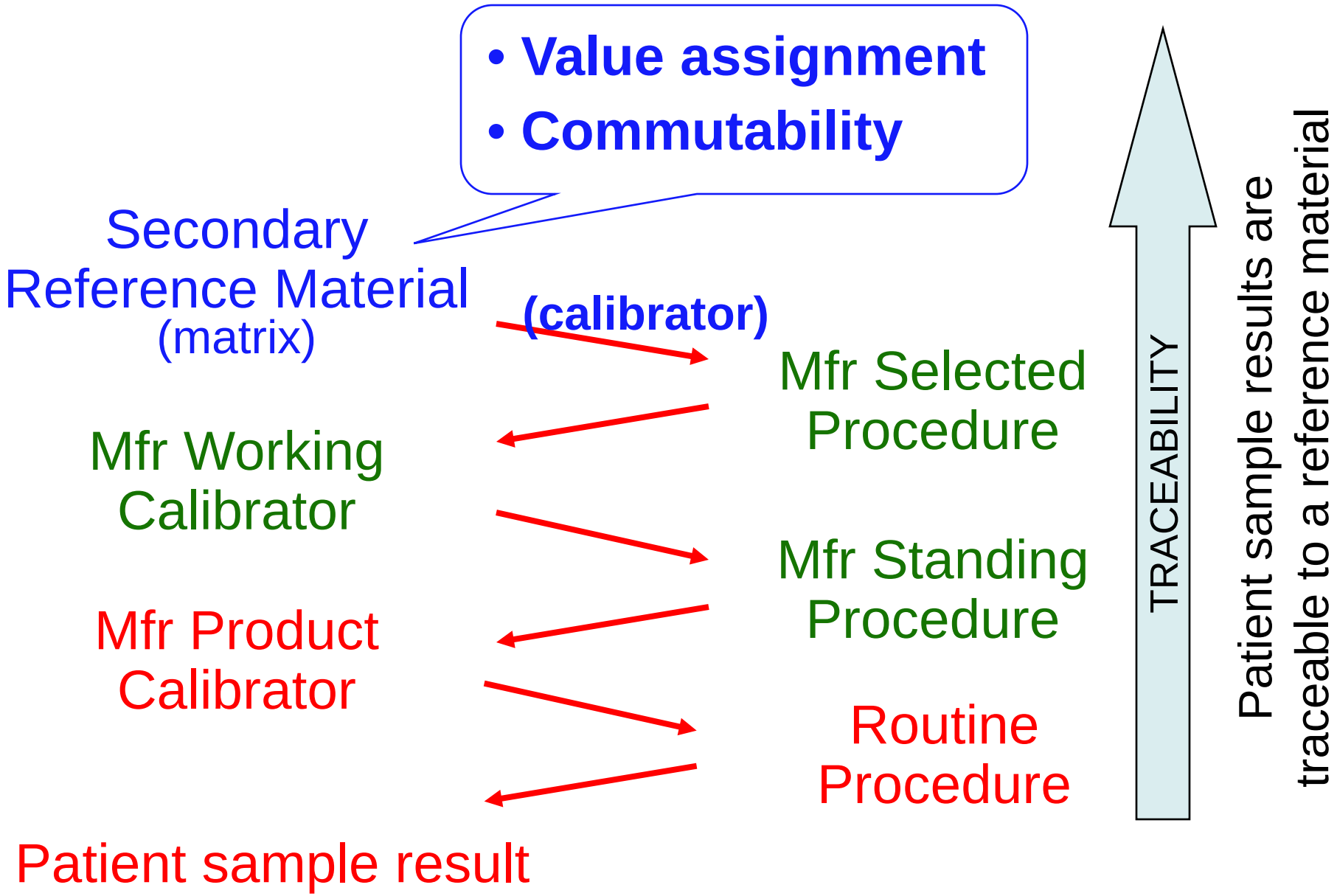
Harmonization: challenges related to commutability

Greg Miller, PhD
Virginia Commonwealth University
Richmond, VA, USA

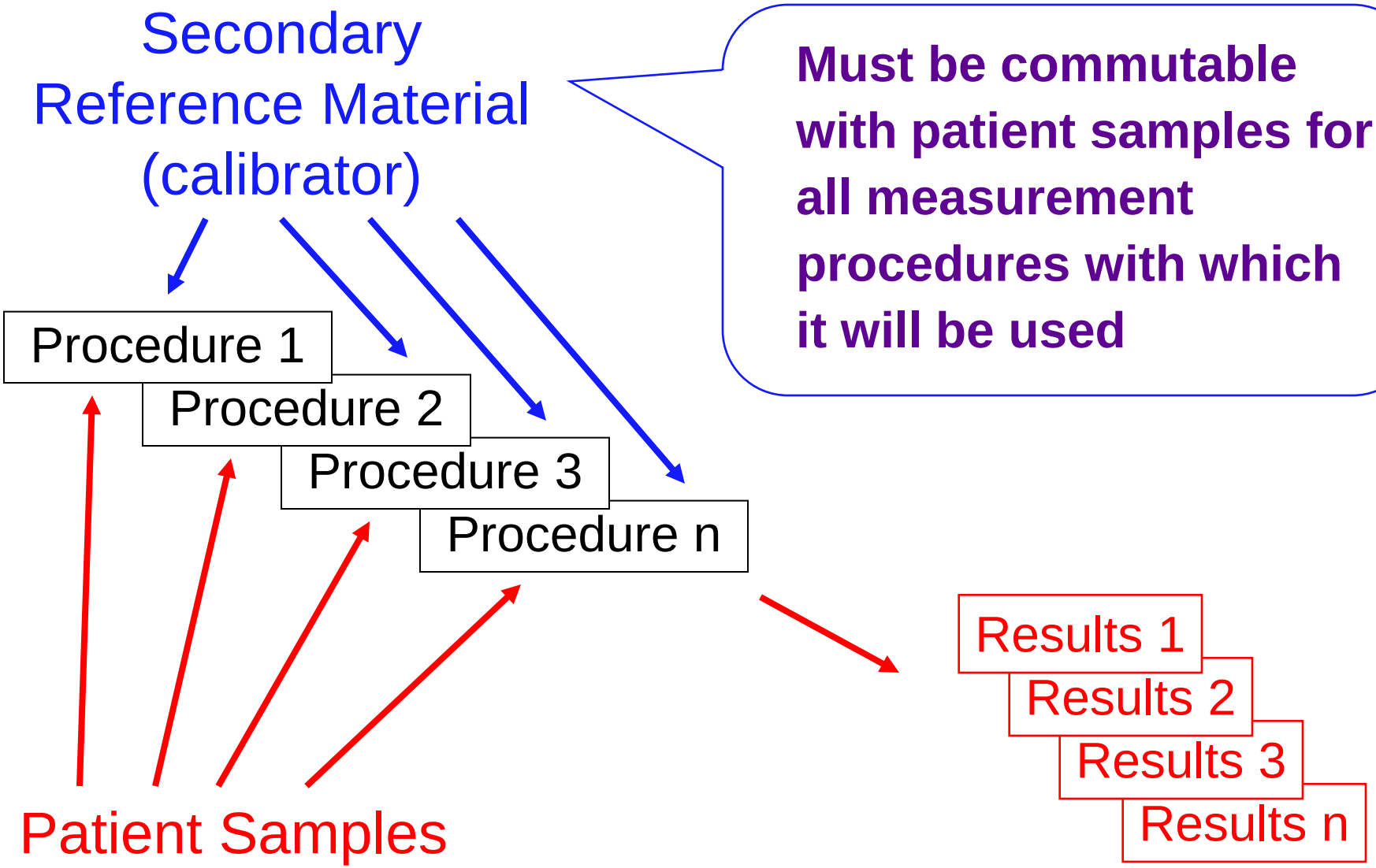
Financial disclosures:

Research grant from Abbott Diagnostics

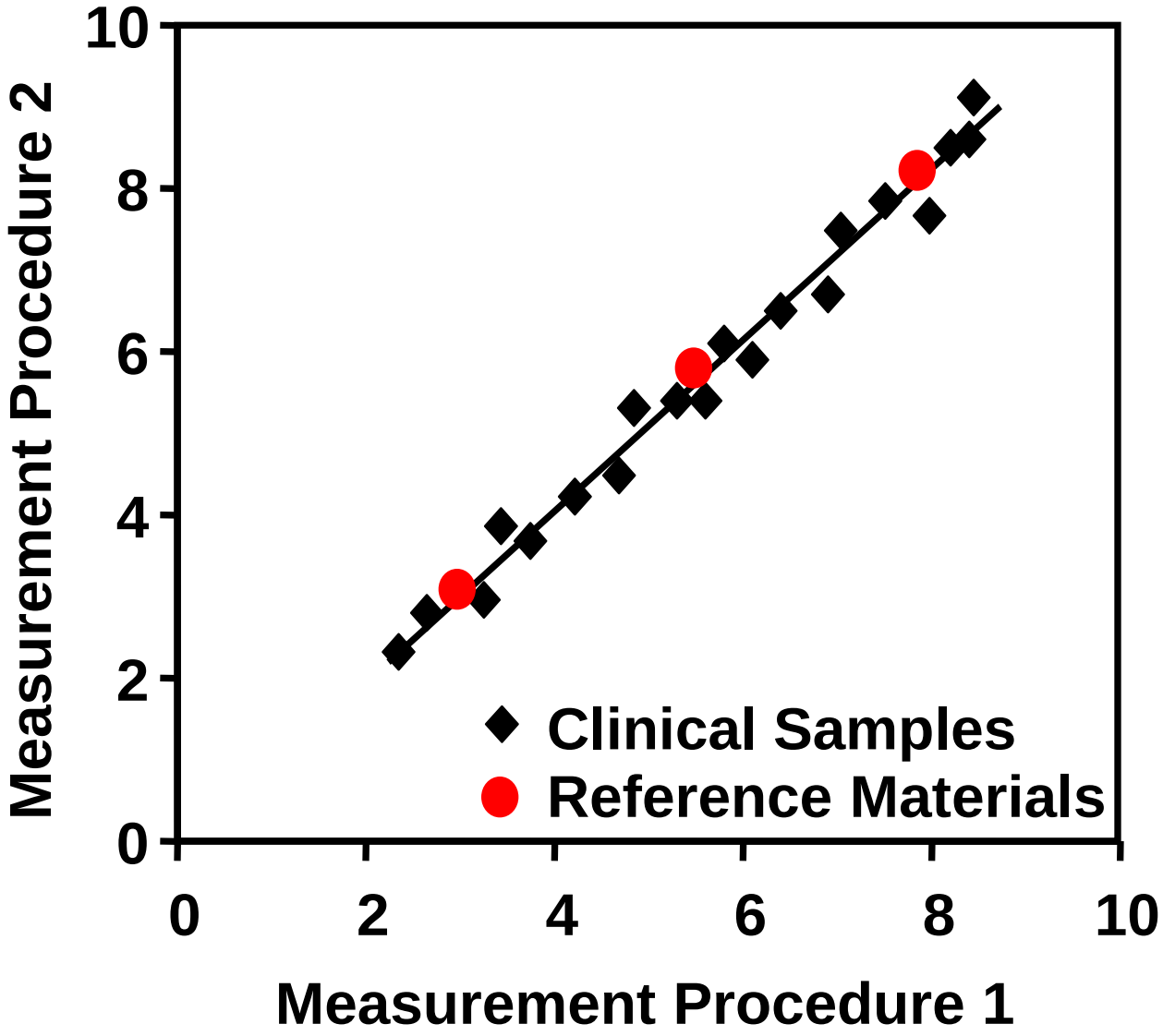
Traceability (based on ISO 17511)



