

Harmonization: why you should care!

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- Siemens Healthcare Diagnostics, consultant
- Roche Molecular Diagnostics, focus group
- Abbott Diagnostics, research grant



Cooperation

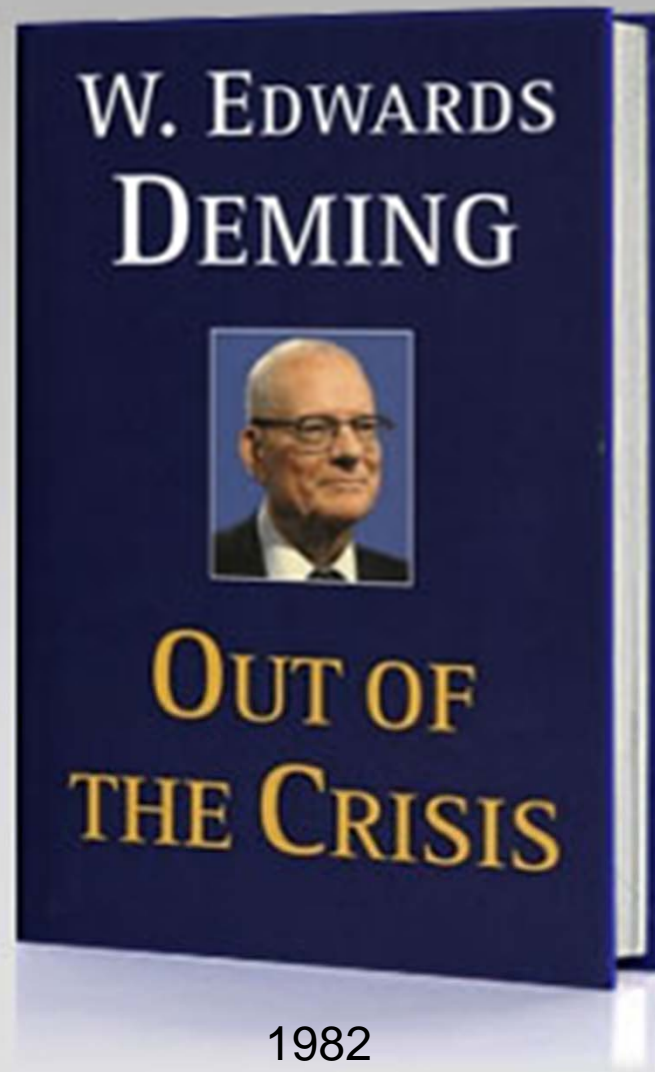


Harmonization



Regulation

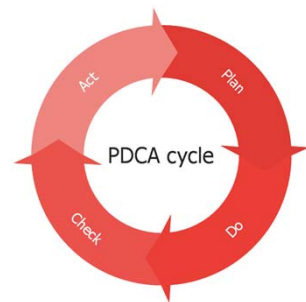
Cooperation



1982

Deming's Key Principles

- ❖ Cooperation improves quality, productivity, profit
- ❖ Understand and eliminate variation
- ❖ Use statistical process control, not inspection
- ❖ Value customer - supplier relationships
- ❖ Implement continuous quality improvement



Institute of Medicine

1999: *To Err Is Human: Building a Safer Health System*

- ❖ Mistakes happen
- ❖ Caused by lack of systematic work practices
- ❖ Teamwork, practice guidelines, checklists

Cooperation

Clinical practice guidelines

Based on cooperation

to eliminate variation

to achieve uniform quality

How has the lab been involved

1988

JAMA Internal Medicine

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January 1, 1988, Vol 148, No. 1 >

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ARTICLE | January 1988

Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults

Did not know
cholesterol was not
standardized

CRMLN



Still ignoring laboratory medicine

1993



The NEW ENGLAND
JOURNAL of MEDICINE

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ORIGINAL ARTICLE

The Effect of Intensive Treatment of Diabetes on the Development and Progression of Long-Term Complications in Insulin-Dependent Diabetes Mellitus

The Diabetes Control and Complications Trial Research Group*

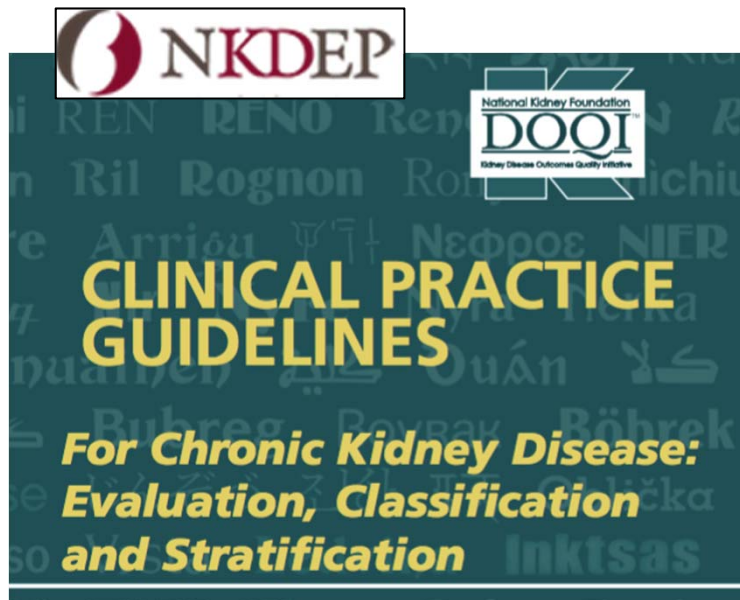
N Engl J Med 1993; 329:977-986 | September 30, 1993 | DOI: 10.1056/NEJM199309303291401

