Criteria for assignment of reference method values

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EMPOWERIVD●GLOBE

Introduction

Reference method/measurement procedure (RMP) values

In all situations where
"trueness and nothing but trueness"
is required

Points of care!

Introduction

Reference Method Values & [Reference] Materials

Must be viewed together!

< Right values on >

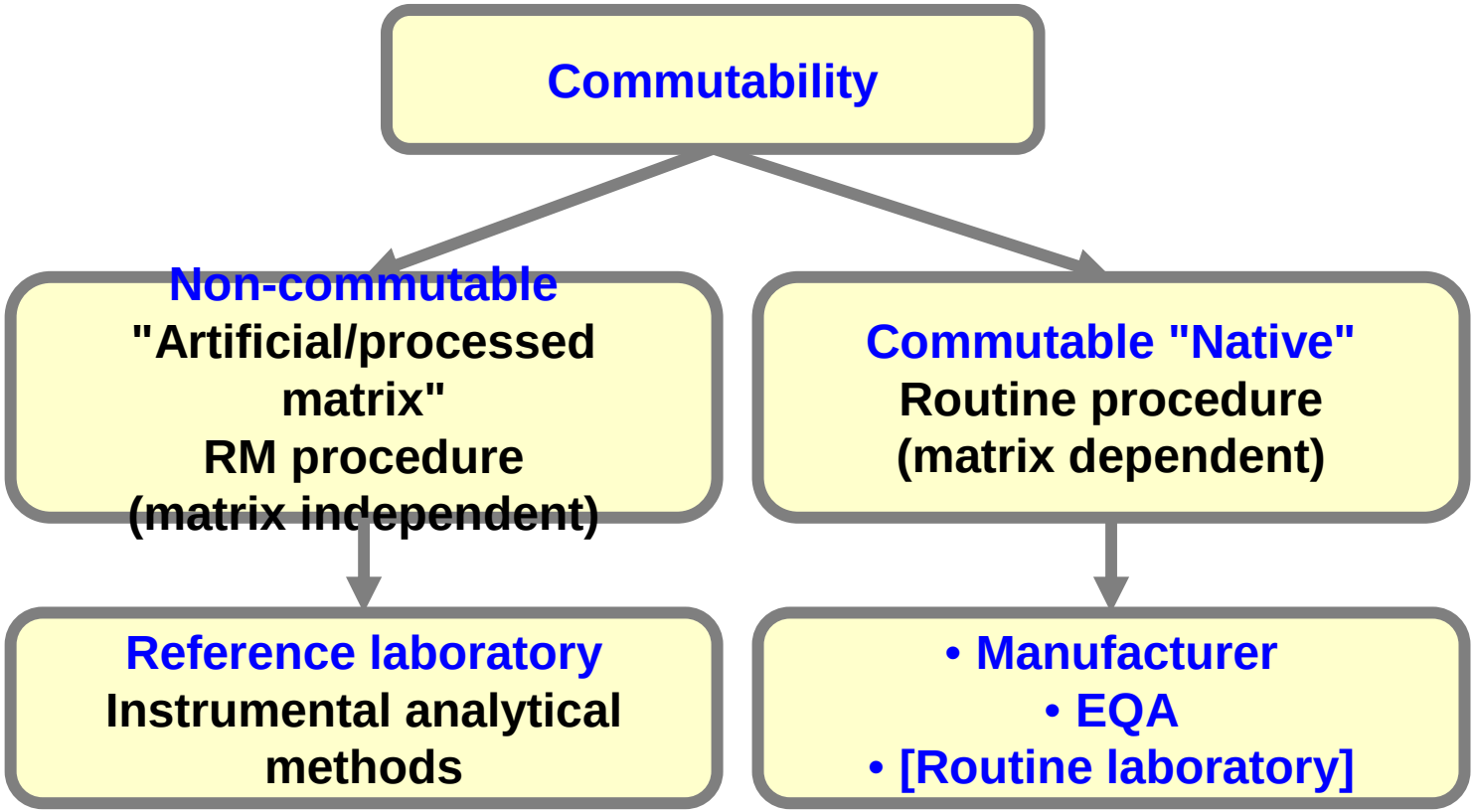
< Right materials in the >

< Right hands for >

< Right applications >

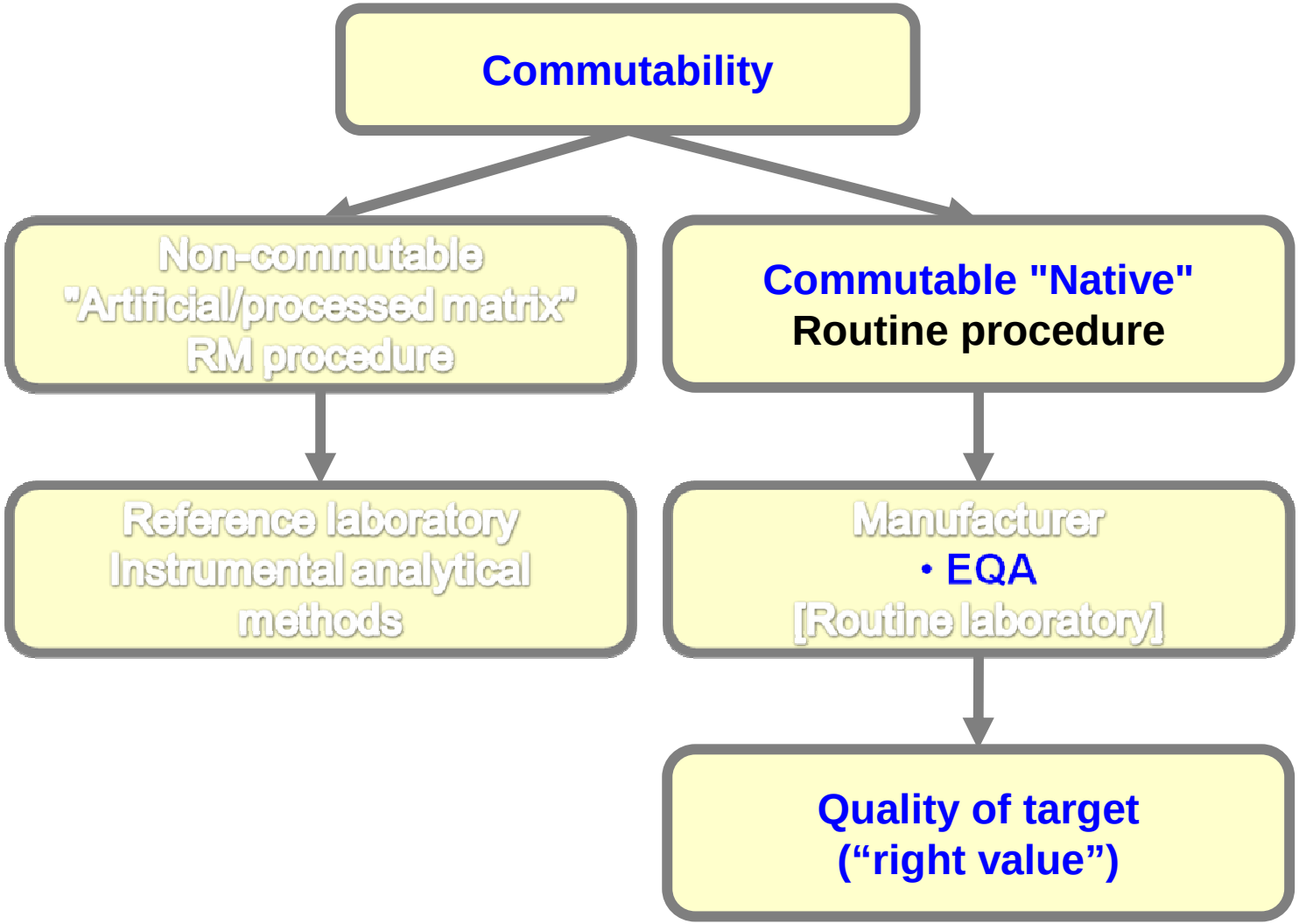
Introduction

Reference method value & commutability of material



Introduction

Focus of this presentation *"Criteria for assignment of reference method values"*



Quality of target – Concept

General requirements

- **Analytically *valid* RM procedure (ISO 15193)**
- ***Competent* RM laboratory (ISO 17025/15195)**

➔Joint Committee for Traceability in Laboratory Medicine JCTLM

"Procedure Manual": ISO 15193 & 15195

Concept "quality of a target set by a RMP"

ISO 15193: Reference Measurement Procedure
"… measurement procedure accepted as providing measurement results fit for their intended use in assessing measurement trueness of measured quantity values obtained from other measurement procedures for quantities of the same kind, …"
➔Quality specifications?

Quality of target – Concept

Proposed quality specifications