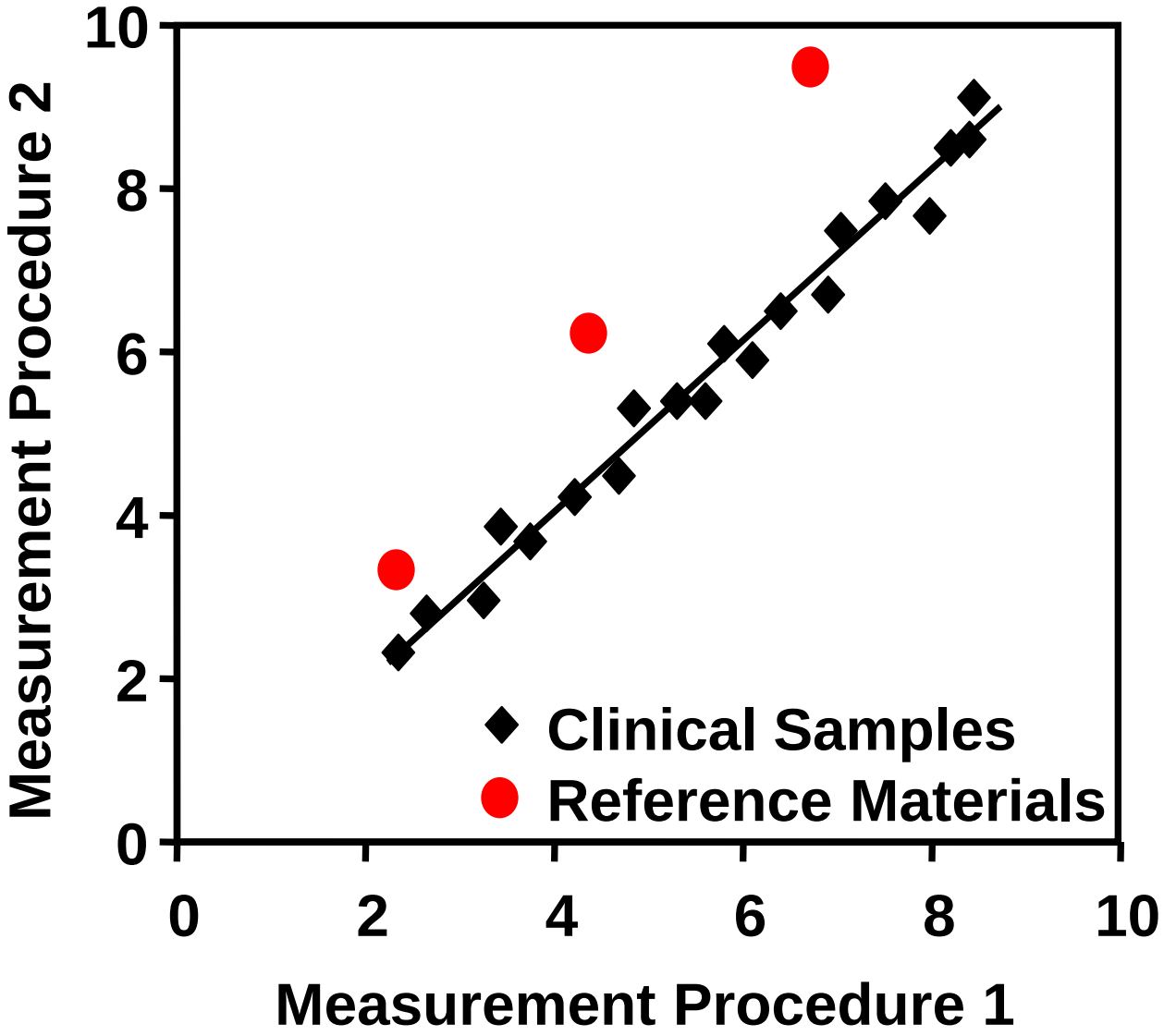
Traceability to a Reference Material



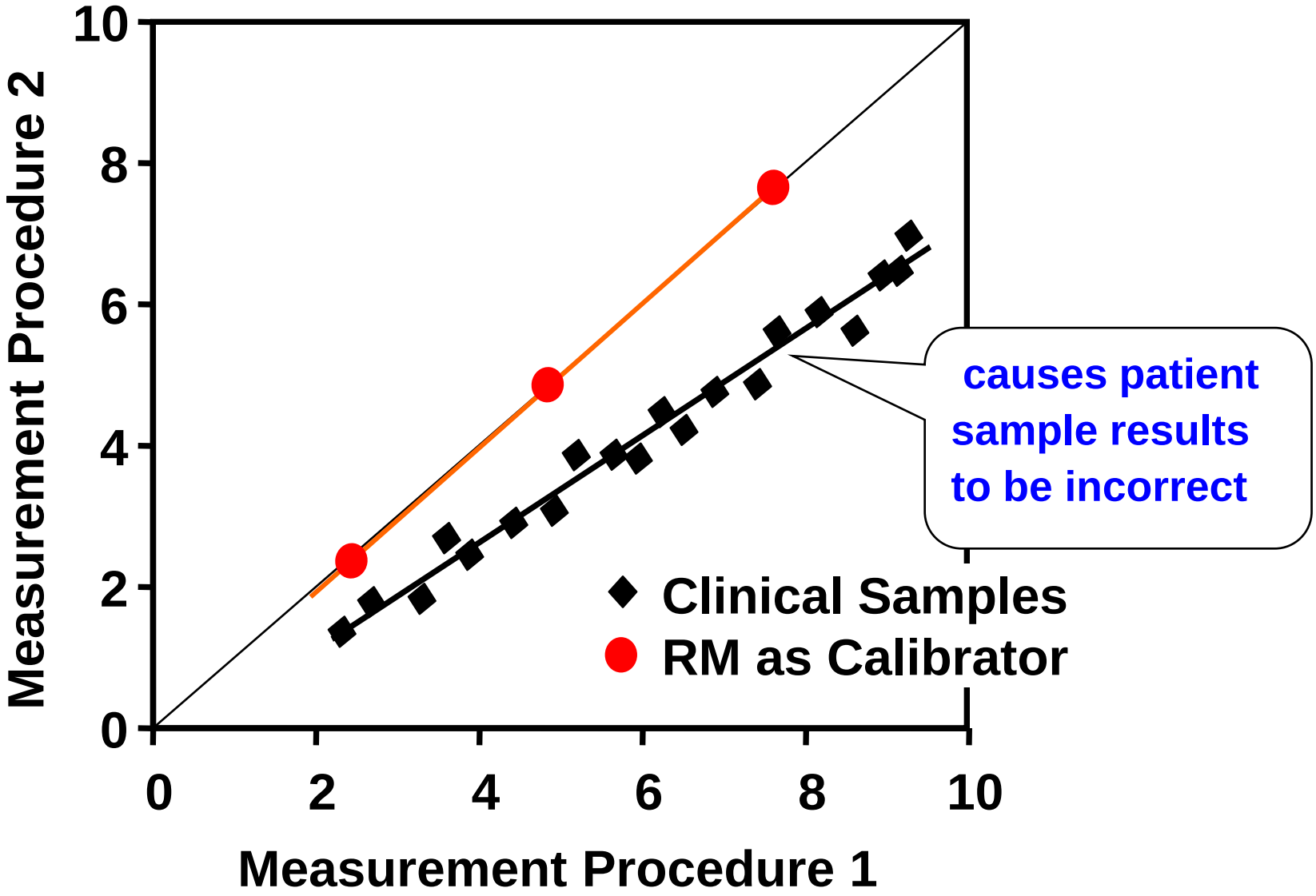
Commutable: same relationship for clinical samples and reference materials



