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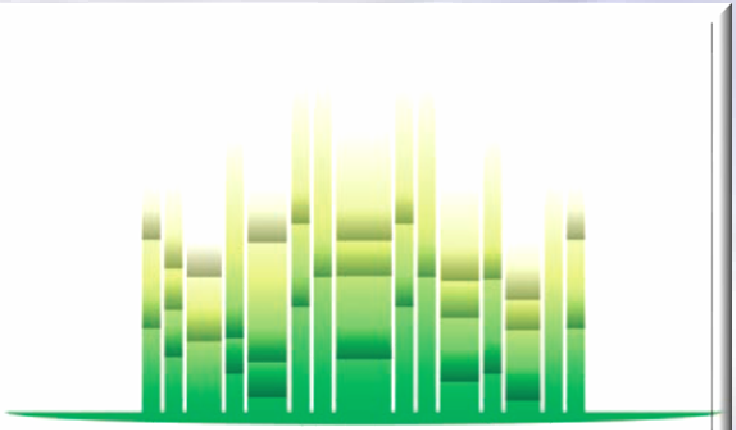
Centre for Metrological Traceability in Laboratory Medicine (CIRME)

Director: Prof. Mauro Panteghini

site: http://users.unimi.it/cirme



9th International Scientific Meeting

STRUCTURING EQAS FOR MEETING METROLOGICAL CRITERIA: READY FOR PRIME TIME

MILANO, ITALY
November 27th, 2015

Performance specifications in EQAS

Mauro Panteghini

Table 3. Evaluation capabilities of PT/EQA related to scheme design.

	Sample characteristics			Evaluation capability						
				Accuracy						
				Individual laboratory					Standardization or harmonization[b]	
					Relative to participant results		Reproducibility		Measurement procedure calibration traceability	
Category	Commutable	Value assigned with RMP[a] or CRM	Replicate samples in survey	Absolute vs RMP or CRM	Overall	Peer group	Individual laboratory intralab CV	Measurement procedure interlab CV	Absolute vs RMP or CRM	Relative to participant results
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			No		X	X		X		X
5			Yes			X	X	X		
6			No			X		X		

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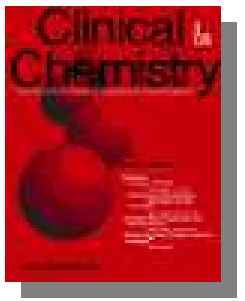
Miller WG et al. Clin Chem 2011;57:1670



EQAS performance specifications

- Currently wide variation in practice
- Range between very “tight” and very “loose”
- May be based on:
  - Clinical
  - Biological variation
  - State of the art (different definitions)
  - Statistical
  - Regulatory
  - Combination of models (e.g. state of the art and BV)
  - Other (e.g. professional recommendations)

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EQAS performance specifications

(looser)
e.g. regulatory
All labs pass

(tighter)
e.g. biological
A portion of labs fail

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Accred Qual Assur (2008) 13:145–148
DOI 10.1007/s00769-008-0364-z

Marjan Van Blerk et al.

GENERAL PAPER

Comparison of evaluation procedures used by European external quality assessment scheme organizers for haemoglobin concentration and leukocyte concentration

Table 1 Criteria used for acceptable performance for haemoglobin concentration in blood and leukocyte concentration (deviation from the target value)

Scheme	Haemoglobin concentration	Leukocyte concentration
Belgium	±2*s*	±2*s*
France	±2*s*	±2*s*
Spain (two organizers)	±2*s*	±2*s*
Croatia	±1*s*	±1*s*
Germany	±6%	±18%
Finland	±5%	±10%
Hungary: consensus mean	±3%	±6%
Hungary: target value set by reference labs or manufacturers	±5%	±15%
Russia	±1.64*s*	±1.64*s*
Slovenia	±4%	±10%
Switzerland: QUALAB (official for licensing)	±9%	±25%
Switzerland: CSCQ (scientific approach)	±3%	±8%
New York State, USA	±7%	±15%

Table 2 Percentages of unsatisfactory results reported by the participating EQAS organizers for a fixed set of 262 results of haemoglobin concentration in blood and leukocyte concentration

Scheme	Haemoglobin concentration	Leukocyte concentration
Belgium	6.9	7.3
Croatia	14.9	15.3
Finland	1.5	3.1
France	5.4	4.6
Hungary: consensus mean method	13.5	19.8
Russia	15.6	19.8
Spain 1	7.6	4.6
Spain 2	3.1	2.3
Switzerland: QUALAB (official for licensing)	0.4	0
Switzerland: CSCQ (scientific approach)	0.8	2.0
New York State, USA	0.8	2.3

Requirements for the applicability of EQAS results in the evaluation of the performance of participating laboratories in terms of traceability of their measurements

Feature	Aim
EQAS materials value-assigned with reference procedures by an accredited ref. laboratory	To check traceability of commercial system to reference systems
Proved commutability of EQAS materials	To allow transferability of participating laboratory performance to the measurement of patient samples
Definition and use of the clinically allowable measurement error	To verify the suitability of laboratory measurements in clinical setting

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Panteghini M, CCLM 2010;48:7
Infusino I et al., CCLM 2010;48:301
Braga F & Panteghini M. CCLM 2013;51:1719
Braga F & Panteghini M, Clin Chim Acta 2014;432:55

Analytical performance specifications: definition

Criteria that specify (in numerical terms) the quality required for analytical performance in order to deliver laboratory test information that would *satisfy clinical needs* for *improving health outcomes*.

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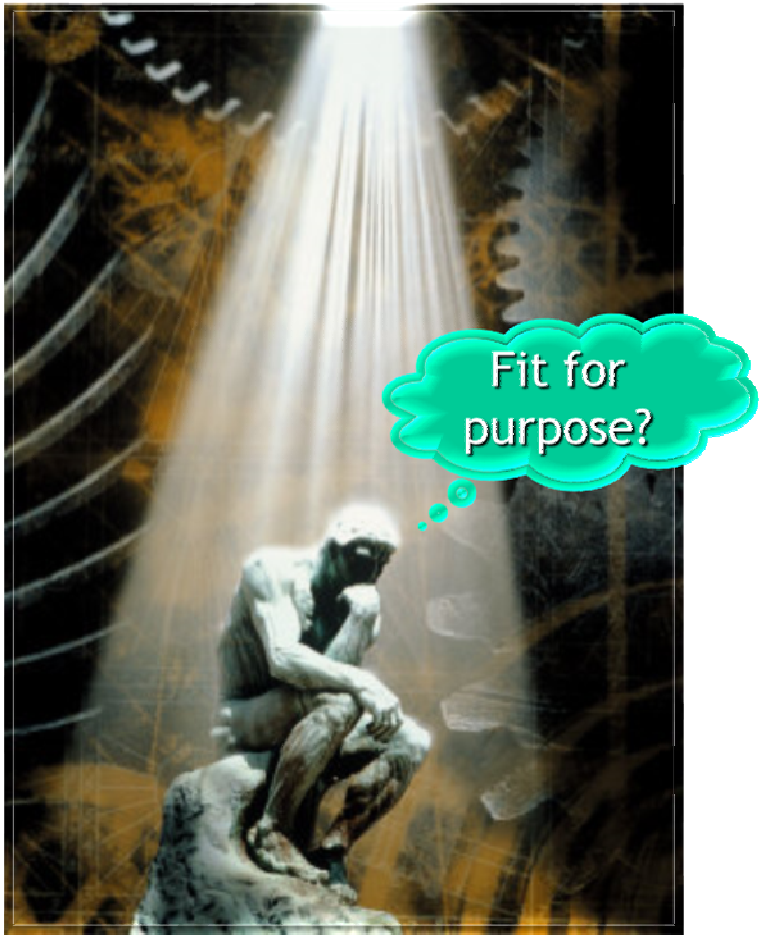
The Essential Question…



"What amount of medical harm due to analytical error is it OK to let go undetected?"

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Steps of the process and different responsibilities in implementing traceability of patient results and defining their uncertainty

Profession
(e.g., JCTLM, IFCC, EFLM):

Define analytical objectives: reference measurement systems (traceability chain) and associated clinically acceptable uncertainty (fit for purpose)

Diagnostic manufacturers:

Implement suitable analytical systems (platform, reagents, calibrators, controls) fulfilling the above established goals

End users (clinical laboratories):

Survey assay and laboratory performance through IQC and EQA redesigned to meet metrological criteria

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Adapted from Panteghini M, Clin Chem Lab Med 2010;48:7

STRATEGIES TO SET GLOBAL QUALITY SPECIFICATIONS IN LABORATORY MEDICINE

WORLD HEALTH ORGANIZATION ORGANISATION MONDIALE DE LA SANTE

International Union of Pure and Applied Chemistry

ifcc International Federation of Clinical Chemistry and Laboratory Medicine

Nobelforum, Karolinska Institutet Stockholm April 24-26, 1999

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1999 Stockholm Consensus revised in Milan 2014

Although the essence of the hierarchy established in Stockholm was supported, new perspectives have been forwarded prompting simplification and explanatory additions.

