International Developments in Standard Materials for Clinical Laboratory Testing

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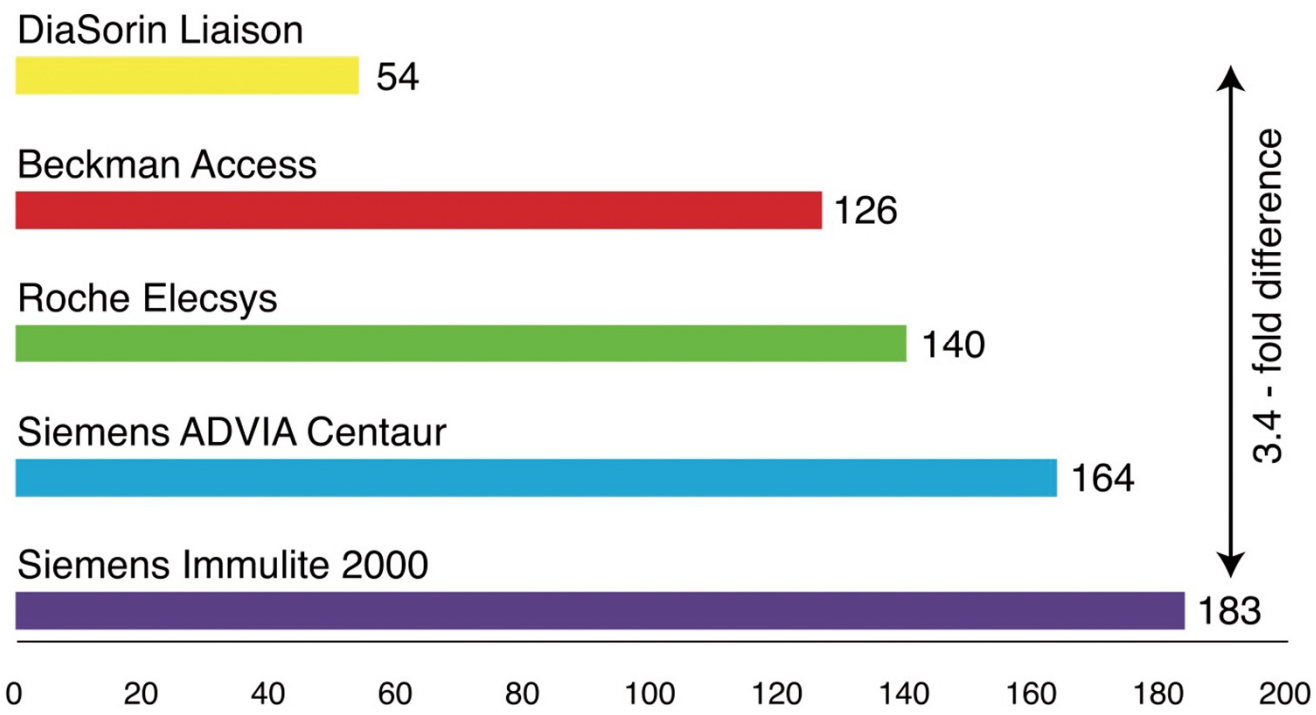
PTH results - single patient



Results in pmol/L.
1 pmol/L ~ 9.5 ng/L

In the patients studied, differences ranged from 1.4-fold to 4.2-fold (mean 2.8-fold) although manufacturers' reference ranges are similar.

Almond, Walker & Ellis. Ann Clin Biochem 2012; 69: 43-7

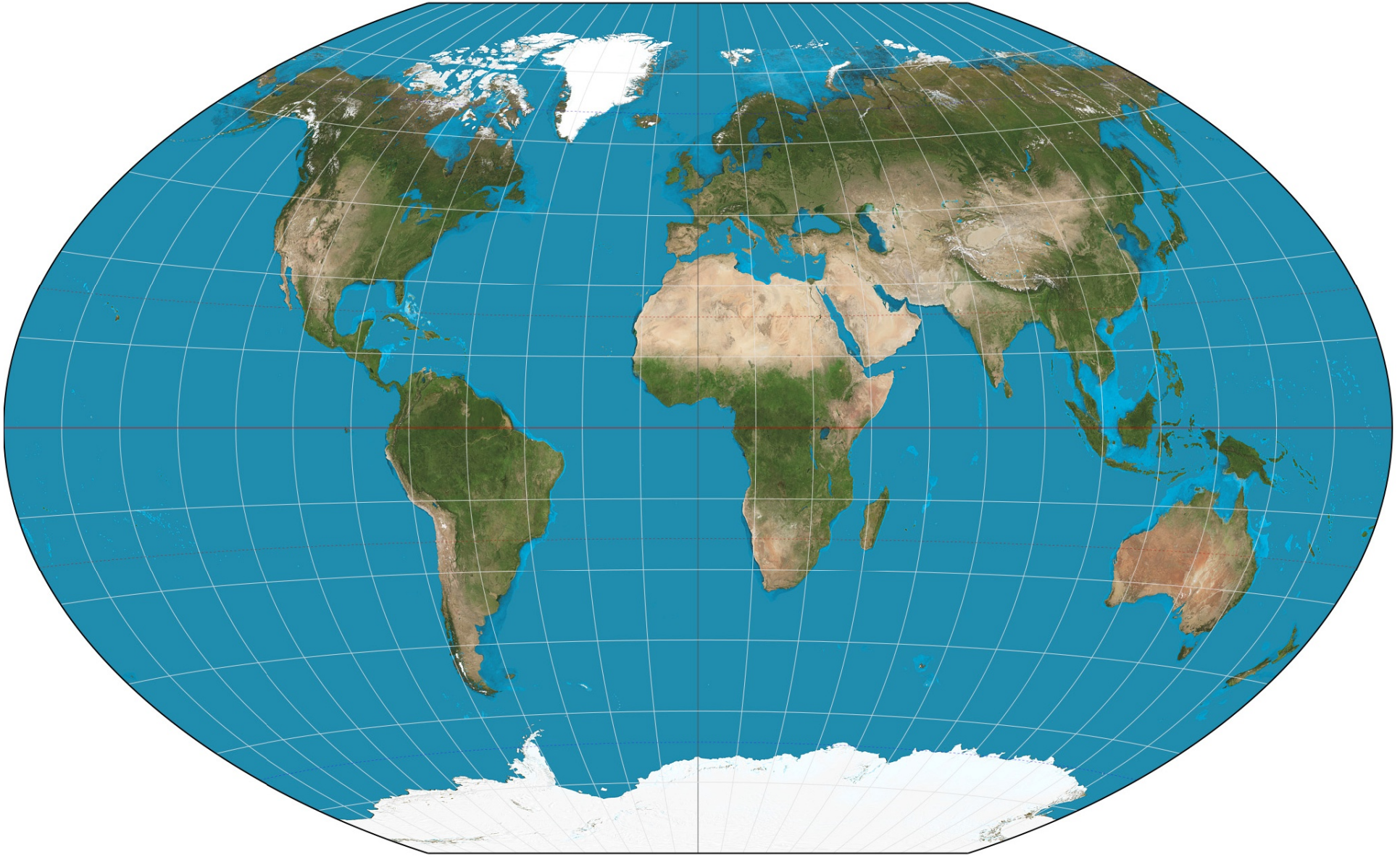
Why do we need comparable results

- If different measurements give different results for the same patient sample:
  - ⇨ Clinicians and patients may become confused
  - ⇨ Interpretive guidelines become less useful
  - ⇨ **Patients may receive incorrect treatment**

KDOQI Clinical Practice Guidelines for Bone Metabolism and Disease in Children With Chronic Kidney Disease

