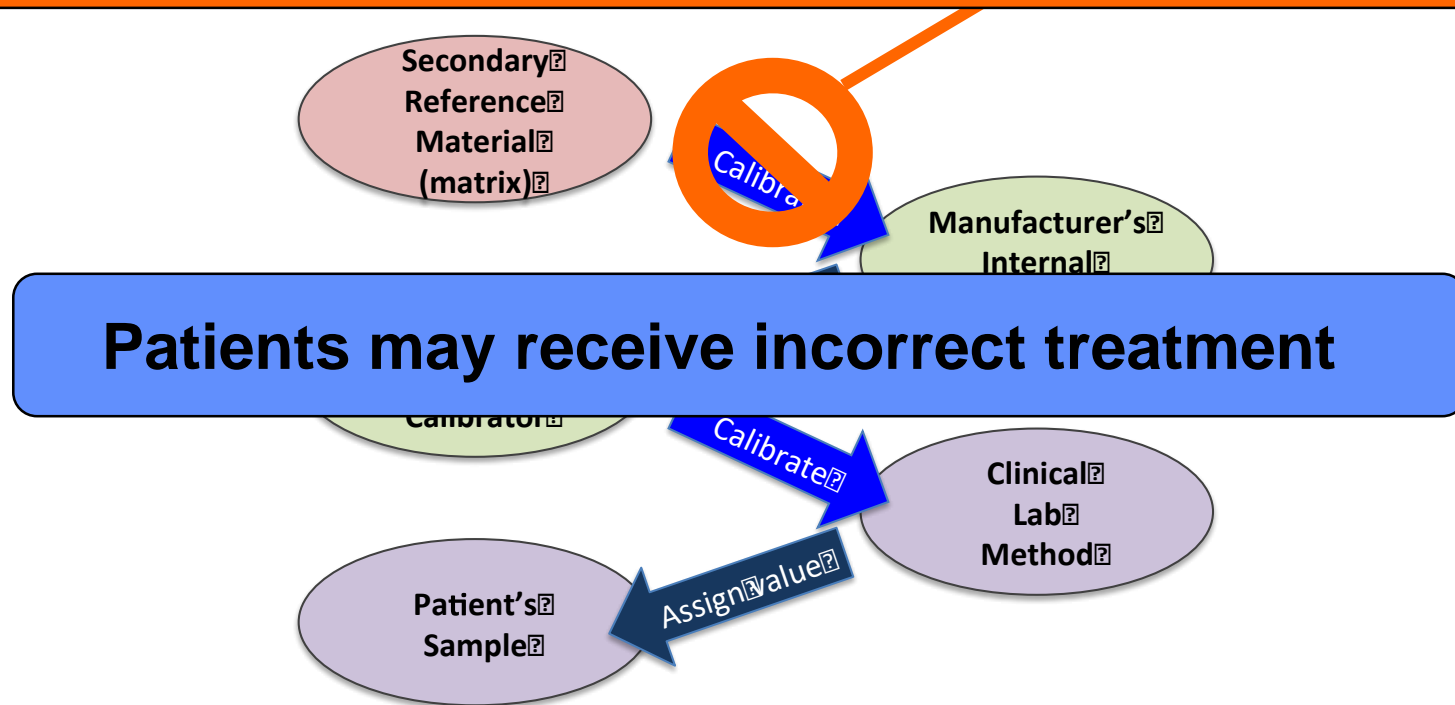
Patient's
Result

Traceability Chain

Patient's result is equivalent to
result from the reference procedure

Why commutability matters

Even though manufacturers show traceability, if reference material is non-commutable the process will fail to provide equivalent results for patient samples among different measurement procedures



IFCC Working Group on Commutability

(established March 2013)

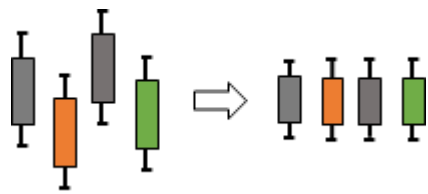
Chair: Greg Miller, PhD, Virginia Commonwealth University

- Establish operating procedures for the formal assessment of commutability of a reference material
- Establish criteria for commutability taking into account the intended use of a reference material
- Propose standard terminology to describe commutability characteristics
- Provide guidance on specific information to be provided regarding commutability
- Develop educational materials on commutability for manufacturers, laboratories, and end users

Global challenges in implementing traceability in laboratory medicine

Lack of Global Coordination

- No definitive list of biomarkers used across laboratory medicine
- No systematic process to identify and prioritize measurands in need of harmonization
- Traceability activities among different organizations is not coordinated on a global level



International Consortium for the Harmonization of Clinical Laboratory Results

Primary Functions:

- 1. Prioritize measurands by medical importance**
- 2. Maintain a website that will serve as a resource for information on traceability activities of different global organizations**
- 3. Promote processes for harmonization when there is no reference measurement procedure or reference material**



The International Consortium for Harmonization of Clinical Laboratory Results

OUR VISION

- ✓ Clinical laboratory test results will be equivalent independent of the clinical laboratory that produced the results

OUR MISSION

- ✓ To provide a centralized process to organize global efforts to achieve harmonization of clinical laboratory test results

Our specific objectives

- ✓ to improve the harmonization of results from clinical laboratory measurement procedures for measurands (analytes) that do not have reference measurement procedures
- ✓ to provide a resource center for information on global activities to harmonize and standardize clinical laboratory measurement procedures

Organization

Operating Procedures for the International Consortium for Harmonization of Clinical Laboratory Results describe the program. The governing body is a Council made up of organizations from around the world that contribute financially to support the administration of the program. A Harmonization Oversight Group (HOG) is responsible to manage the harmonization activities.