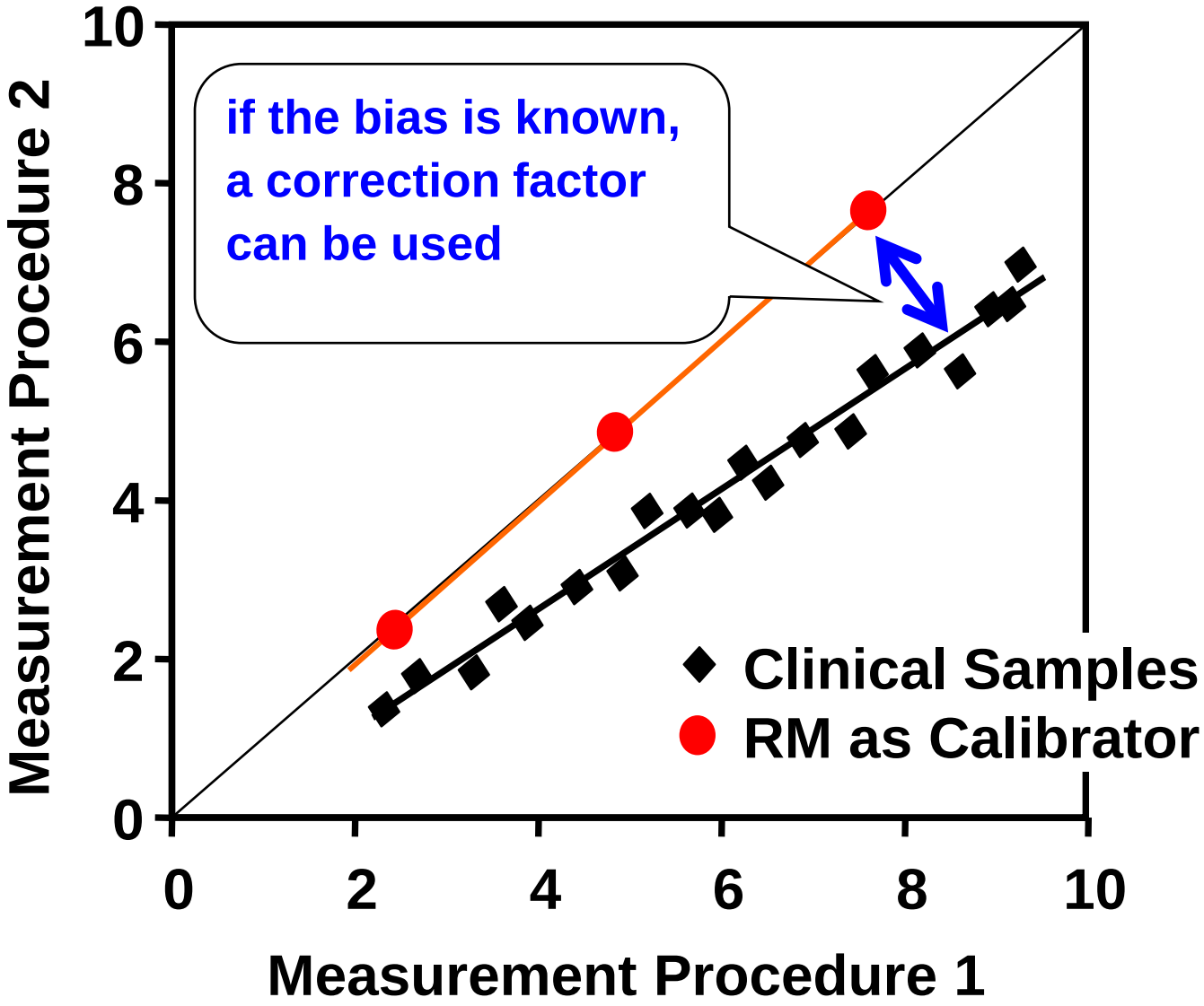
Non-commutable: different relationship for clinical samples and reference materials



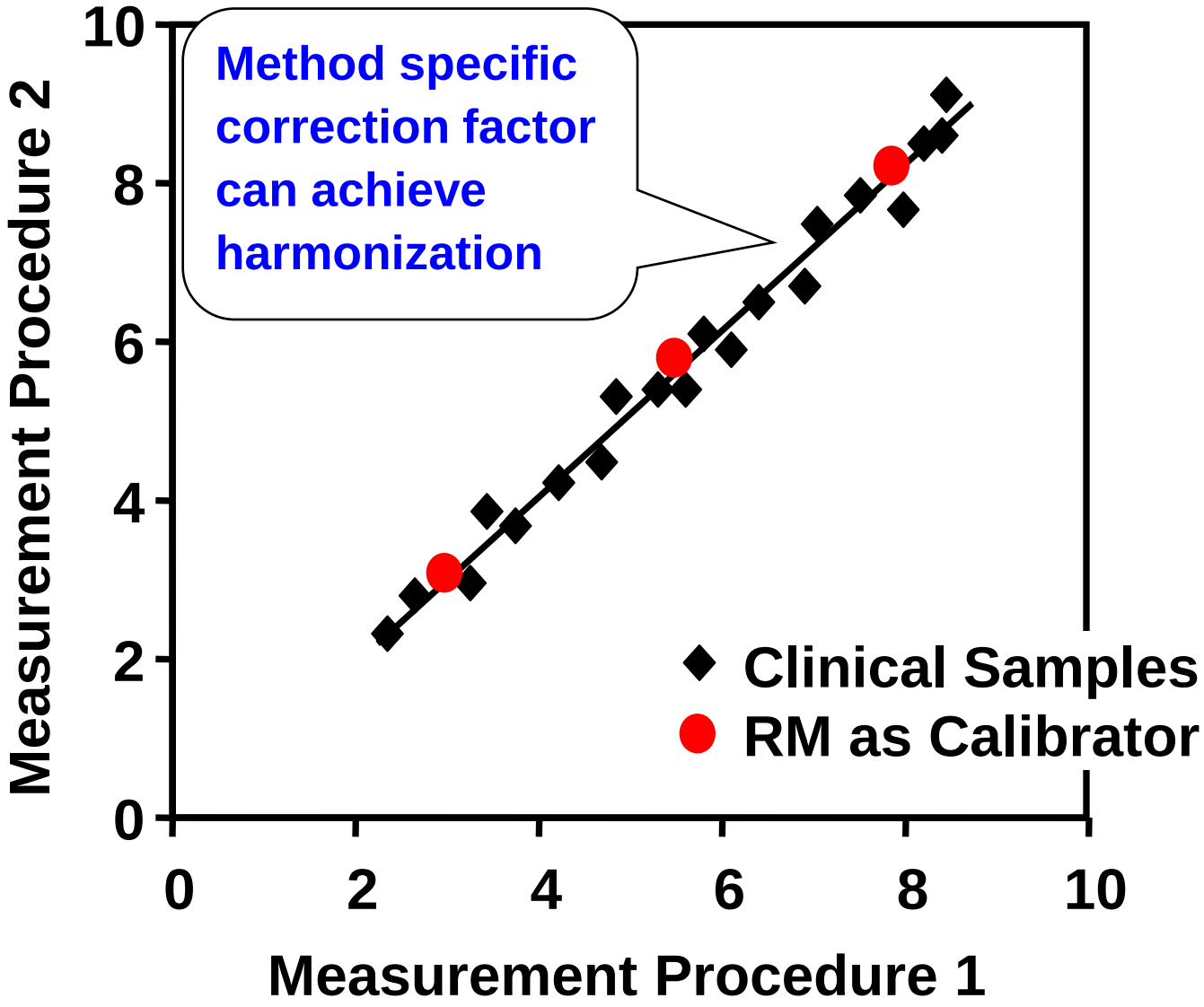
Calibration with non-commutable materials



