Post-market surveillance of the implementation of result traceability in clinical enzymology

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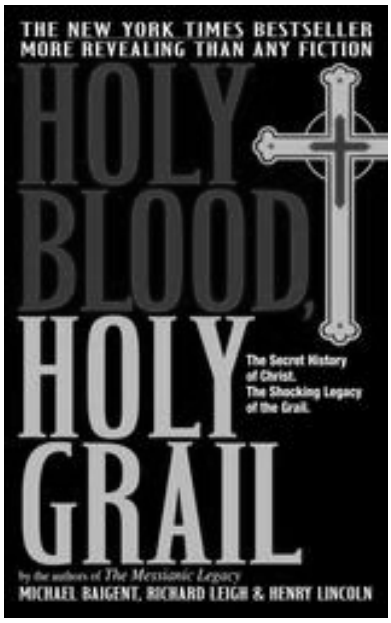
Which criteria should the surveillance fulfill?

- Which samples?
- Which references?
- What variation is allowable?

Looking for a Grail?



Searching the Grail
1. Samples

- Commutable
- Stable
- Concentration range covering clinical range

Calibration 2000

- Commutable material proven by twin-study
- Reference values
- Covering range of clinical interest
- Stable

Holy Grail

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Searching the Grail
2. Reference

- Reference system IVD
- Reference method targets

IVD directive

- Traceability to reference systems
- 80 category A analytes
- JCTLM defines reference methods and reference materials

Traceability

- Reference system
  - Reference method
  - Reference materials
  - Reference laboratories
- Industry calibrate kits and reagents
- Surveillance (EQA) trueness verification
  - Commutable materials

Example Enzymes

- IFCC reference procedures for 6 enzymes
- Commercial systems should be traceable
- International study for trueness verification
  - R. Jansen e.a. Clin Chim Acta 368 (2006) 160-167

International enzyme study

- Commutable material Calibration 2000
  - Calibration 2000, Weykamp
- 70 laboratories Italy, Germany Netherlands
- Reference laboratories targets
  - Panteghini, Schumann, Franck
- NEQAs organizers
  - Franzini, Kruse, Baadenhuijsen, Kuypers

Trueness verification

- Commutable material Calibration 2000
- Reference method target values
- Allowable area of deviation based on biological variance concept

Searching the Grail
3. Allowable variation

- Reference method targets
- Variance limits based on biological variance

Biological

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Biological variation

- CVw within-person variation
- CVb between-person variation
- CVa desirable analytical variation
  = 0.5 x CVw
- B maximum allowable bias
  = 0.25 $\sqrt{(CVw^2 + CVb^2)}$
- TE total allowable error
  = 1.65 x CVa + B

Statistics

- (1.65 * SDbl + |X – T|)< AB (P=95%)
- SDbl max = (AB - |X – T|) /1.65
- SDwl max = (TAE – 1.96*SDbl - |X – T|) / 1.96
- a = [(T+1.96*SDbl max) – X] / SDbl
- b = [X – (T-1.96*SDbl max)] / SDbl
- |D(a) – D(b)| * 100% is perc. Labs measuring within limits

IVD Trueness verification

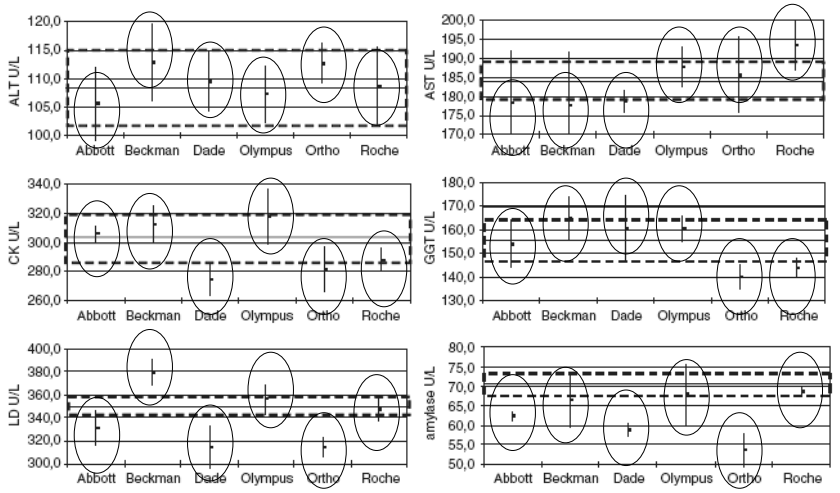


Fig. 1. Target value (fat line), means ± SD_M (U/L) for each company system, and the area (dashed) of maximum allowable SD_{bl} in absence of significant bias.