Interested stakeholders may become Organizational Members of the consortium or join the Strategic Partners Group to support and contribute to the harmonization activities.

The AACC is the secretariat for administration of the program.

[Read more](#)

Council Members

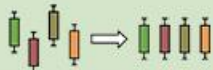
American Association for Clinical Chemistry

Japanese Committee for Clinical Laboratory Standards

Korean Society for Laboratory Medicine

Organizational Member

College of American Pathologists



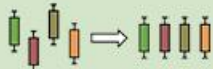
Measurands

[Frontpage](#) / [Measurands](#)

This section provides information on the status of harmonization or standardization of measurands. Priorities based on medical impact are provided for measurands for which harmonization is needed or that have an incomplete or inactive implementation of a harmonization activity. Additional information regarding the harmonization status and medical impact is available by clicking on the measurand name. Information on reference materials, reference measurement procedures, and reference laboratory services is provided by the links in the JCTLM column. Links to organizations actively addressing harmonization of particular measurands are provided for additional information on those projects.

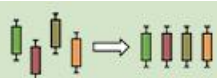
Comments on measurand status can be sent using the [Contact Us](#) tab. [Download the form to submit a new measurand.](#)

Summary of Measurand Harmonization Activities



Measurands

Measurand	Matrix	Medical Impact of Harmonization ¹	Harmonization Status ²	JCTLM Listed ³	Organization
Akaline Phosphatase (ALP)	Serum	Medium	Incomplete		IFCC
Alanine Aminotransferase (ALT)	Serum	Medium	Incomplete		IFCC EU-JRC (IRMM)
Albumin	Urine		Active		NKDEP IFCC JSCC
Albumin	Serum	Medium	Needed		
Amylase	Serum		Active		IFCC
Aspartate Aminotransferase (AST)	Serum	Medium	Incomplete		IFCC
B-type Natriuretic Peptide (BNP)	Serum	High	Needed		
Bilirubin, conjugated	Serum	Medium	Needed		
Bilirubin, total	Serum		Adequate		
Blood gasses (pH, pO2, pCO2, oximetry)	Blood		Adequate		
C-Reactive protein, high sensitivity	Serum		Adequate		



International Consortium
for Harmonization of Clinical Laboratory Results

HOME ABOUT OVERSIGHT

Measurands

Measurand

Akaline Phosphatase (ALP)

Alanine Aminotransferase (ALT)

Albumin

Albumin

Amylase

Aspartate Aminotransferase (AST)

B-type Natriuretic Peptide (BNP)

Bilirubin, conjugated

Bilirubin, total

Blood gasses (pH, pO₂, pCO₂, oximetry)

C-Reactive protein, high sensitivity

Alanine Aminotransferase (ALT)

The IFCC has developed reference measurement procedures for AST and ALT enzymes. The IFCC reagent formulation is generally used by IVD manufacturers with some adaptation for the technology of a given instrument system. Standardization is thus easily achievable. The harmonization issue is whether or not pyridoxyl-5-phosphate (P5P) is included in reagents from IVD manufacturers. P5P is needed to fully activate the enzymes in situations when a patient has a deficiency in this vitamin as may occur in kidney failure and other conditions. A technical issue is that adding P5P to reagents reduces the reagent stability. Consequently P5P is supplied in a separate container to be mixed at the time a reagent is put into use. Furthermore, laboratories may prefer not to add P5P because there may be reagent waste in lower testing volume situations. Some countries do not typically include P5P and in other countries there is a mix of inclusion and exclusion in reagents. Differences in vitamin deficiency between countries may contribute to different practices. The ICHCLR recommends that manufacturers make available reagents that include P5P so that laboratories can determine if their population would benefit from its use in the reagents. A medium priority was assigned because these two analytes are well standardized except for the P5P inclusion and the need for P5P may vary among different regions of the world.

Schumann G, Bonora R, Ceriotti F, Ferard G, Ferrero CA, Franck PF, et al. IFCC primary reference procedures for the measurement of catalytic activity concentrations of enzymes at 37 degrees C. International Federation of Clinical Chemistry and Laboratory Medicine. Part 4. Reference procedure for the measurement of catalytic concentration of alanine aminotransferase. *Clin Chem Lab Med.* 2002;40:718-24.



