How EQA can be used to check whether laboratory performance is clinically appropriate

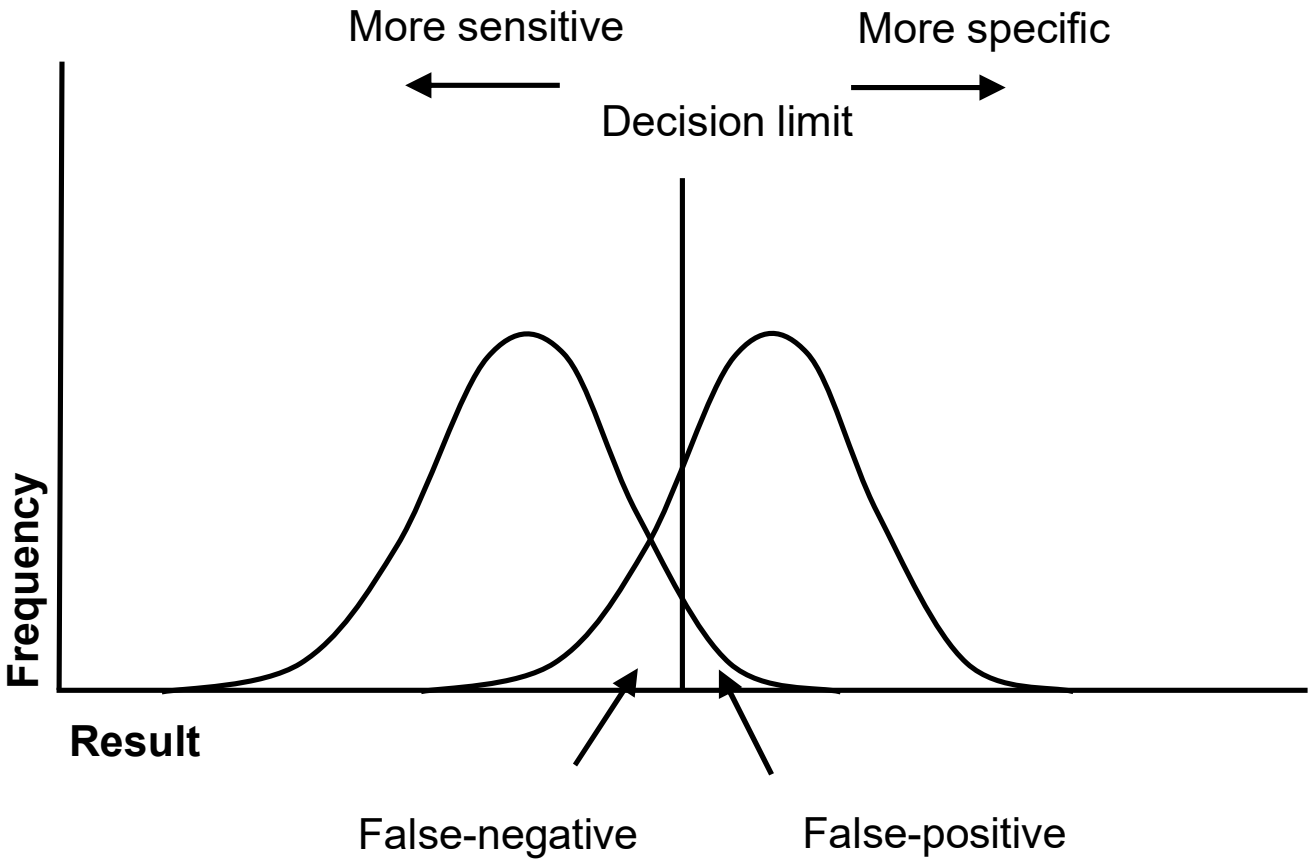
Prof. Marc Thelen PhD, SKML, the Netherlands

Session: Clinical performance specifications and misclassification of patients
EQALM Symposium, Vienna 2024