Wide disparity in
HbA1c results
among labs



“They” did it again

2002

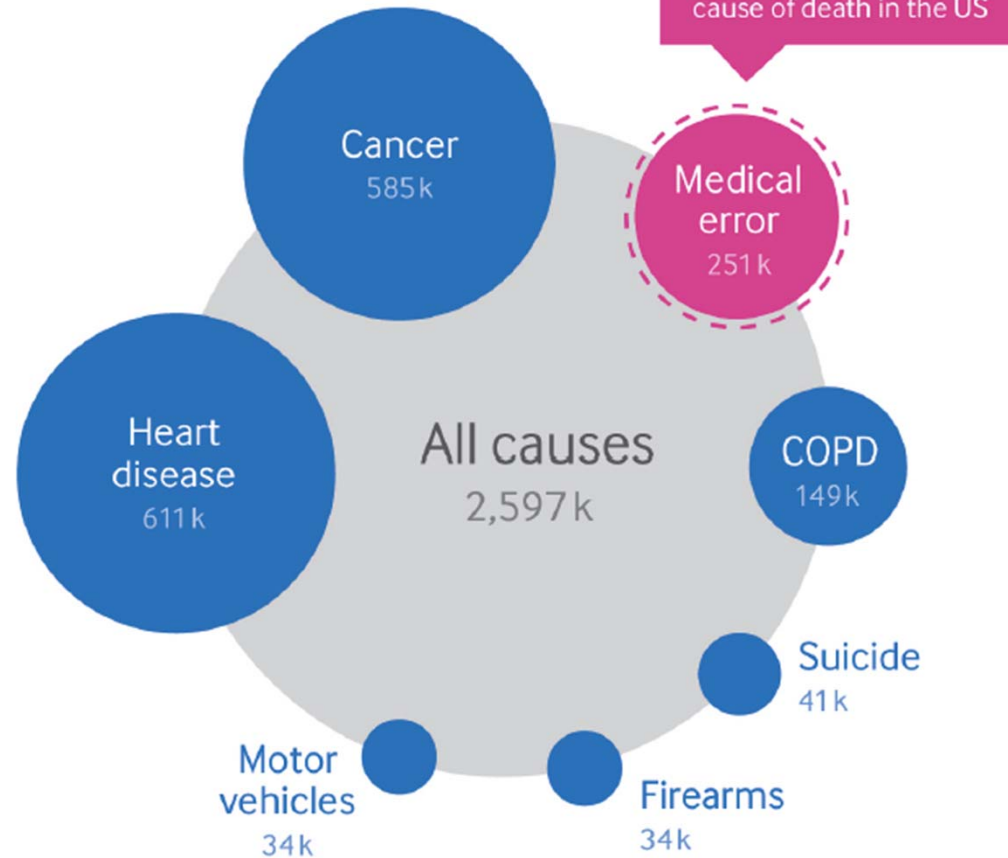


- Asked labs to report eGFR
- Creatinine was not standardized



Laboratory Working Group

Causes of death, US, 2013



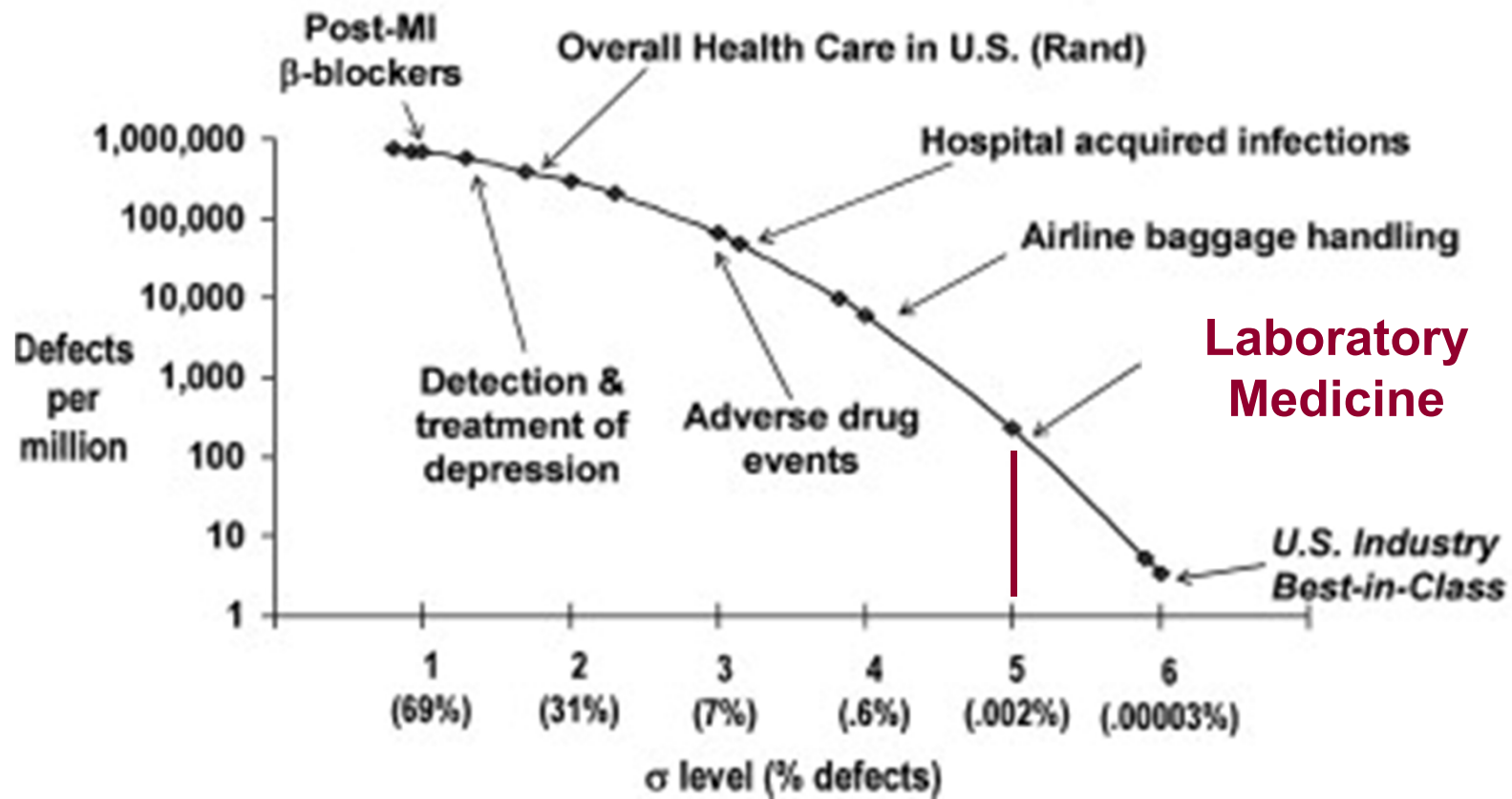
However, we're not even counting this - medical error is not recorded on US death certificates

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Data source:

http://www.cdc.gov/nchs/data/nvsr/nvsr64/nvsr64_02.pdf

Defect rate in laboratory medicine



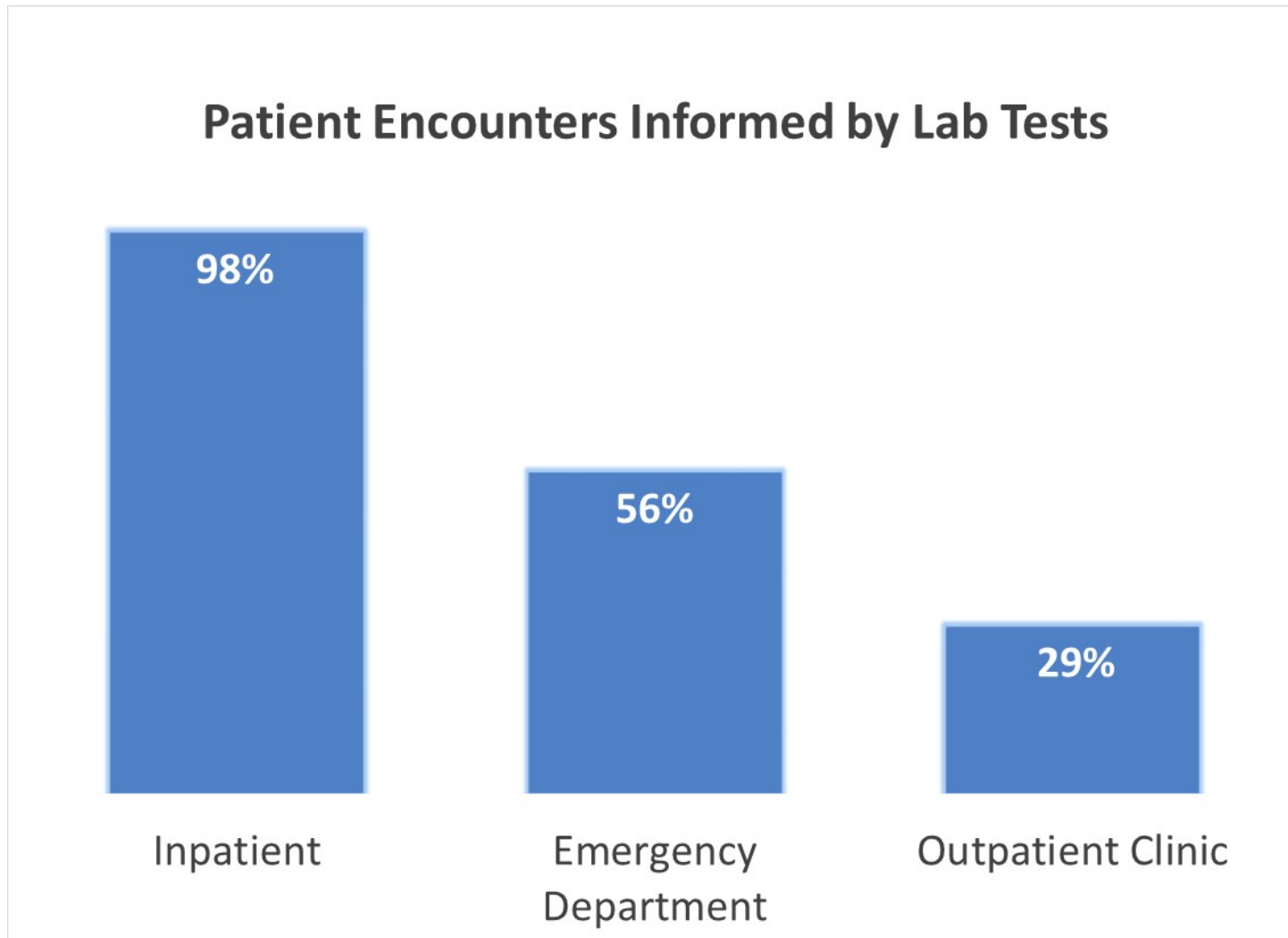
20 defects per 1 M test results

Leape LL. Clin Chim Acta 2009;404:2-5. (review: Plebani. Ann Clin Biochem 2010;47:101-10)

- ❖ **Defect creates a hazardous condition (risk)**
- ❖ **Harm only if the hazardous condition affects patient care**



Lab tests are important



Ngo A, Gandhi P, Miller WG. J Applied Lab Med 2017;1:410-4.

Source of lab testing errors



3-12% of errors caused adverse events (4 reports)

Institute of Medicine

2015: *Improving Diagnosis in Health Care*

- ❖ Reinforced guidelines and cooperation
- ❖ **The clinical laboratory is part of the team**

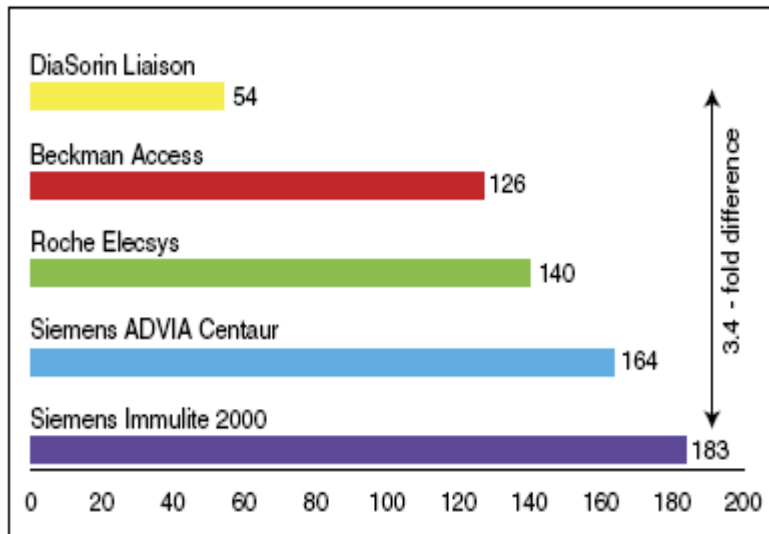


Institute of Medicine

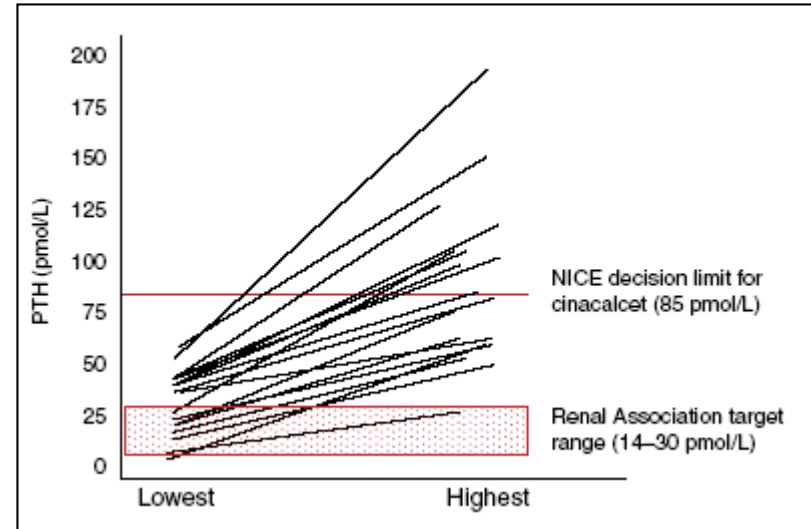
2015: *Improving Diagnosis in Health Care*

Failed to mention that when applying guidelines, **non-harmonized lab results can cause errors** in diagnosis or in decisions for treatment / non-treatment

PTH: Between Method Variability



PTH concentration (pmol/L) in a single patient.