Table 3. Target Range of Serum PTH by Stage of CKD

CKD Stage	GFR Range (mL/min/1.73 m²)	Target Serum PTH
2	60-89	35-70 pg/mL (OPINION)
3	30-59	35-70 pg/mL (OPINION)
4	15-29	70-110 pg/mL (OPINION)
5	<15 or dialysis	200-300 pg/mL (EVIDENCE)



National Metrology Institutes

National Societies

WHO

IFCC

Diagnostics Industry

Regulators

JCTLM

International Harmonization Consortium

About the IFCC

- A worldwide, non-political organization for clinical chemistry and laboratory medicine
- Global standard setting in collaboration with other international organizations
- Supporting its members through scientific and educational endeavour
- Providing a series of congresses, conferences and focussed meetings in order for laboratory medicine specialists to meet and present original findings and best practice

IFCC-SD – Working in Partnership

- IFCC Divisions
- Corporate members
- Metrology institutions
- Governmental bodies and non-Governmental organisations
- Other professional bodies
- Clinicians and clinical organisations

IFCC SD

Mission: to advance the science of Clinical Chemistry and to apply it to the practice of Clinical Laboratory Medicine

- By identifying technical innovations and diagnostic strategies and assisting the transfer of these to the profession
- By promoting the standardization of laboratory tests and the comparability of patient results through the development of reference measurement systems, or harmonization activities where this is not currently possible
- By establishing standards for scientific and technical aspects of good laboratory practice

Scientific Division

Committees	Working Groups
Theme orientated	Task orientated

How to achieve comparable results

- Harmonization / standardization
- Calibration of all measurement procedures is traceable to a common reference system
- Performance is monitored and maintained by surveillance using PT, EQA or a certification program

Traceability categories from ISO 17511

Standardization

Category	Reference measurement procedure	Primary (pure substance) reference material	Secondary (value assigned) reference material	Examples
1	Yes	Yes	Possible	Electrolytes, glucose, cortisol
2	Yes	No	Possible	Enzymes
3	Yes	No	No	Hemostatic factors
4	No	No	Yes	Proteins, tumor markers, HIV
5	No	No	No	Proteins, EBV, VZV

Harmonization

Terminology

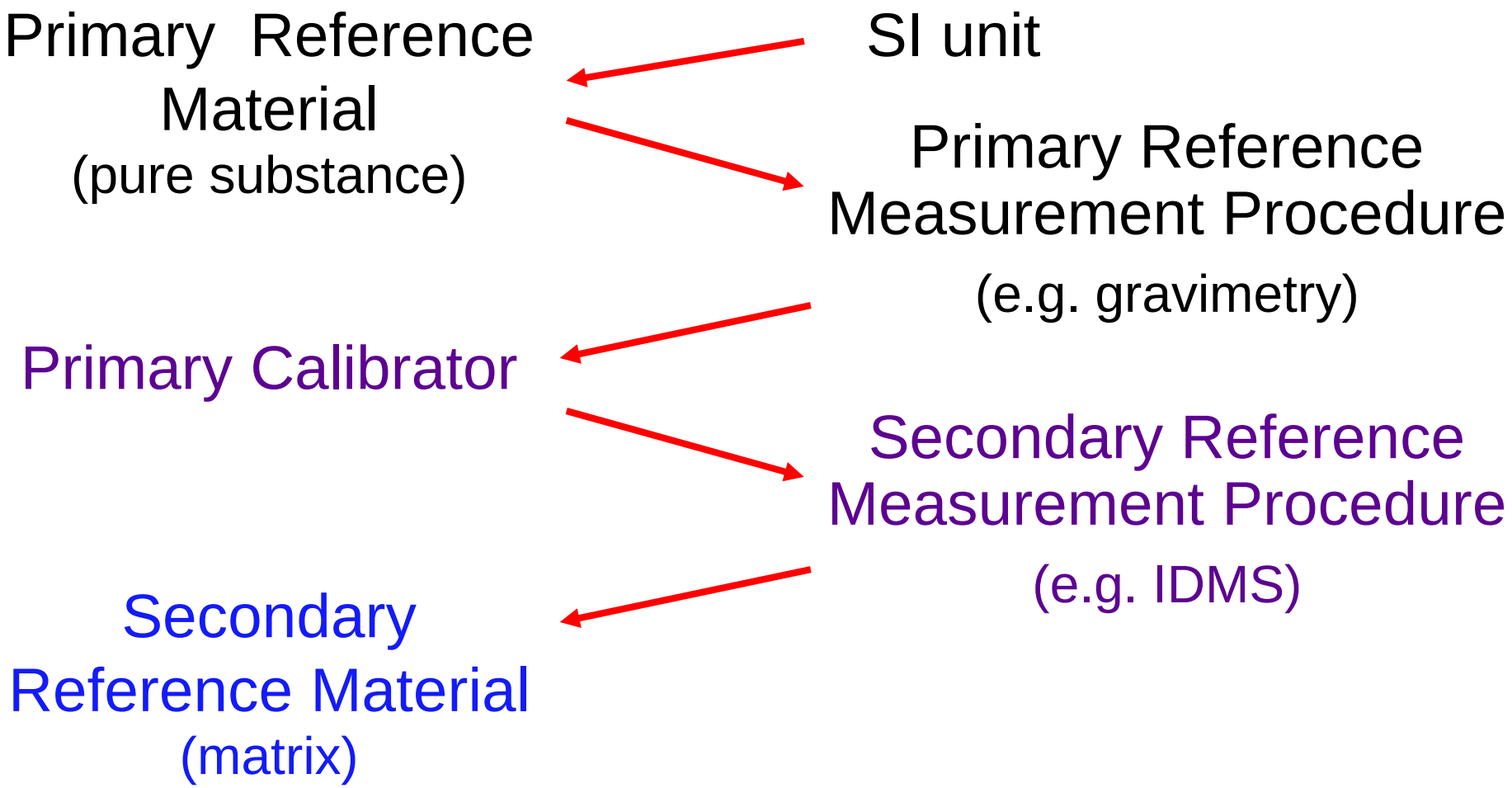
- **Standardization**: results are uniform among measurement procedures
  - ⇨ traceability is established to SI using a reference measurement procedure
- **Harmonization**: results are uniform among measurement procedures
  - ⇨ NO reference measurement procedure and no "pure substance" reference material exists

Advantages of standardization

- Trueness-based results with a firm and consistent anchor are possible
- New analytical procedures should give consistent results
- Long term continuity of results is easier to maintain