Stöckl D, et al. Diskussionsvorschlag für ein einheitliches Referenzmethodenkonzept auf der Grundlage der "Richtlinien der Bundesärztekammer zur Qualitätssicherung in medizinischen Laboratorien". Lab Med 1991;15:336-9.

Stöckl D, Reinauer H. Development of criteria for the evaluation of reference method values. Scand J Clin Lab Invest Suppl 1993;212:16-8.

Stöckl D, Franzini C, Kratochvila J, Middle J, Ricos C, Siekmann L, Thienpont LM. Analytical specifications of reference methods – Compilation and critical discussion (from the members of the European EQA-Organizers Working Group B). Eur J Clin Chem Clin Biochem 1996;34:319-37 [Review].

Quality of target – Concept

Quality specifications (Stöckl et al, 1996)
"Outcome-related"
Total allowable error 1/5 of the *German* EQA limit,
resulting in a false discrimination rate of 0.7%

Analyte	CV (%)#	Bias (%)#
Chloride	1	0.5
Calcium	1.5	0.5
Creatinine	1.5	0.6
Thyroxine	2	0.9
Cortisol	2	1.4
#Together with specified *n* measurements		

Quality of target – Concept

General model: Relate the desired quality to %-increase of false decisions

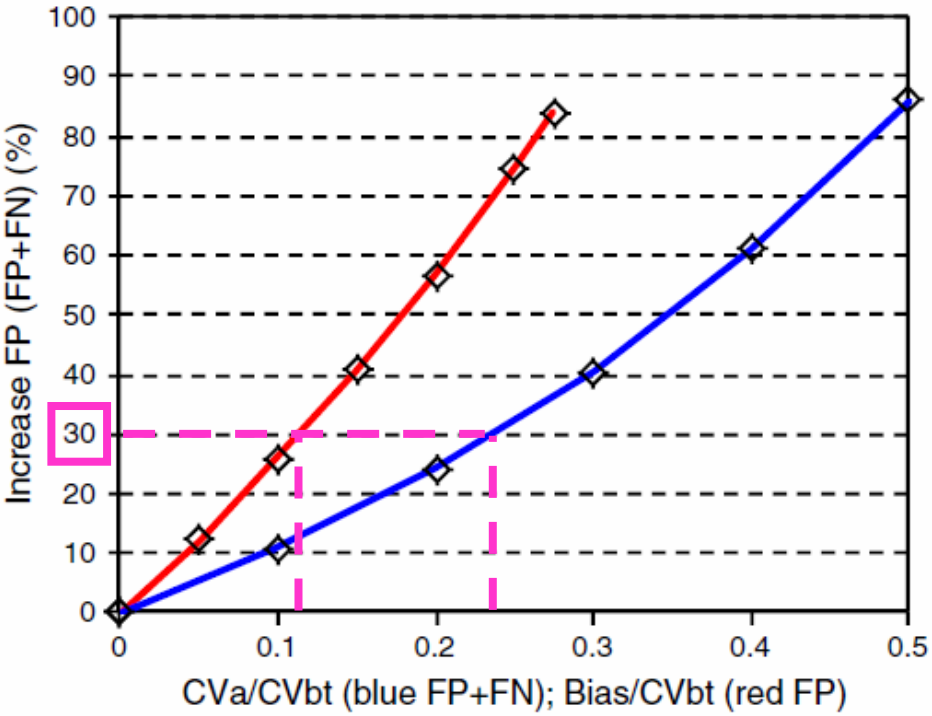


Fig. 1. %-FP plus %-FN for the ratio CVa/CVb (blue) and %-FP for the ratio bias/CVb (red) beyond the 1.96 σ decision points for Gaussian distributed data. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Stepman HC, Stöckl D, Twomey PJ, Thienpont LM. A fresh look at analytical performance specifications from biological variation. Clin Chim Acta 2013;421:191-2.