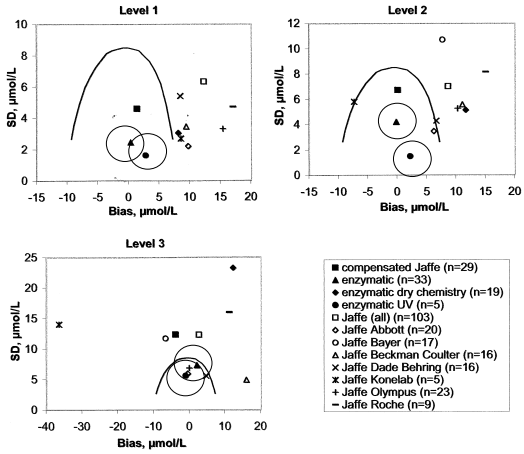
% Labs expected to measure within limits

	ALT	AST	CK	GGT	LD	Amy
Abbott	94%	50%	>95%	90%	37%	1%
Beckm	89%	48%	>95%	79%	12%	49%
Dade	>95%	95%	73%	73%	12%	0%
Olymp	>95%	88%	85%	>95%	73%	50%
Ortho	>95%	68%	81%	62%	0%	0%
Roche	>95%	52%	>95%	92%	81%	>95%

Example Creatinine

- IFCC reference method
- Commercial systems should be traceable
- International study for trueness verification
  - J. DeLanghe e.a. CCLM 2008, submitted

Creatinine Total error budget



Delanghe e.a. CCLM 2008, submitted

Consequenses

- EFCC/IFCC define allowable variation
- Industry: traceability
- Abandon non-specific methods
- EQA: commutable materials
  - Calibration 2000
- EQA: Biological variation concept
  - Introduced in SKML survey's
- Individual laboratories: TAE

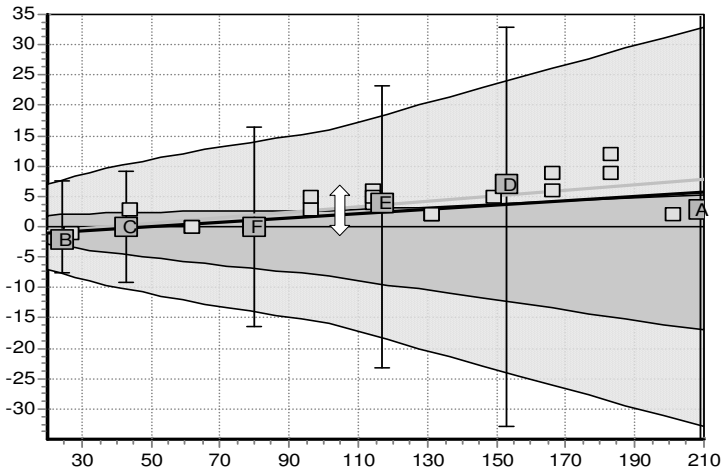
Searching the Grail
3. Allowable variation in EQA

- Commutable materials
- Reference method targets
- Variance limits based on biological variance
- Comparison with state of the art

EQA in The Netherlands

- Commutable control sera
- Target values by reference methods
- Variance criteria based on biological variance concept
- Comparison with state of the art