The most innovative aspect of the new consensus is that it is recognized that some models are better suited for certain measurands than for others; the attention is therefore primarily directed towards the measurand and its biological and clinical characteristics.

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Sverre Sandberg*, Callum G. Fraser, Andrea Rita Horvath, Rob Jansen, Graham Jones, Wytze Oosterhuis, Per Hyltoft Petersen, Heinz Schimmel, Ken Sikaris and Mauro Panteghini

Defining analytical performance specifications: Consensus Statement from the 1st Strategic Conference of the European Federation of Clinical Chemistry and Laboratory Medicine

Model 1: Based on the effect of analytical performance on clinical outcomes

a. Done by direct outcome studies – investigating the impact of analytical performance of the test on clinical outcomes;

b. Done by indirect outcome studies – investigating the impact of analytical performance of the test on clinical classifications or decisions and thereby on the probability of patient outcomes, e.g., by simulation or decision analysis.

Model 2: Based on components of biological variation of the measurand.

Model 3: Based on state of the art of the measurement (i.e., the highest level of analytical performance technically achievable).

Model 1. Based on the effect of analytical performance on clinical outcomes

- *Advantage*: to address the influence of analytical performance on clinical outcomes that are relevant to patients and society.
- *Disadvantage*: it is only useful for examinations where the links between the test, clinical decision-making and clinical outcomes are straightforward and strong. Furthermore, it may be influenced by the current measurement quality and results may vary according to the actual test method used, the investigated population and health care setting.

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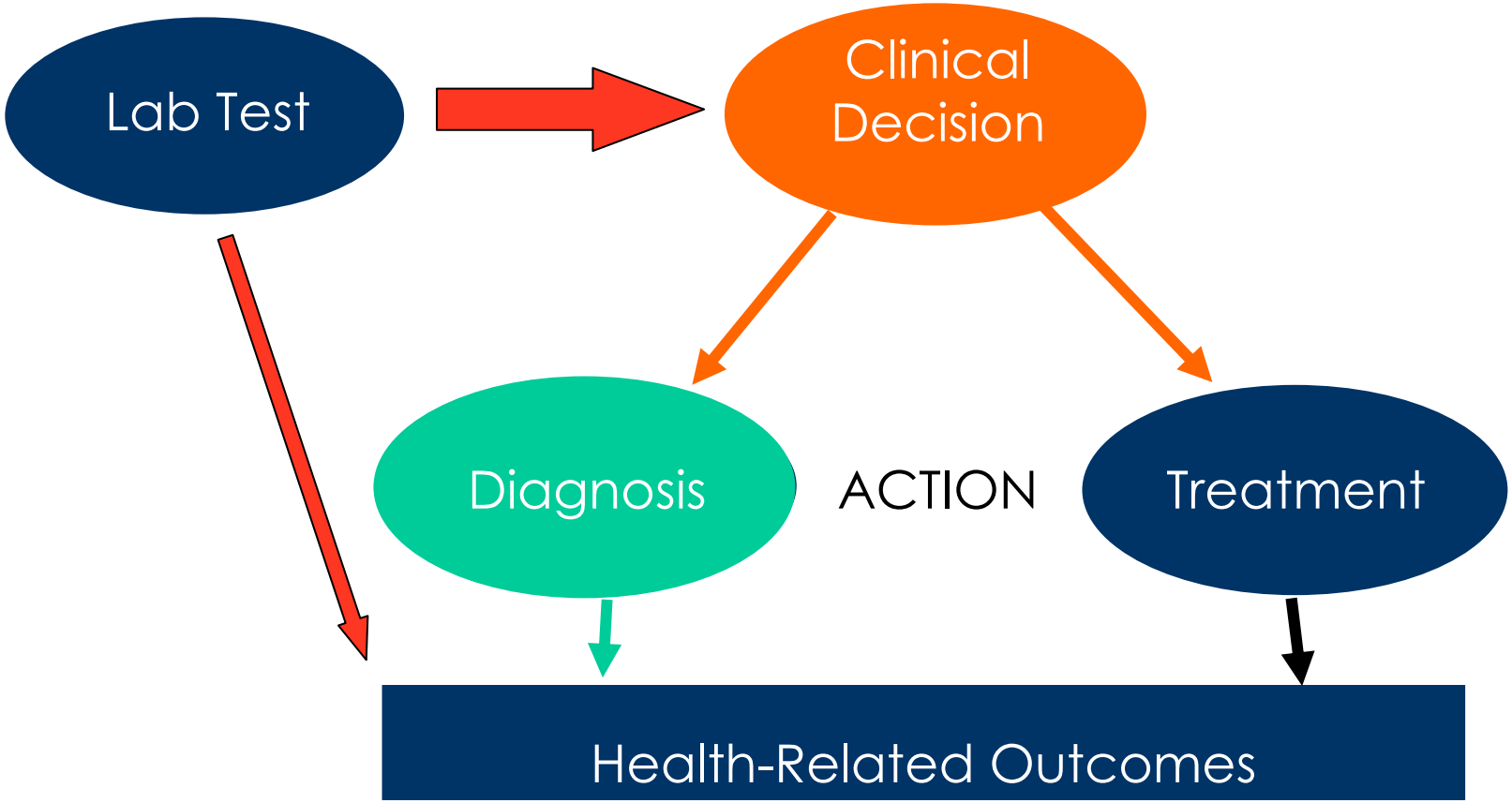
Challenge: Connecting Laboratory Testing to Outcomes



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Demonstrating the value of lab tests on health outcomes is reliant on linking the test with processes that directly impact outcomes

Performance specifications based on clinical needs defined in terms of allowable misclassification rates

Table. Recommended analytical performance goals for cardiac troponin measurement for definition of the limit of quantitation of assays.

Quality level	Imprecision goal (as CV)			Bias goal[a]
	Outcome-based	Biological variability[a]	Expert opinion	
Minimum	<13%[b]	<7.3%	<20%	±21.6 %
Desirable	<10%[c]	<4.9%	<10%	±14.4 %
Optimum	<6%[d]	<2.4%	–	±7.2 %

[a] Calculated according to Fraser CG, Hyltoft Petersen P, Libeer JC, Ricos C. Proposal for setting generally applicable quality goals solely based on biology. Ann Clin Biochem 1997;34:8-12.
[b] Assuming a diagnostic misclassification of 1.8%, [c] 1.0%, and [d] 0.5%.

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aacb testing for health

Panteghini M, AACB Troponin Monograph 2012

Model 2. Based on components of biological variation of the measurand

- *Advantage*: it can be applied to most measurands for which a "steady state" biologic model can be established.
- *Disadvantage*: need to carefully assess the relevance of biological variation data.

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HOME ▸ CLIA & QUALITY ▸ QUALITY REQUIREMENTS ▸ DESIRABLE BIOLOGICAL VARIATION DATABASE SPECIF

DESIRABLE BIOLOGICAL VARIATION DATABASE SPECIFICATIONS

Updated for 2014! Desirable Specifications for imprecision, inaccuracy, and total allowable error, calculated from data on within-subject and between-subject biologic variation. This database is updated and compiled by Dr. Carmen Ricos and colleagues. We are honored to be able to host this database.

DE GRUYTER Clin Chem Lab Med 2015; 53(2): 299–305

Carmen Perich, Joana Minchinela, Carmen Ricós*, Pilar Fernández-Calle, Virtudes Alvarez, María Vicenta Doménech, Margarita Simón, Carmen Biosca, Beatriz Boned, José Vicente García-Lario, Fernando Cava, Pilar Fernández-Fernández and Callum G. Fraser

Biological variation database: structure and criteria used for generation and update