Quality of target – Concept

Variance propagation & outcome concepts compared

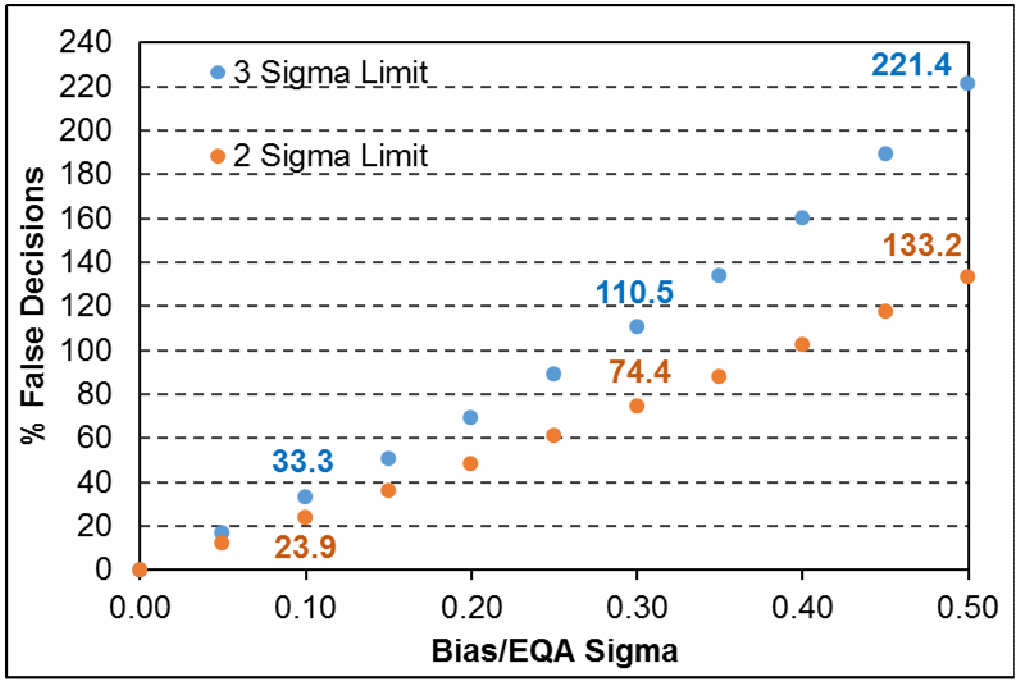
	Variance propagation	Outcome
CVa/CVb	%-increase CVt	%-increase FP+FN
0.25 (optimum)	3	32
0.5 (desirable)	12	86
0.75 (minimum)	25	167
Bias/CVb	%-out each limit	%-increase FP
0.125 (optimum)	3.3/1.8	33
0.25 (desirable)	4.4/1.4	75
0.375 (minimum)	5.7/1	126

Quality of target – Concept

Application to EQA

- **Limit for [potential] bias of the target by a RMP**
- **Fraction of the EQA-limit (different σ-limits)**
- **False Positives (FPs) & False Negatives (FNs) (%)**

Example: 2σ-limit, if bias = 0.3σ, (FPs+FNs) = 74.4%
(3.4% false discrimination relative to 4.6% out without bias)



Quality of target – Concept

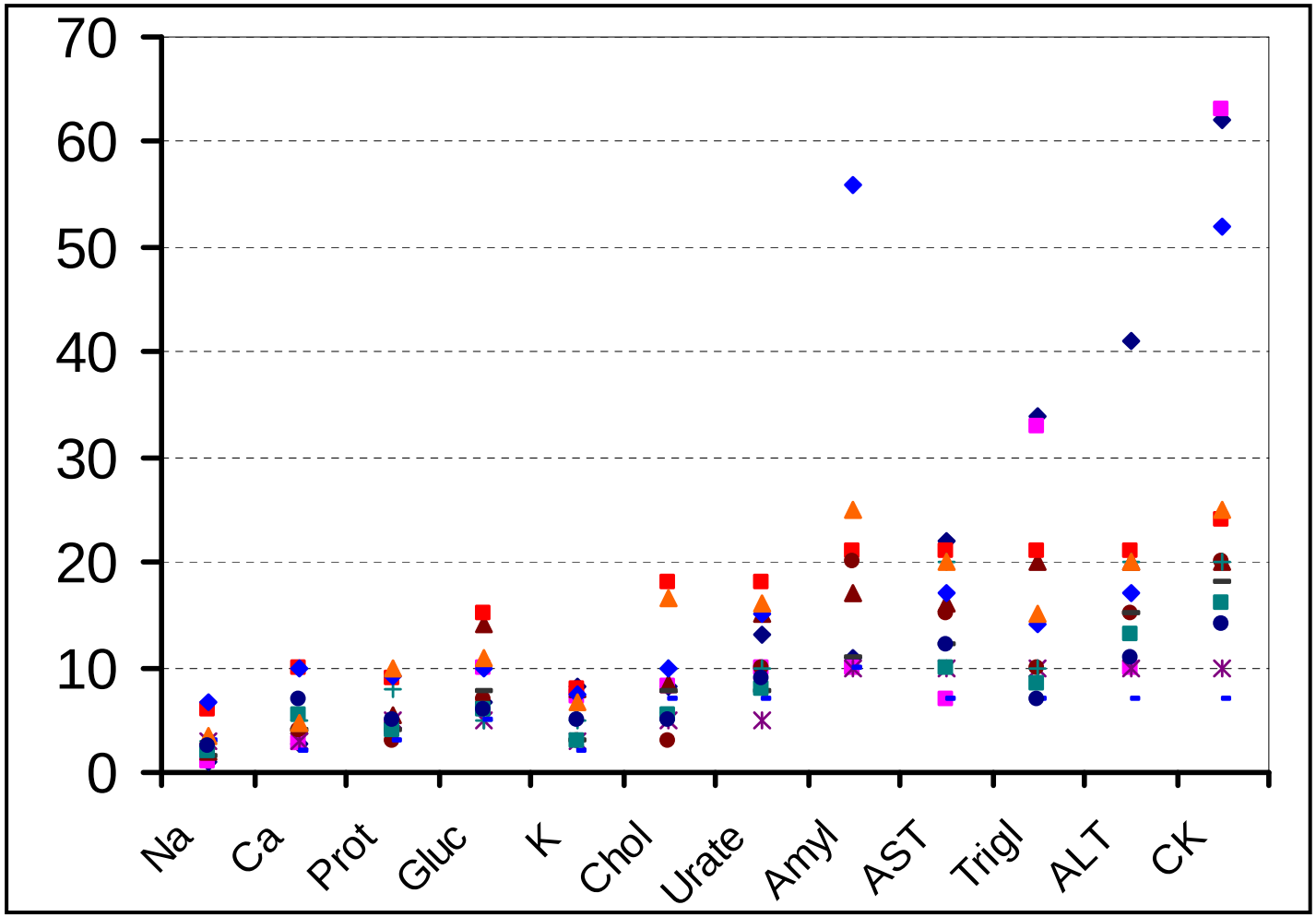
“Relate the desired quality to the % of false decisions on performance in EQA”