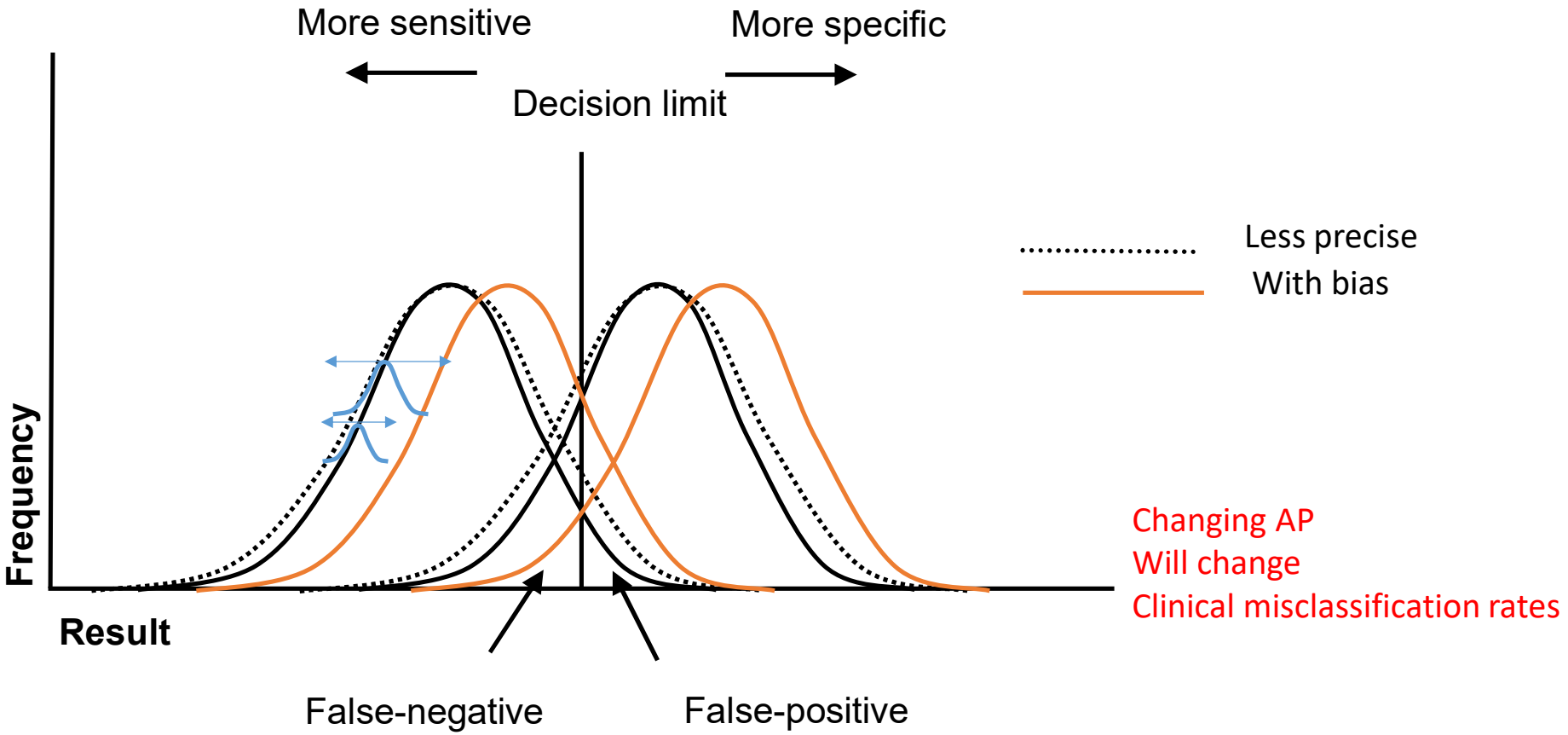
Content

- Introducing the players in the relationship between analytical performance and clinical misclassification
  - **Analytical performance** in terms of bias and imprecision
  - Patient **result distribution** around decision limits
  - Appropriateness of the **decision limits**
- Example: EQA study on AP albumin for classification on protein-loss
- Example: EQA study on AP Chloride for classification acidosis
- Example: EQA study on AP hs-c-trop for NSTEMI classification
- Example: EQA study on interaction between ref-interval and AP