More than 240 articles
More than 350 measurands

Generation of estimates of CV_I and CV_G using the MEDIAN of all data compiled

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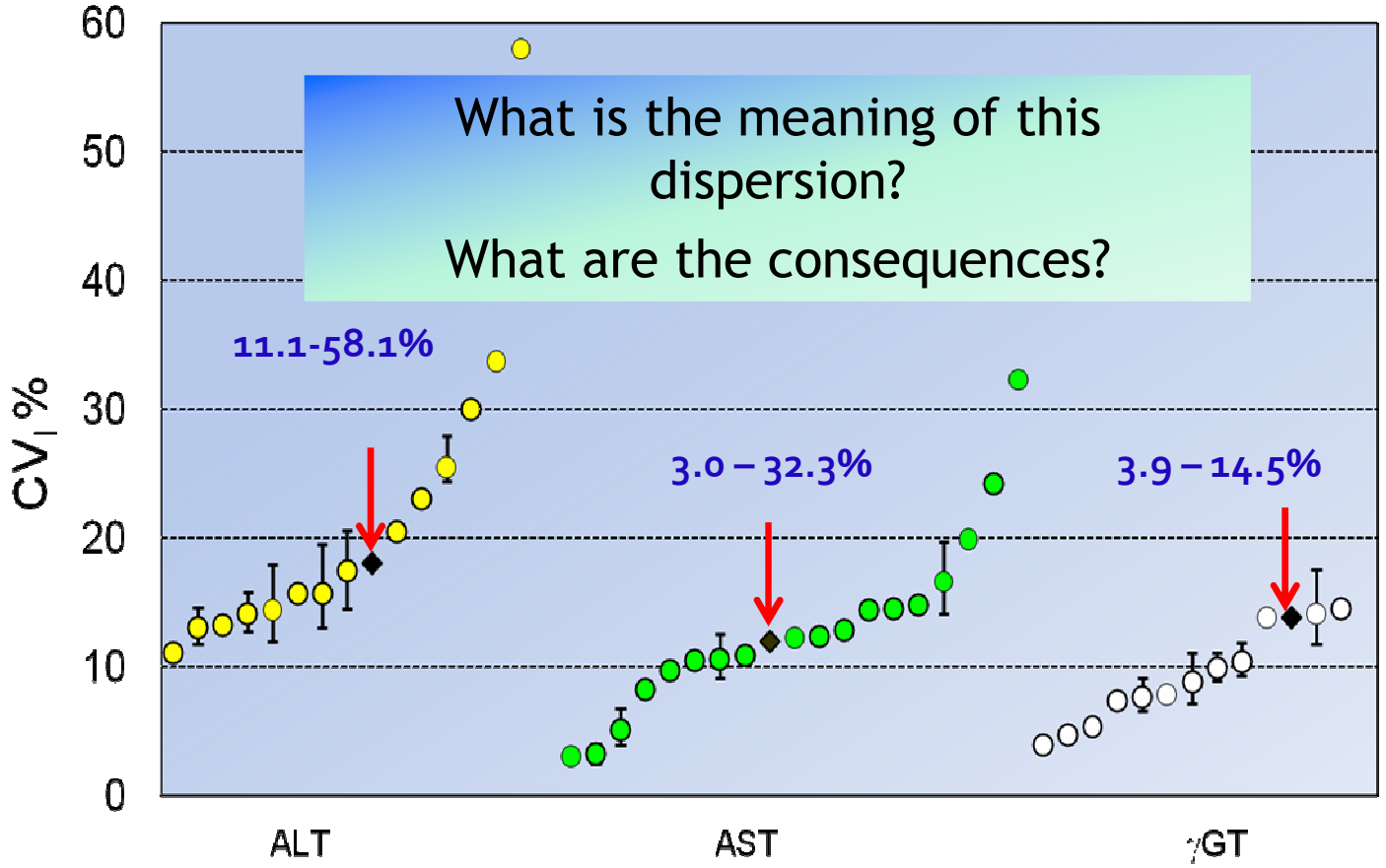
ALT, AST and γGT

Within-subject biological variation (CVI)



The arrows show the values currently present in the Ricos' database

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Carobene A et al., Clin Chem Lab Med 2013;51:1997

Quantifying Biological Variation

How do you do the experiment?

✓ Subjects	How many?
✓ Collect specimens	Number? Frequency?
✓ Analyse specimens	Minimise analytical variation?
✓ Analyse data	Outliers? Statistics?

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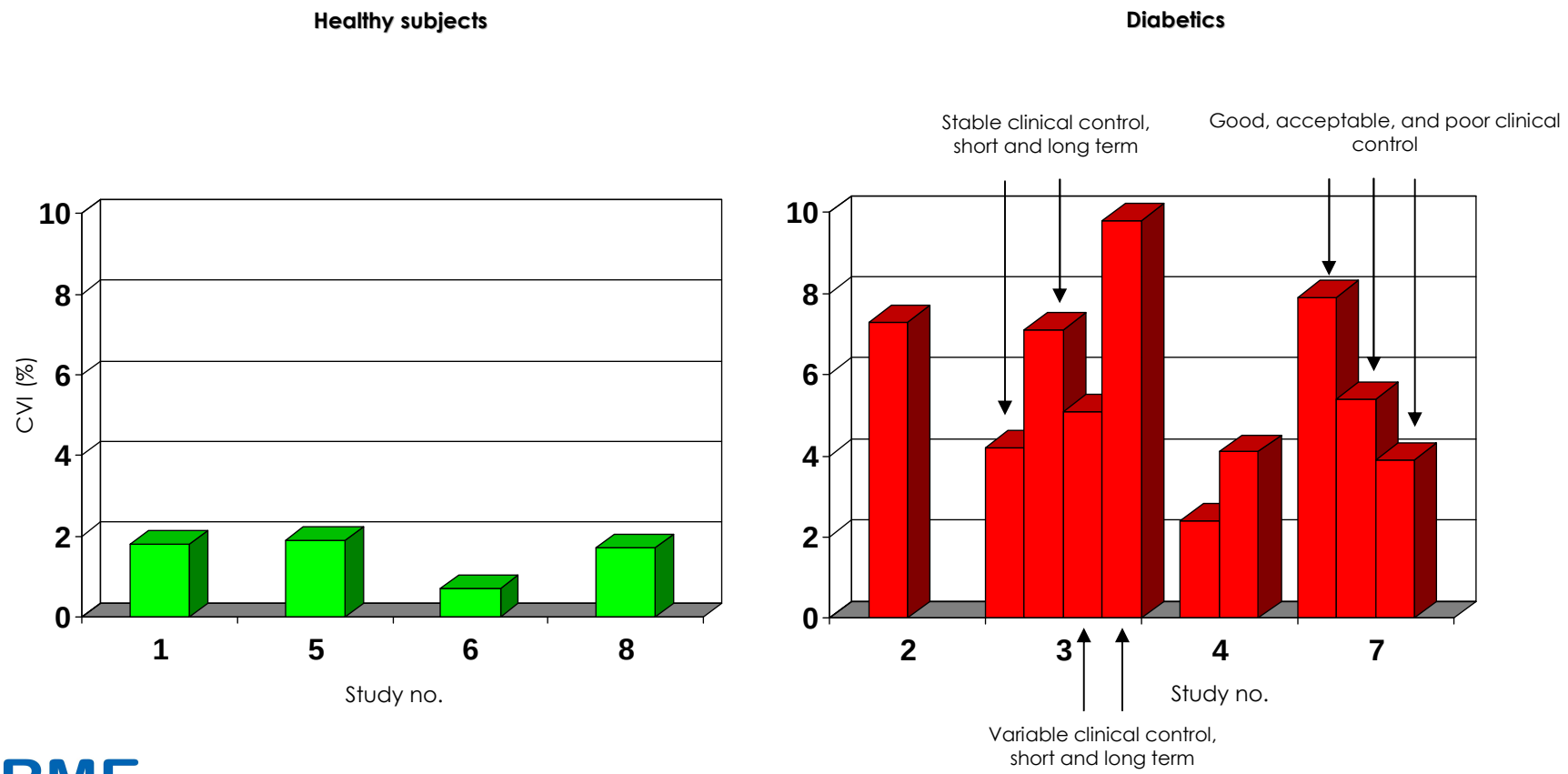
Biological variation from patients
Should they be used?



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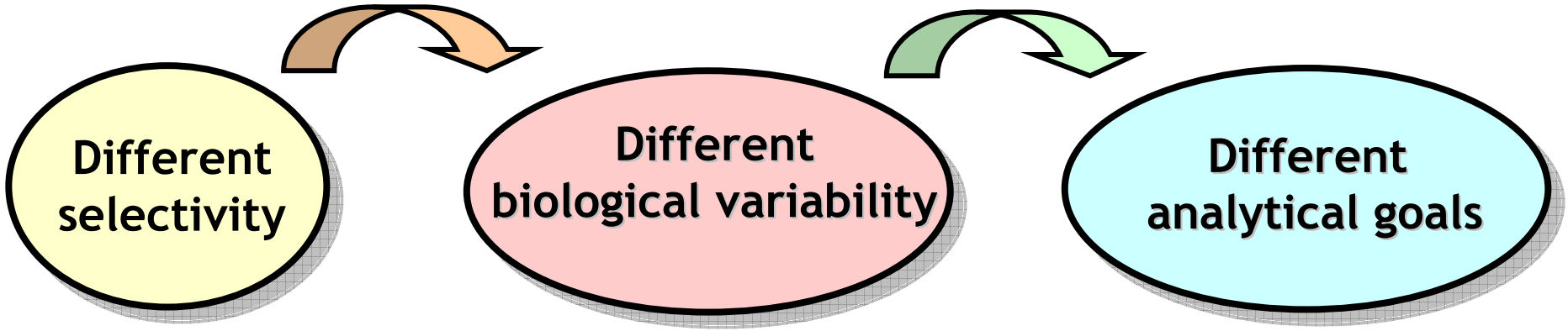
Intra-individual variation in pathology >> CV_I of healthy individuals

Braga F et al, Chim Clin Acta 2010;411:1606

Assay selectivity is an important biological variation qualifier

If the used methodology has different specificity for the measured analyte, one can expect that also the biological variability, a property closely associated with the characteristics of the analyte itself, significantly changes. And, if the biological variability changes, the analytical goals derived from it may be different.