Treatment variation caused by comparing highest and lowest PTH concentrations in 18 patients.

Almond A, Ellis AR, Walker SW. Current parathyroid hormone immunoassays do not adequately meet the needs of patients with chronic kidney disease.

Ann Clin Biochem 2012; 49: 63–67

Human growth hormone

Tumor markers

Testosterone

Estradiol

Viral load

Troponin I

BNP

AST

LDH

Amylase

Lipase

Albumin

“We” need to engage “Them”

Lab specialists cannot wait to be asked to collaborate on guidelines

- ✧ **Engage clinical colleagues**
- ✧ **Join rounds teams in hospitals**
- ✧ **Establish consultative lab orders**
- ✧ **Talk to patient advocate groups**

Cooperation



Harmonization

**One of the most important
challenges in laboratory medicine**

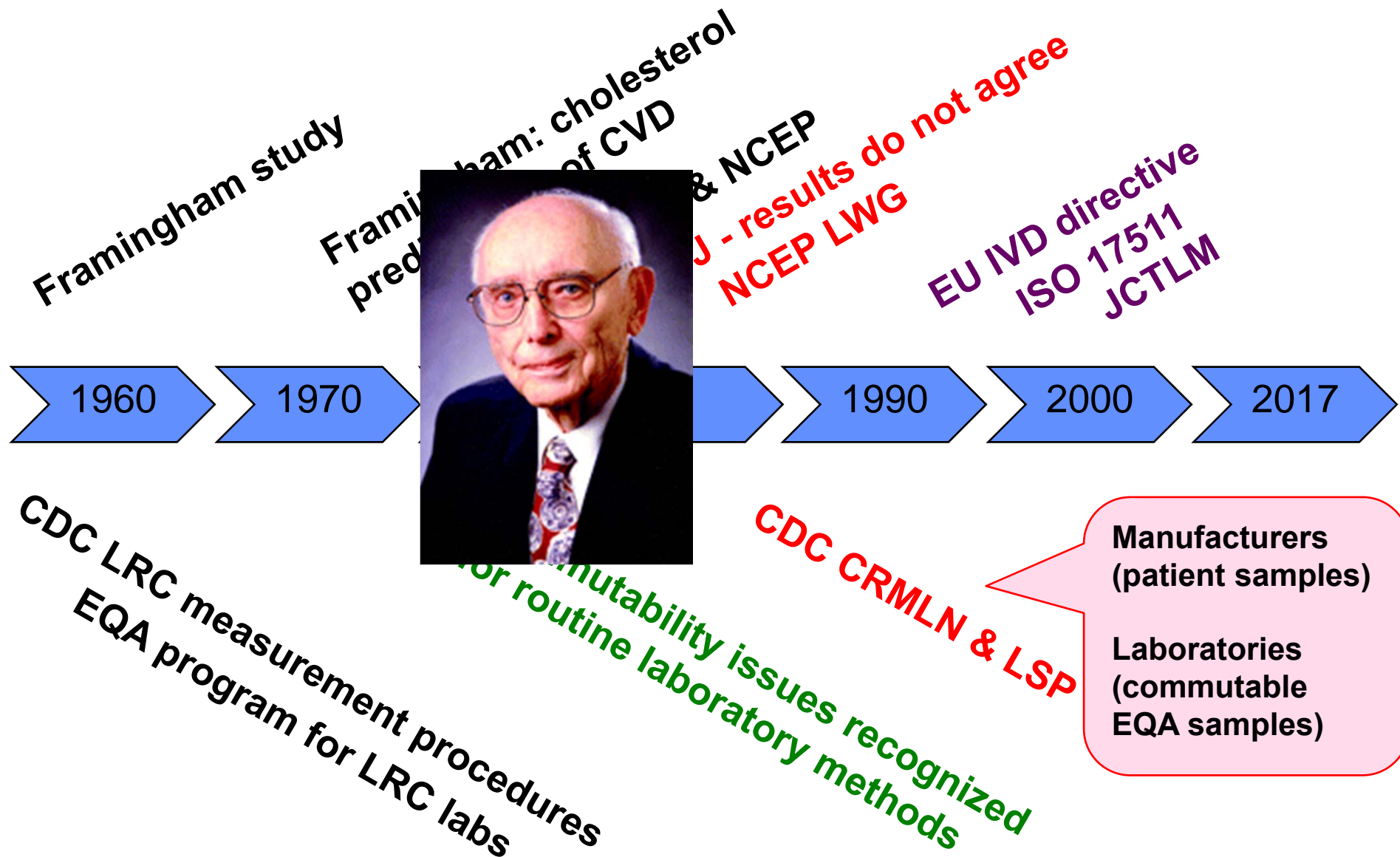
What is harmonization

Equivalent results, within clinically meaningful limits, among different measurement procedures for the same laboratory test

Terminology

- **Harmonization:** achieving equivalent results among different measurement procedures
 - ❖ Implies there is no reference measurement procedure or certified reference material
- **Standardization:** achieving equivalent results by having calibration traceable to a higher order reference system

Cholesterol: first integrated program



What's the problem; we have infrastructure for harmonization



- 17511:2003, Calibration Traceability
- 15193:2003,2009, Reference Measurement Procedures
- 15194:2003,2009, Certified Reference Materials
- 15195:2003, Reference Measurement Laboratories



Database of reference materials, reference measurement procedures, and reference (calibration) laboratories that conform to the ISO standards

ISO built on a legacy of harmonization infrastructure

Belk, Sunderman. A survey of the accuracy of chemical analyses in clinical laboratories. Am J Clin Pathol 1947; 17:853 – 61.

Standard Methods of Clinical Chemistry. AACC, seven volumes 1953-1972

Radin. What is a standard? Clin Chem 1967;13:55-76.

Bergmeyer, Bowers, Horder, Moss. IFCC method for AST. Clin Chim Acta 1976;70:F19-29.

A national understanding for the development of reference materials and methods for clinical chemistry. Conference sponsored by CDC, FDA, NBS/NIST, 1978

National Reference System for the Clinical Laboratory. NCCLS/CLSI, 1978

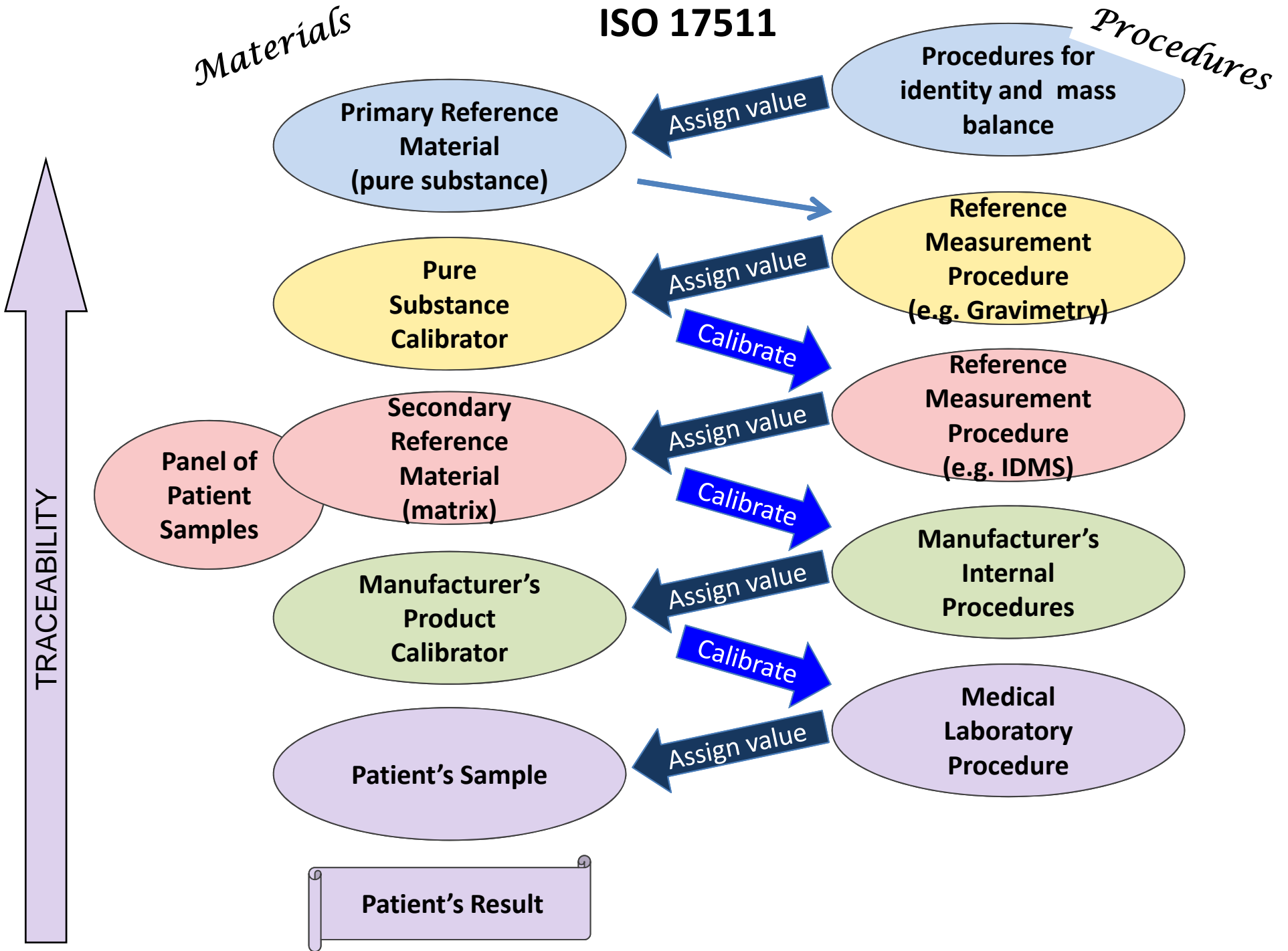
How to achieve equivalent results

1. **Calibration of all measurement procedures is traceable to a common reference system**

- ❖ **ISO 17511:2003**

2. **All measurement procedures measure the same quantity (the same molecular form)**

- ❖ **Analytical selectivity for the measurand**



How many tests are in ARUP's directory?

