Leids Universitair Medisch Centrum

The road to a perfect EQA-programme

The Dutch SKML experience

Christa Cobbaert

DEPARTMENT OF CLINICAL CHEMISTRY AND LABORATORY MEDICINE,
LEIDEN UNIVERSITY MEDICAL CENTRE, LEIDEN, THE NETHERLANDS

skml
Stichting Kwaliteitsbewaking Medische Laboratoriumdiagnostiek
CALIBRATIE 2.000

JCTLM
Accurate results for patient care
WG on TRACEABILITY
EDUCATION and PROMOTION

Content

I. Rationale for EQA

II. Legislation and regulations affecting EQA

III. Evaluation capabilities of EQA programmes

IV. Dutch EQA & the road to perfection:

- Calibration 2000 since 1998
- Trueness verification for general chemistry since 2005
- Accuracy-based scoring & reporting since 2014
- Achievements

V. Conclusions

I. Meaning of Life of an EQAS organizer

The client perspective

ISO 15189 accredited labs need:

- 4.12 continuous improvement
- 5.3.1.4 metrological traceability, ISO17511
- 5.5.1. selection, validation and verification of methods
- 5.5.1.4 measurement uncertainty
- 5.6.3 interlaboratory comparison including corrective action

fundamental tool for independent evaluation & continuous quality improvement of lab services

Risk management of accuracy

1. Method validation, verification
   - T=0
     Trueness and imprecision within Analytical Performance Specifications?
     (desirable/ minimum/ optimum)

2. Internal QC
   - Performance as on T=0 still true?

3. External QC
   - What can be wrong?

Goals for perfect EQAS

Goals:

- Verification of trueness and imprecision (SEPARATELY!)
- Verification of harmonisation
- (Verification of quality of Total Testing Process)

Materials as intended by ISO17043: commutable, homogenous, stable

- Material cannot be blamed

Value assignment by reference labs using reference methods

- Value assignment cannot be blamed

Smart reporting

- Participant knows what to do

II. (Inter)national legislation and regulation affecting EQA

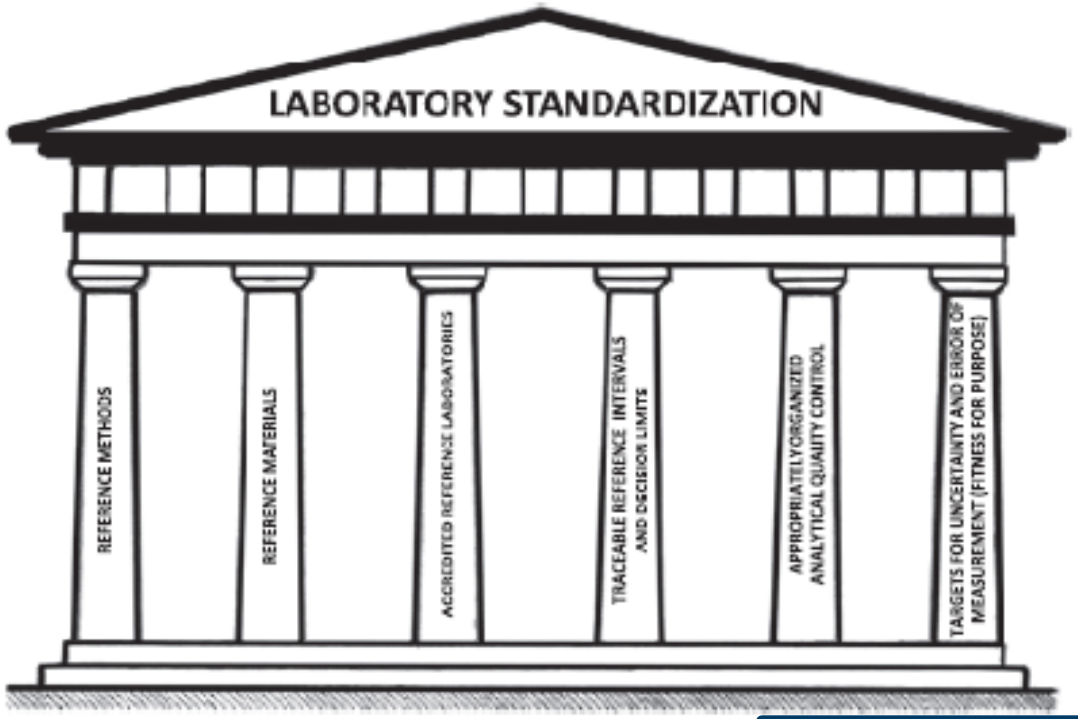
History of EQA:

- Belk and Sunderman, 1947 → 1ste EQA-survey
- Industrial quality control concepts were adapted for use in medical labs and in EQA schemes at the end of the sixties/ early seventies.

Upcoming regulation/ legislation affecting current EQA-programmes:

- **Standards** < authoritative bodies:
  - ✓ISO 15189:2012 and ISO 17025 for accreditation of medical labs;
  - ✓EN 14136 and ISO 17043 for accreditation of EQA-/PT-providers
- **Guidelines** < scientific organizations: e.g. RiliBÄK
- **EU directive IVD 98/79/EC** → revised IVD regulation since June 2016
- **Establishment of JCTLM**, 2002

Commutable EQA-materials enable trueness verification



The temple of lab standardization and its six pillars

Braga et al., CCA 2014

Trueness verification ←

1. Reference methods
2. Reference materials
3. Accredited reference labs
4. Traceable RI & DL
5. Commutable, value -assigned EQA-samples
6. Targets for uncertainty and error of measurement