Correction factor is possible



Correction factor is possible



The Problem

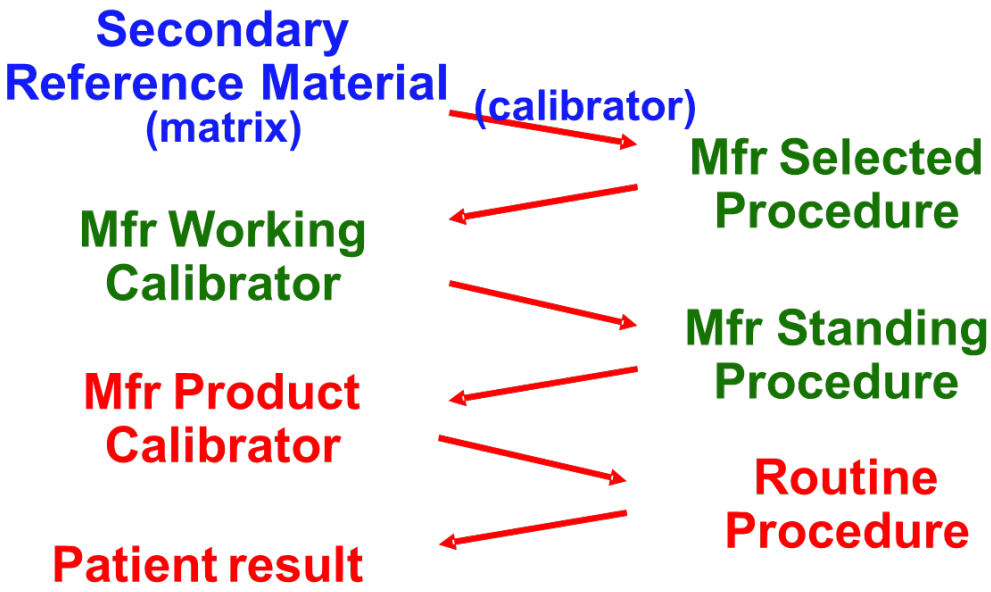
Many secondary reference materials are not commutable with clinical samples for routine clinical laboratory procedures

The Problem

Many secondary reference materials are not commutable with clinical samples for routine clinical laboratory procedures

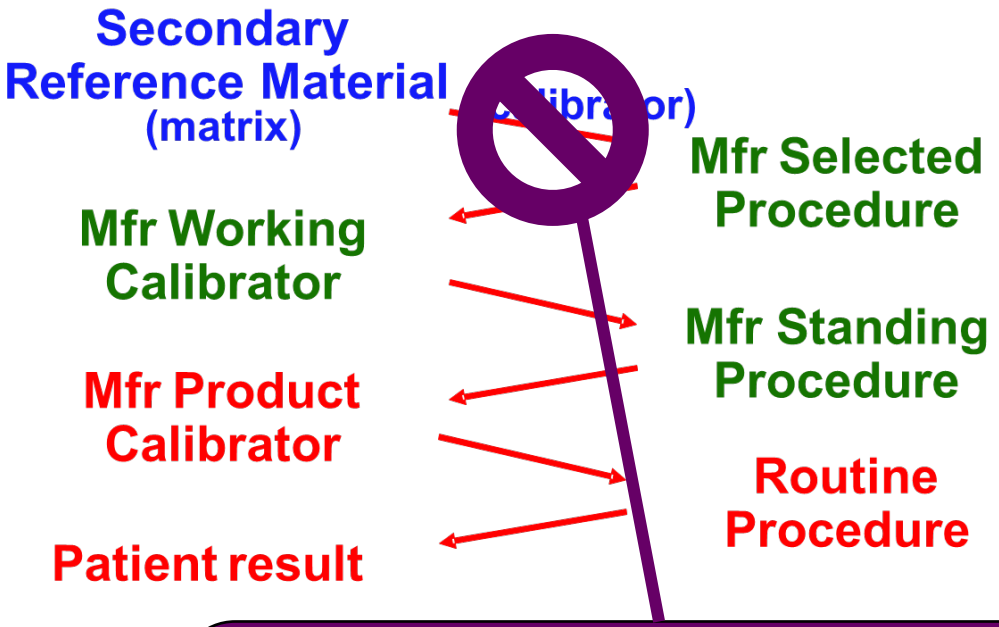
- Historically, commutability of reference materials was not validated for use with routine clinical laboratory measurement procedures

Why commutability matters



The manufacturer's procedures used for value assignment may be the same as the routine procedure

Why commutability matters



The manufacturer's procedures used for value assignment may be the same as the routine procedure