Leads us to the problem of currently used EQA-limits!

There are as many limits as there are EQA-providers

EQA limits

Comparison of EQA-limits (%) from 13 countries



Analytes arranged by increasing biological variation.
From: Ricos et al. Eur J Clin Chem Clin Biochem 1996;34:159-65.

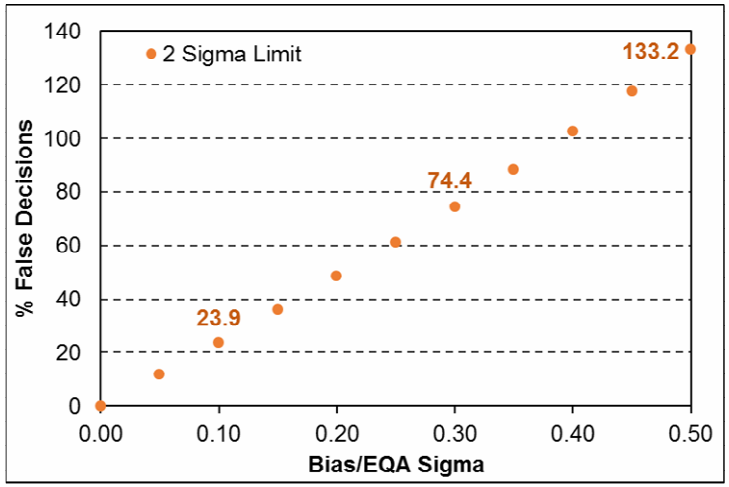
Quality of target – Examples

Only [potential] bias considered!
Calculations 2-sided: FP+FN

Calcium *EQA limit 2%*, understood as "2σ"
EQA fail >2σ → 4.6% outside (without bias)

Maximum bias of reference method/RMP

FP+FN	Bias
23.9%	0.1%
74.1%	0.3%



Currently, beyond capabilities!

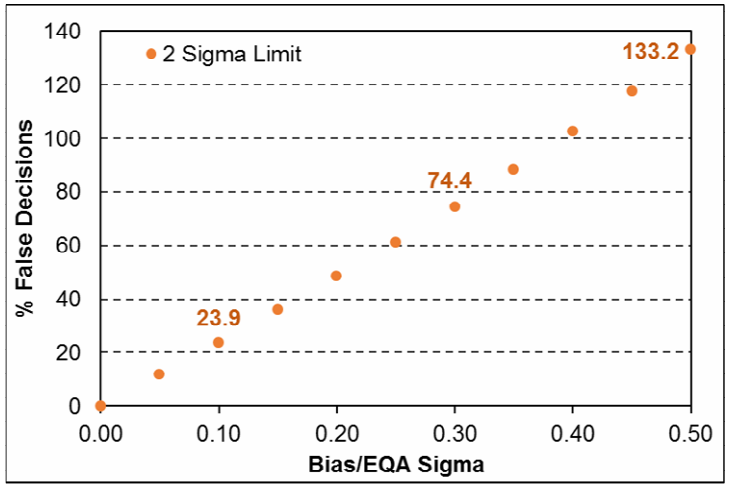
Quality of target – Examples

Only [potential] bias considered!
Calculations 2-sided: FP+FN

Calcium *EQA limit 10%*, understood as "2σ"
EQA fail >2σ → 4.6% outside (without bias)

Maximum bias of reference method/RMP

FP+FN	Bias
23.9%	0.5%
74.1%	1.5%



Realistic ~50%

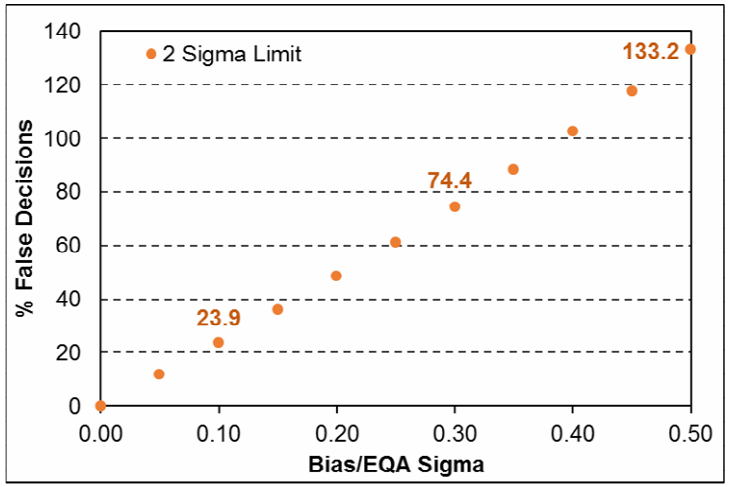
Quality of target – Examples

Only [potential] bias considered!
Calculations 2-sided: FP+FN

ALT *EQA limit 10%*, understood as "2σ"
EQA fail >2σ → 4.6% outside (without bias)

Maximum bias of reference method/RMP

FP+FN	Bias
23.9%	0.5%
74.1%	1.5%



Currently, beyond capabilities!