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Clinica Chimica Acta 413 (2012) 1179–1183

Contents lists available at SciVerse ScienceDirect

Clinica Chimica Acta

journal homepage: www.elsevier.com/locate/clinchim

Invited critical review

Biologic variability of C-reactive protein: Is the available information reliable?

Federica Braga *, Mauro Panteghini

Table 2
Summary of the characteristics of studies on biologic variability of C-reactive protein (CRP) evaluated in this systematic review.

Study no.	Assay sensitivity	Recruitment of healthy subjects	Optimal study duration and sampling frequency	Appropriate sample type	Optimal protocol of sample analysis	Statistical test for outliers	Testing normal distribution of data
1	No	Yes	No	Yes	No	Yes	No
2	No	Yes	No	Yes	No	Yes	No
3a	No	Yes	No	No	NA	No	No
3b	No	No	No	No	NA	No	No
4	Yes	Yes	No	No	NA	Yes	No
5	Yes	±[a]	No	No	NA	No	No
6	Yes	Yes	Yes	Yes	Yes	Yes	No
7	Yes	No	Yes	Yes	Yes	No	Yes
8	Yes	Yes	No	Yes	No	No	No
9	Yes	±[b]	No	No	No	Yes	No
10	Yes	No	No	No	NA	No	No
11	NA	No	No	Yes	No	Yes	No

NA, information not available.

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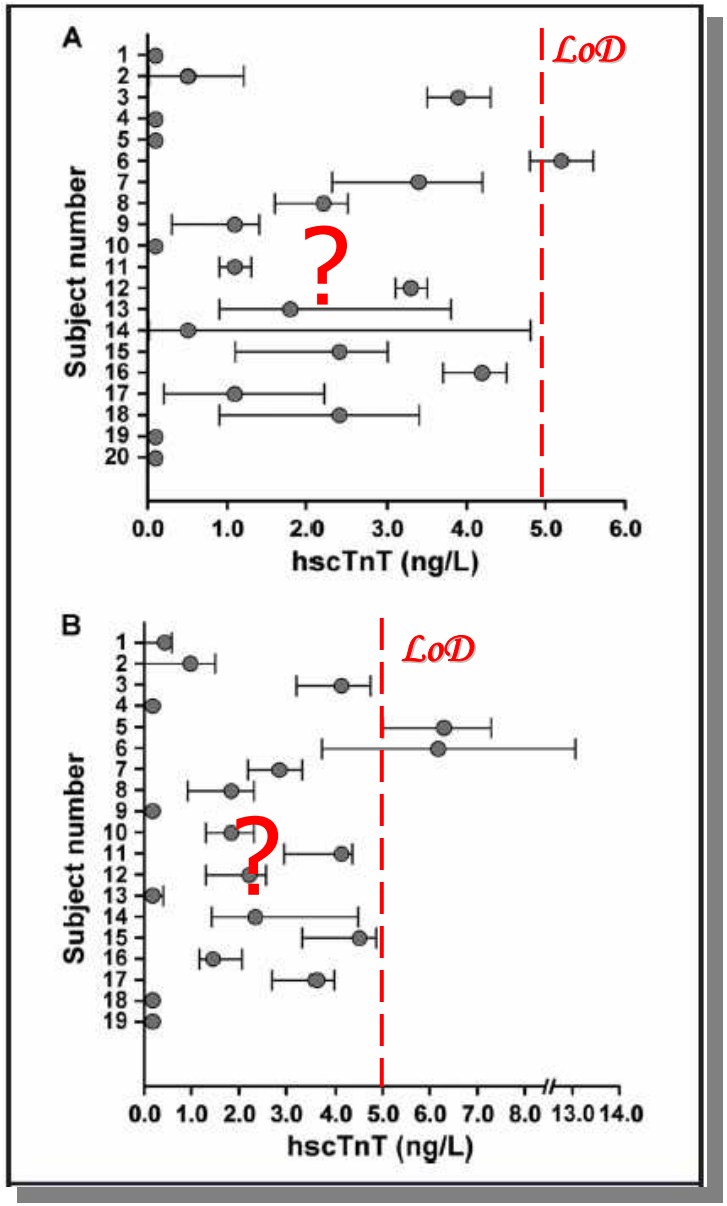
Is available information on biological variability of troponin T reliable?



Short-term

Long-term

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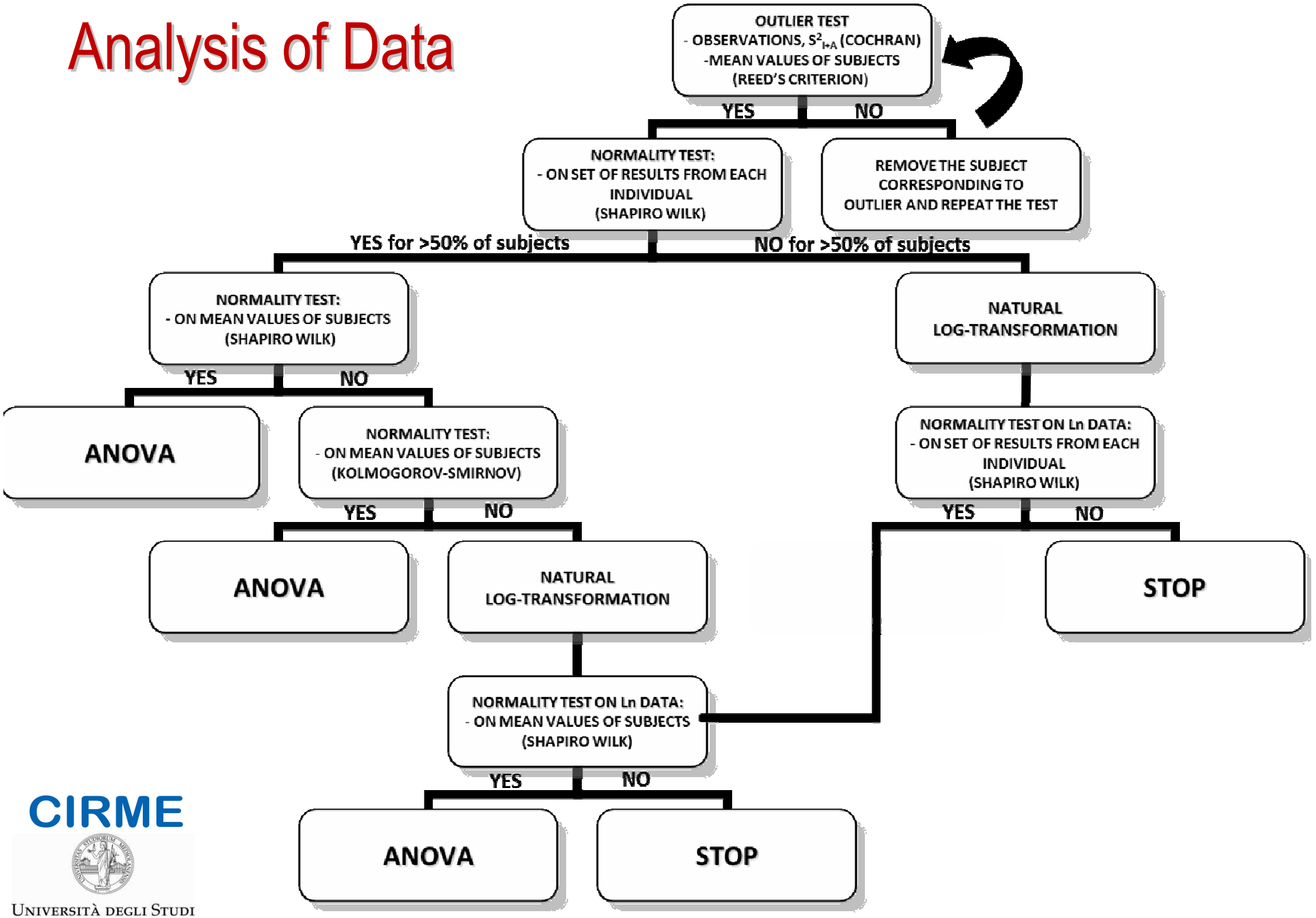
Vasile VC et al., Clin Chem 2010;56:1086

Analysis of Data



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1	No	Yes	No	Yes	No	Yes	No
2	No	Yes	No	Yes	No	Yes	No
3a	No	Yes	No	No	NA	No	No
3b	No	No	No	No	NA	No	No
4	Yes	Yes	No	No	NA	Yes	No
5	Yes	±[a]	No	No	NA	No	No
6	Yes	Yes	Yes	Yes	Yes	Yes	No
7	Yes	No	Yes	Yes	Yes	No	Yes
8	Yes	Yes	No	Yes	No	No	No
9	Yes	±[b]	No	No	No	Yes	No
10	Yes	No	No	No	NA	No	No
11	NA	No	No	Yes	No	Yes	No

NA, information not available.