JCTLM lists CRM and RMP for 80 analytes

Infrastructure: what's needed

Reference Measurement Laboratories

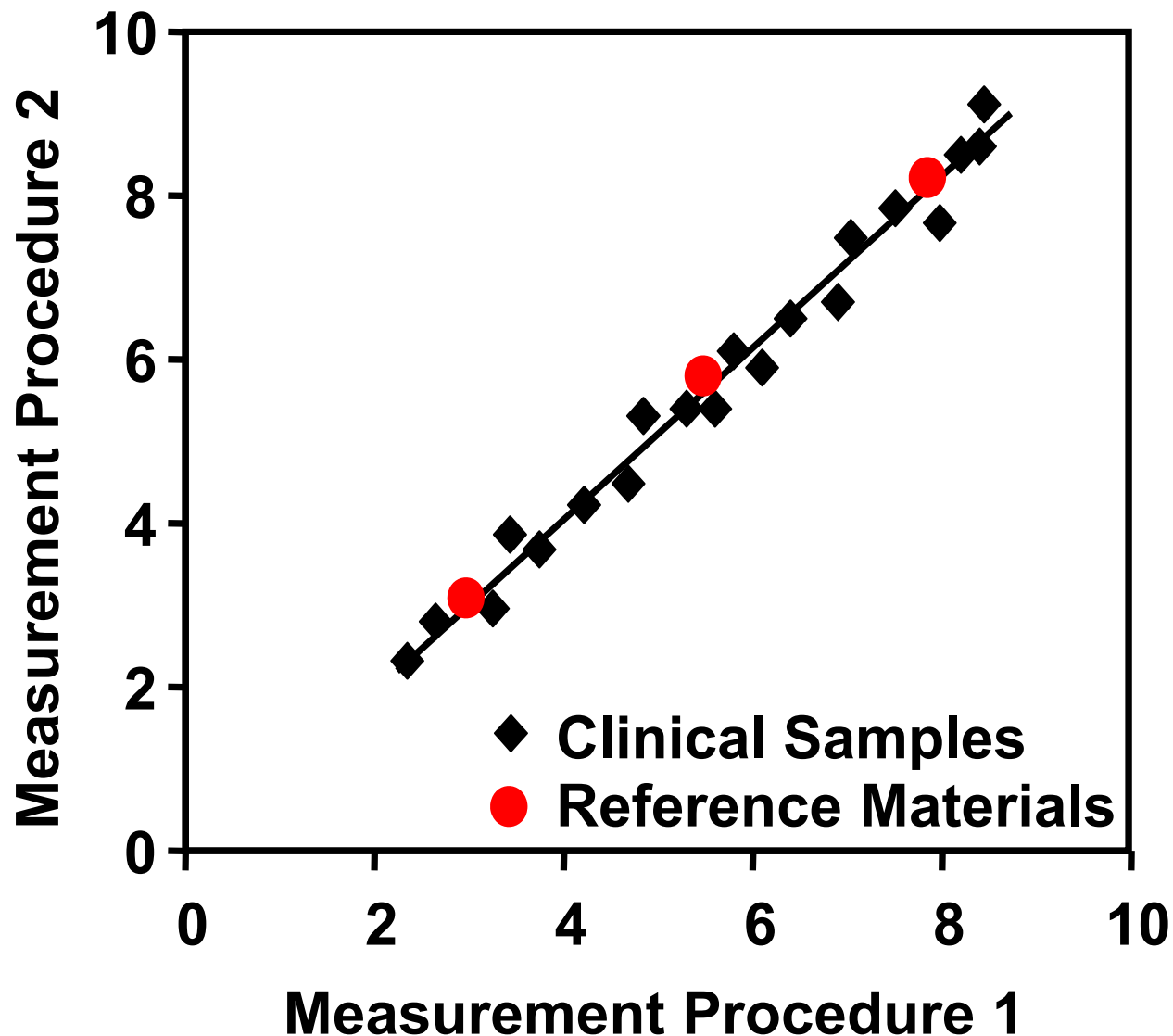
No JCTLM listed reference lab in US that IVD manufacturers can use to establish traceability

- Accredited by an ILAC approved organization
 - e.g. American Association for Laboratory Accreditation (www.A2LA.org)
- Participate in IFCC ring trials for reference labs

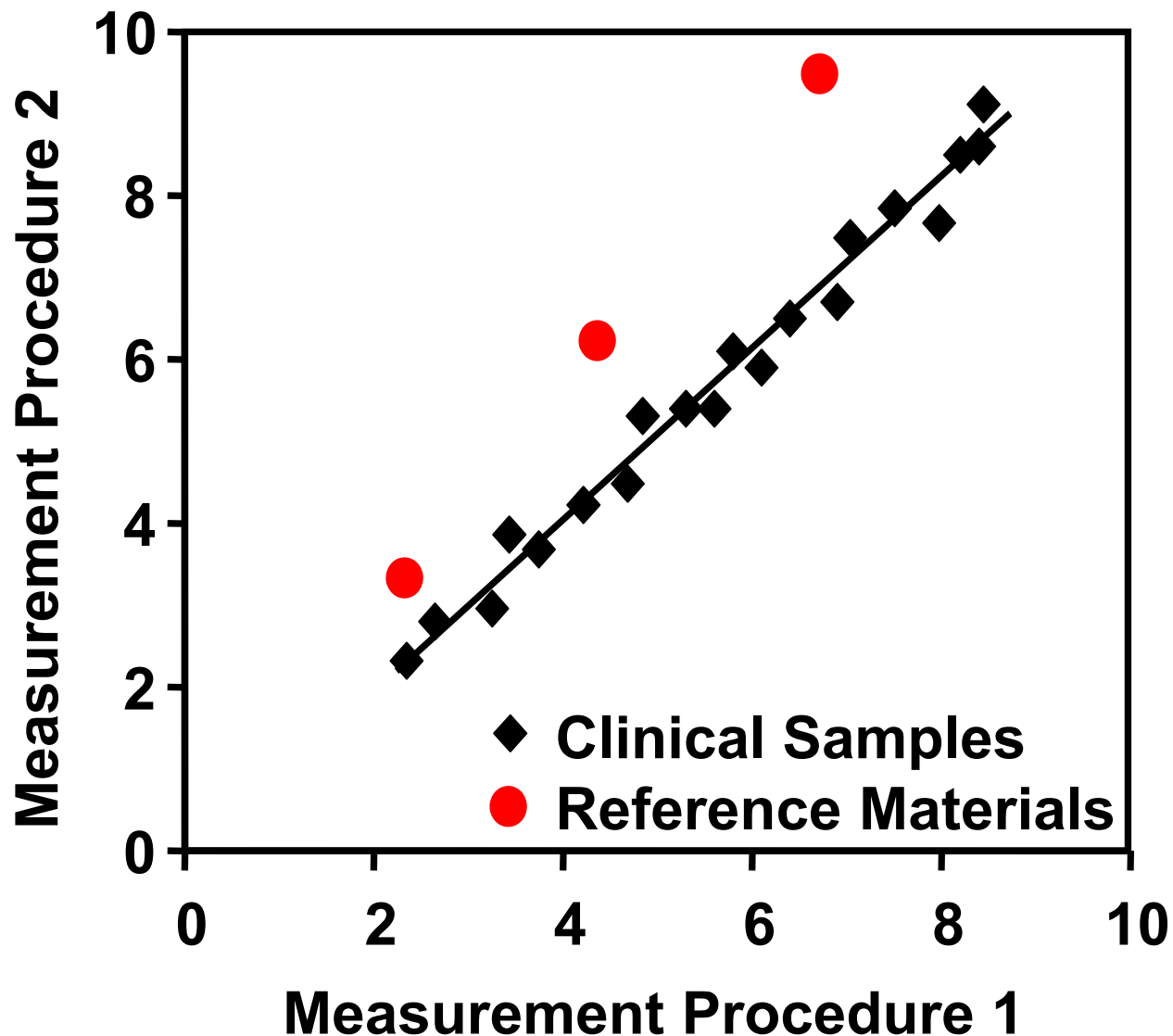
Infrastructure: what's needed

Commutable Reference Materials

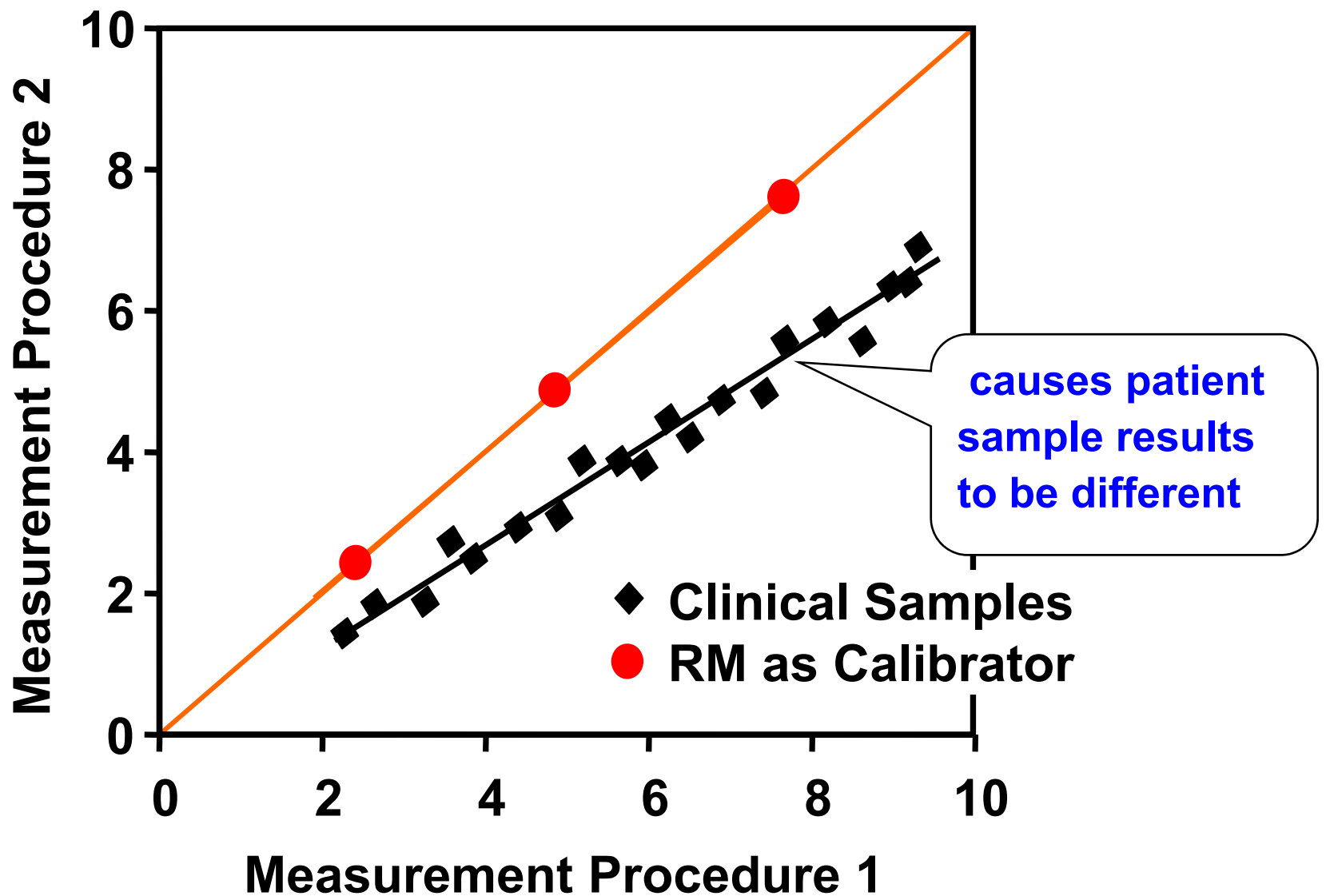
Commutable: same relationship for clinical samples and reference materials