III. Evaluation Capabilities of EQA-surveys related to Scheme Design

Clin Chem. 2011 Dec;57(12):1670-80

Category	Sample Characteristics			Evaluation Capability						
				Accuracy			Reproducibility		Standardization / Harmonization.	
	SKML			Absolute	Relative		Individual lab	Method	Absolute	Relative
Category	Commuta -ble	Target RMP CRM	Replicate Samples	RMP CRM	Overall	Peer group	Intra lab CV	Method Inter lab CV	RMP-CRM	Mean Labs
1	Yes	Yes	Yes	X	X	X	X	X	X	X
2	Yes	Yes	No	X	X	X		X	X	X
3	Yes	No	Yes		X	X	X	X		X
4	Yes	No	No		X	X		X		X
5	No	No	Yes			X	X	X		
6	No	No	No			X		X		

IV. Dutch EQA and the road to perfection

Calibration 2000

1. **Commutable EQA-materials**
2. **Value-assigned**
3. **Accuracy-based reporting & scoring system** based on analytical performance criteria defined at the 1st strategic EFLM Milan consensus.

Developed and evaluated since 1998.

Formally introduced for general chemistry since 2005.

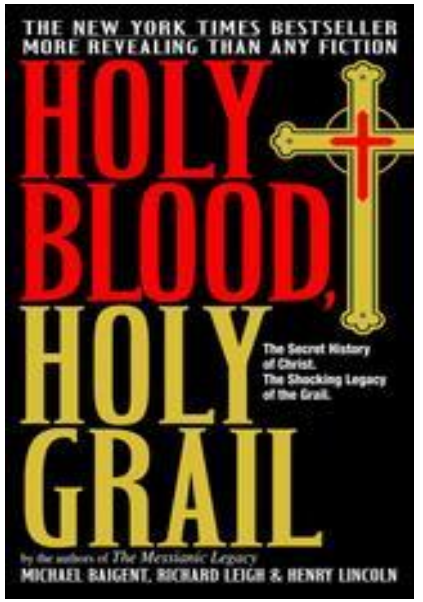
Standardization /harmonization initiative "avant la lettre".

Dutch EQA: fresh frozen EQA-materials for general clinical chemistry since 2005

Scope: type 1 analytes with available RMS for standardization

1. Human serum matrix
2. Not or minimally processed:
   - ✓ CLSI C37A single donor pools for lipids/apo's!
   - ✓ Regular pool procedure for chemistry with spiking;
   - ✓ For enzymes: spiking with human recombinant enzymes
3. Systematic concentration range (donor selection /spiking)
4. 24 interdependent samples per year (12 pairs; linear relation!)
5. Liquid frozen
6. Stored at - 70 °C (enzyme stability!)
7. Values assigned with (JCTLM-listed) RMPs

CCLM 2005; 43: 304-7.



Holy Grail
San Greal
Sang Real

Certified EQA Production Centre

CERTIFICATE

Number: 2135450

The management system of:

MCA Laboratory
Streekziekenhuis Koningin Beatrix

Beatrixpark 1
7101 BN Winterswijk
The Netherlands

including the implementation meets the requirements of the standard:

ISO 13485:2003

Scope:
The development, manufacturing, distribution and sales of calibrators, controls, specimens and reference materials used for In Vitro Diagnostic Devices and External Quality Assessment schemes in medical laboratories

Certificate expiry date: 1 March 2019
Certificate effective date: 1 October 2016
Certified since: 1 October 2010

Samples	*Commutable*
	Range
	Stability
	Replicates
	Homogeneity
Targets	*RMS*
	Mean Labs
	(Uncertainty)
Evaluation	*Poor Performer policy*
	Scores
	Reports
	Monitoring Standardization

EQA-Design

Frozen Human Serum

-24 Samples/Year
-12 Replicates
-Linearity Panel
-Shipment on Dry ice
-Storage < -70 ° C

Assigned values

-Biweekly Assay

MUSE & sigma metrics

-Day report
-Trimester Report
-Annual Report
-Annual Letter

MUSE:

Multiple Sample Evaluation

accuracy-based EQA-scoring system

Submitted

MUSE Scoring & Reporting System

Essential features of MUSE:

1. Regression analysis & time weighting

2. Predefined tolerance ranges

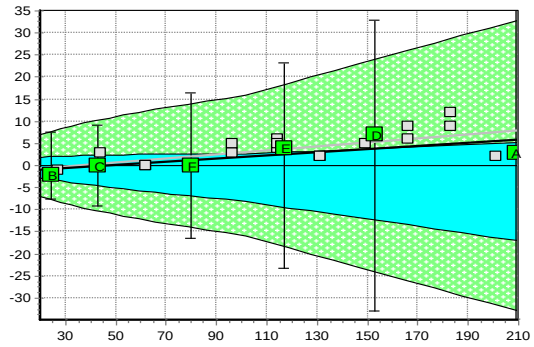
3. Sigma metrics & sigma values

4. Performance scores based on sigma values

Regression analysis

Regression lines through differences of EQA-results minus Target Values (TVs) against TVs:

- reference values
- expert lab values
- consensus method group averages



→ Slope and intercept depict bias!