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Have data not normally distributed been appropriately transformed?

1) This is a critical aspect! Studies using statistical parametric approach on data not normally distributed should not be considered! Otherwise we will continue to have CV >>33%!

2) When a not normal data distribution is present, a log-transformation of data is recommended, but this approach does not always solve the distribution problems!

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Westgard QC http://www.westgard.com/biodatabase1.htm

	Analyte	Number of papers	Biological Variation		Desirable specification		
			CVw	CVg	I(%)	B(%)	TE (%)
S-	C reactive protein	3	42.2	76.3	21.1	21.8	56.6

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Summary

- BV published data are of varying quality
- Safe application for deriving performance specifications requires prior critical appraisal
- Need for standards (i.e. a set of attributes to enable the data to be effectively transmitted and applied)

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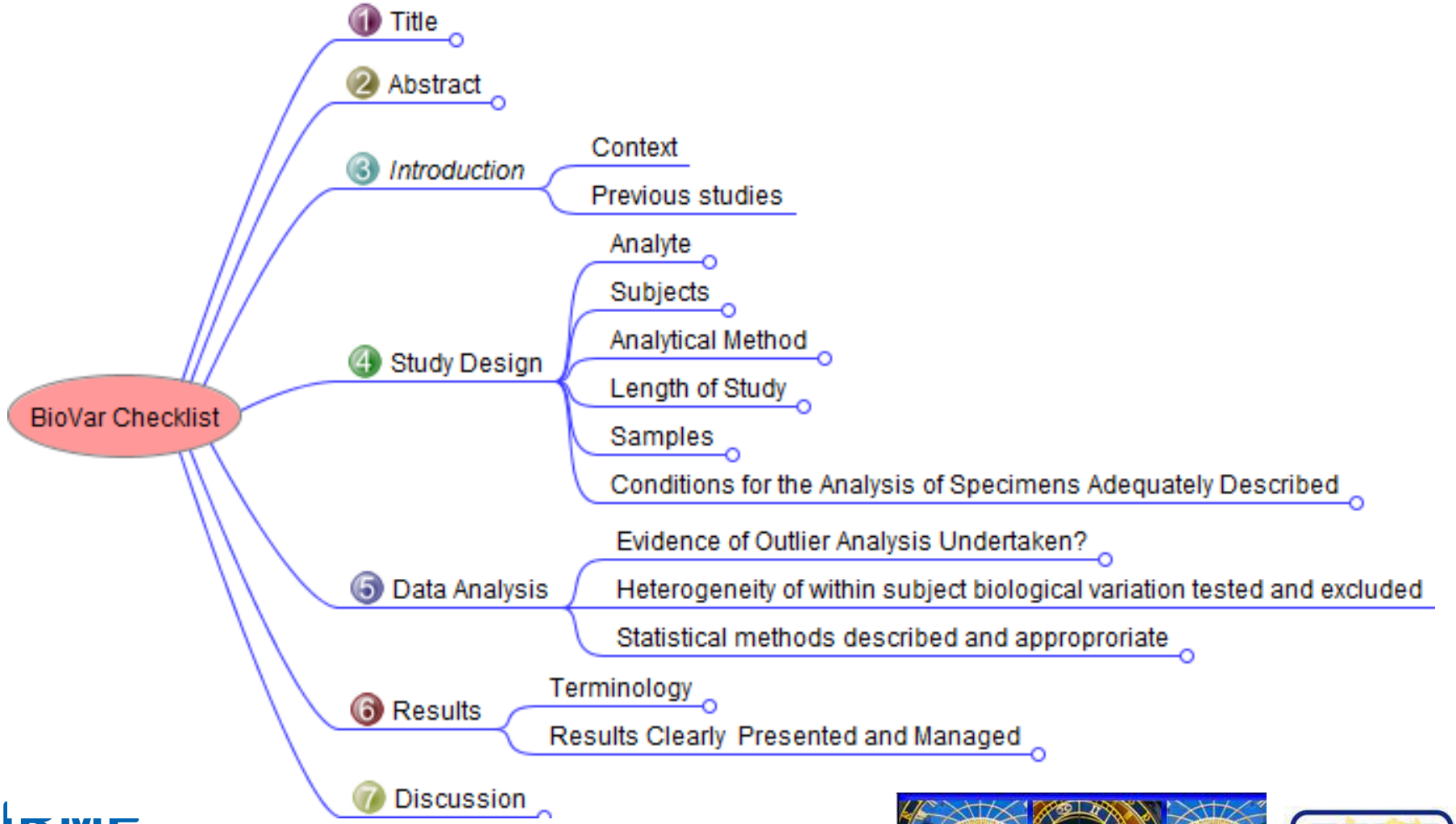
A checklist for critical appraisal of studies of biological variation



Bartlett WA et al. Clin Chem Lab Med 2015;53: 879

Biological Variation Working Group

Model 3. Based on state-of-the-art

This relates to the highest level of analytical performance technically achievable
[but someone defines it as the analytical performance achieved by a certain percentage of laboratories]

- *Advantage:* numbers are readily available.

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Problems with the state-of-the-art concept

- No scientific reasoning
- Often based on „old“ data which may be outdated
- Lack of transparency
- Lack of neutrality (dependency on industry)
- No relationship between what is achievable and on what is needed clinically

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Possible criteria for allocation of laboratory tests to different Milan models for performance specifications

1. The measurand has a central role in diagnosis and monitoring of a specific disease $\Rightarrow$ outcome model
2. The measurand has a high homeostatic control $\Rightarrow$ BV model
3. Neither central diagnostic role nor sufficient homeostatic control $\Rightarrow$ state-of-the-art model

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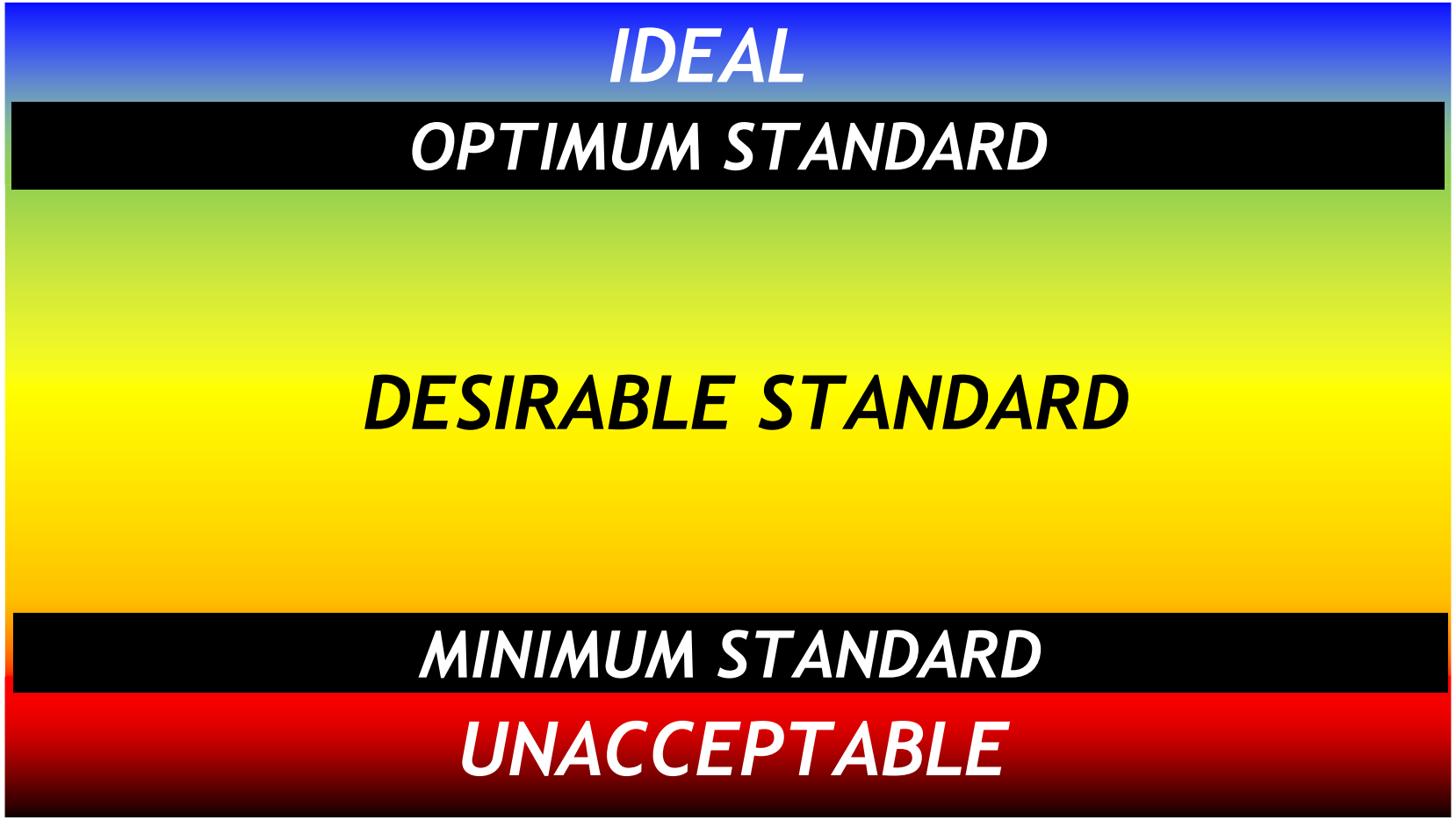
Grading different quality levels



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Result interpretation in EQAS

- There should be two types of specifications, depending on the number of measurements of EQAS samples participants do.
- If participants measure in singlicate, a TE specifications is needed (when only a single measurement is performed, it is impossible to separate the different causes of measurement's deviation from the reference value).
- If EQAS ask for multiple measurements of the same sample, a bias specification should be used for judgement of an EQAS result, providing that the scheme is also able to independently estimate the random component of the measurement uncertainty of individual participants.