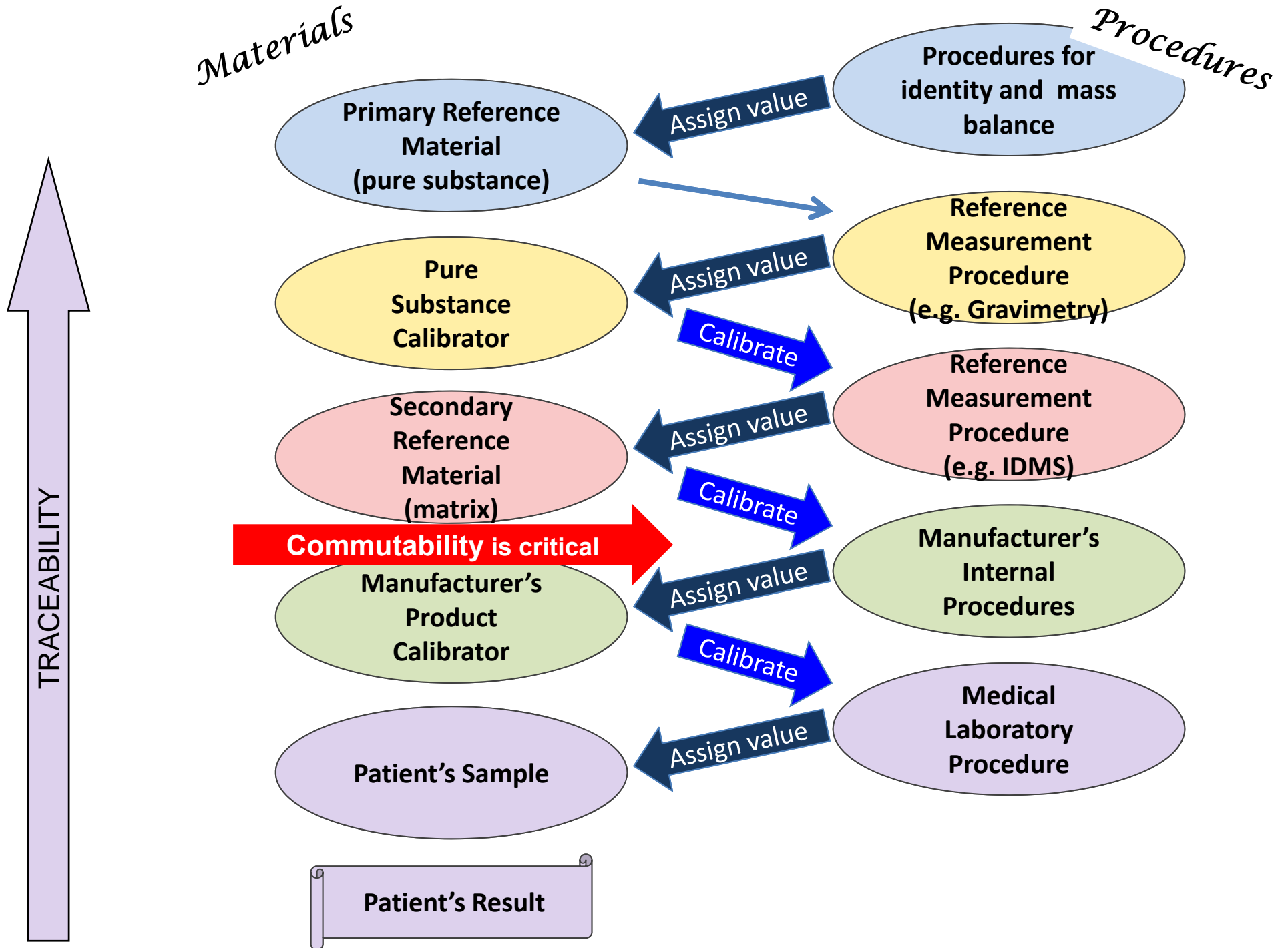


Non-commutable: different relationship for clinical samples and reference materials



Calibration with non-commutable materials





Materials

Procedures

Primary Reference Material

Assign value

Procedures for identity and mass balance

A non-commutable calibrator breaks the traceability chain

Calibrator

Calibrate

Secondary Reference Material (matrix)

Assign value

Reference Measurement Procedure (e.g. IDMS)

Commutability is critical

Calibrate

Manufacturer's Product Calibrator

Assign value

Manufacturer's Internal Procedures

Calibrate

Patient's Sample

Assign value

Medical Laboratory Procedure

Patient's Result

TRACEABILITY

Materials

Procedures

Procedures for
identity and mass

Primary Reference

Assign value

Even though manufacturers show traceability, the process fails to provide equivalent results for patient samples among different measurement procedures

Calibrator

Calibrate

Secondary
Reference
Material
(matrix)

Assign value

Reference
Measurement
Procedure
(e.g. IDMS)