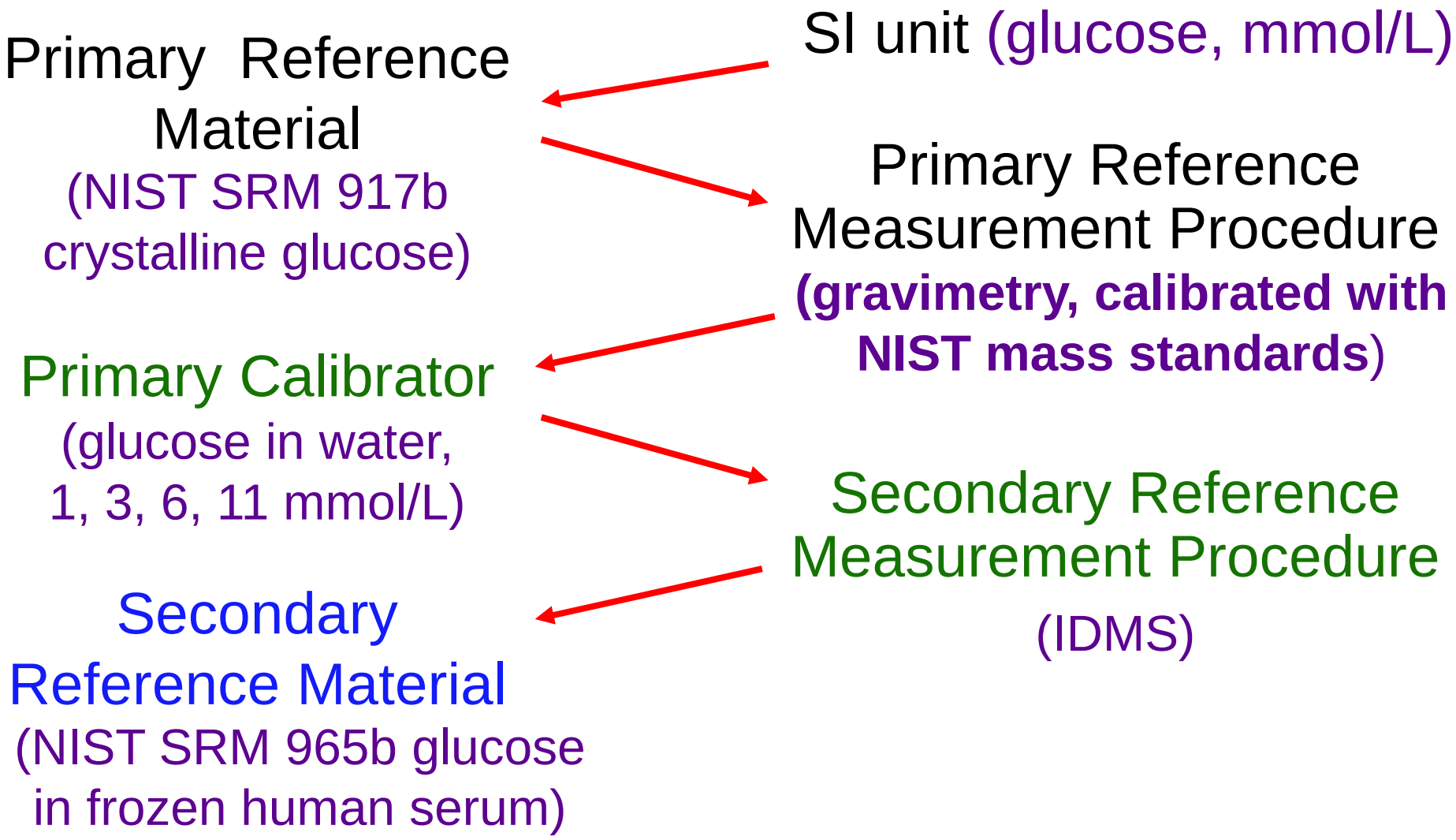
Traceability (based on ISO 17511)

A reference system (ideal)

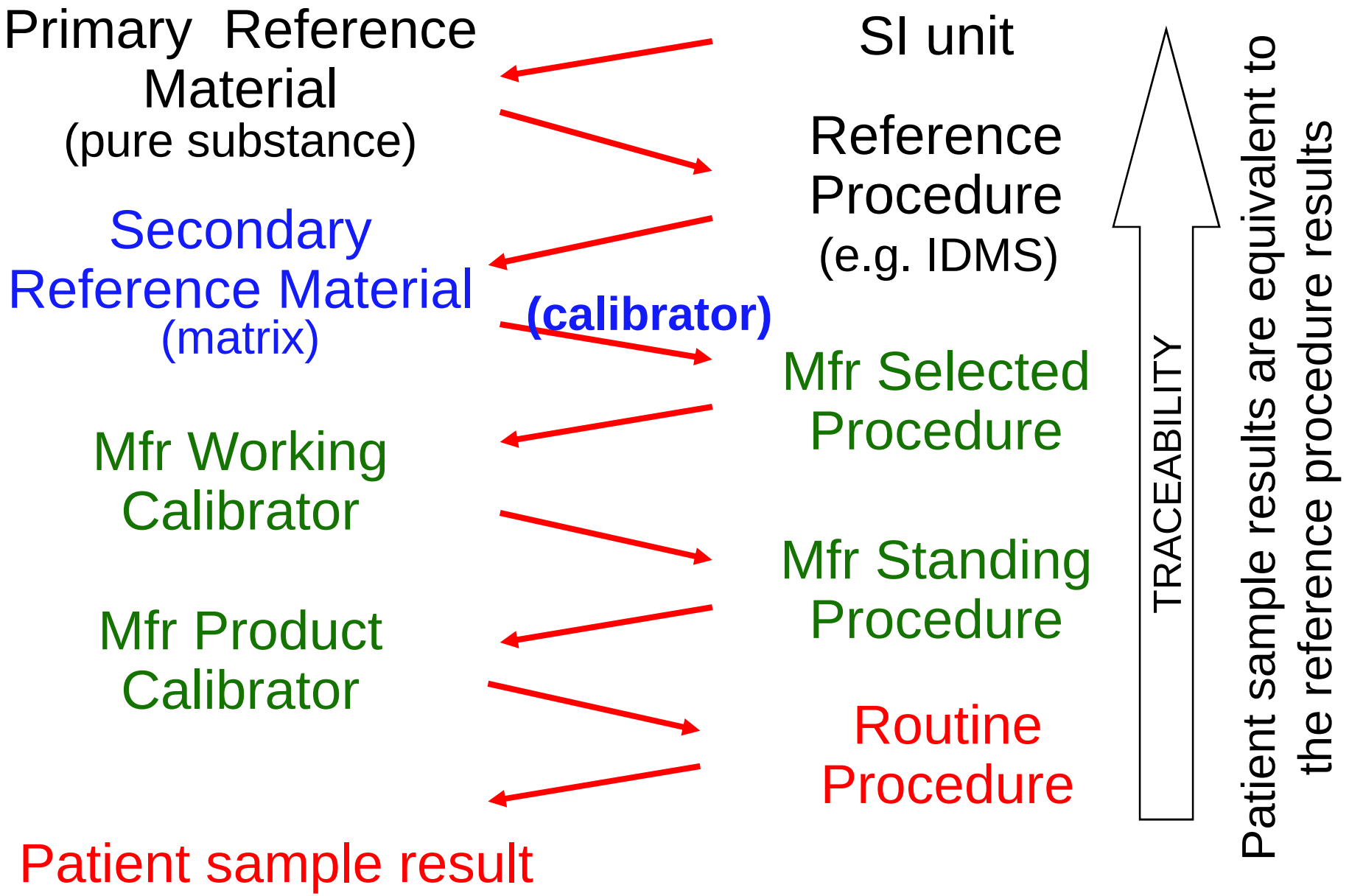


Traceability (based on ISO 17511)