Box 1 Factors influencing choice of External Quality Assessment (EQA) Scheme

- Accreditation status of provider. Preference should be given to schemes accredited to ISO 17043 or equivalent (eg, those still Clinical Pathology Accreditation (CPA) accredited within the UK). If a non-accredited provider is chosen, the reason(s) should be clearly documented. Under International Laboratory Accreditation Cooperation (ILAC),[11] accreditation bodies should support the use of appropriate proficiency testing programmes which meet the essential requirements of ISO/IEC 17043, where applicable.
- Appropriateness of distribution frequency. Distributions should be at a frequency sufficient to identify performance issues in a timely manner. For core tests, this probably equates to at least monthly distributions.
- Range and number of EQA samples. Samples within the distribution cycle should cover an appropriate range of values for each analyte to verify performance across clinically relevant concentrations. Each cycle should supply sufficient samples to provide evidence of reproducibility; 3–4 samples in each distribution would probably fulfil this requirement. Samples should be 'blinded' to participants in relation to expected results.
- Scheme management and development. The scheme should be designed and overseen by appropriately competent professionals (clinical, technical and statistical). The scheme should also have an independent medical and scientific committee.[12]
- Poor performance issues. Mechanisms should be in place for reporting of poor performance to the appropriate regulatory/oversight body.
- Variety of sample provided. 'Challenging' samples should be included in selected distributions.
- Education. Educational input should be provided.
- Manufacturers. Participation of the EQA provider in postmarketing vigilance of in vitro diagnostics.[12]
- Materials. EQA providers should demonstrate use of commutable materials.[13]

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James D et al., J Clin Pathol 2014;67:651

EQAS categorization

				Evaluation capability				
				Accuracy				
				Individual laboratory				
	Sample characteristics				Relative to participant results		Reproducibility	
Category	Commutable	Value assigned with RMP[a] or CRM	Replicate samples in survey	Absolute vs RMP or CRM	Overall	Peer group	Individual laboratory intralab CV	Measurement procedure interlab CV
1	Yes	Yes	Yes	X	X	X	X	X
2	Yes	Yes	No	X	X	X		X

Category 1A → Milan model 1 or 2 as basis for PS

Category 1B → Other models

The role of the Profession: “check”

1. Availability and quality of information about IVD metrological traceability and uncertainty

2. Daily surveillance of IVD system traceability

Verification of the consistency of declared performance during routine operations performed in accordance with the manufacturer’s instructions

Participation to appropriately structured EQAS (“meeting metrological criteria”)

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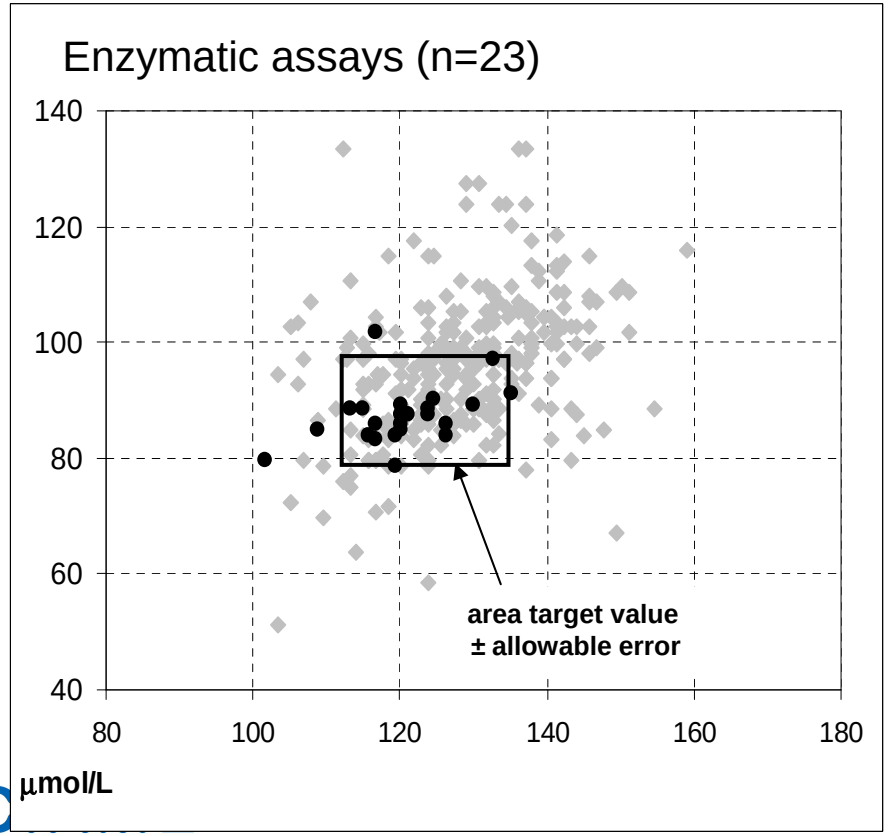
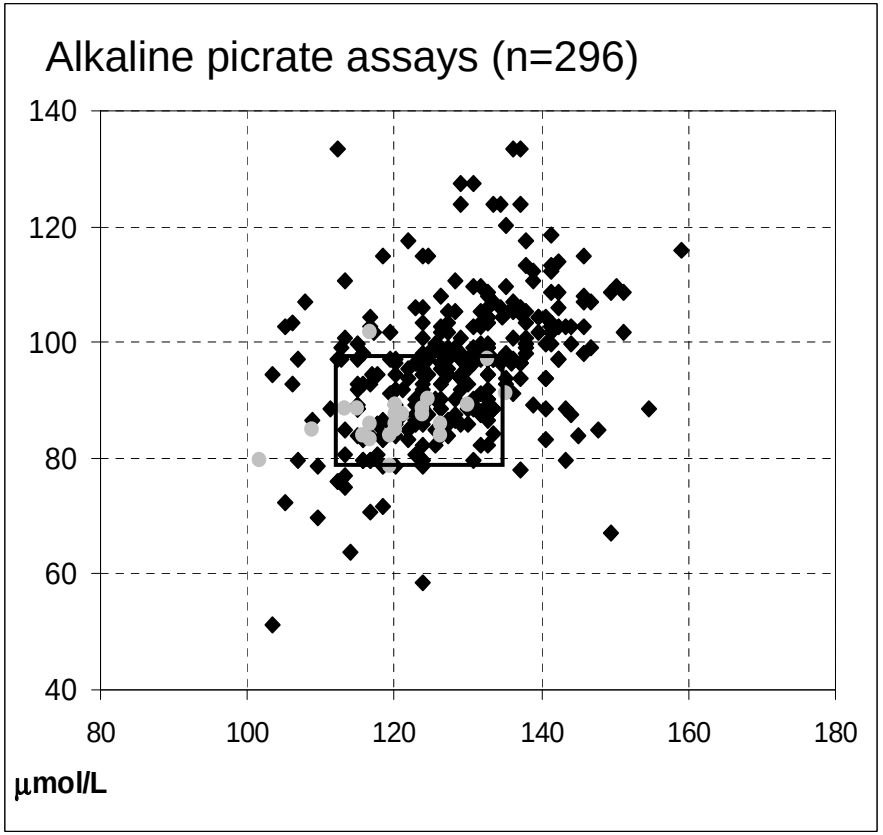
Braga F & Panteghini M, Clin Chim Acta 2014;432:55

EQAS materials with physiologic (88.4 µmol/L) and borderline (123.8 µmol/L) creatinine concentrations vs. the desirable goal.

The vast majority (87%) of laboratories using systems employing enzymatic assays were able to fulfill the desirable performance, while only one third of laboratories using picrate-based systems were able to meet the target.