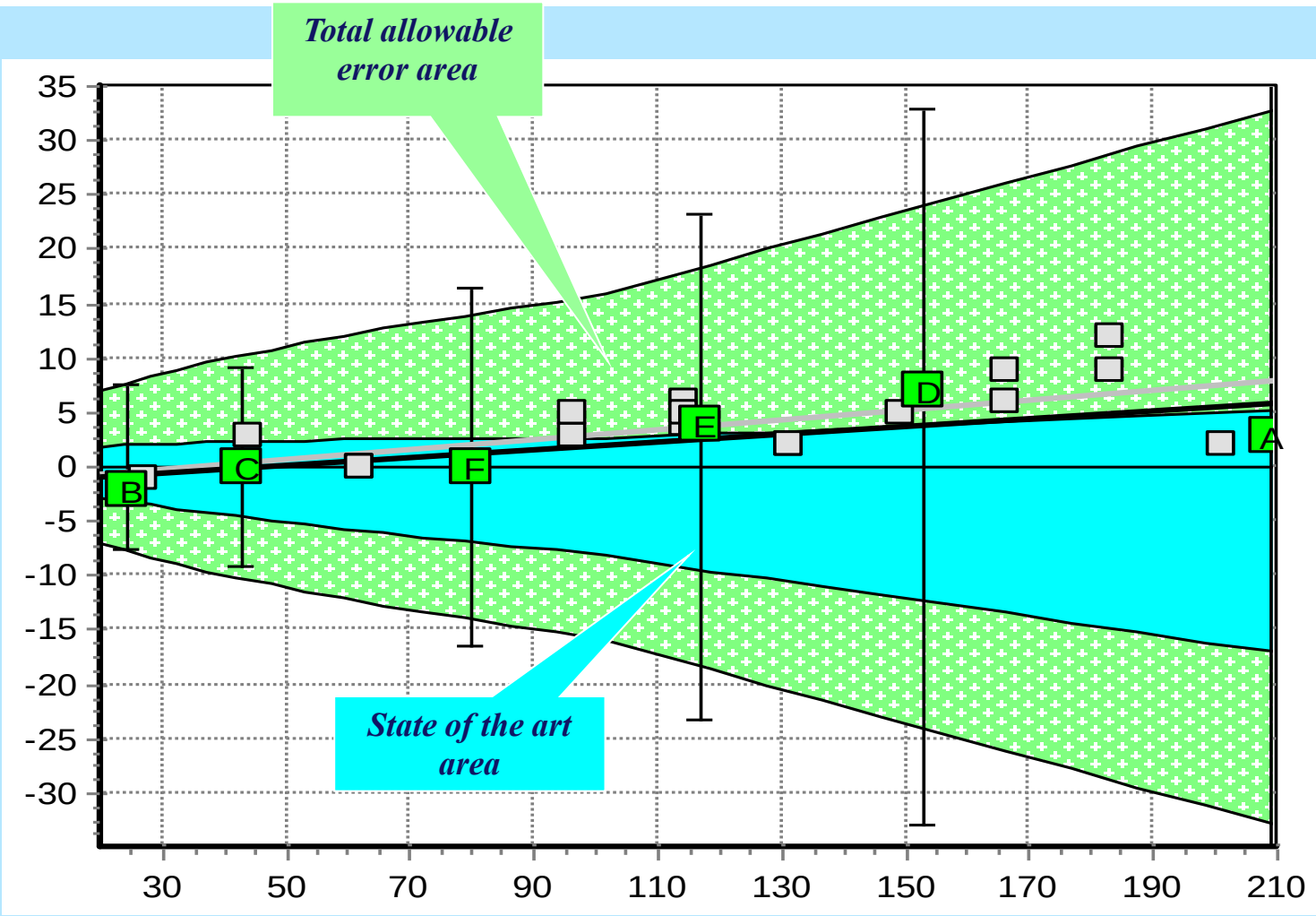
→ Dispersion around regression line is a measure of within-lab imprecision!

Two regression lines:

- last quarter and last year;
- time weighted for last quarter (= moving regression analysis of multiple samples)

→ Vivid PDCA cycle

MUSE: graphical presentation of tolerance ranges



MUSE features

Lab performance measured against predefined tolerance ranges:

1. **State-of-the-art tolerance range = mean ± 3SD_{SA}**
   - SD_{SA} is selected so that 90% of the results of participating labs from the last 3 year evaluation period are within SA tolerance limits, after clean-up *of non state-of-the-art* results.
   - Shape is function of the concentration and determined by the precision profile.

2. **Total allowable error tolerance range = mean ± [(1.65 x CV_a) + B]**
   - Based on desirable specifications dbase < Ricos and Westgard:
     - CV_a <u>desirable</u> analytical variation = 0.5 x CV_w
     - B maximum allowable bias = 0.25 $\sqrt{(CV_w^2 + CV_b^2)}$*
   - TE_a value from the dbase is used at the reported level
   - Extrapolation to other concentration levels using precision profiles