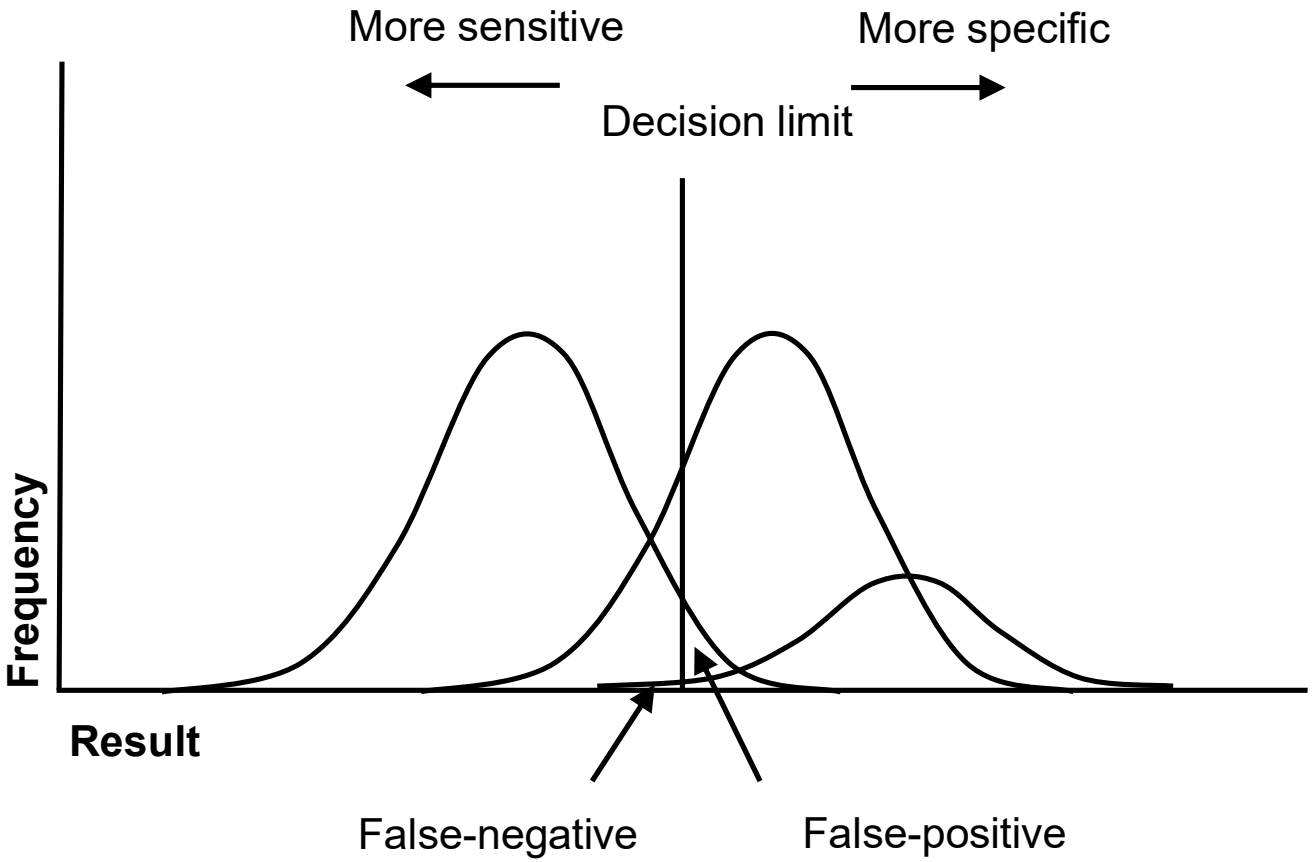
The players in classification



1. Analytical performance: Bias and imprecision

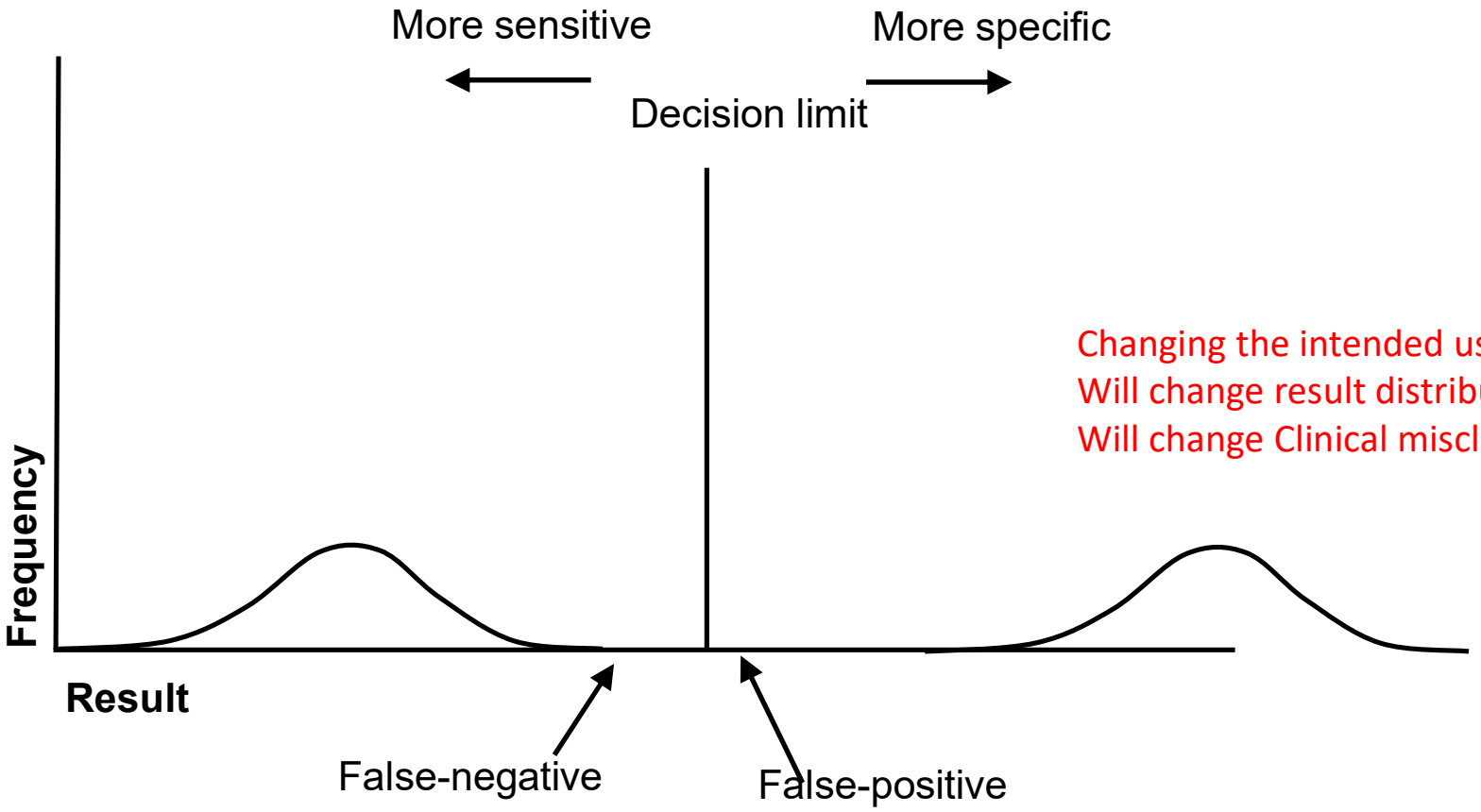


2. Result distribution in test population



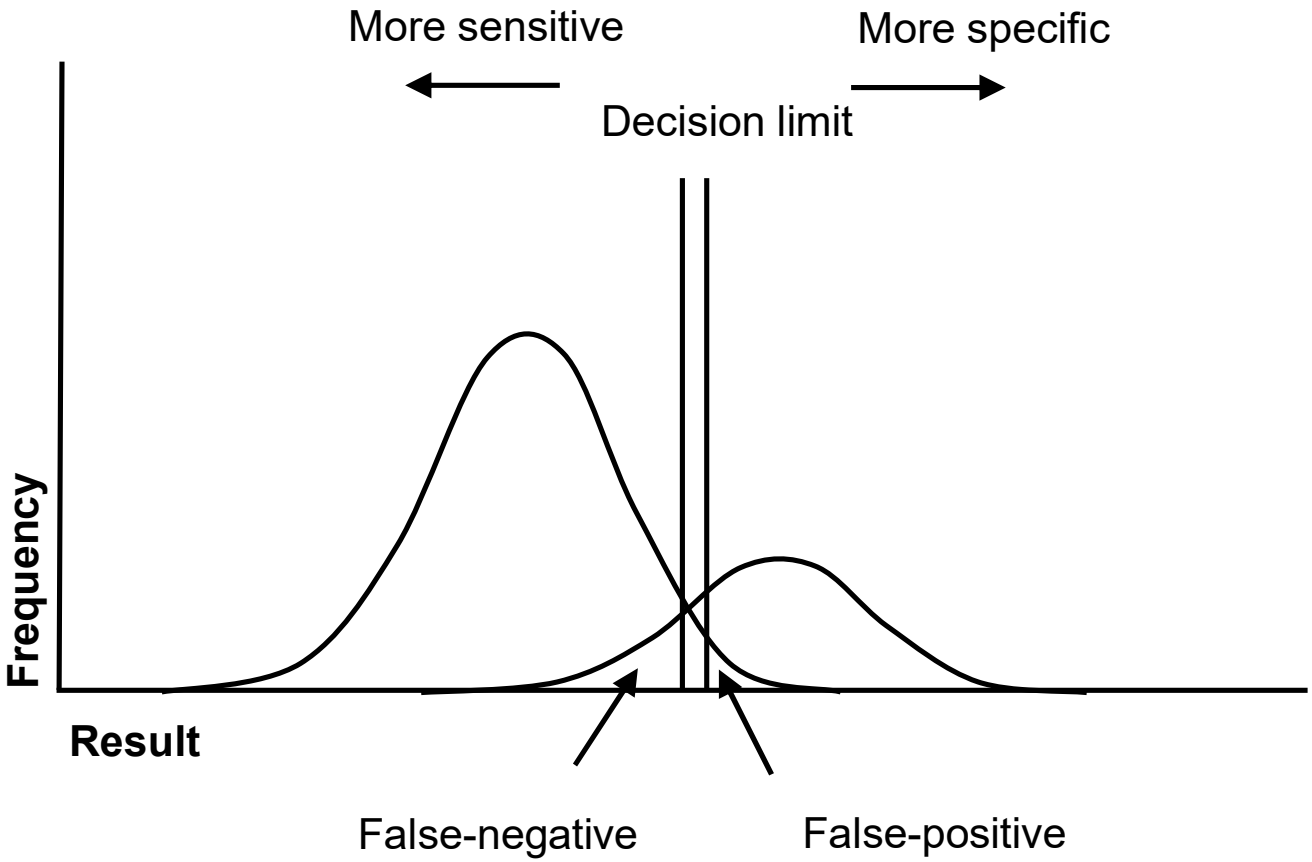
Changing result distribution
Will change
Clinical misclassification rates

2. Result distribution in test population: intended use



Changing the intended use
Will change result distribution
Will change Clinical misclassification rates