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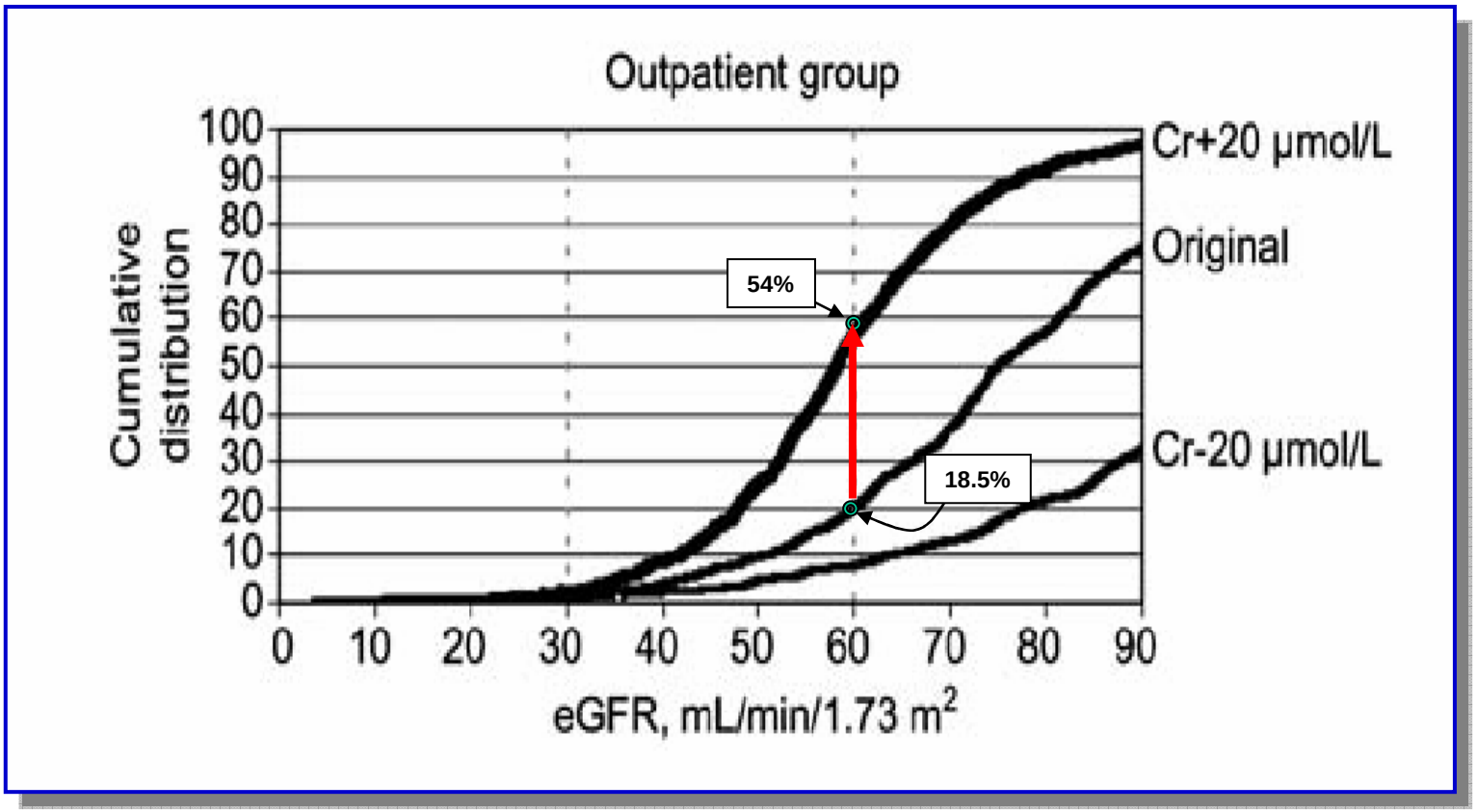
Carobene A et al., Clin Chim Acta 2014;427:100.

Effect of analytic bias in creatinine on the distribution of estimated GFR values



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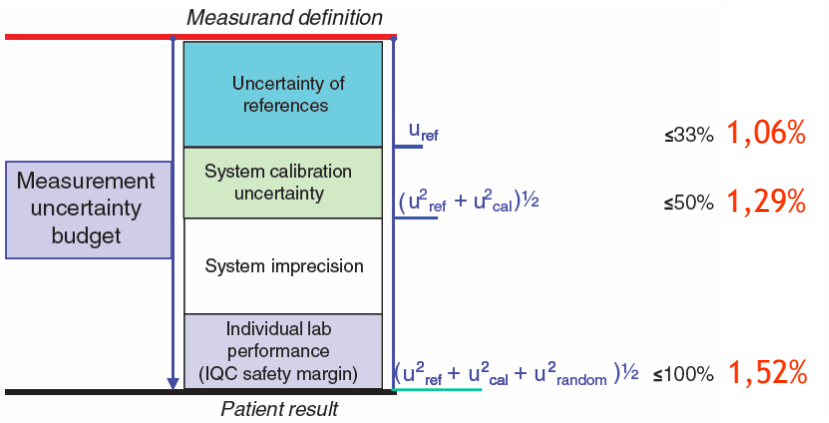
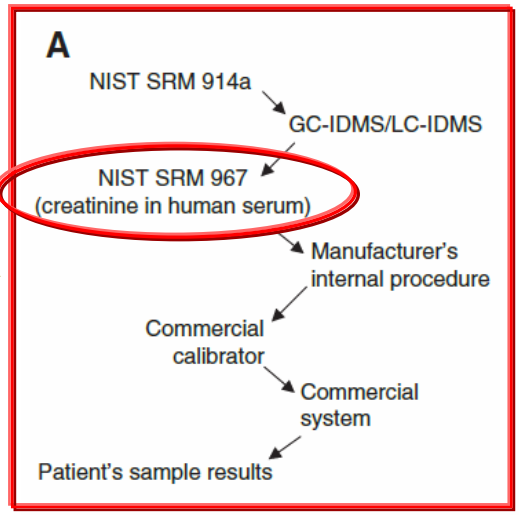
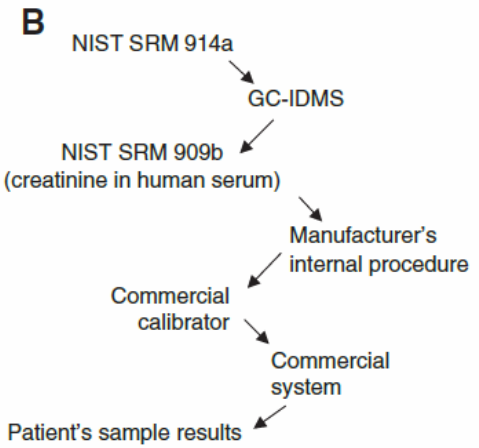
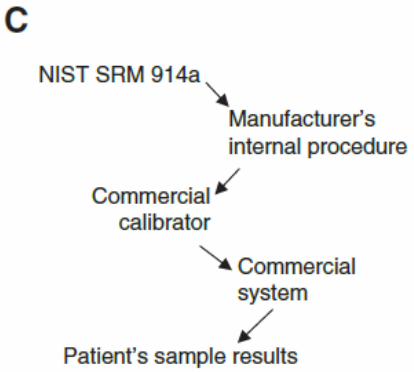
Klee GG et al., Clin Chem Lab Med 2007;45:737

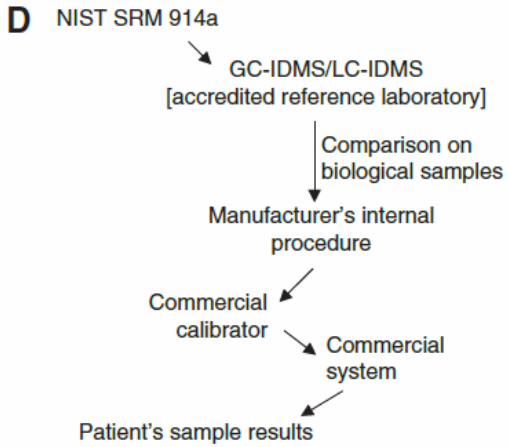
ABBOTT
Creatinine enzymatic assay (cod. 8L24)
Clin Chem Calibrator (LN 6K30)











vs. 3,0% (desirable goal)