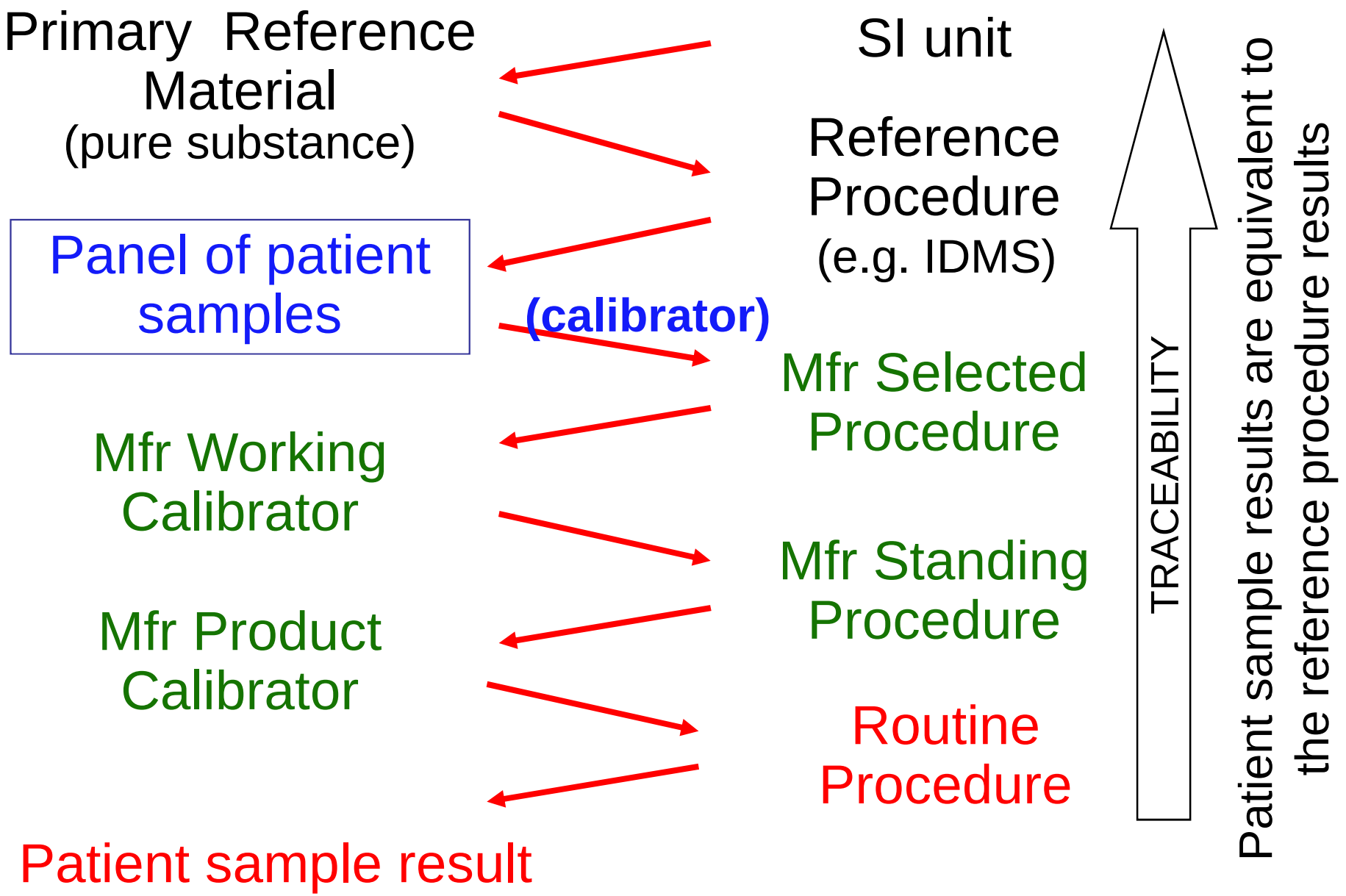
A reference system for glucose



Traceability (based on ISO 17511)

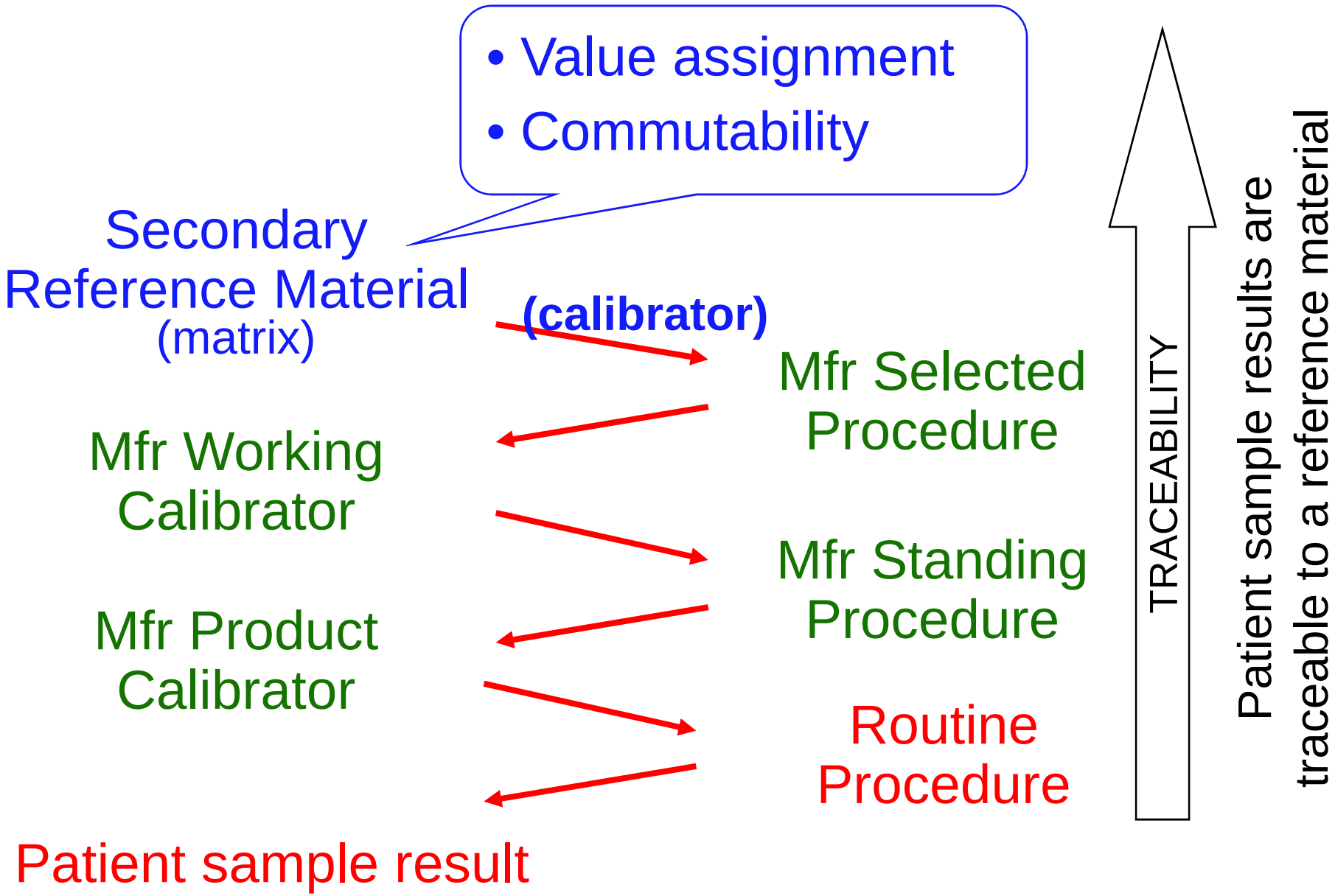


Traceability (based on ISO 17511)



What happens when there is no reference measurement procedure

Traceability (based on ISO 17511)



Value assignment when there is no reference measurement procedure

International conventional calibrator (reference material)

- ⇨ Arbitrary e.g. U/L
- ⇨ Bioassay for hormone activity
- ⇨ An arbitrary designated comparison procedure

Traceable to an international conventional reference material

- The true value is not known
- Since the goal of harmonization is comparable results irrespective of the measurement procedure used,
- **Clinical guidelines can still be implemented**