3. Adequate decision limits



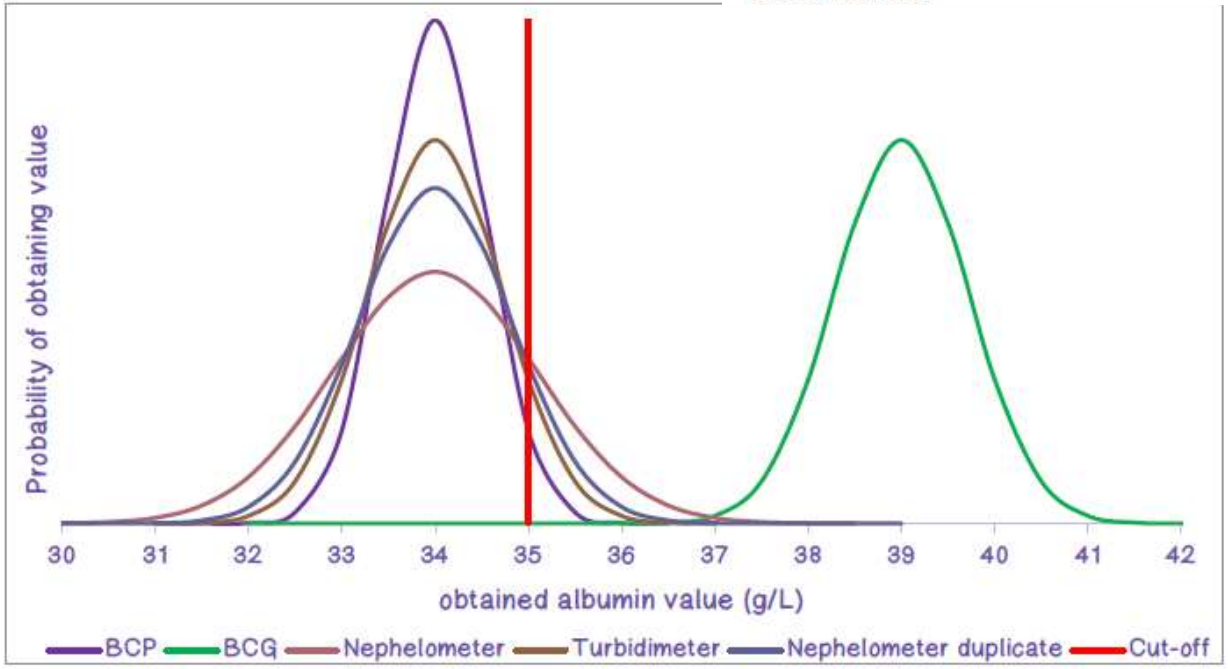
Changing decision limits
Will change
Clinical misclassification rates

First example: Albumin

Nephrol Dial Transplant (2022) 37: 1792–1799
doi: 10.1093/ndt/gfaa375
Advance Access publication 24 December 2020

Serum albumin measurement in nephrology: room for improvement

Marith van Schrojenstein Lantman [1,2,3], Anne-Els van de Logt[4], Marc Thelen[1,2,3], Jack F. Wetzels[4] and Miranda van Berkel[1]



Albumin method comparison in Patient samples with different CKD stage

DE GRUYTER

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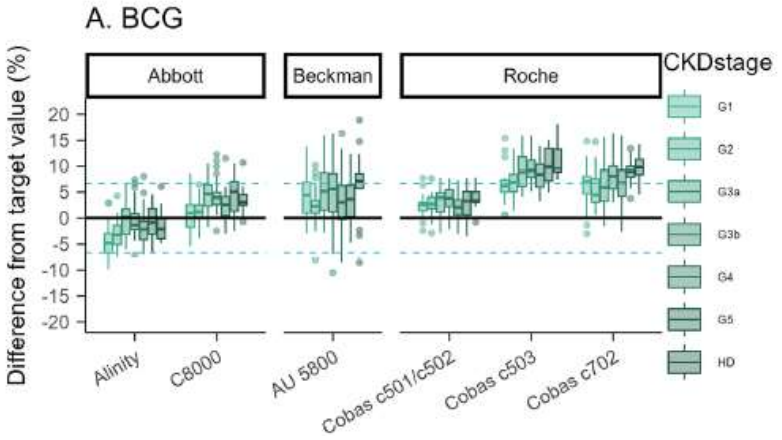
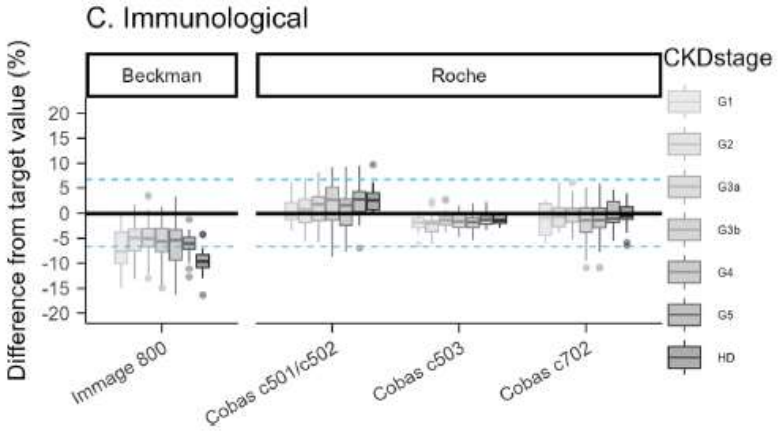
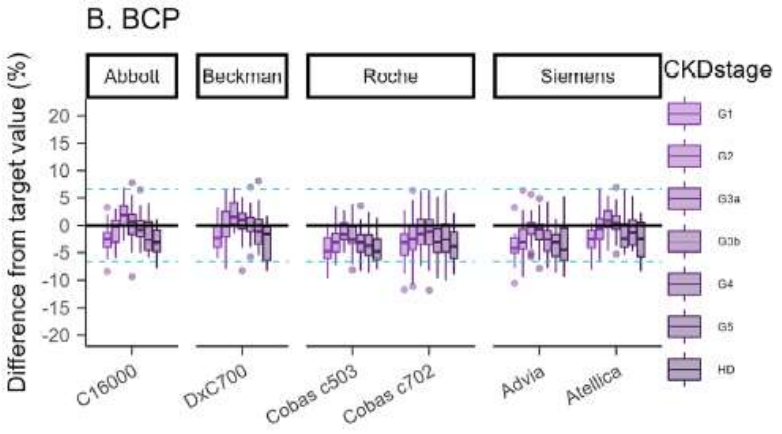
Marith van Schrojenstein Lantman*, Anne-Els van de Logt, Elma Prudon-Rosmulder, Marloes Langelaan, Ayşe Y. Demir, Steef Kurstjens, Armando van der Horst, Aldy Kuypers, Aram Greuter, Jenny Kootstra-Ros, Eline van der Hagen, Marlies Oostendorp, Roseri de Beer, Christian Ramakers, Dirk Bakkeren, Fokke Lindeboom, Dennis van de Wijngaart, Marc Thelen, Jack Wetzels and Miranda van Berkel