* CV_w within-person variation; CV_b between-person variation

MUSE features

Sigma metrics concept

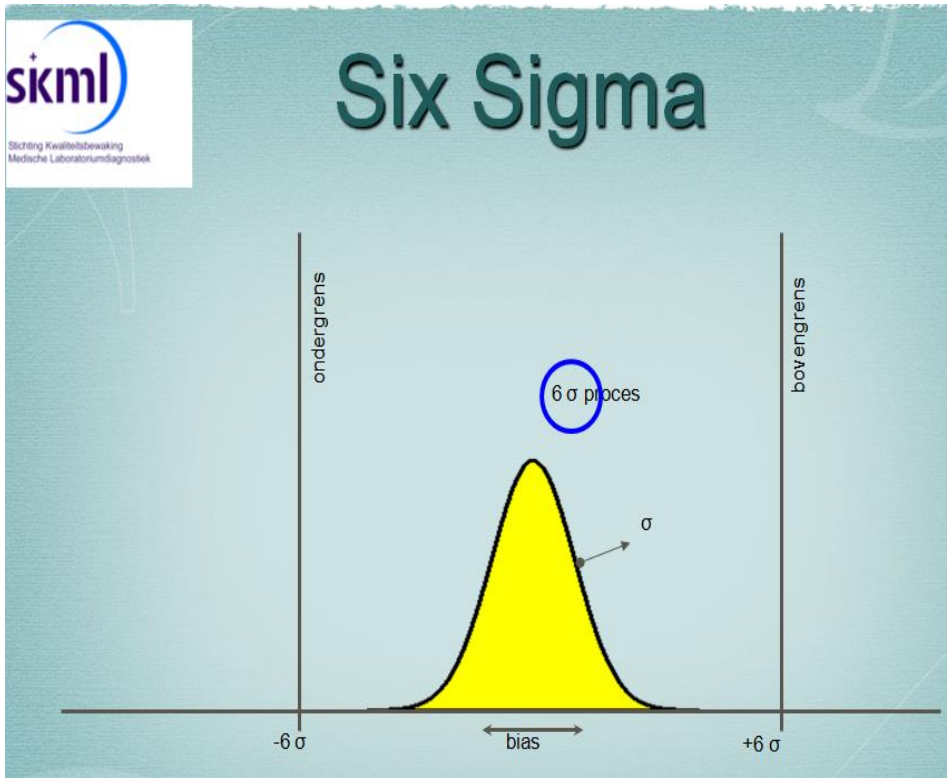
Used worldwide to quantify the quality of a production process

Six sigma process:

6 SDs are within the tolerance limits and less than 1 out of 10^6 products does not meet the quality standard.

Six sigma concept:

Accepts a shift of 1.5 sigma after some time → SKML tolerance limits based on 4.5 sigma



SIGMA value calculation

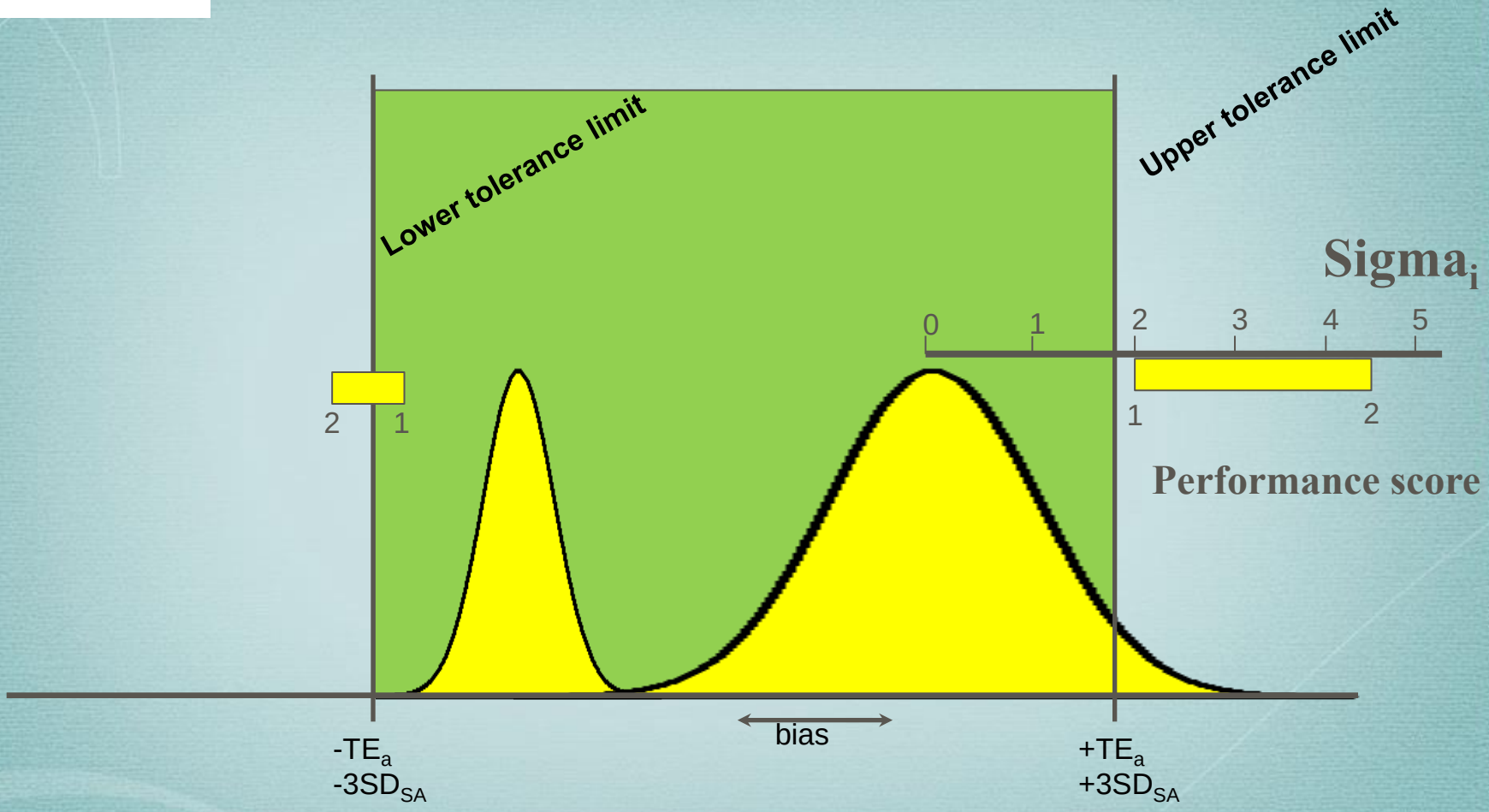
$$Sigma_i = (TL - |x_j - T_i|) / SD_{wl} + \sqrt{2}/\pi$$

- ✓TL is the tolerance limit (TE_a or SD_{SA});
- ✓x_j the measured EQA-value;
- ✓T_i the target for the sample (reference value where possible, otherwise method group consensus).