Examples: traceable to a reference material

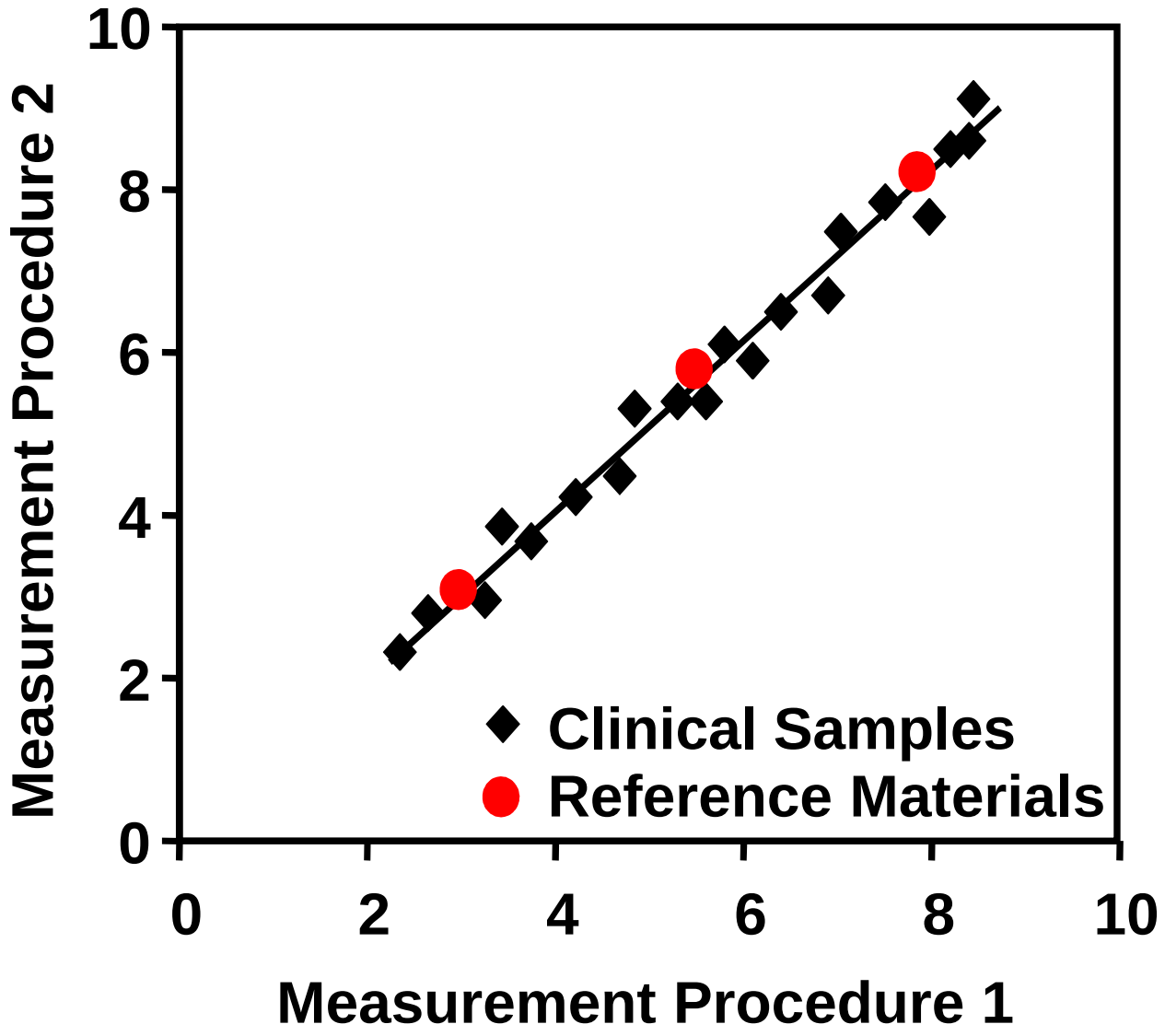
(no reference measurement procedure)

- Human chorionic gonadotropin
- Prostate-specific antigen
- Thyroid stimulating hormone
- Human immunodeficiency virus

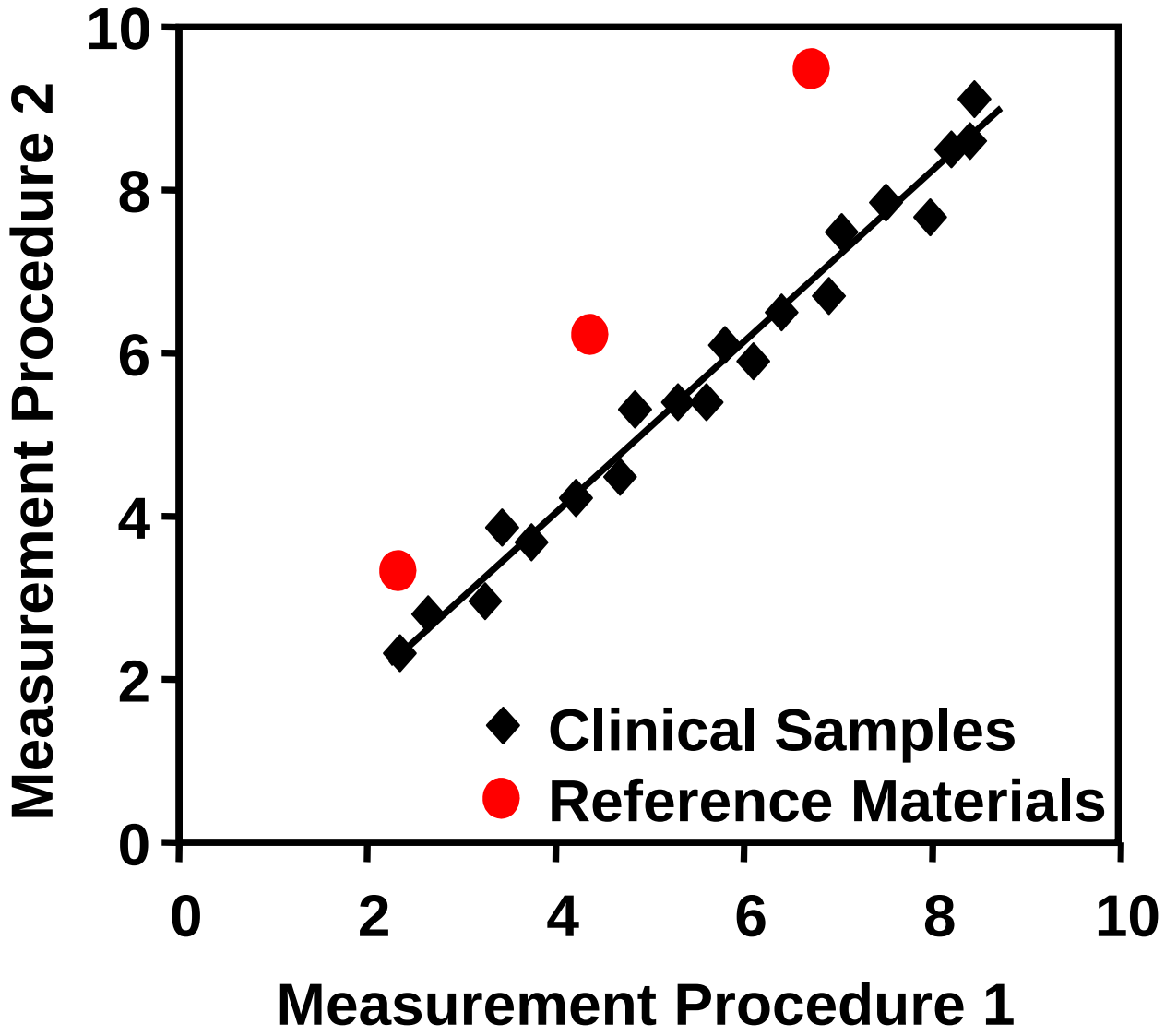
Traceability requires commutable calibration materials

Commutable means that values measured for a calibration material and for native clinical samples have the same relationship between two, or more, measurement procedures for the same measurand.