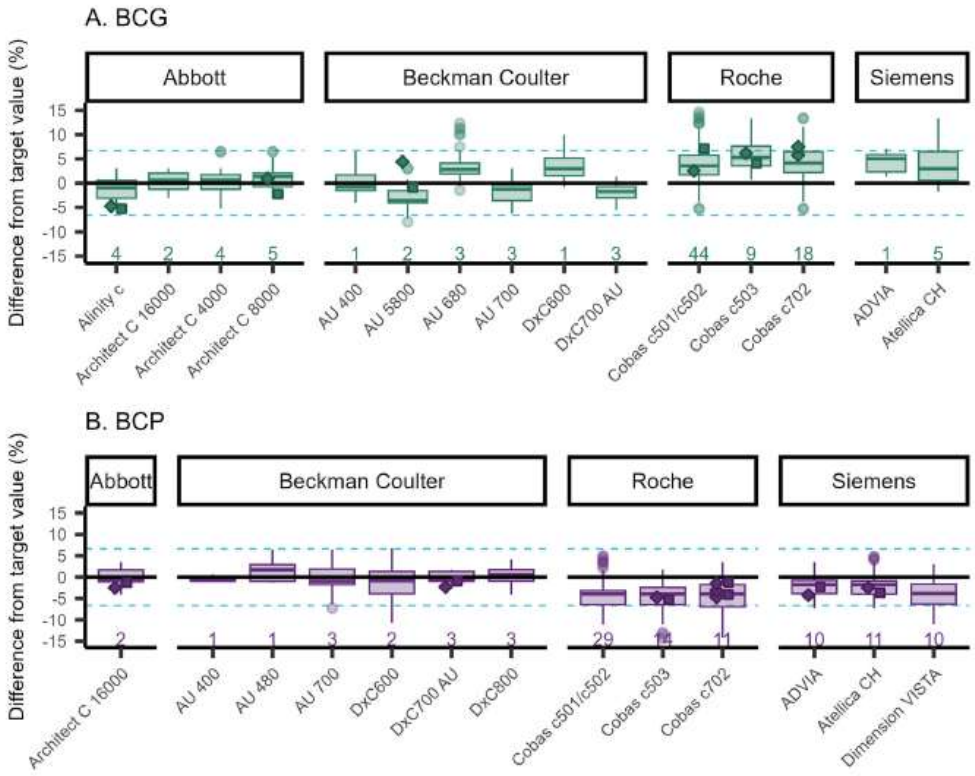
Albumin determined by bromocresol green leads to erroneous results in routine evaluation of patients with chronic kidney disease

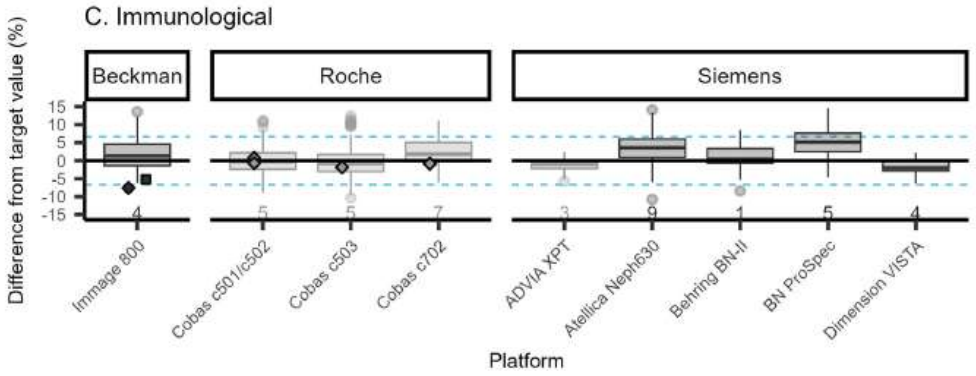






Can EQA be used to monitor method specific bias?