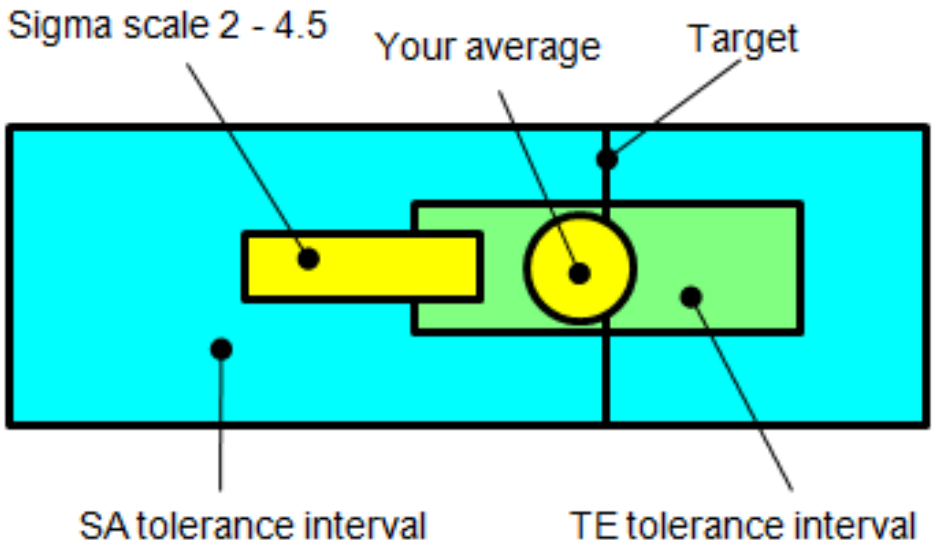
The term $\sqrt{2}/\pi$ (≈ 0.7979) is a correction for the fact that sigma of each individual sample is not calculated from the bias of the mean of multiple measurements of that sample, but from a single estimate of that bias.

Stichting Kwaliteitsbewaking
Medische Laboratoriumdiagnostiek

Sigma values



MUSE report: score pictograms and 2-point P-scores



Sigma	P-score	% Accept
0-2	0	<95%
2-4.5	1	95-99.9997%
>4.5	2	>99.9997%

= Adequate score (1 or 2 points)

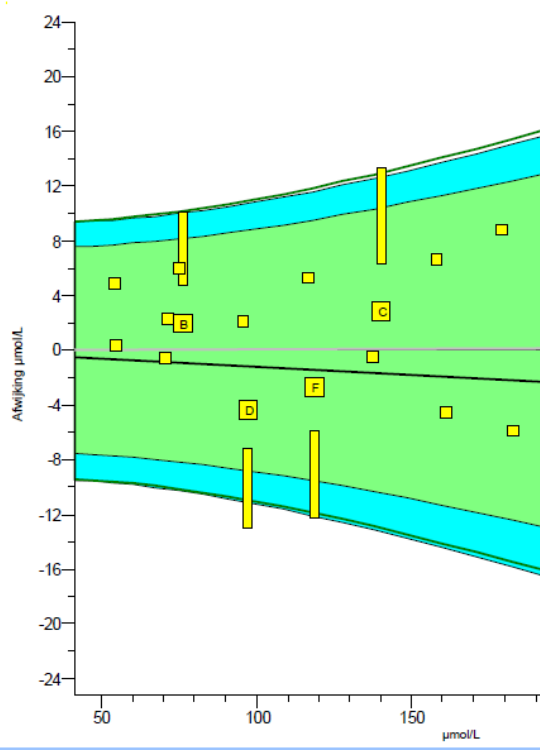
= Inadequate score (≤ 0 points)

= No result submitted, does not count for MAP

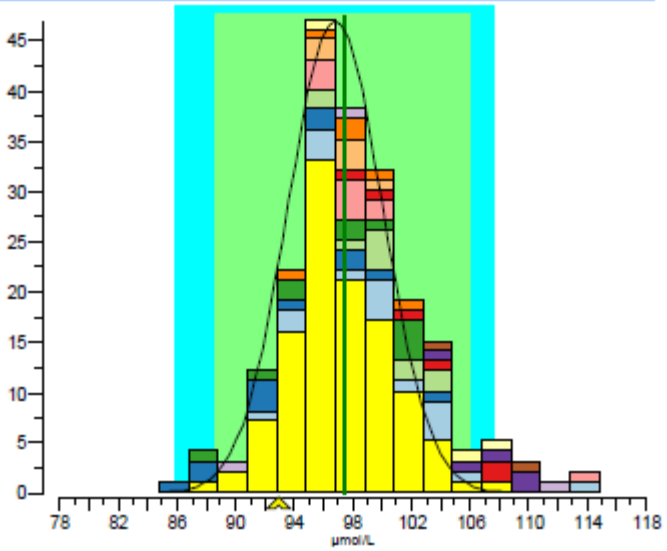
Example:

1st, 2nd, 4th and 6th result correctly measured, 3rd result is incorrect.