Commutability is critical

Calibrate

Manufacturer's
Product
Calibrator

Assign value

Manufacturer's
Internal
Procedures

Calibrate

Patient's Sample

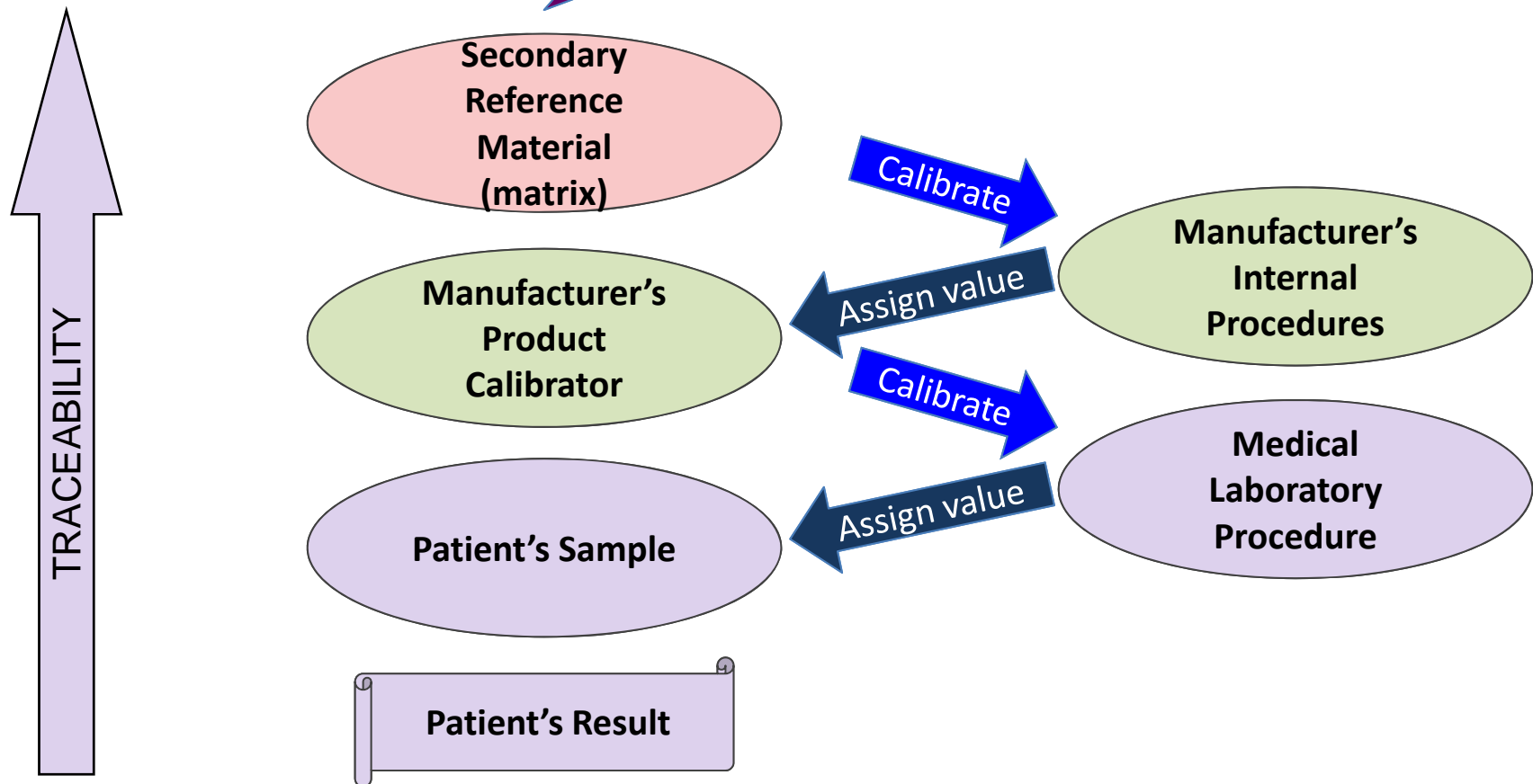
Assign value

Medical
Laboratory
Procedure

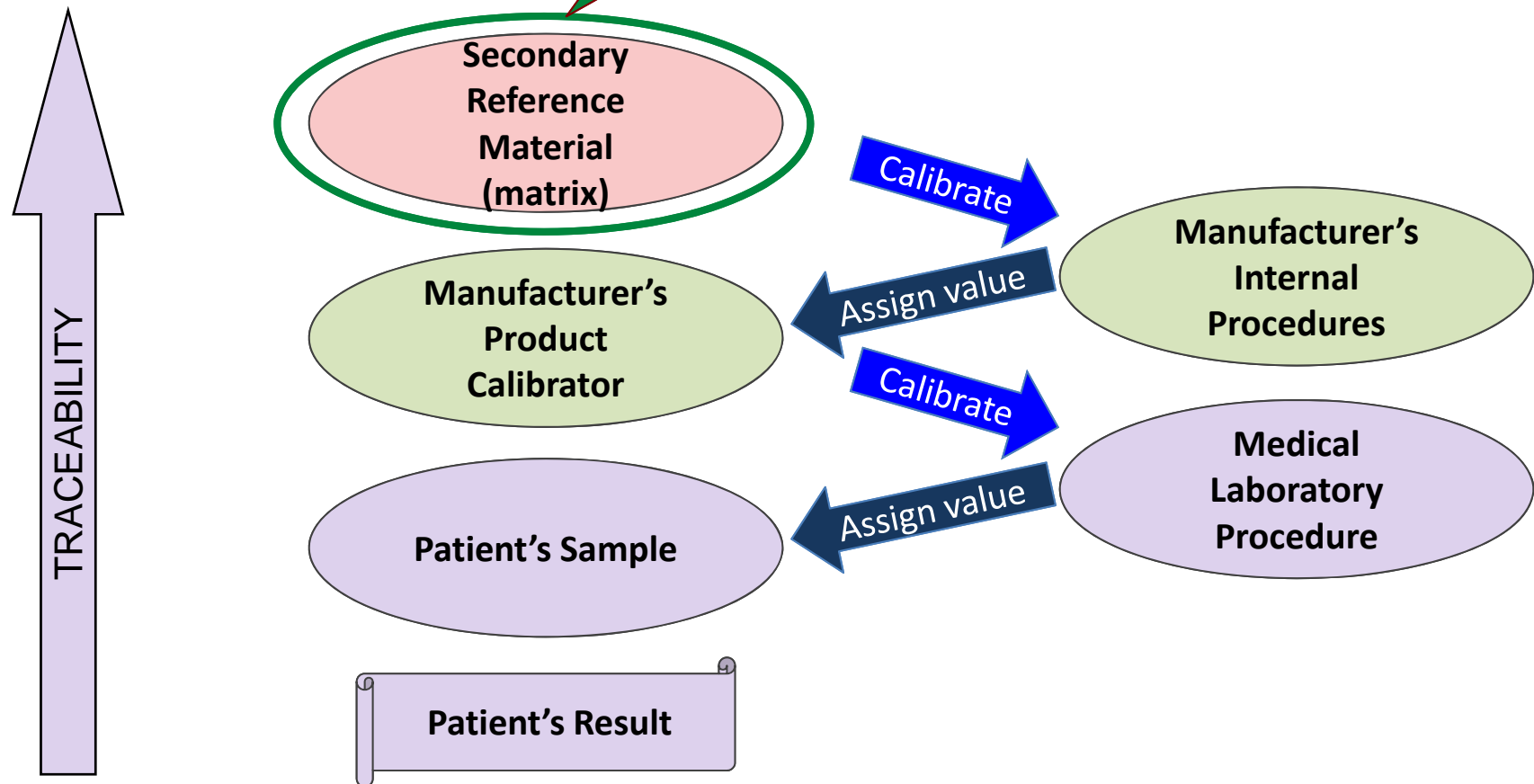
Patient's Result

TRACEABILITY

**Traceability stops here when
no primary reference material
or reference measurement
procedure**



- Must be commutable
- Hasn't always happened



Commutability: now an expectation

Face, Rej, Copeland, Vanderlinde. A discussion of enzyme reference materials: applications and specifications. Clin Chem **1973**;19:5–9.

College of American Pathologists Conference XXIII: Matrix Effects and Accuracy Assessment in Clinical Chemistry, June 1992; Miller, Kaufman, eds. Arch Pathol Lab Med **1993**;117:343-436.

Miller, Myers, Rej. Why commutability matters. Clin Chem **2006**;52:553-4.

Consultation on Commutability of World Health Organization Biological Reference Preparations for *In Vitro* Detection of Infectious Markers, **2013**.

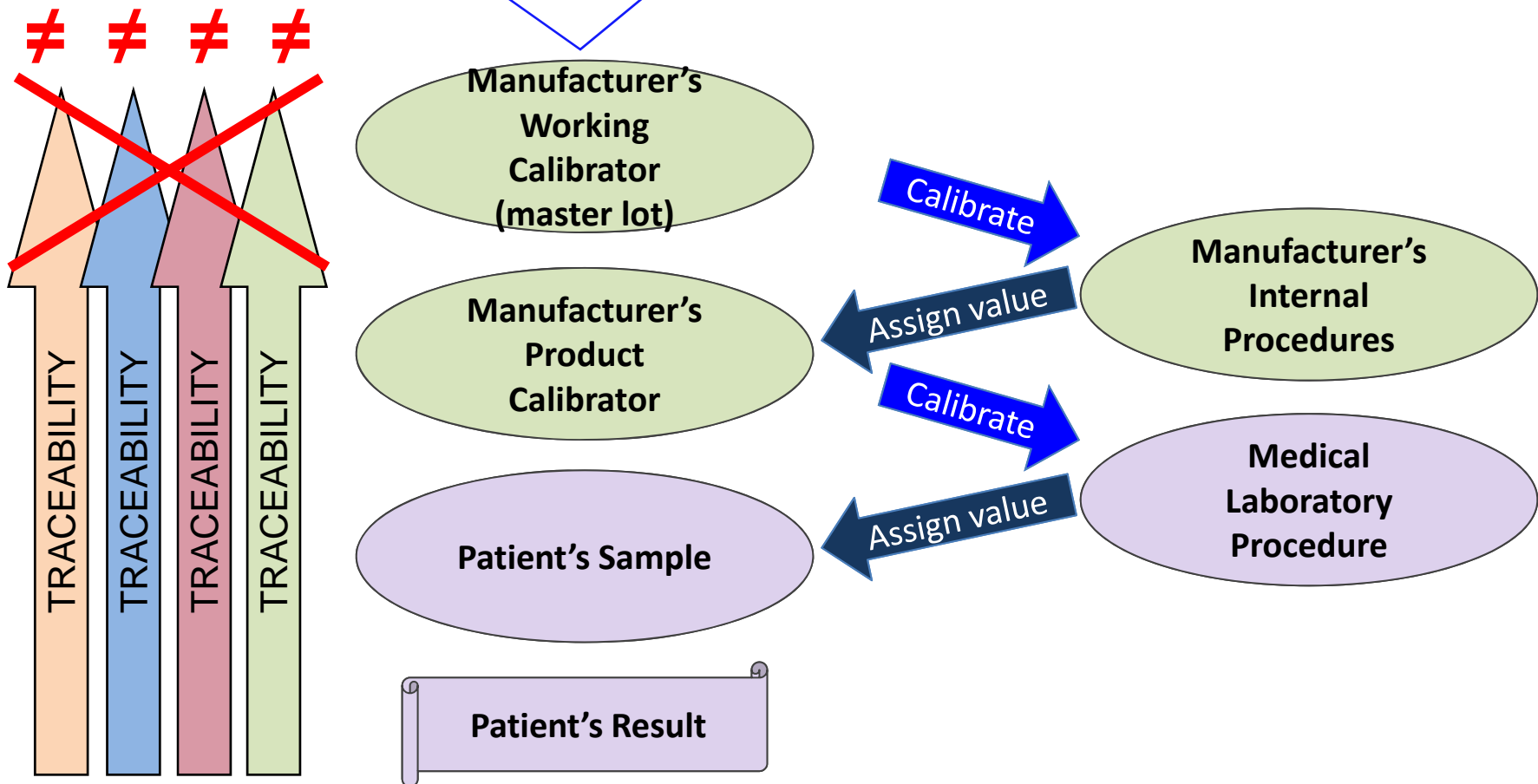
2014, JCTLM requires commutability data when indicated by the intended use of a reference material

What happens when there is both:

- no reference measurement procedure
- no certified reference material

**Traceability is established to to a material selected by
the producer of a measurement procedure**

No coordination among producers (IVD or LDT)



Roadmap for Harmonization of Clinical Laboratory Measurement Procedures

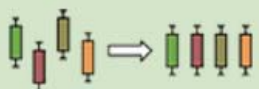
W. Greg Miller,^{1*} Gary L. Myers,² Mary Lou Gantzer,³ Stephen E. Kahn,⁴ E. Ralf Schönbrunner,⁵
Linda M. Thienpont,⁶ David M. Bunk,⁷ Robert H. Christenson,⁸ John H. Eckfeldt,⁹ Stanley F. Lo,¹⁰
C. Micha Nübling,¹¹ and Catharine M. Sturgeon¹²

- ✧ **International Forum organized by AACCC in October, 2010**
- ✧ **Representation from 62 organizations & manufacturers**
- ✧ **90 participants from 12 countries**

The Roadmap

Develop an infrastructure to coordinate harmonization activities world wide:

- 1. Prioritize measurands by medical importance**
- 2. Coordinate the work of different organizations**
- 3. Promote processes for harmonization when there is no reference measurement procedure or certified reference material**



International Consortium
for Harmonization of Clinical Laboratory Results



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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



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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

www.harmonization.net



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Measurands

Measurand	Matrix	Medical Impact of Harmonization ¹	Harmonization Status ²	JCTLM Listed ³	Organization
Alkaline 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		

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Measurands

Measurand

Alkaline 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.