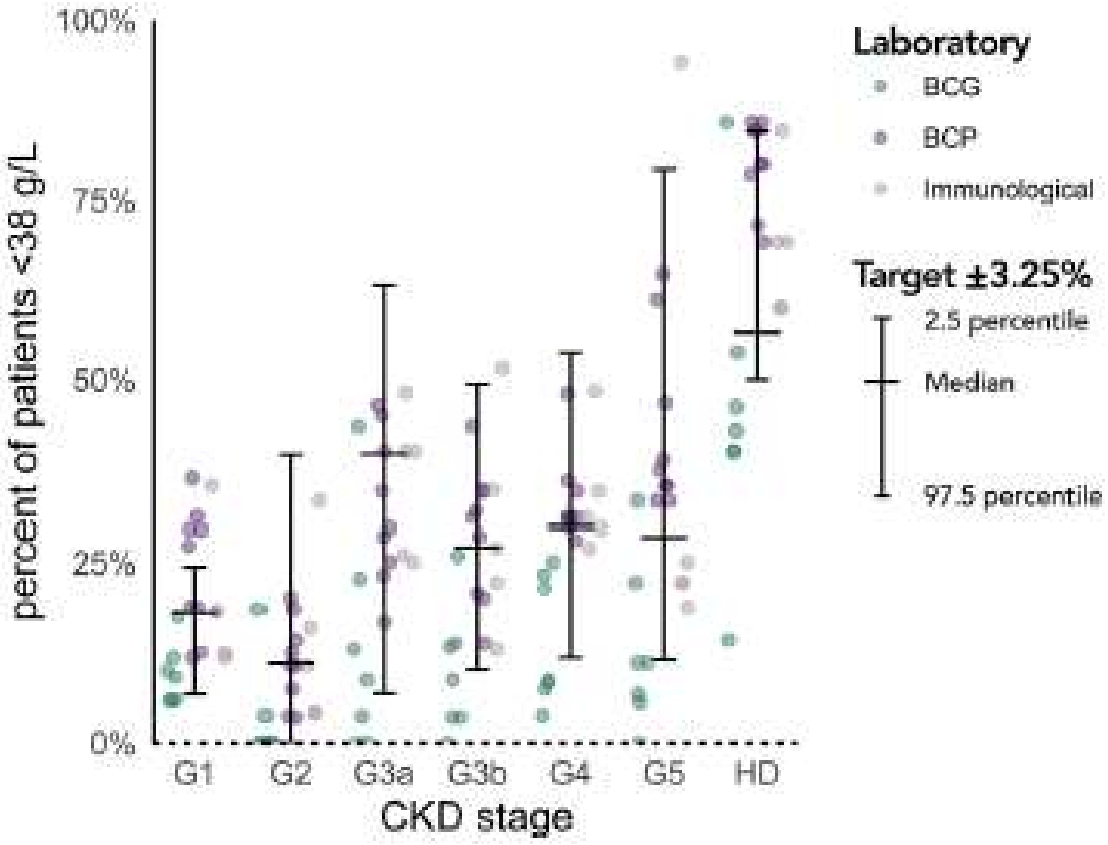




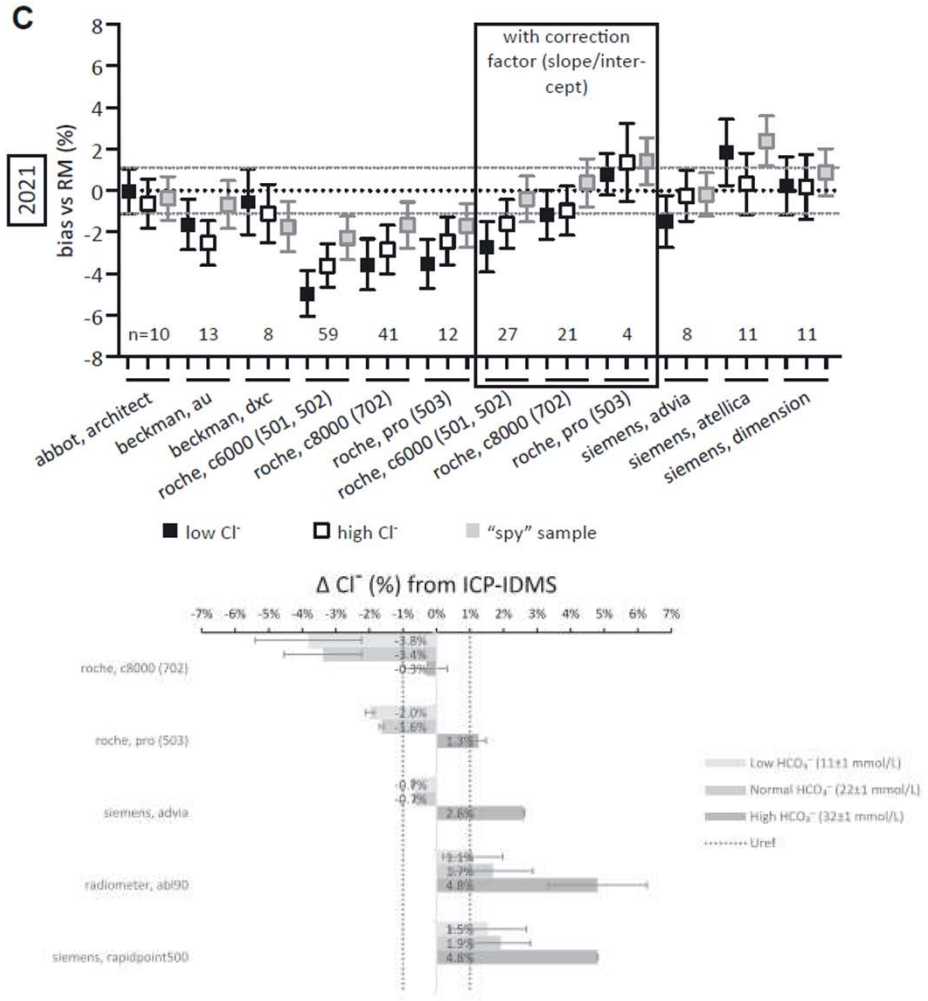
BCG underclassification of protein wasting

Misclassifiation due to

1. AP: biased methods
2. AP: imprecise methods
3. Result distribution
4. Improper decision limits (in combination with 1)



Second example: Chloride



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Letter to the Editor

Jenny E. Kootstra-Ros*, Eline A.E. van der Hagen, Marith van Schrojenstein Lantman, Marc Thelen and Miranda van Berkel, on behalf of the SKML General Clinical Chemistry Group

(In)direct chloride ISE measurements, room for improvement

Some have **positive** bias in **high** bicarbonate samples
Others have **negative** bias in **low** bicarbonate samples
What do you prefer?

Intended use determines which non-selectivity bias is preferable

- Calculate anion gap in metabolic acidosis
- Calculate anion gap in metabolic alkalosis

“You are the only EQA with these findings”

Eqalm survey
Do you see Neg Bias in Roche Chloride?

1. Hmm, now that you mention it, we see it
2. No, we only compare to method group and Roche agrees with Roche
3. No

Follow up EQALM survey
Let us know the bicarbonate concentration in your Chloride samples

Misclassification due to
1. AP: non-selectivity bias