Commutable: same relationship for clinical samples and reference materials



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



Use of a non-commutable material for calibration traceability will cause:

- Incorrect value assignment for a routine (field) measurement procedure calibrator
- Incorrect results for patient samples

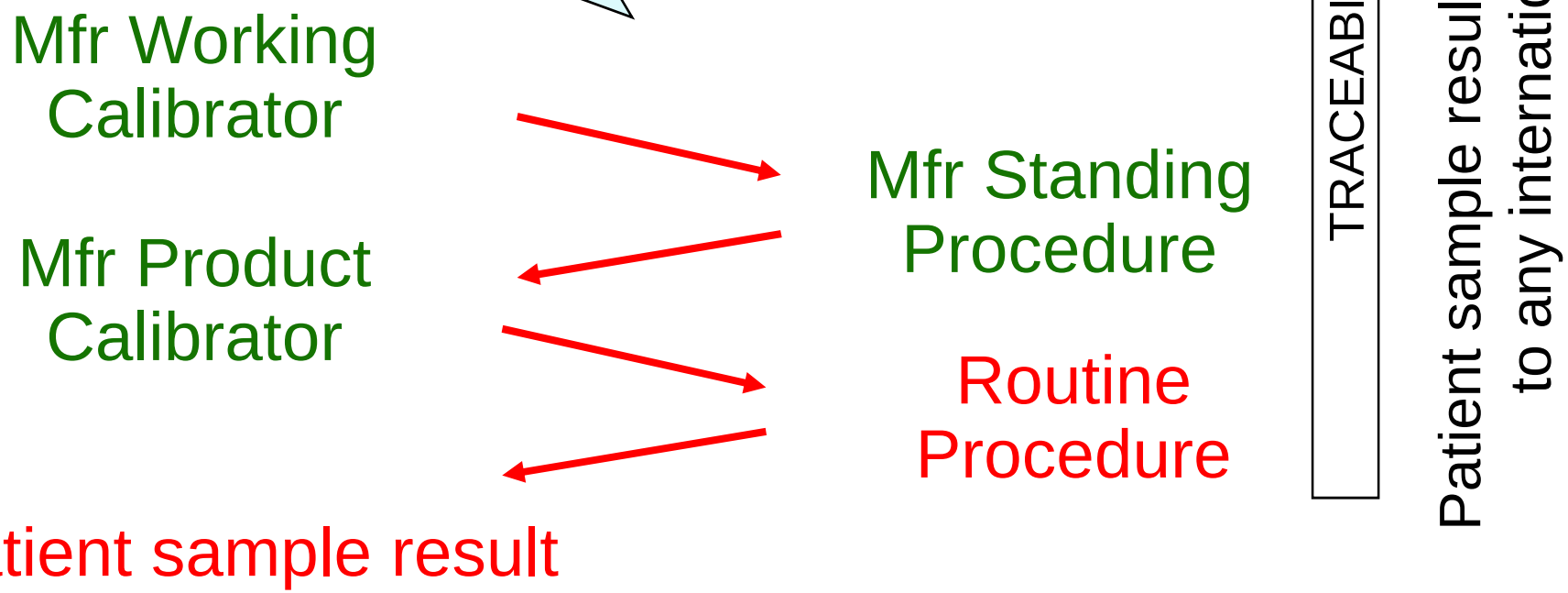
Miller, Myers, Rej. Why commutability matters. Clin Chem 2006; 52: 553-4 .

What happens when there is both:

- no reference measurement procedure
- no reference material

Traceability (based on ISO 17511)

- **There is no coordination among manufacturers**
- **Method specific reference intervals or decision values are used**



Examples: traceable to a manufacturer's working calibrator

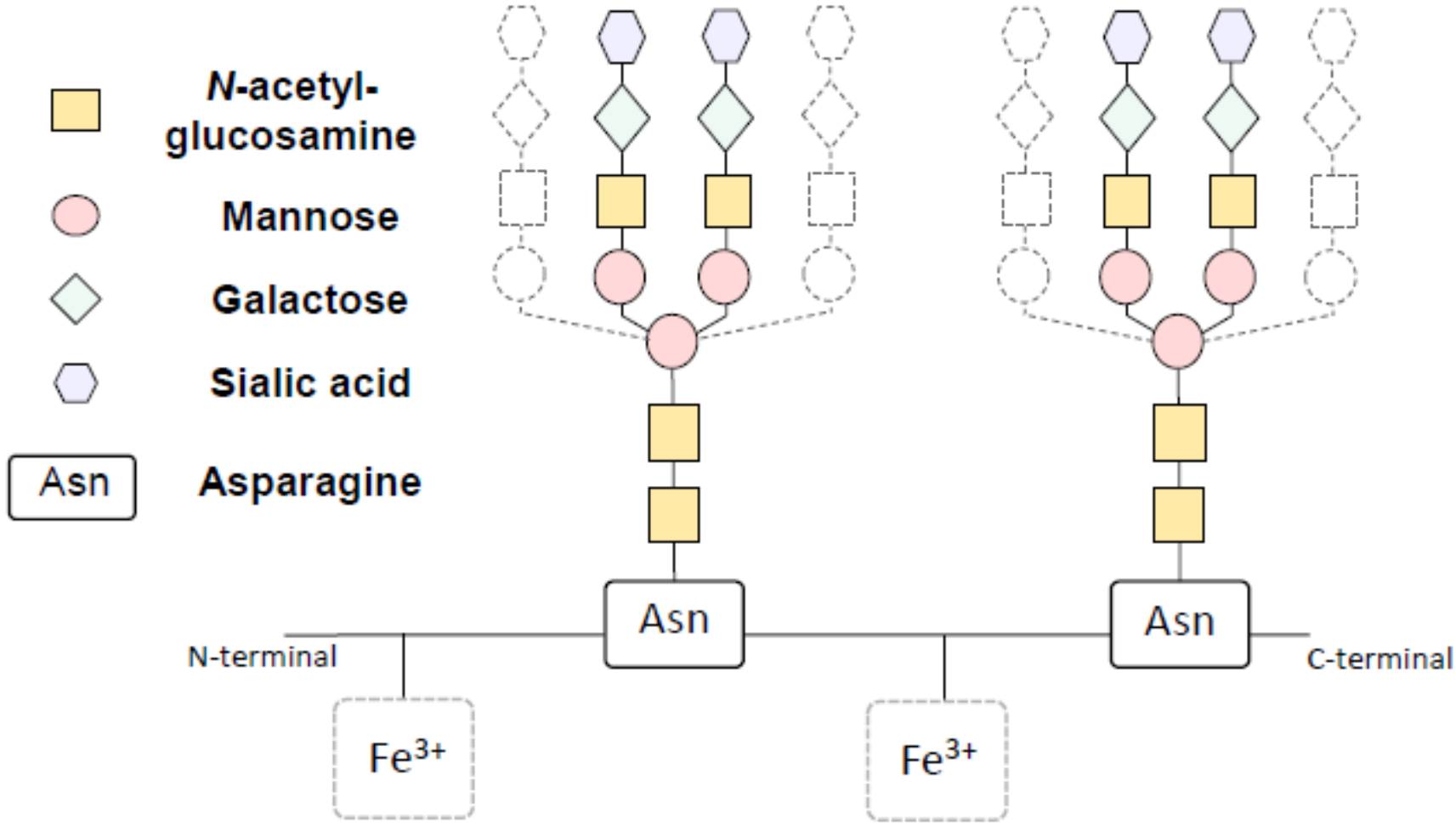
(no reference material nor reference measurement procedure)

- B-type natriuretic peptide
- CA-125
- Epstein-Barr virus
- Varicella zoster virus

The example of Carbohydrate Deficient Transferrin (CDT)

- **CDT is the generic term that refers to the transferrin glycoforms whose concentration in blood is temporarily increased by sustained alcohol consumption**
- **Tetrasialotransferrin, consists of two biantennary chains and represents approximately 80% of the total.**