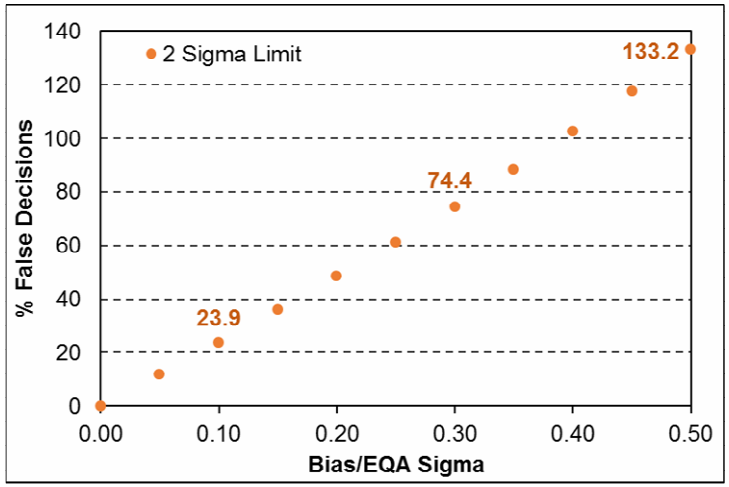
Quality of target – Examples

Only [potential] bias considered!
Calculations 2-sided: FP+FN

ALT *EQA limit 30%*, understood as "2σ"
EQA fail >2σ → 4.6% outside (without bias)

Maximum bias of reference method/RMP

FP+FN	Bias
23.9%	1.5%
74.1%	4.5%



Realistic ~50%

Quality of target

Significant target uncertainty

When the target uncertainty is significant, typically, we expand our EQA limits by that uncertainty

Expanded Limits Master comparison 2012

EQA limits for laboratory bias to AMTM/REF c-AMTM% estimates								
	ALP	**ALT***	**AST***	**GGT**	**LDH***	**CL**	**K**	**NA**
Bias (state-of-the-art)	5.0	7.5	5.0	7.5	5.0	1.5	2.0	1.0
AMTM/REF c-AMTM uncertainty	5.2	2#	2#	2#	2#	0.4	1	0.4
Bias (expanded)	10.2	9.5	7.0	9.5	7.0	1.9	3.0	1.4

* Limits are used for both ALT/AST with and without PP, but only for LDH FW
# Estimates refer to REF c-AMTM targets

Target uncertainty – Another look

Disadvantages of reference methods/RMPs

RMPs often apply instrumental analytical procedures (e.g., mass spectrometry), require extensive sample clean-up, and involve manual steps (e.g., RMPs for enzymes). These features may make them vulnerable to increased measurement imprecision, low-throughput and high measurement costs. Particularly the latter is prohibitive for RMPs performing a significant number of replicate measurements to reduce the analytical random error component.

Advantages of the “all method trimmed mean” (AMTM)

Routine procedures generally are characterized by very low within-run measurement imprecision in the order of 1–2% and performance at a relatively low cost, which favors a high number of measurements.

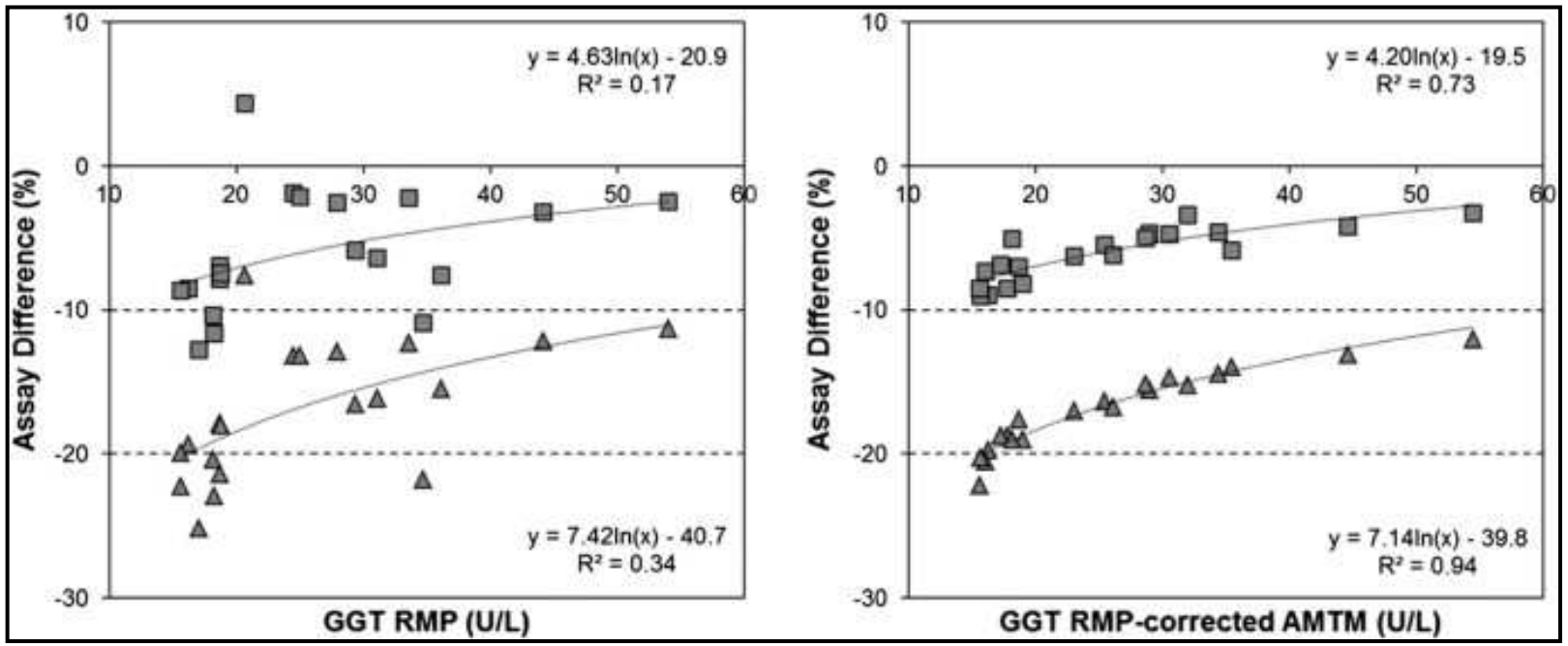
“Best of two worlds”

Method comparison studies between a RMP and several routine procedures can combine “the best of two worlds”, i.e., the high trueness provided by the RMP and the low dispersion of the AMTM inferred from the results by the routine procedures **(RMP-corrected AMTM)**.