A non-commutable calibrator breaks the traceability chain

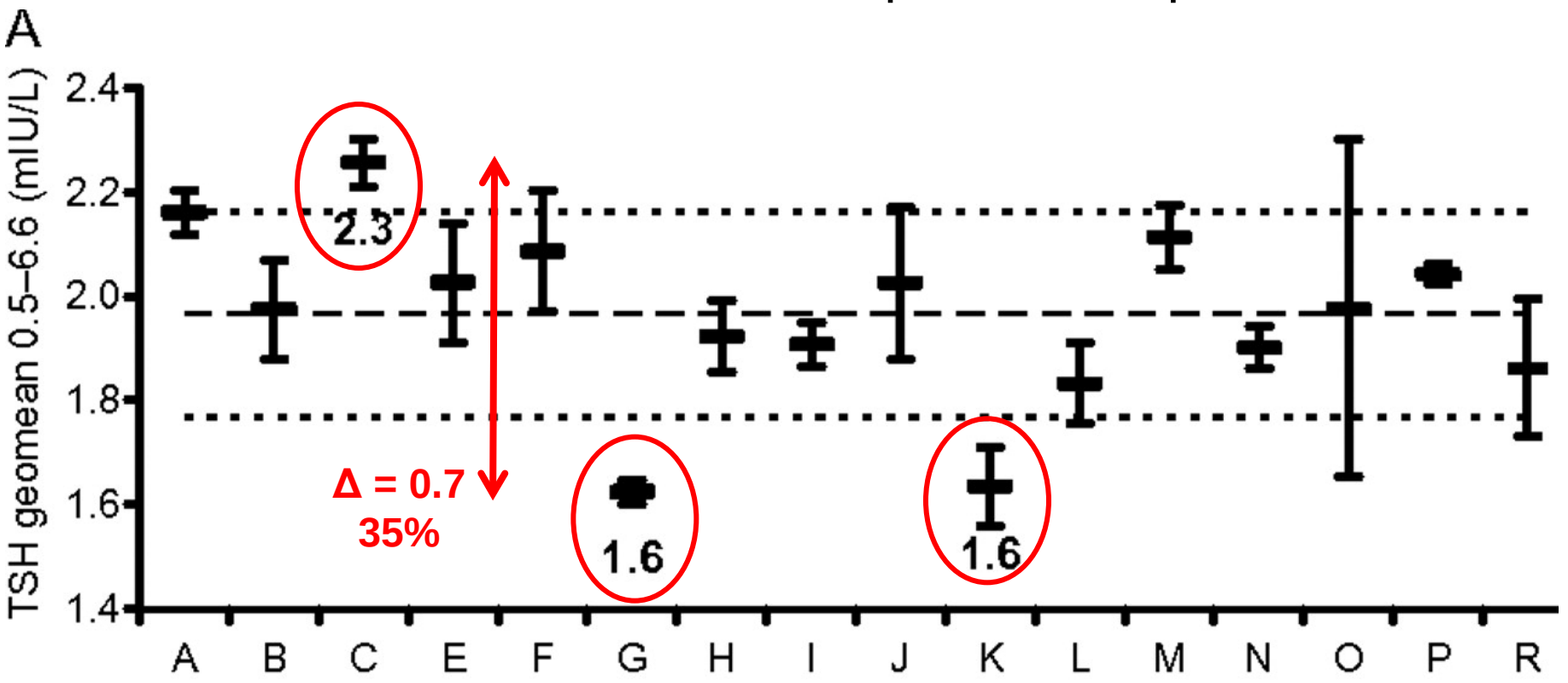
The Problem

Many secondary reference materials are not commutable with clinical samples for routine clinical laboratory procedures

- Even though manufacturers show traceability, the process fails to provide equivalent results for patient samples when different measurement procedures are used

TSH methods
All traceable to IS 94/674 (WHO)

Mean ±95% CI for 40 patient samples



Thienpont et al. Clin Chem 2010; 56: 902-911.

Other examples:

- **Follicle stimulating hormone** (Clin Chim Acta 1998;273:103-17)
- **Prostate-specific antigen** (Clin Chem 2006;52:59-64. Clin Chem 2011;57:1776-7)
- **C-peptide** (Clin Chem 2008;54:1023-6)
- **Insulin** (Clin Chem 2009;55:1011-1018, 2009)
- **Human chorionic gonadotropin** (Clin Chem 2009;55:1484-91)
- **Cytomegalovirus** (Clin Chem 2009;55:1701-10)
- **Troponin I** (Pathology 2010;42:402-8)


What do we do?

Must change practice to require commutability validation for reference materials intended for use with:

- Manufacturer's standing procedures
- Routine clinical laboratory procedures

A guideline is available: CLSI EP30-A Characterization and Qualification of Commutable Reference Materials for Laboratory Medicine (2010 as C53-A)

Validating commutability

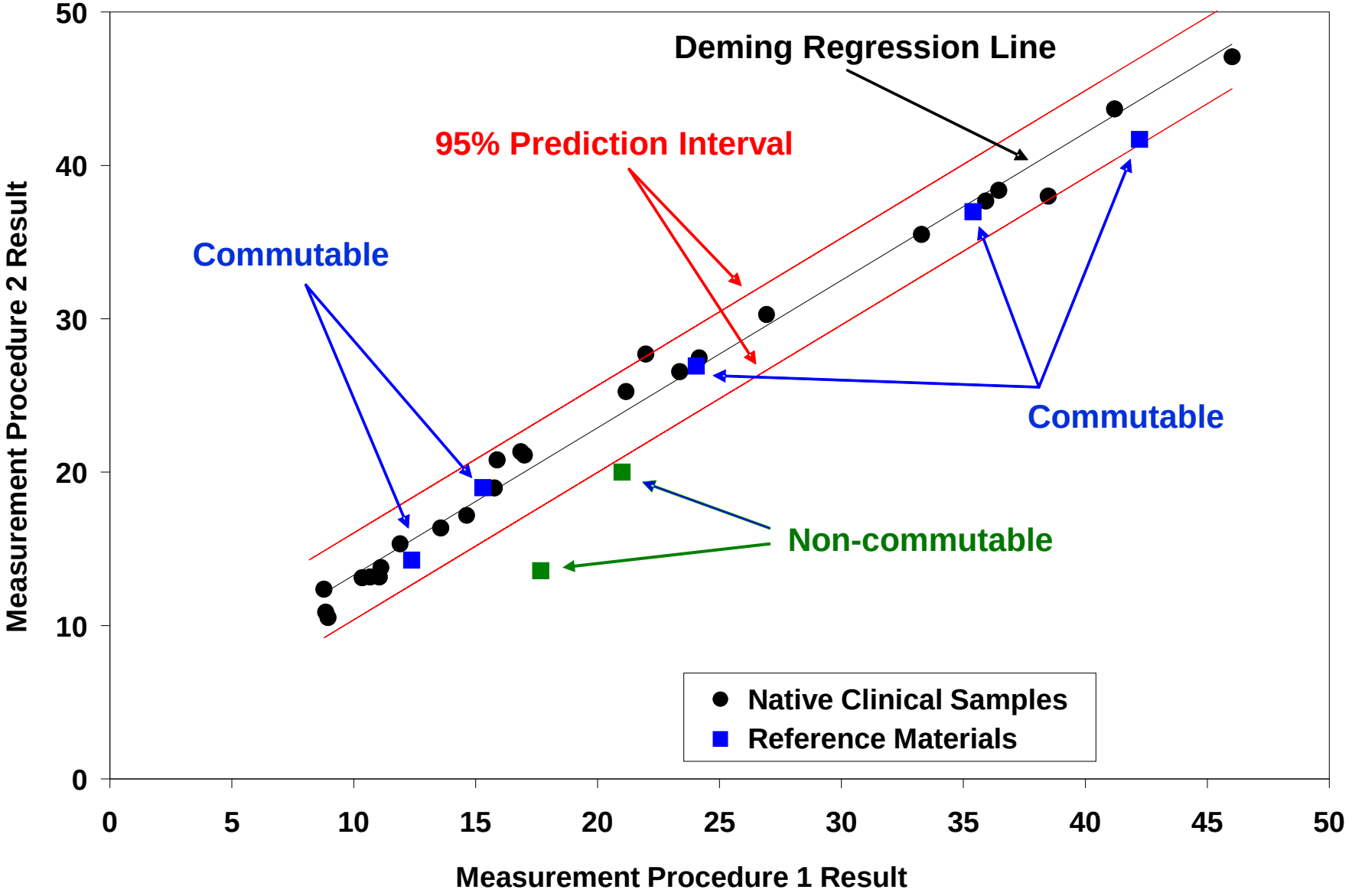
1. Representative clinical samples
2. Candidate reference materials
3. Measure clinical samples and reference materials with all measurement procedures for a measurand