LM
ted 3

Organization

IFCC

IFCC EU-JRC (IRMM)

NKDEP IFCC JSCC

IFCC

IFCC



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Resources

/ Resources

Below are resources to support global harmonization of clinical laboratory measurement procedures.

External link

**International Consortium for
Harmonization of Clinical
Laboratory Results – Current
Status and Future Promise**

Lecture presented at the IFCC 2014
WorldLab Conference

[Read more](#)



Content

**Council/HOG Meeting
Summaries**

Council/HOG Meeting Summaries

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Content

**Strategic Partners Group
Update Reports**

Strategic Partners Group Update
Reports

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Document

**Toolbox of technical
procedures for developing a
process to achieve
harmonization for a
measurand**

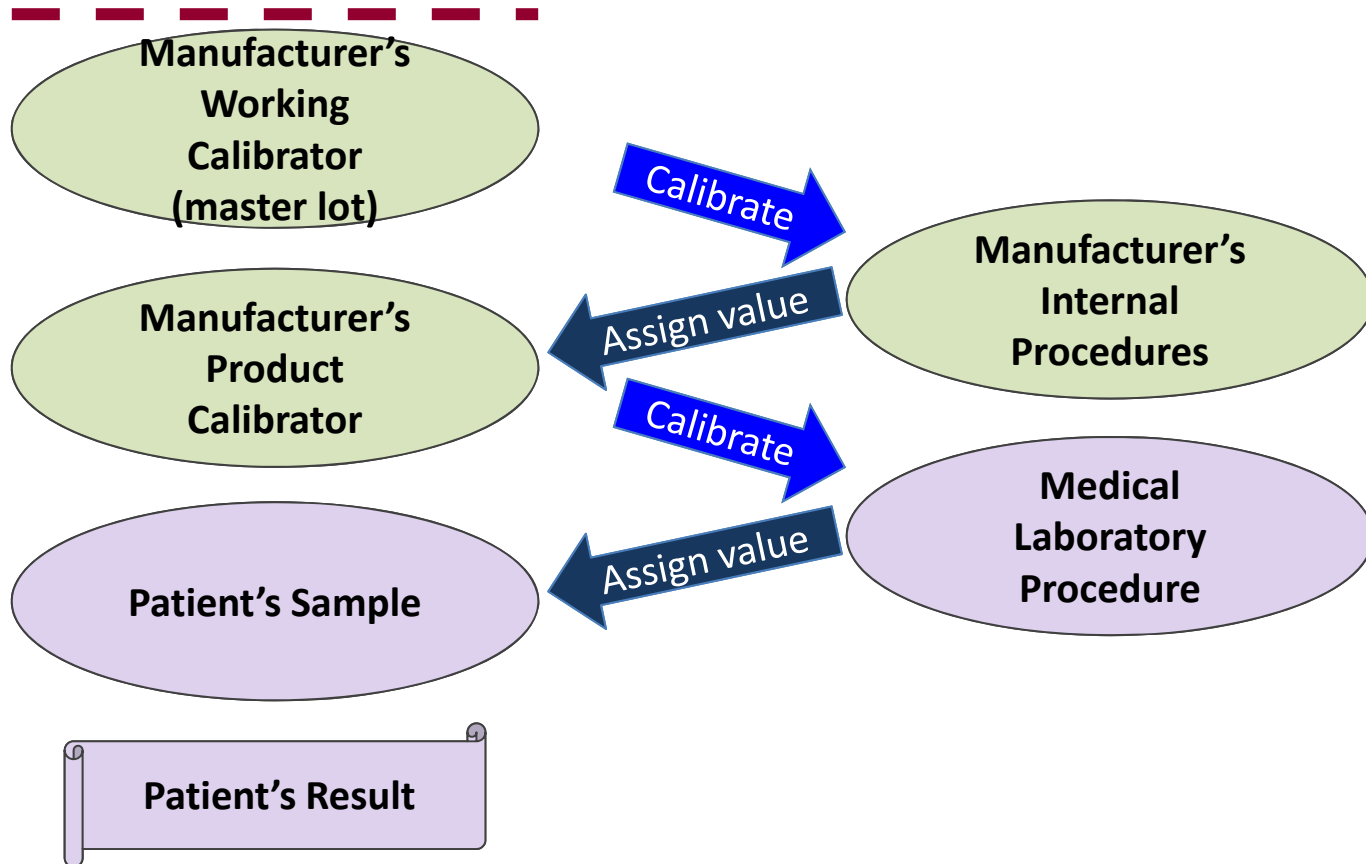
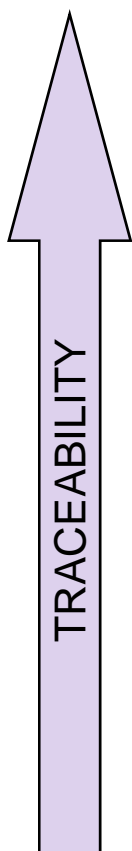
[Read more](#)