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Organization

IFCC

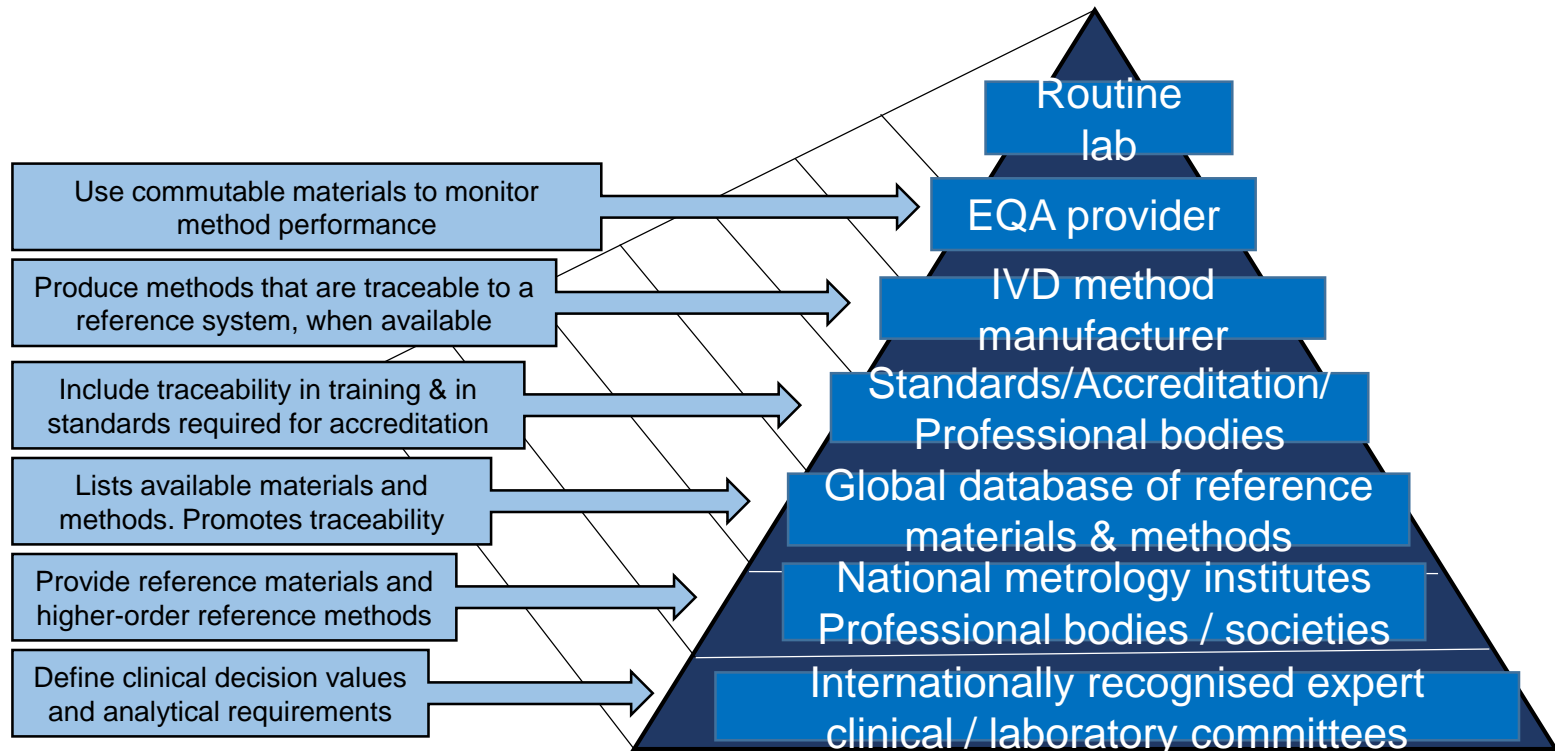
IFCC EU-JRC (IRMM)

NKDEP IFCC JSCC

IFCC

IFCC

Support actions for the routine lab to achieve traceability



What can you do as a laboratory medicine specialist in your lab to assure method traceability?

1. Check the traceability status of the methods that you use. If uncertain check with your supplier
2. Encourage key colleagues to learn more about traceability in laboratory medicine
3. Check whether your EQA scheme provider is using commutable materials
4. Analyse your EQA performance critically to assess the extent to which the lack of traceability may be negatively impacting laboratory results obtained

Where can you find more information?

Websites

- JCTLM database of reference materials and measurement procedures www.bipm.org/jctlm/
- Joint Committee for Traceability in Laboratory Medicine (JCTLM): www.jctlm.org
- International Consortium for Harmonization of Clinical Laboratory Results
www.harmonization.net

In Summary

How to reduce between method variability

- Calibration of all procedures is traceable to a common reference system (**traceability chain**)
- All measurement procedures measure the same quantity
- Surveillance (PT or EQA) is needed to monitor and maintain consistent performance
- Materials for calibration and surveillance purposes should be commutable

Thank You!!



Accurate results
for patient care