Validating commutability

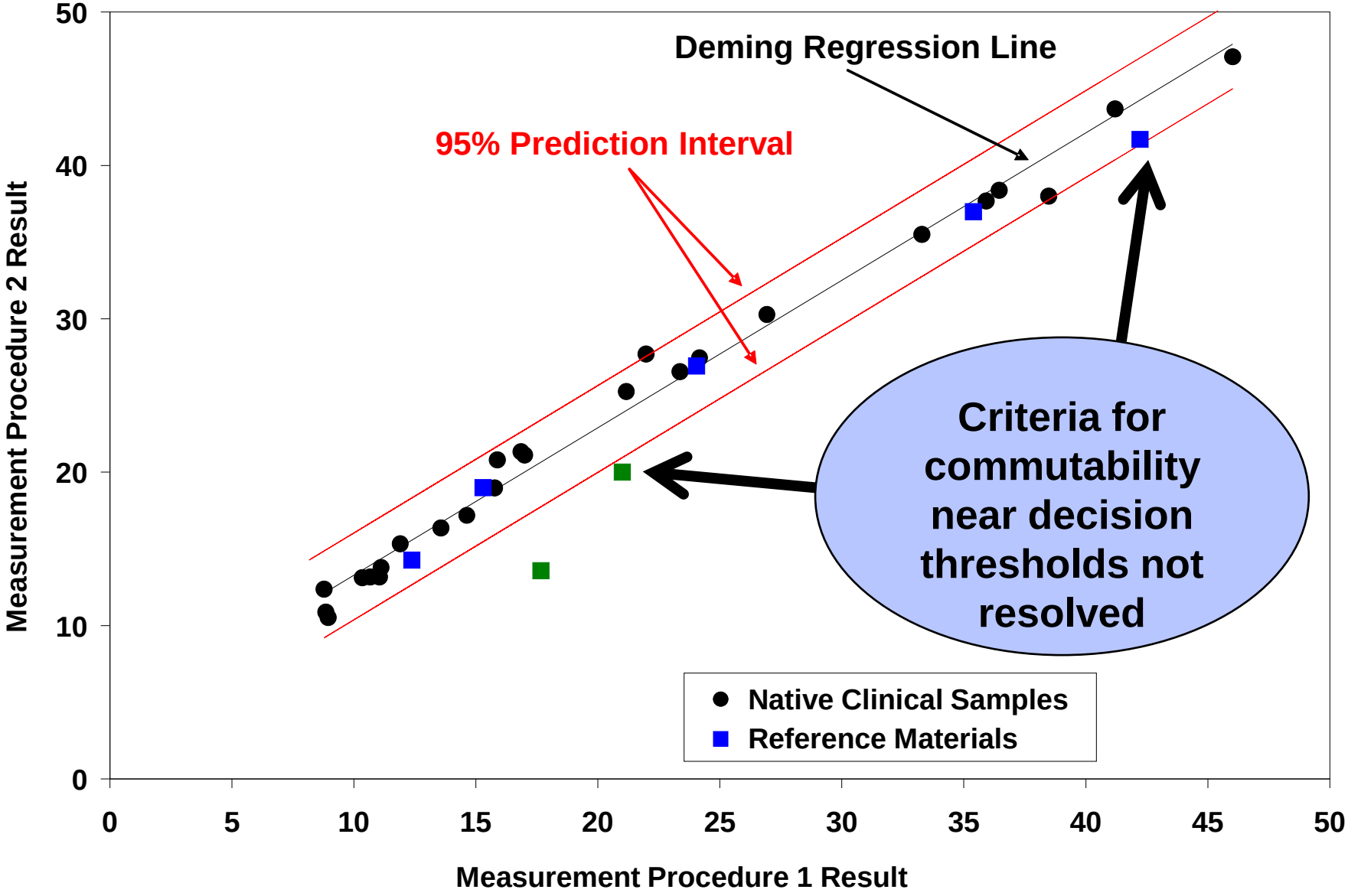
4. Establish the numeric relationships between the measurement procedures for the clinical samples

5. Determine if the RMs have the same relationships

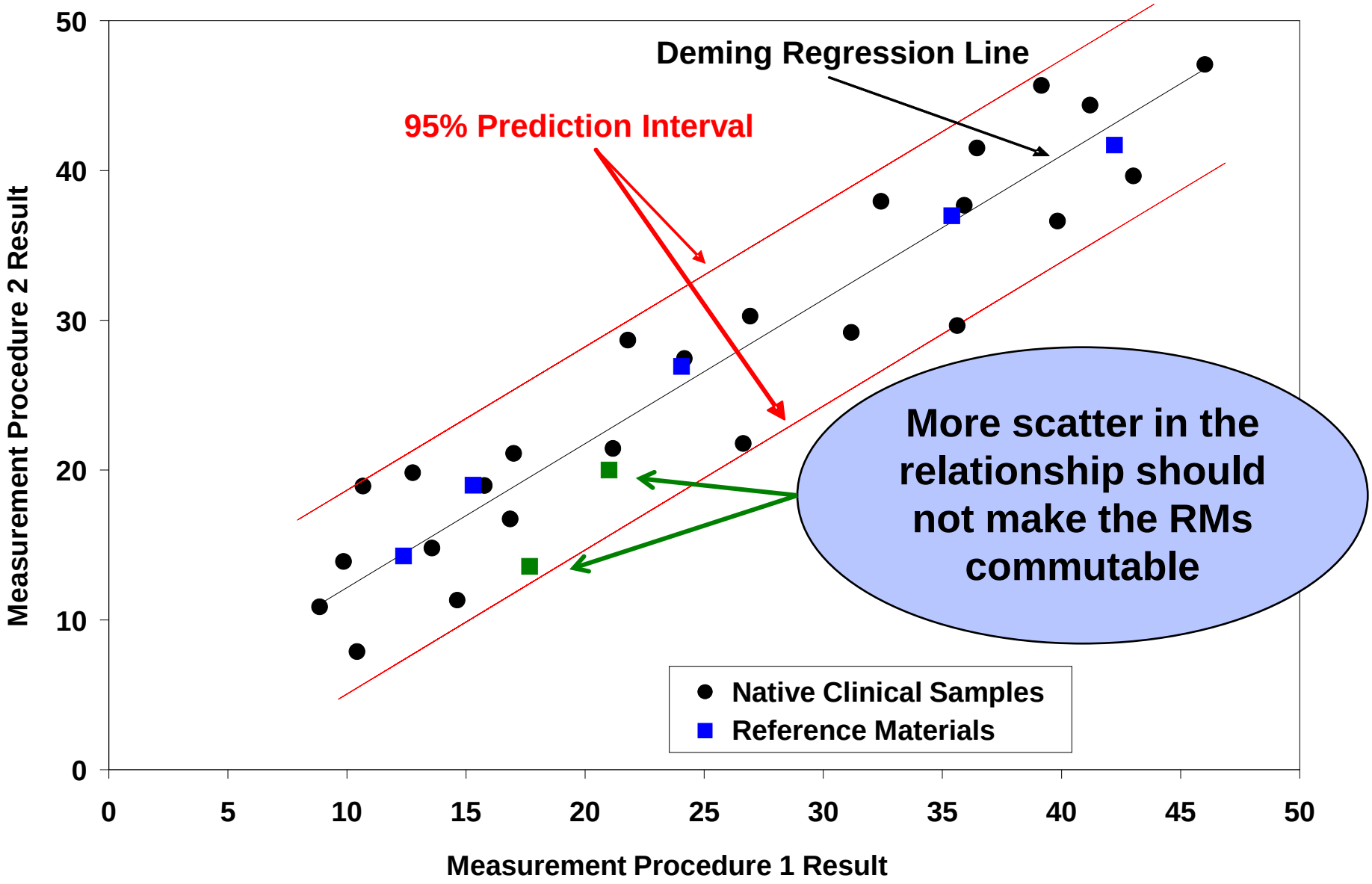
   - If a reference measurement procedure (RMP):
     - Compare each routine procedure to the RMP
     - Also evaluates traceability to the RMP
   - If no RMP, all combinations of two routine procedures must be examined