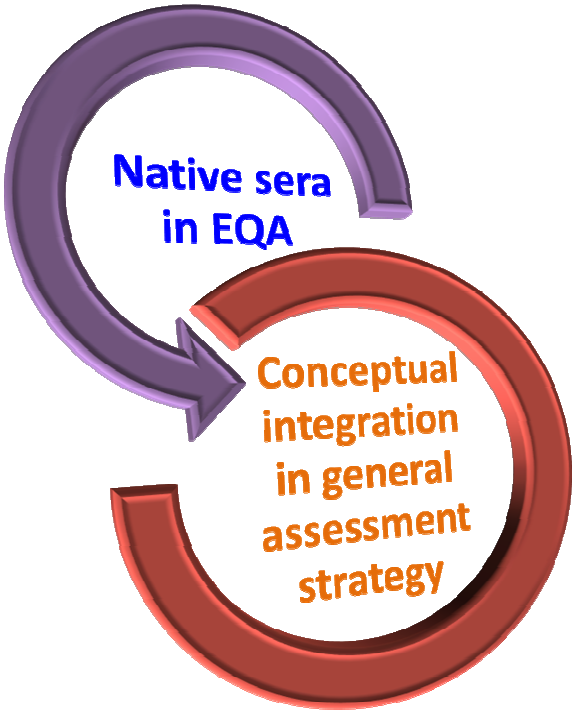
Goossens K, Thienpont LM. Reference measurement procedure corrected all method trimmed mean - The best of two worlds. Clin Chim Acta 2015;440:55-6.

Best of two worlds

Demonstration of the effect of using RMP and RMP-corrected AMTM values on data dispersion around regression lines (logarithmic relationship); %-difference plots of results for γ-glutamyltransferase (GGT) by 2 different routine procedures compared to RMP (left) and RMP-corrected AMTM values (right). The squared symbols and triangles used in the plots represent the differences of the respective routine procedures.



Commutable samples in PT – Our start



Stöckl D, Thienpont LM. The combined target approach - A way out of the proficiency testing dilemma [Letter]. Arch Pathol Lab Med 1994;118:775-6.

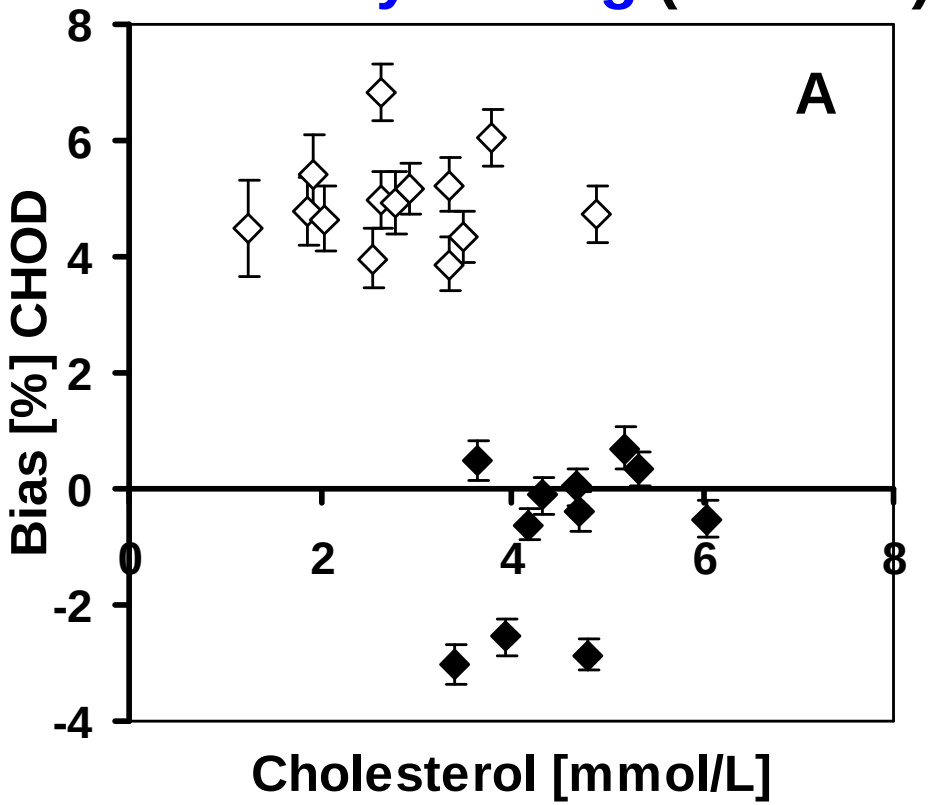
Commutable samples in PT – Our start

INSTAND e.V.

Stöckl D, Libeer J-C, Reinauer H, Thienpont LM, De Leenheer AP. Accuracy-based assessment of proficiency testing results using serum from single donations: possibilities and limitations. Clin Chem 1996;42:469-70.

Applications

SEKK: pilot study (2003)
Commutability testing (◊ native)



Thienpont LM, Stöckl D, Kratochvíla J, Friedecký B, Budina M. Pilot external quality assessment survey for post-market vigilance of in vitro diagnostic medical devices and investigation of trueness of participants' results. Clin Chem Lab Med 2003;41:183-6.