Tetrasialo-Tf

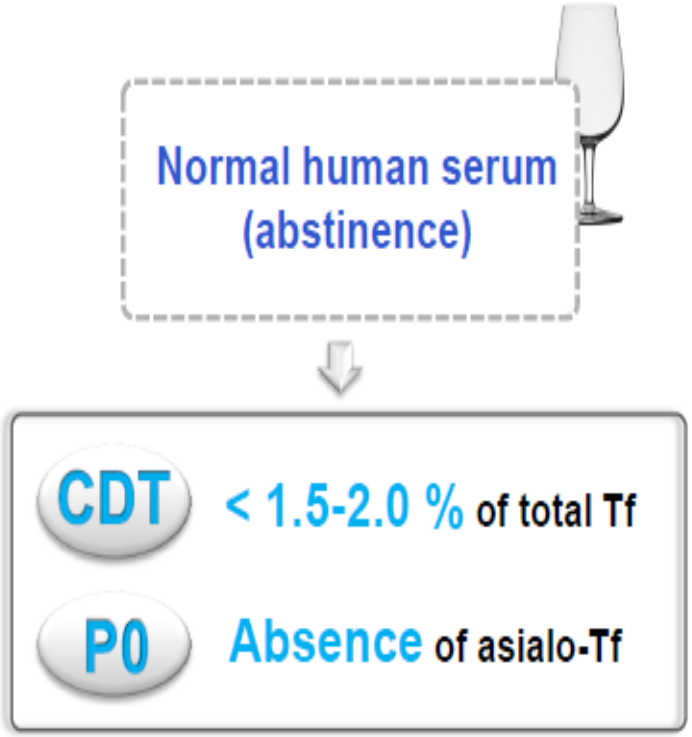


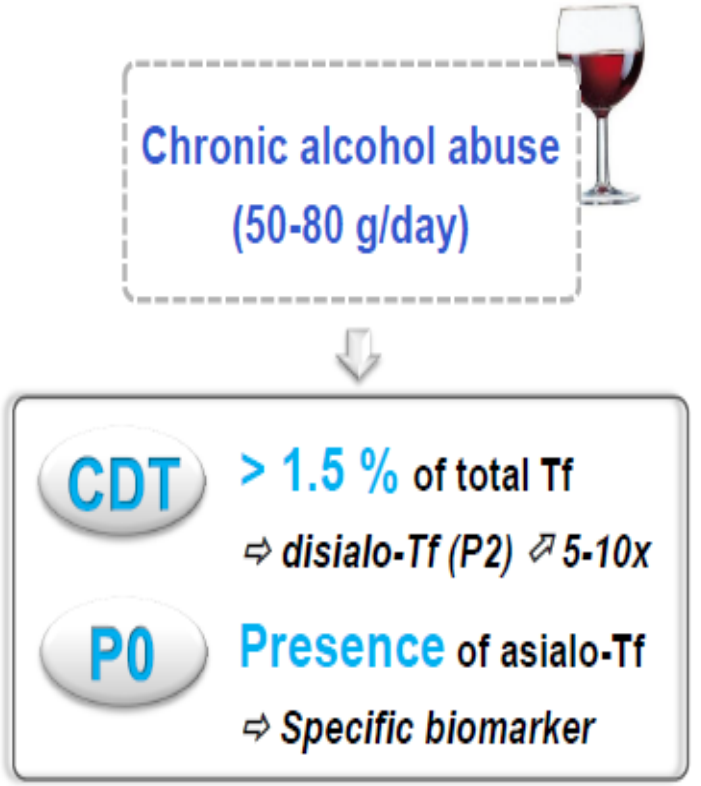
Other glycoforms of CDT

- pentasialotransferrin (≈15%)
- trisialotransferrin (≈4%)
- disialotransferrin (≈1.5%)
- hexasialotransferrin (≈1%)

Effect of alcohol consumption on CDT

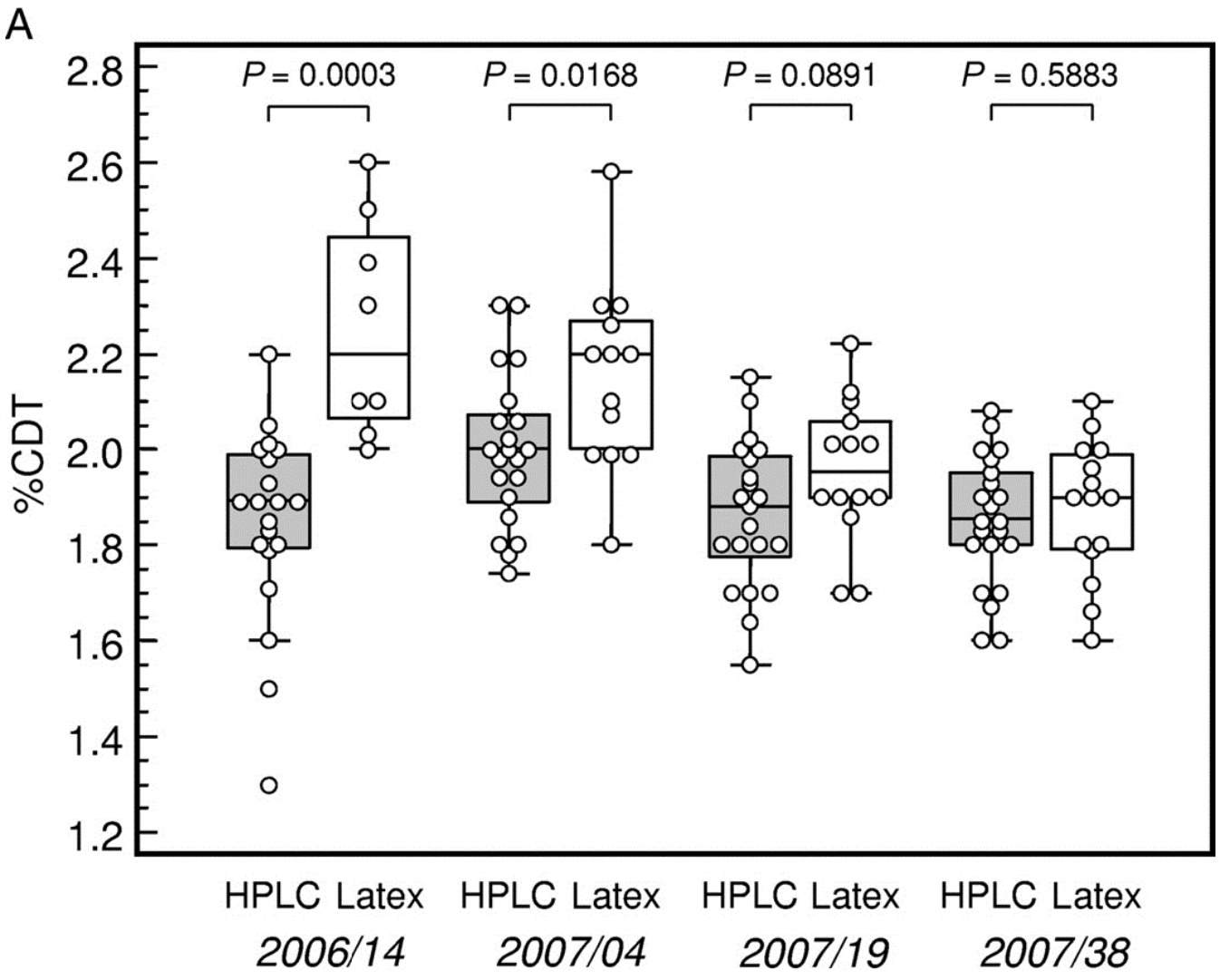
- **Alcohol consumption of more than 60 g/d for more than two weeks leads to a relative increase of disialotransferrin.**
- **When disialotransferrin level reaches approximately twice the initial level, asialotransferrin becomes detected.**





Stibler H., Allqulander C., Borg S., Kjellin KG., Acta Med Scand 204 (1978)49

Need for CDT standardization



CDT standardization

- **Disialotransferrin (disialylated monoglycan transferrin) was defined as the measurand and the target analyte for standardization**
- **HPLC with photometric detection was proposed as the candidate reference method**
- **A network of reference laboratories running this method was formed that demonstrated good within- and between-laboratory performance**