Adapted from CLSI C53-A (used with permission)



Adapted from CLSI C53-A (used with permission)



Modified from CLSI C53-A (used with permission)

Issues in criteria for commutability

1. **Intended use of a reference material**
   - Calibrator for traceability
   - Trueness control
   - External Quality Assessment

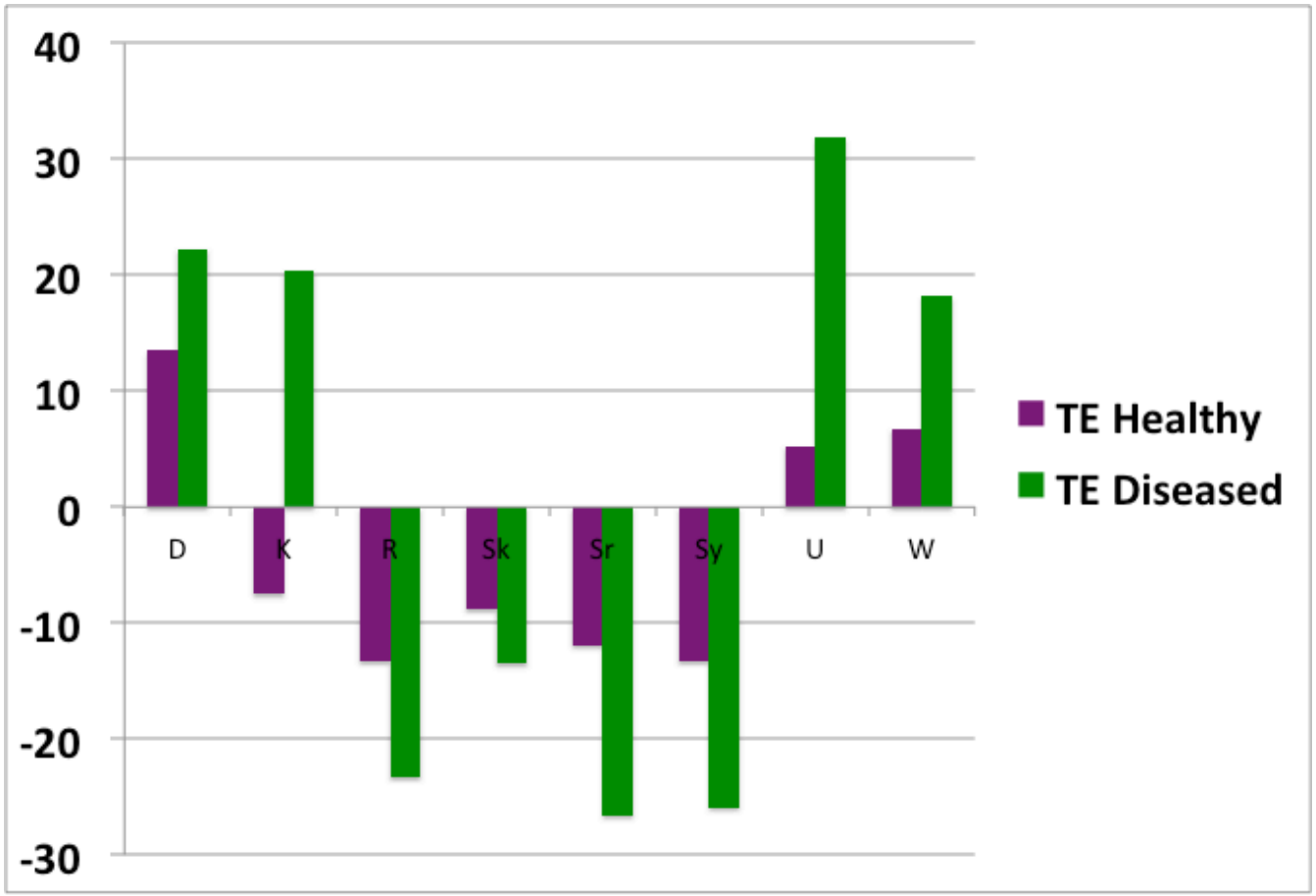
Issues in criteria for commutability

2. **Confounding measurement limitations with acceptance criteria**
   - Imprecision
   - Specificity for the measurand (sample specific influences)

Issues in criteria for commutability

3. **What are the properties for a set of representative clinical samples**
   - Healthy vs. diseased
   - Common vs. rare molecular forms
   - Potential interfering substances
   - Single vs. pooled samples
   - Freeze-thaw artifacts

Healthy vs. diseased; total error for 8 direct LDLC methods



Adapted from Miller et al. Clin Chem 2010;56:977-86

Issues in criteria for commutability

4. Uncertainty of decision thresholds

- Should criteria be based on clinical performance requirements rather than the statistical distribution of a small number of clinical samples

Issues in criteria for commutability

5. **For what fraction of available clinical laboratory measurement procedures should criteria be met to have “adequate” commutability**

   - How to address those measurement procedures for which a RM is non-commutable

Issues in criteria for commutability

6. **What is the minimum number of clinical samples for “adequate” assessment**
   - Cost and availability of samples
   - Cost and feasibility to conduct the assessment

IFCC Working Group on Commutability

(established March 2013)

- Operating procedures for the formal assessment of commutability
- Criteria for commutability taking into account the intended use of a reference material
- Standard terminology to describe commutability characteristics
- Information to be provided regarding commutability
- Education of manufacturers, laboratories, end users

Commutability: who is responsible

- Reference material manufacturer
  - Cannot know all procedures in use
  - Should make a material likely to be commutable
  - Should address commonly used procedures
- Measurement procedure manufacturer
  - Must confirm commutability for an intended use

Perfect

- is the enemy of good

- Goal is a reference material that is fit for purpose
- How to define fit for purpose