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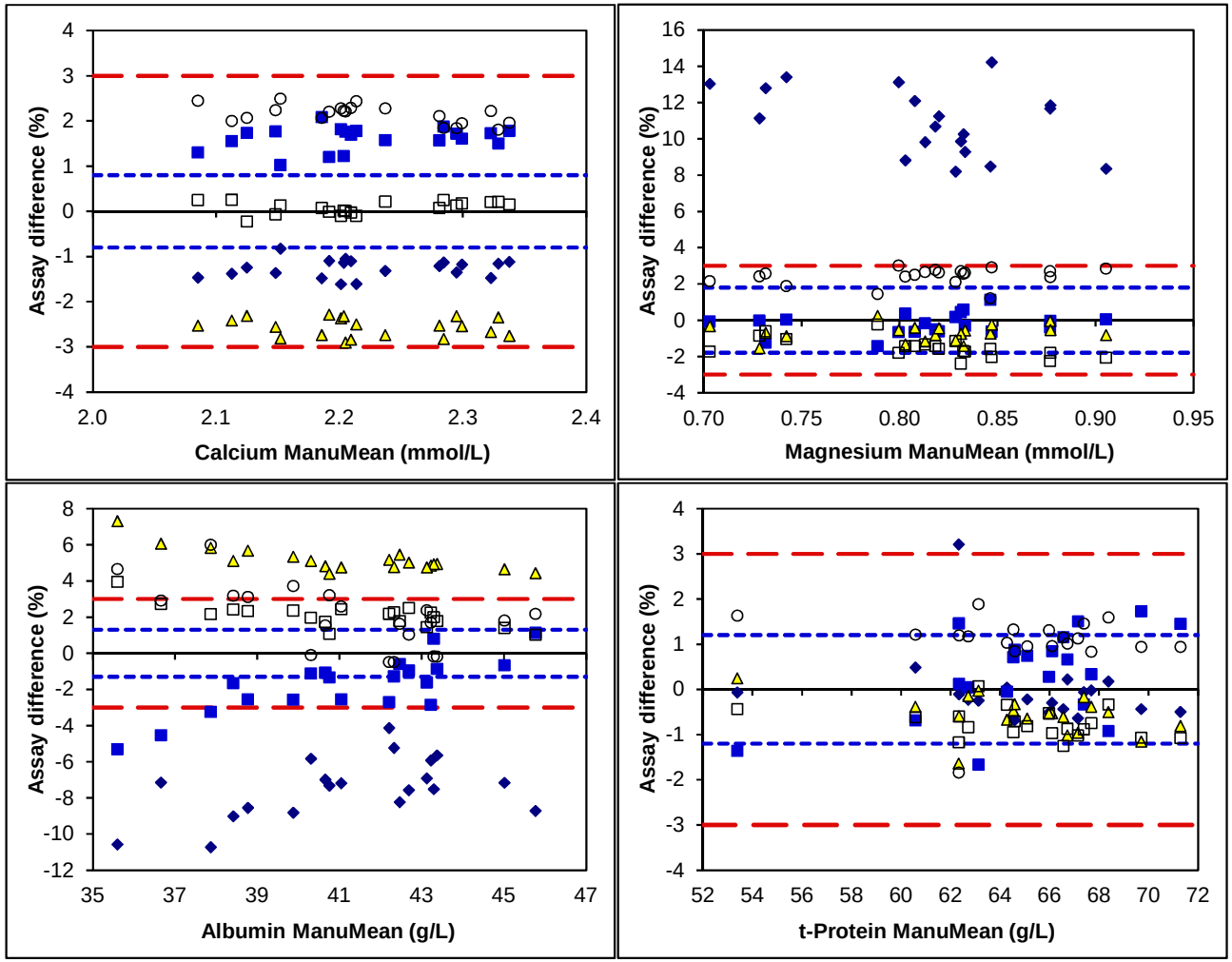
Applications