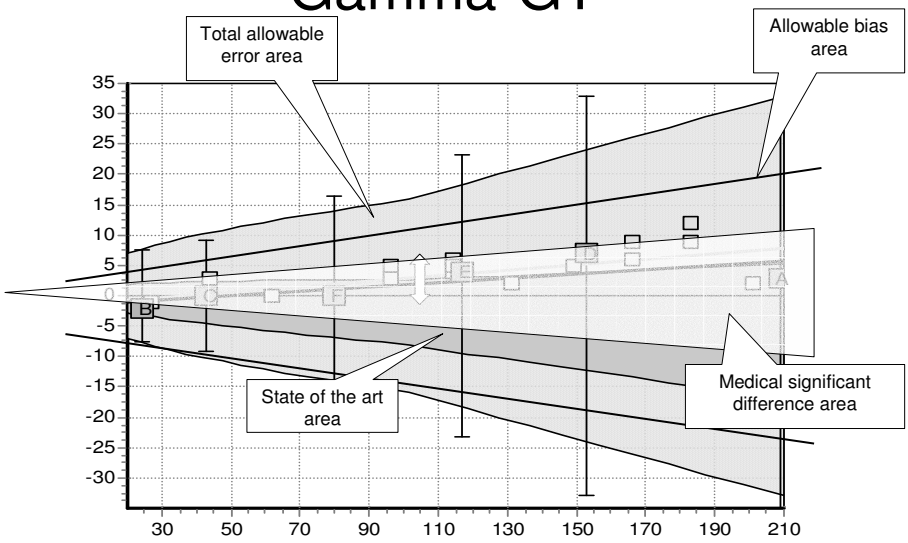
Gamma-GT



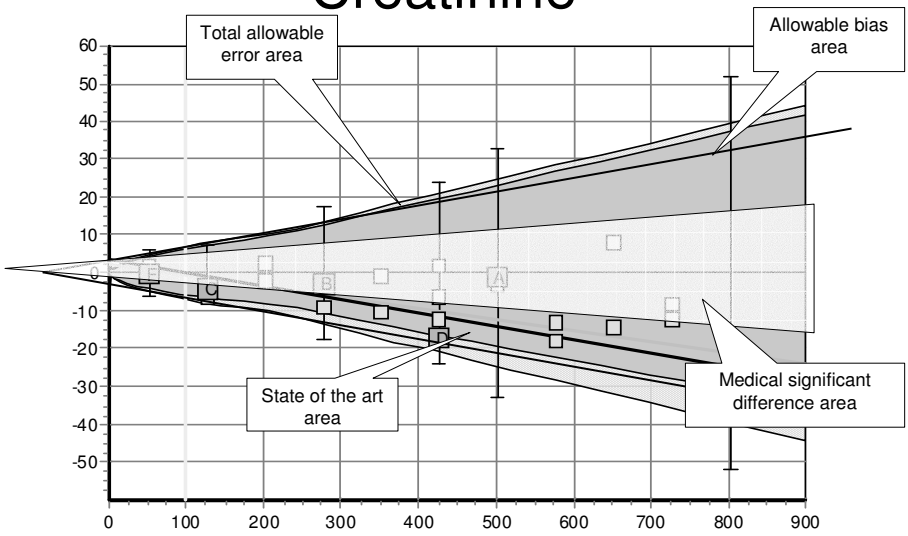
Which criteria?

- Total allowable error 1.65 x CVa + B
- Desirable SD CVa = 0.5 CVw
- Allowable bias $B = 0.25 \sqrt{(CVw^2 + CVb^2)}$
- Medically significant difference
  $\Delta med = 2.77 \times \sqrt{(CVa^2 + CVw^2)} + \Delta SE$
  $\Delta med = 3.1\ CVw$ if $\Delta SE = 0$
  $\Delta SE < 0.33\ CVw$ if $CVa = 0$

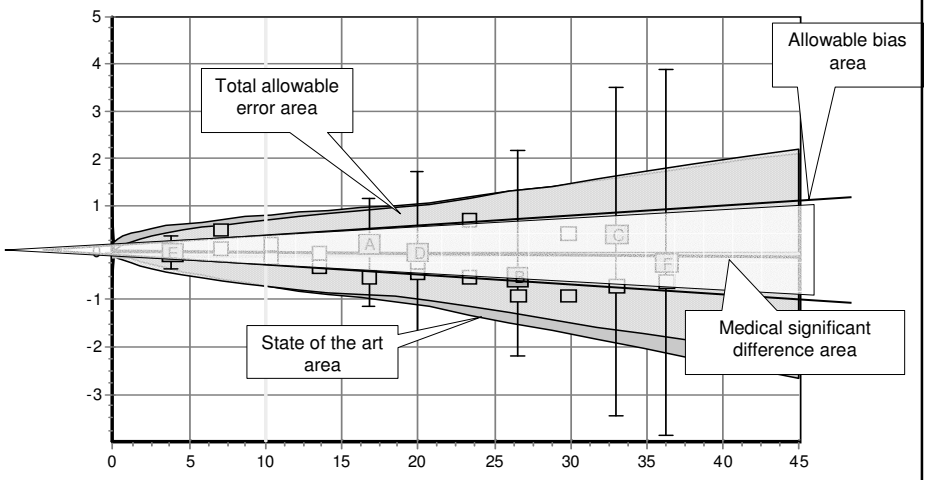
Gamma-GT



Creatinine

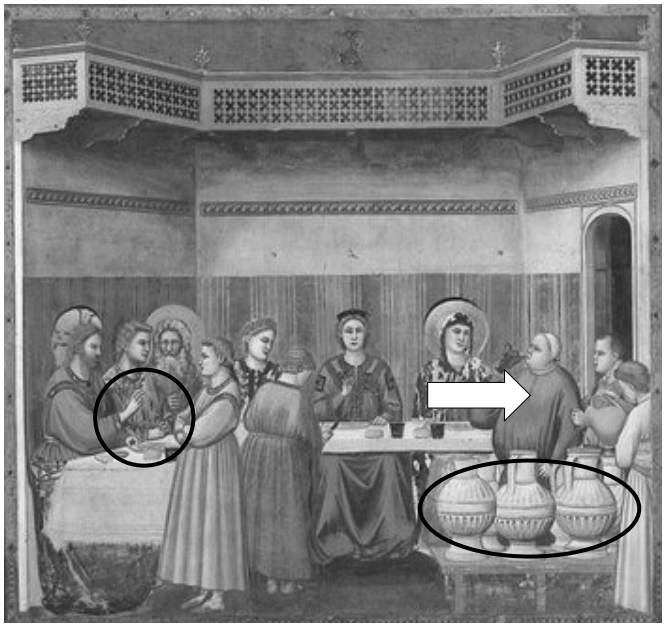


Glucose



Did we find the Grail?

- Post marketing surveillance is possible
- Does the traceability system guarantee patient security?



Post marketing surveillance is started but the Grail is not yet found

- Commutable plasma instead of serum?
- Reference method targets
- Variance criteria based on allowable bias and medically significant difference?