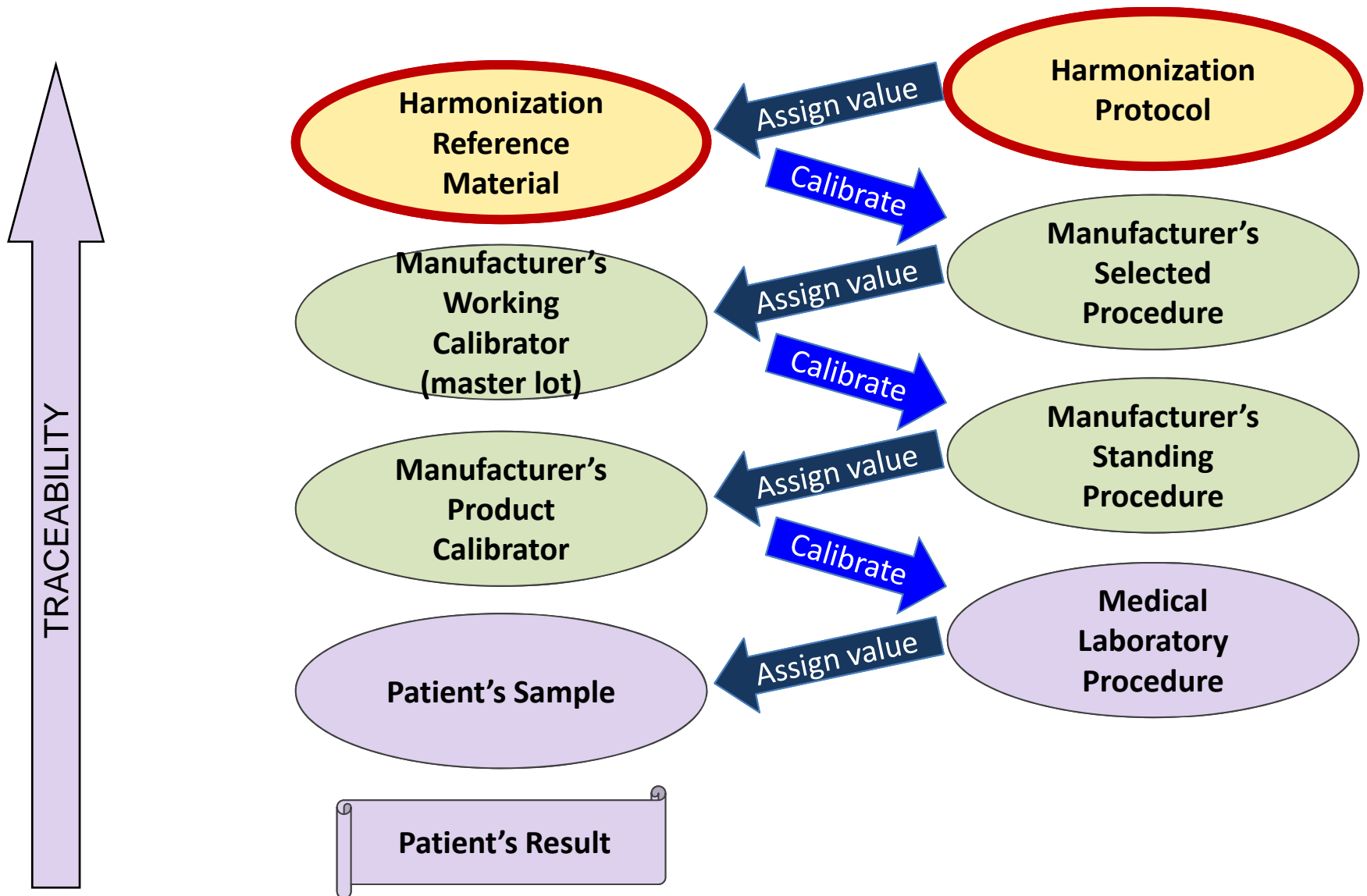




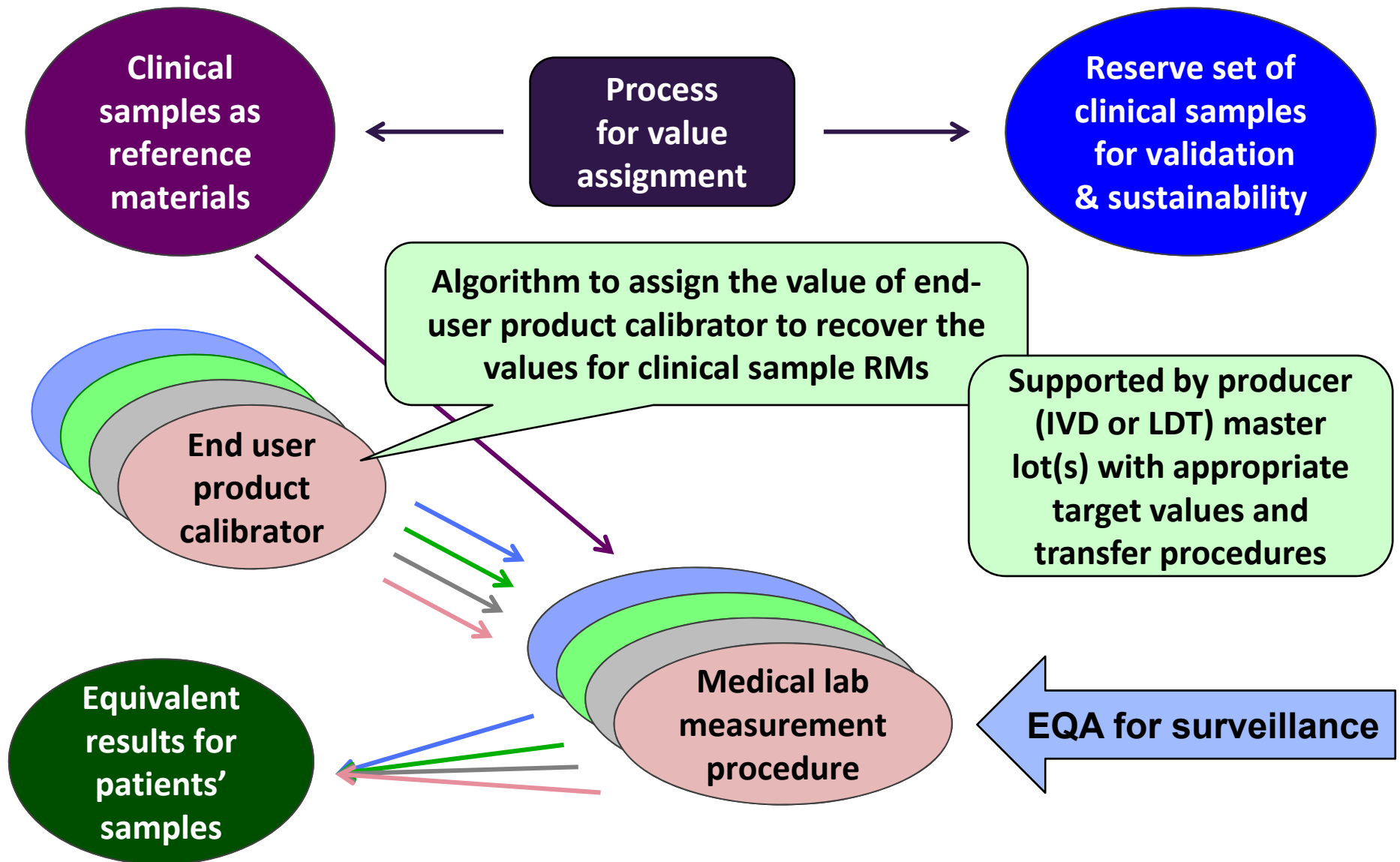
NP 21151: *In vitro diagnostic medical devices -
Measurement of quantities in samples of
biological origin - **Requirements for
international harmonization protocols**
intended to establish metrological traceability
of values assigned to product (end user)
calibrators and human samples*

Will enable JCTLM listing





Example: harmonization protocol





Perfect is the Enemy of Good

We need fit for purpose solutions

What is the ROI for harmonization

Cholesterol and lipids program

- ✧ CDC LSP-CRMLN **cost \$1.7M** in 2007
- ✧ Reduction in deaths during 1980-2000 attributable to statin therapy **saved \$338M to \$7.8B** per year in USA

(Hoerger et al. A cost-benefit analysis of lipid standardization in the United States. Preventing Chronic Disease 2011;8:A136)

Harmonization is inadequately funded

We need to raise public awareness



Theranos attracted millions based only on marketing:

- Less blood volume
- Lower cost testing

Harmonization is inadequately funded

We need to raise public awareness



Harmonization can:

- **Avoid medical errors in diagnosis and treatment**

Other Harmonization Needs

- ✧ **Nomenclature for test orders**
- ✧ **Reporting units**
- ✧ **Interpretive information – decision values and reference intervals**

Electronic Health Record

Focused attention on nomenclature and units

- **RCPA – Australian Pathology Units and Terminology Standards**
- **UK Pathology Harmony**
- **USA – global; Unified Code for Units of Measure; part of Regenstrief Institute**
- **IFCC and IUPAC collaboration**

What is the recommended lab test:

Vitamin D

Vitamin D2

Vitamin D3

25 hydroxy Vitamin D

25-OH vitamin D

1,25 dihydroxy vitamin D

Which digoxin result is critical:

3 ng/mL

0.3 µg/dL

3.8 nmol/L

Interpretive Information

Decision values

Reference Intervals

Decision values

- ❖ Derived from clinical outcomes studies
- ❖ Or from clinical classification systems for diagnosis or therapy
- ❖ **Preferred to reference intervals**
- ❖ **Key lab requirement is harmonization of results and units**

Reference Intervals

- ❖ Central 95% of results from “reference individuals”
 - *why not use the central 99%?*
 - *or the lower and upper confidence limits?*
- ❖ How to qualify a “reference individual”
- ❖ Risk of adverse outcome may be different than the reference interval

Creatinine Example

- ✧ **CKD has no symptoms until approaching kidney failure**
- ✧ **“Adult” RI is misleading:**
 - **How many adult “reference individuals” have CKD**
 - **What was the distribution of muscle mass**
 - **What were the ages: GFR goes down with age**

Upper limit of RI is consistent with loss of one-half of kidney function – NOT NORMAL

AST, RI = 10-40 U/L

- Does a value of 45 U/L mean liver disease or undetected hemolysis? What about 50 U/L?

Albumin, RI = 3.5-5.0 g/dL

- Does a value of 32 g/L mean nutritional deficiency, sub-clinical inflammation, or posture (inpatients vs. outpatients)?

Reference Intervals

- ✧ Current practice is a mess
- ✧ Many IVD manufacturer RIs are from literature; may not even be for the same measurement procedure
- ✧ Labs are expected to establish or verify RIs but do not have resources

Common Reference Intervals



Common Reference Intervals

Prerequisites:

- **Harmonized results**
- Similar population characteristics

Common Reference Intervals

- New Zealand: SIQAG, ARQAG, LNIQAG
- Australia: AACB Committee for Common Reference Intervals
- UK: Pathology Harmony
- Nordic Reference Interval Project 2000
- IFCC Committee on Reference Intervals and Decision Limits

Common but not Universal

Analyte	Unit	AACB	Nordic	UK
Sodium	mmol/L	135-145	137 -145	133 -146
Potassium	mmol/L	3.5-5.2	3.6- 4.6	3.5-5.3
Bicarbonate	mmol/L	22-32	22-32	22- 29
Calcium	mg/dL	8.4-10.4	8.8- 10.0	8.8-10.4
ALP	U/L	30-110	35- 105	30- 130

Adapted from an AACB Special Report (2014); www.aacb.asn.au/documents/.../3201



Harmonization

**One of the most important challenges
in laboratory medicine**

**Non-harmonized results contribute to
medical errors**



Regulation

A challenge to harmonization

Regulation

Medical laboratories are regulated to:

- ✧ **Protect public safety**
- ✧ **Ensure appropriate health care is available**

FDA

Premarket Notification (510K) and FDA clearance required to sell medical devices in USA

- ✧ **Safe and effective**
- ✧ **Substantial equivalence to a predicate device**
- ✧ **Required for significantly changed or modified device to the extent that its safety or effectiveness could be affected**

FDA

Recalibration to conform to a national or international harmonization recommendation has been interpreted to be **a significant change**

Cost to resubmit is millions of dollars

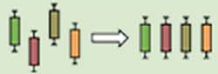




Cooperation



- ✧ **AACC, FDA and AdvaMed sponsored a forum in 2013 to address recalibration issues**
(www.harmonization.net/Resources)
- ✧ **IFCC C-STFT has arranged coordination between FDA and IVD manufacturers**



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Resources

/ Resources

Below are resources to support global harmonization of clinical laboratory measurement procedures.

External link

Roadmap for Harmonization
of Clinical Laboratory
Measurement Procedures
Clinical Chemistry 2011 v. 57,
p. 1108–1117.

[Read more](#)



External link

AACC Position Statement on
Harmonization of Clinical
Laboratory Test Results

[Read more](#)



Document

AACC/AdvaMedDx/FDA
Forum on Regulatory Issues
in Harmonization, 2013

[Read more](#)



Document

International Consortium
for Harmonization of
Clinical Laboratory Results:
Operating Procedures

[Read more](#)



www.harmonization.net

What has changed by recalibration

- **Numeric value**
- **Reference interval**
- **Measuring interval**

Changes will be proportional to the numeric value change

Nothing else is changed by recalibration

- **Precision**
- **Selectivity**
- **Interfering substances**

Should not require a full resubmission

The important change is that **harmonized laboratory results reduce medical errors**

Patient safety is improved

❖ **FDA agrees with these concepts**

❖ **FDA concerns are**

✧ **Coordination of implementation among measurement procedure producers**

✧ **Education of laboratories and clinical care providers to ensure a smooth transition to harmonized results**

- ❖ **FDA is willing to develop guidance to simplify the process for clearance of recalibrated measurement procedures**
- ❖ **FDA has suggested that manufacturers coordinate their submissions for recalibrated measurement procedures**
- ❖ **FDA has requested to be kept informed and involved in harmonization activities**

Remember

- **Non-harmonized results cause medical errors**
- **Medical and economic impact is poorly studied**
- **“We” need to pay more attention to this defect**



- **Practitioners**
- **IVD Industry**
- **Public health organizations**
- **Metrology institutes**
- **Regulators**
- **Patient advocacy groups**

The road ahead

- ✓ **Be part of the health care team**
- ✓ **Cooperate with other stakeholders**
- ✓ **Engage in legislative and regulatory processes**
- ✓ **Engage with patient advocate groups**





Cooperation



Harmonization



Regulation