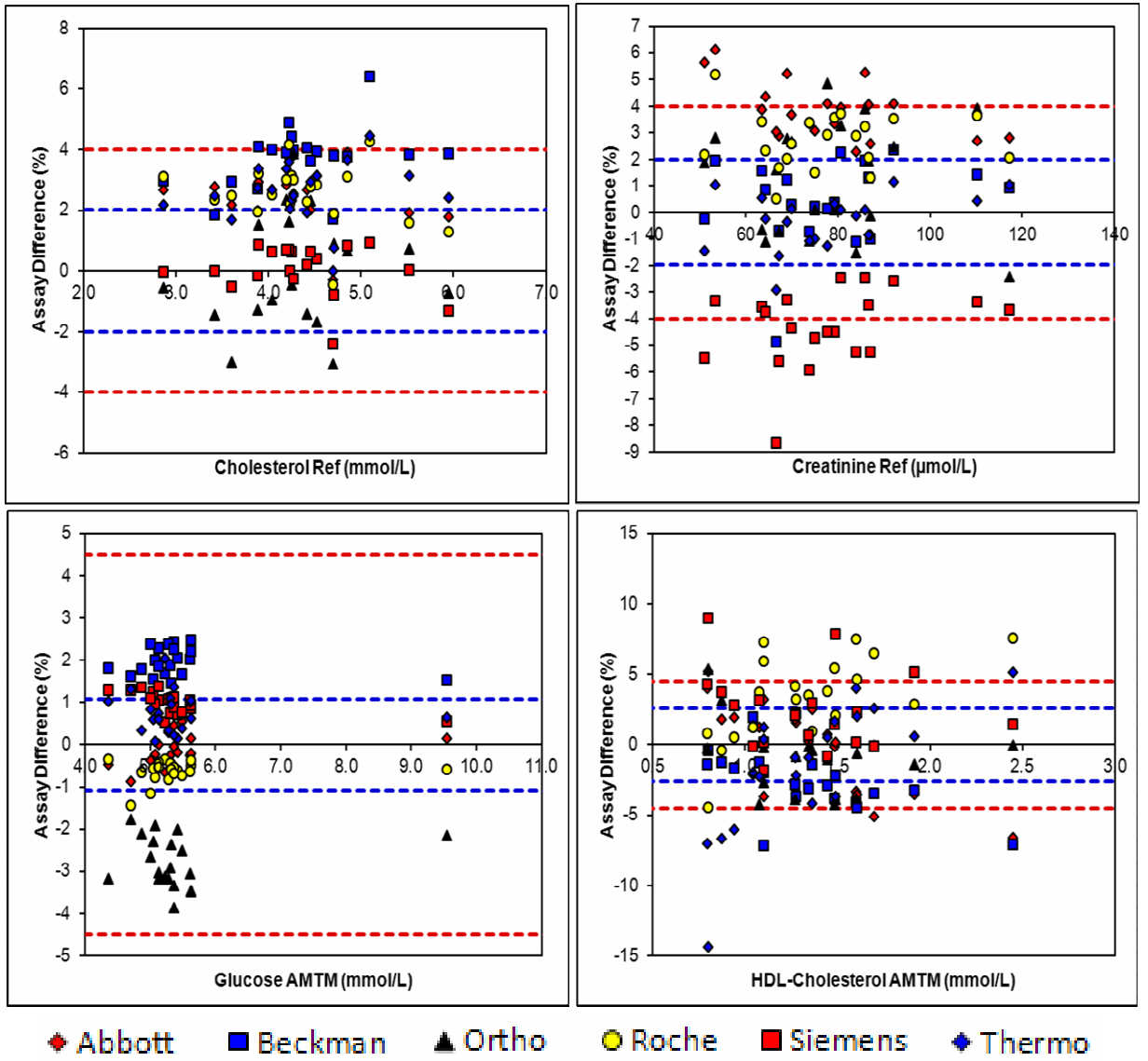
Master comparison NKK 2011



Van Houcke et al. Clin Chem 2012;58:1597-9.

Applications

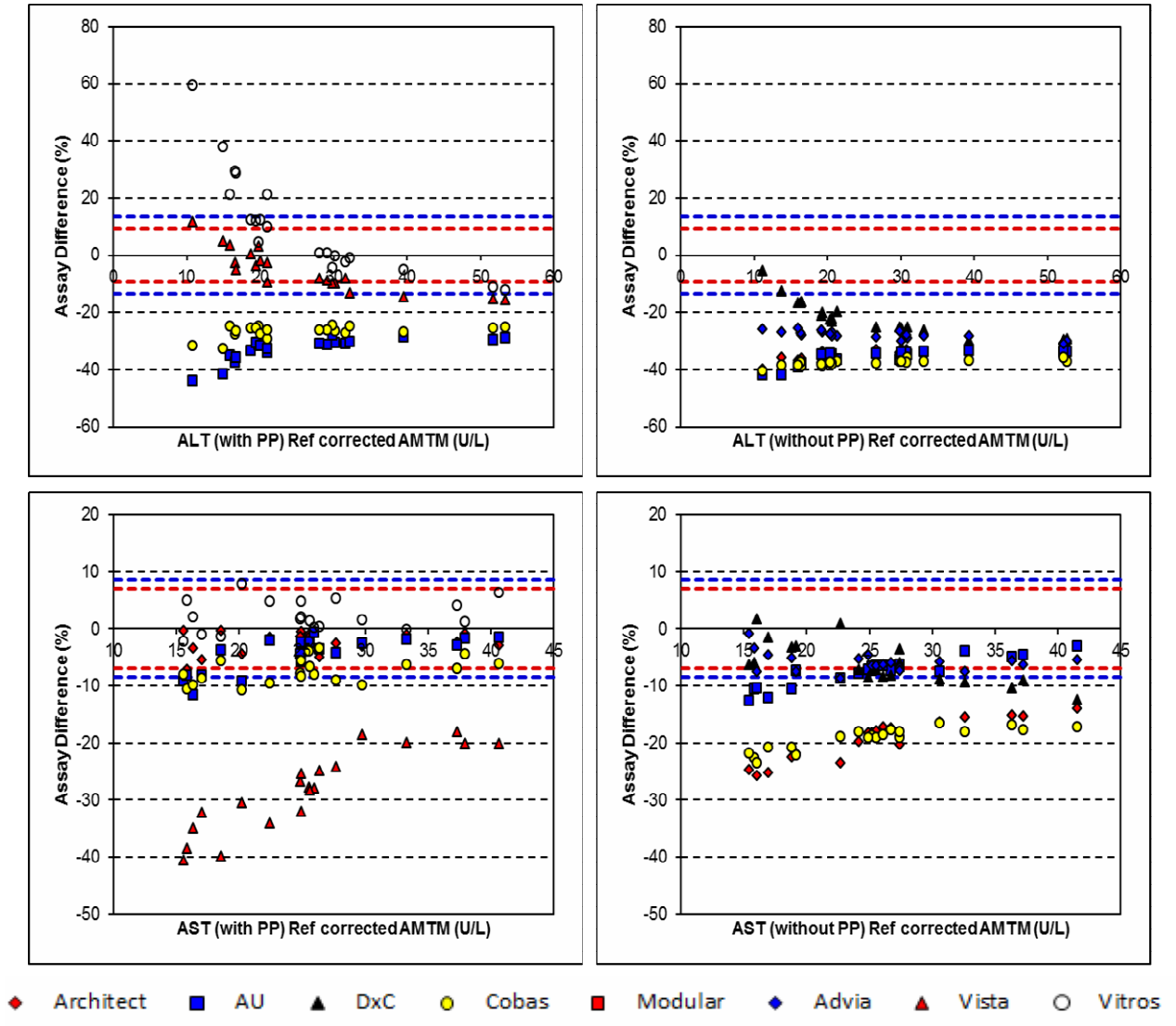
Master comparison Labquality 2012



Stepman HCM et al. Clin Chem 2014;60:855-63.

Applications

Master comparison UGent 2014



Goossens K et al. Clin Chim Acta 2015;442:44-5.

Conclusion

Criteria for assignment of reference method values for use in EQA

- **Quality of targets set by RMPs must be commensurate with the intended use**
- **Quality should not be taken for granted:**
  - **-[Potential] bias**
  - **-Uncertainty dependent on n of measurement protocols**
- **Quality specifications are needed – bias**
- **Outcome-related model (EQA-limits; % FDs)**
- **Alternatives to cope with the high demands for the quality of the targets**

In the end

Ceterum censeo Carthaginem esse delendam*

*Cato Censorius (called Cato The Elder) °234 - †149 BC

And by the way, I am of the opinion that commutable samples must be used in EQAS intended for the assessment of traceability!