MUSE quarter report for serum creatinine



2016.2 D



	cons.	meth.	ref.	lab
gem.	96.8	96.7	97.4	93
SD	3.2	3.3		
n	160	114		
nu	4	1		

eenheid : µmol/L

cumulatief

+0.25%
2.7%
24
0
3.1
4.0

0.0 + 1.001.x

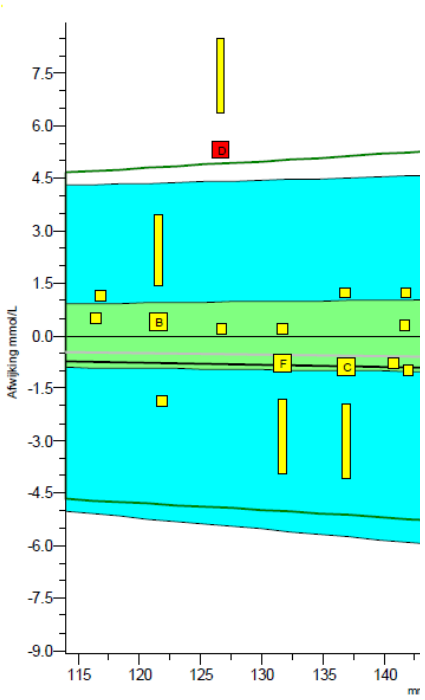
ch
ymatisch
dular

vijzigd gedurende rapportage periode.
nsusgroep ook gewijzigd is,
hebben voor de score berekening.

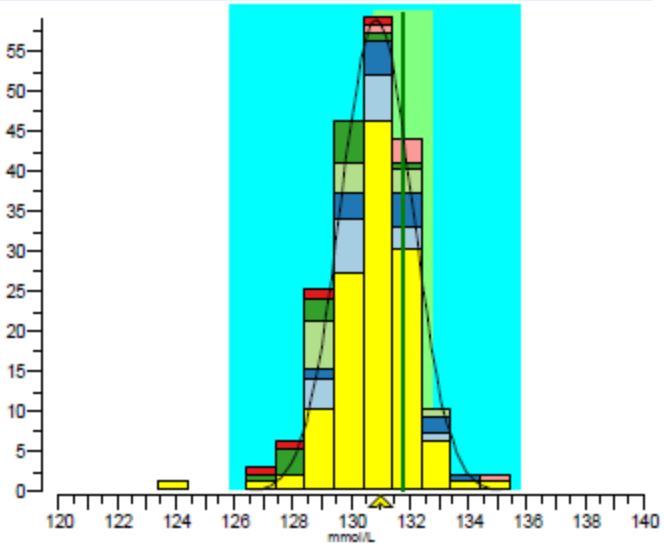
Legenda

Roche enzymatisch	Beckman Coulter Jaffe	Siemens Dimension enzymatisch	Beckman Coulter Olympus enzymatisch	Roche Jaffe
Abbot enzymatisch	Siemens Dimension Jaffe	Beckman Coulter enzymatisch	Siemens Advia 1800 enzymatisch	Overige methoden
Abbott Jaffe	Overigen enzymatisch	Beckman Coulter Olympus Jaffe	Siemens Advia 1800 Jaffe	

MUSE quarter report for serum sodium



2016.2 F



	cons.	meth.	ref.	lab
gem.	130.9	130.9	131.8	131
SD	1.2	1.1		
n	194	125		
nu	18	3		

eenheid : mmol/L

.2	cumulatief
%	-0.39%
%	0.63%
6	24
1	1
2	0.6
7 2	5.3 2
994.x	0.0 + 0.996.x

Modular
000.x
000.x
gewijzigd gedurende rapportage periode.
sensusgroep ook gewijzigd is,
gen hebben voor de score berekening.

Legenda

- Roche
- Beckman Coulter
- Siemens Dimension
- Beckman Coulter Olympus
- Abbott
- Siemens Advia
- Overige methoden

MUSE report: cover page & score summary at a glance

Analyte		Trueness				Precision		Performance				
		your mean	ref.	cons.	SDwl	your prec.	SDbl	this survey	PS	cumulative	PSc	
Urea	mmol/L	15.8		15.5	0.5	0.6	0.4		2			2
Creatinine	µmol/L	155.1	152.4	151.5	4.3	3.1	3.0		1			1
Sodium	mmol/L	140.2	143.8	142.7	1.5	1.8	1.2		1			1
Potassium	mmol/L	5.21	5.37	5.39	0.07	0.09	0.06		1			1
Chloride	mmol/L	100.9	102.3	100.8	1.8	1.2	1.0		2			2
Calcium	mmol/L	2.377	2.230	2.242	0.060	0.117	0.042		0			1
Inorg. Phosphate	mmol/L	1.635		1.574	0.034	0.066	0.029		1			1
Magnesium	mmol/L	1.204	1.167	1.163	0.029	0.076	0.024		1			1
Urate	mmol/L	0.336	0.348	0.346	0.010	0.015	0.007		2			2
Bilirubin	µmol/L	40.1	37.1	36.6	1.3	2.4	1.1		1			2
ASAT	U/L	72.1	74.6	74.6	2.9	2.5	1.7		2			2
ALAT	U/L	76.3	82.3	80.6	3.8	2.7	2.0		2			2
LD	U/L	390	448	454	30	27	16		0			0
Alk. Phosphatase	U/L	144	155	152	9	8	5		2			2
Gamma-GT	U/L	68.9	67.5	68.0	2.4	2.0	1.7		2			2
Amylase	U/L	186	189	184	7	8	4		2			2
Lipase	U/L	25.2		26.8	1.3	1.4	0.9		2			2
CK	U/L	231	245	243	11	6	5		2			2
Total Protein	g/L	65.9	65.4	65.5	1.4	1.6	1.0		2			1
eGFR (F, 55, white)	mL/min/1,73m²	23.6	24.1	23.0	1.2	0.9	0.7		2			2
Glucose	mmol/L	13.85	13.39	13.56	0.35	1.15	0.28		1			1
Albumin	g/L	46.1		46.7	1.3	1.6	0.9		1			1
Osmolality	mOsmol/kg	310.6		313.9	3.9	5.4	2.9		1			1
Iron	µmol/L	36.2		36.1	0.9	0.9	0.8		2			2
								Total :		35		36