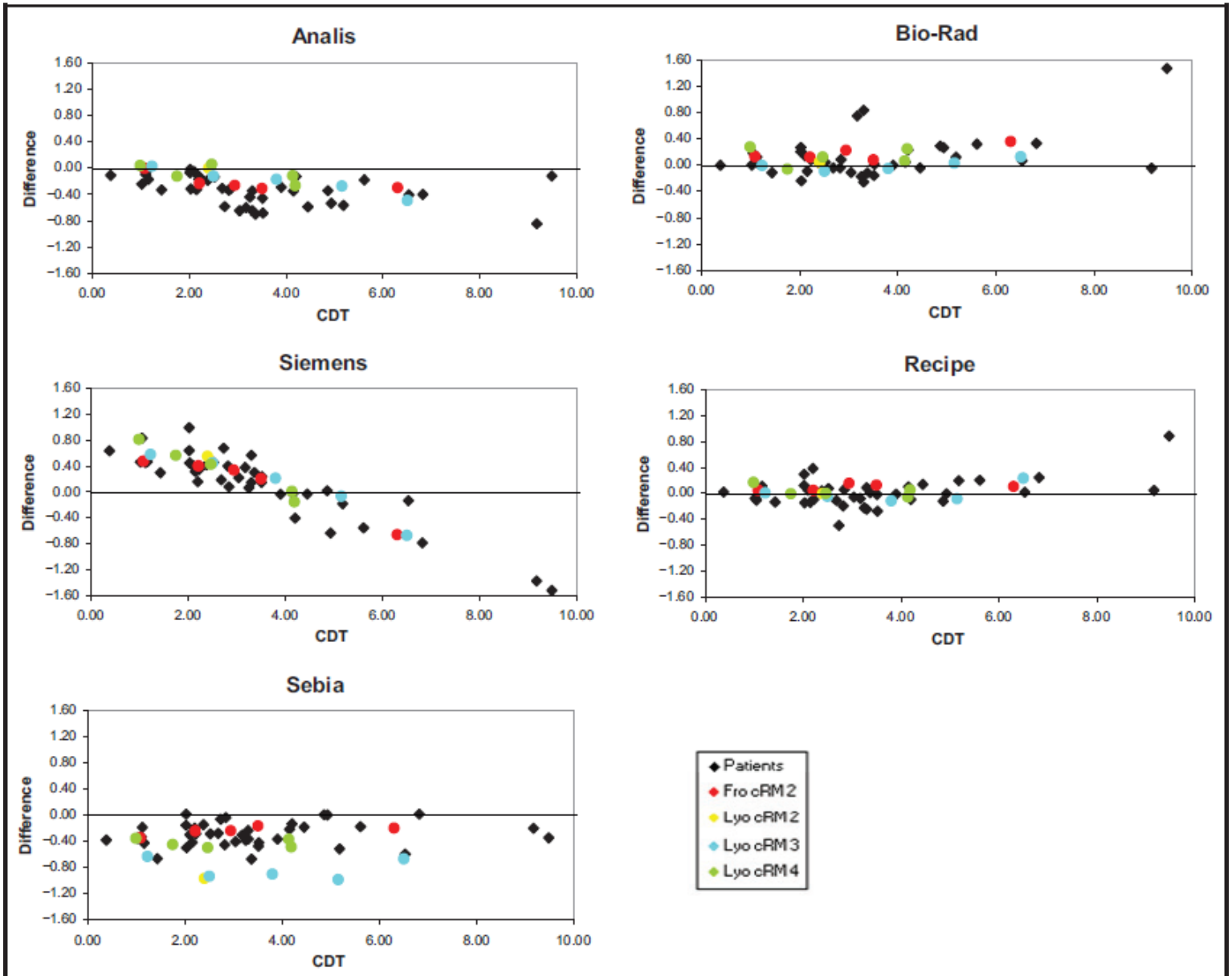


Fig. 1. Bland–Altman plots for commutability. Commutability of the 3 batches of lyophilized cRMs (Lyo cRM 2, 3, 4) and 1 batch of frozen cRMs (Fro cRM 2) for the routine MPs.

CDT concentrations in IFCC CDT units are on the *x* axis. Differences in CDT between the respective routine MPs and the cRMP in IFCC CDT units are on the *y* axis.

Table 4. Success of harmonization of CDT routine MPs: intermethod CV and recovery target values after calibration with frozen cRMs.

		All routine measurement procedures									
		Inter-MP CV		Recovery target[a]		Recovery target individual routine MP[a]					
Samples	n	Uncalibrated, %	Calibrated, %	Mean MPs	Target reference labs	Analis	Bio-Rad	Helena	Siemens	Recipe	Sebia
Patient sera	20	8.8	3.4	3.07	3.09	3.02	3.07	2.97	3.10	3.04	3.13
Low (<1.3%) CDT	3	21.1[b]	9.6[b]	1.28	1.30	1.34	1.41	1.38	1.30	1.20	1.17
High (>10%) trisialotransferrin	4	13.9[b]	9.3[b]	4.05	4.30	3.52[c]	4.65[c]	4.22	4.05	3.85[b]	4.14

[a] CDT expressed in IFCC CDT units (% disialotransferrin).
[b] Significantly different from patients ($P < 0.05$).
[c] Significant different from target ($P < 0.05$).

Major Challenges

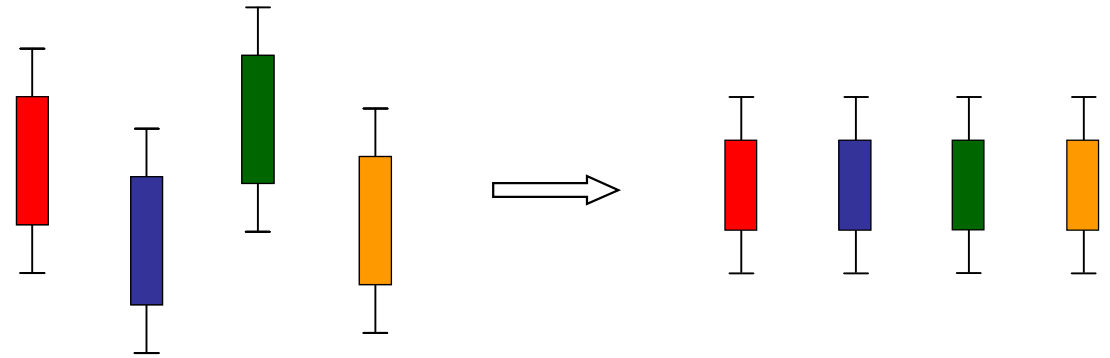
- **International co-ordination of activities**
- **Prioritizing the measurands for which there will be greatest impact**
- **Dealing with new assays**

Co-ordination of International Activities

- Need for a clearing house or registry for standard materials
- Analagous to clinical trials registration
- Might be hosted by JCTLM

International Consortium for Harmonization of Clinical Laboratory Results

Harmonization.net



AACC

http://www.ifcc.org/ifcc-scientific-division/

Prioritizing measurands

- **Approach to date has been piecemeal**
- **Resources are limited**
- **Key factors:**
  - **Frequency of measurement**
  - **Extent of between method differences**
  - **Potential for clinical impact**

Growth Hormone Testing

- Several clinical practice guidelines on the diagnosis and management of adult GHD o refer to published diagnostic cut-off criteria
- The diagnostic accuracy of provocative tests of GH secretion is hampered by a lack of standardization of GH assays
- The same patient blood sample sent to different laboratories can yield different GH concentrations.

Eur J Endocrinol December 1, 2011 165 841-849

Dealing with new assays

- **There is no current requirement for new assays to demonstrate comparability of results**

How to achieve comparable results

- Harmonization / standardization
- Calibration of all measurement procedures is traceable to a common reference system
- Performance is monitored and maintained by surveillance using PT, EQA or a certification program