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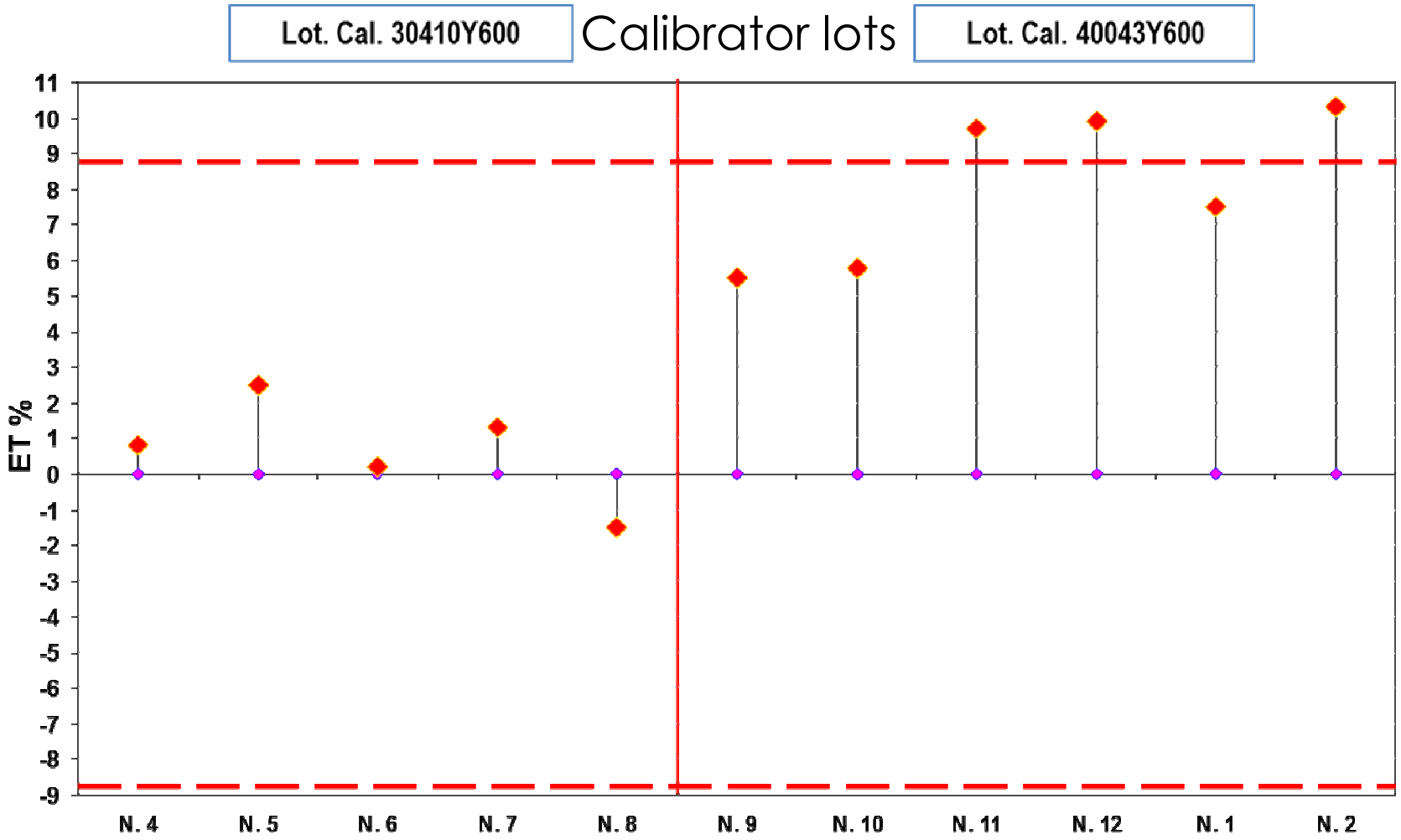

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Pasqualetti S, Infusino I, Carnevale A, Szőke D, Panteghini M.
Clinica Chimica Acta 450 (2015) 125-6

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Letter to the editor

The calibrator value assignment protocol of the Abbott enzymatic creatinine assay is inadequate for ensuring suitable quality of serum measurements

Table 1
Uncertainties for each contributing factor in determination of serum creatinine with Abbott enzymatic assay on Architect *c*16000 platform after calibration with two different lot of system calibrator. Data obtained by measurements of NIST SRM 967a reference material (certified value ± expanded uncertainty: L1, 0.847 mg/dL ± 0.018 mg/dL and L2, 3.877 mg/dL ± 0.082 mg/dL).

	SRM 967a level 1	SRM 967a level 2
Multigent Clin Chem Calibrator lot no. 40043Y600		
Imprecision (u_{Rw})	0.47%	0.40%
Bias (u_{bias})	3.57%	7.05%
Relative combined standard uncertainty [$u_c = (u_{bias}^2 + u_{Rw}^2)^{0.5}$]	3.60%	7.06%
Expanded uncertainty ($U = k \times u_c$)	7.20%	14.12%
Multigent Clin Chem Calibrator lot no. 40496Y600		
Imprecision (u_{Rw})	0.53%	0.42%
Bias (u_{bias})	4.02%	1.71%
Relative combined standard uncertainty [$u_c = (u_{bias}^2 + u_{Rw}^2)^{0.5}$]	4.05%	1.76%
Expanded uncertainty ($U = k \times u_c$)	8.10%	3.52%

Note: For serum creatinine measurements on patient samples, the acceptable limits for combined uncertainty derived from its CVI are 3.0% (desiderable) and 4.5% (minimum quality level), respectively.

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Basis for performance specifications

PROVIDER	MODELS
RCPAQAP Australia	Combination of BV and state of the art
SKML The Netherlands	Combination of BV and state of the art
NOKLUS Norway	Fixed percentage limits and based on a combination of BV, state of the art and expert opinion
SEQC Spain	Combination of BV and statistical results
WEQAS UK	Combination of BV and state of the art
SEHH Spain	Statistical/state of the art/BV
CTCB France	z-score/state of the art/limits given by scientific societies or other/limits based on clinical impact

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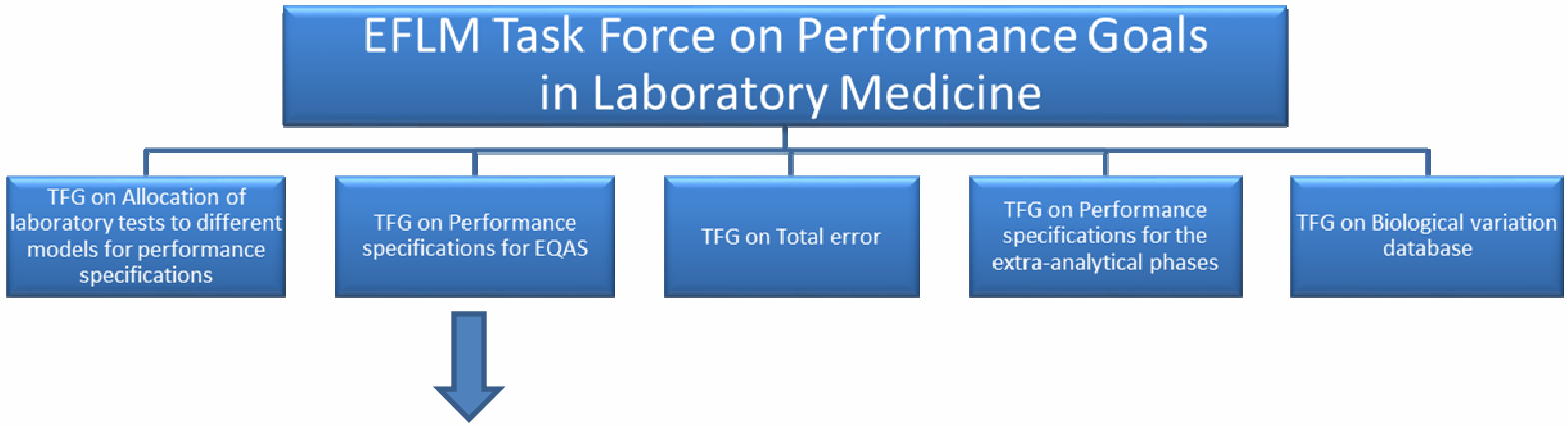
Can these be harmonised?



Chair: Graham Jones (AU - RCPAQAP)
Stéphanie Albarède (FR - CTCB)
Gabriela Gutiérrez (SP - SEHH)
Marc Thelen (NL - SKML)
Anne Vegard Stavelin (NO - NOKLUS)
Annette Thomas (UK - WEQAS)
Finlay Mckenzie (UK NEQAS)
Emma Ventura (SP - SEQC)
Dagmar Kelleler (CH - CSCQ)
Morten Pedersen (DK - DEKS)

TFG on Performance Specifications for EQAS

- Apply Milan models to describe EQAS performance specifications
- Develop common performance specifications based on Milan models
- Focus on “type 1” EQAS (commutable materials, reference measurement for target, repeated samples)

"THE TRACEABILITY REVOLUTION MANIFESTO"

- Definition and approval of reference measurement systems, possibly in their entirety;
- Implementation by IVD industry of traceability to such reference systems in a scientifically sound and transparent way;
- Definition by the profession of the clinically acceptable measurement uncertainty (error) for each of the analytes used in the clinical field;
- Adoption by EQAS providers of commutable materials and use of an evaluation approach exclusively based on trueness;
- Monitoring of the analytical performance of individual laboratories by the participation in EQAS that meet metrological criteria and application of clinically acceptable limits;
- Abandonment by users (and consequently by industry) of nonspecific methods and/or of assays with demonstrated insufficient quality.

Braga F & Panteghini M, Clin Chim Acta 2014;432:55

If these limits are not objectively defined and fulfilled, there is a risk of letting error gain the upper hand, thus obscuring the clinical information supplied by the result and even causing negative effects on patients' outcome.

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