MUSE: from insight to PDCA-support of lab professionals

SKML MUSE reporting and scoring system provides what ISO 15189 & ISO 17043 expect from a type 1 EQAS organizer:

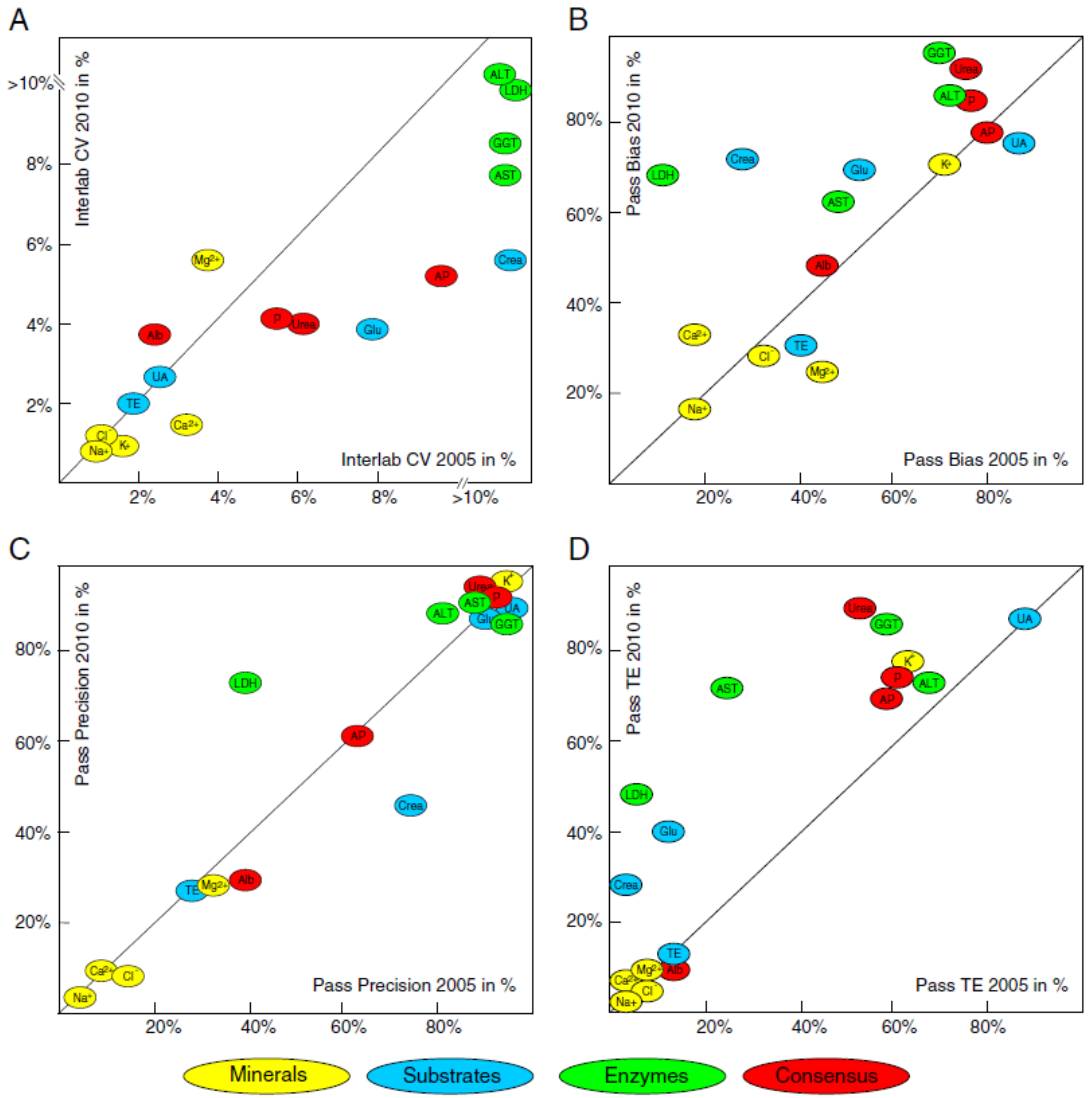
- ✓Insight into bias and imprecision of tests;
- ✓Traceable to the manufacturer!
- ✓Empowering participants to ameliorate trueness or to select more specific tests.

Limitations:

- ✓Data richness of reports demands familiarization;
- ✓No information on the uncertainty of the estimate of bias and imprecision.

First successes: general chemistry in 2005 vs. 2010

C. Cobbaert et al. / Clinica Chimica Acta 414 (2012) 234–240



Clin Chim Acta 2012; 414: 234-40

Transferable: pilots in other European countries

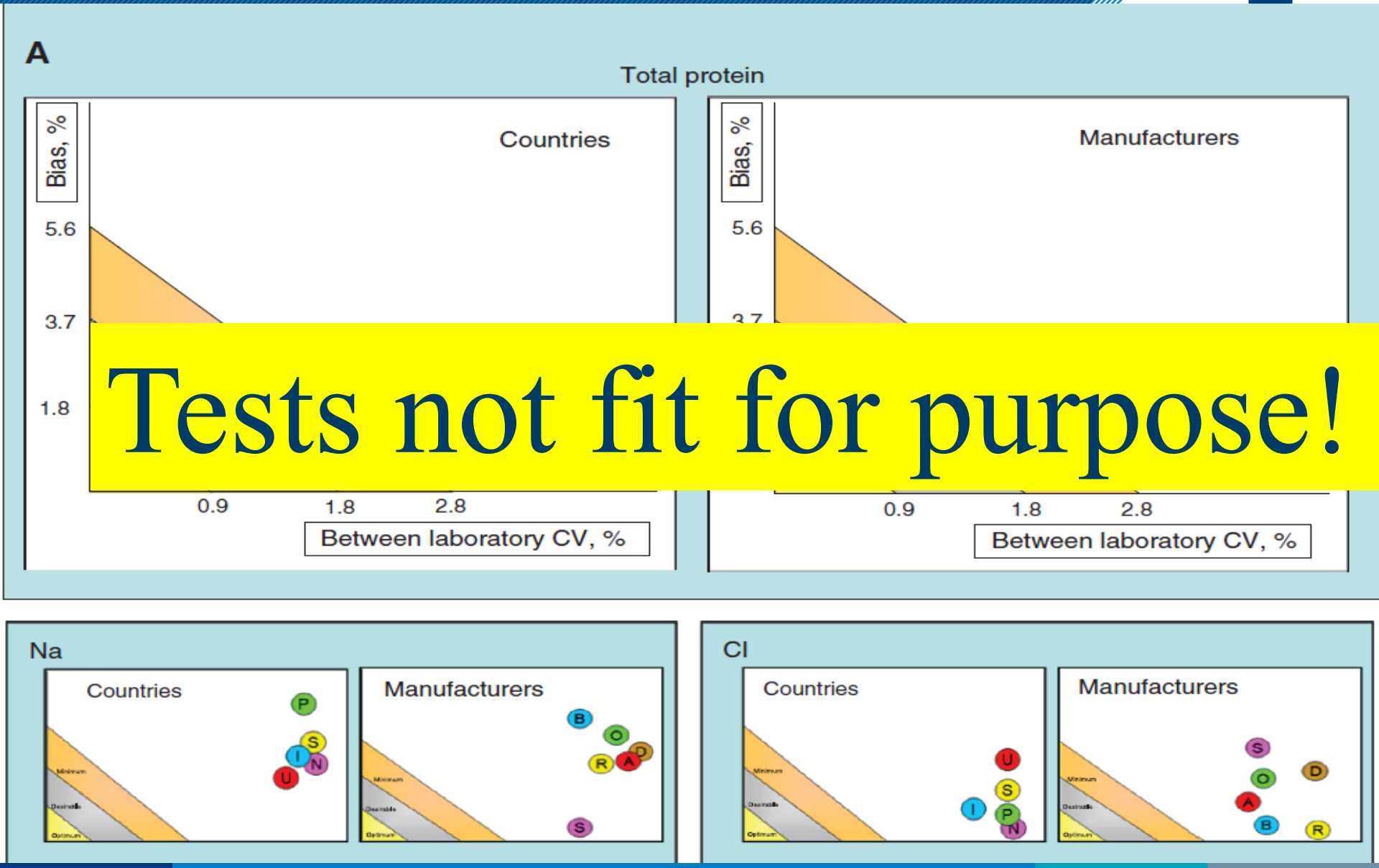
Cas Weykamp*, Sandra Secchiero, Mario Plebani, Marc Thelen, Christa Cobbaert, Annette Thomas, Nuthar Jassam, Julian H. Barth, Carmen Perich, Carmen Ricós and Ana Paula Faria

Analytical performance of 17 general chemistry analytes across countries and across manufacturers in the INPUtS project of EQA organizers in Italy, the Netherlands, Portugal, United Kingdom and Spain

Conclusions: The overall performance of the measurement of 17 general chemistry analytes in European medical laboratories met the minimum performance specifications. In this general picture, there were no significant differences per country and no significant differences per manufacturer. There were major differences between the analytes. There were six analytes for which the minimum quality specifications were not met and manufacturers should improve their performance for these analytes. Standardization of results of enzymes requires ongoing efforts.

CCLM, 2016 (epub ahead of print)

Performance per country and per manufacturer < EQA



Tests not fit for purpose!

V. CONCLUSIONS

1. Since > 10 years SKML runs **a type 1 EQA-programme** for general chemistry based on human, fresh frozen samples which are commutable, value-assigned, interdependent, with 12 pairs per year.
   These EQA-materials enable **trueness verification**.

1. By adding **sigma metrics based performance evaluation** in relation to both **TE_a and SD_{SA} intervals**, SKML provides its participants with a **powerful and actionable check on accuracy**.

CONCLUSIONS

Native samples and the revised Dutch EQA-design resulted in

- ✓ improved between-lab CVs c.q. harmonization (e.g. enzymes);
- ✓ improved trueness c.q. standardization (e.g. creatinine);
- ✓ abandoning of non-selective methods (e.g. creatinine Jaffé).

The innovative scoring and reporting system for chemistry analytes foresees in a Poor Performer Policy of the EQA-provider.

A perfect EQA programme facilitates root cause analysis of inaccurate results

Manufacturer

IVD directive 98/79/EC

JCTLM

Traceability to standards of higher order

EQAS organization

/ SKML chemistry section:

- Intended use: post-marketing vigilance of test performance
- Tools: **trueness verifiers**

Lab professional

- Within TE_a? Within desirable bias?
- Unacceptable lot variation?
- Intended use: temporary (re)calibration in case of unacceptable bias
- Tools: **matrix-based reference materials**

CLUE=

type 1 EQA-provider

Future: effect on patient outcome?

Acknowledgements

Marc Thelen, Medical Director SKML, Nijmegen, NL

Cas Weykamp, Director of the accredited production centre, Winterswijk, NL

Members of the SKML chemistry section

Participating laboratories

Thanks for your attention!