EQA organizer	Sample	Method target	Target target Chloride (mmol/l)	Roche, Cobas (mmol/l)	Abs Bias (mmol/l)
Netherlands, SKML	2021 low	ICP-IDMS	**89.3**	**86.7 (N=112)**	**-2.6**
	2021 spy		**106.1**	**105.2 (N=224)**	**-0.9**
Germany, RfB	KS4/22 A	ICP-OES	**103.6**	**94.9 (N=263)**	**-8.7**
	KS7/22 B		**143.8**	**138 (N=221)**	**-5.8**
Germany, Instand	Jan 22/2	ICP-IDMS	**85.8**	**86.6 (N=258)**	**0.8**
	Oct 22/1		**136.0**	**130 (N=262)**	**-6.0**
France, Biologie Prosp	2022-1b	Mean	**81.2 (N=282)**	**78.2 (N=112)**	**-3.0**
	2022-3a		**82.8 (N=283)**	**81.2 (N=115)**	**-1.6**
Wales, WEQAS	M1011	Mean	**79.6 (N=112)**	**77.9 (N=61)**	**-1.7**
	M1018		**112.7 (N=111)**	**112.4 (N=63)**	**-0.3**
Brasil, PNCQ	459	Mean	**89.8 (N=567)**	**82.5 (N=41)***	**-7.3**
	458		**119.4 (N=567)**	**114.5 (N=41)**	**-4.9**
Austria, OQUASTA	250/C**	Mean	**76.5 (N=195)**	**74.0 (N=103)**	**-2.5**
	250/A**		**107.0(N=225)**	**104.6 (N=116)**	**-2.4**
UK, UKNEQAS	1119/B	ALTM	**95.8 N=525)**	**94.4 (N=288)**	**-1.4**
	1119/C		**104.3(N=525)**	**103.5 (N=288)**	**-0.8**
Australia, RCPAQAP***	22-13	Median	**78 (N=558)**	**75 (N=56)**	**-3**
	22-39		**94 (N=557)**	**96 (N=55)**	**+2**

Example 3: Hs-c-Troponin-T for NSTEMI

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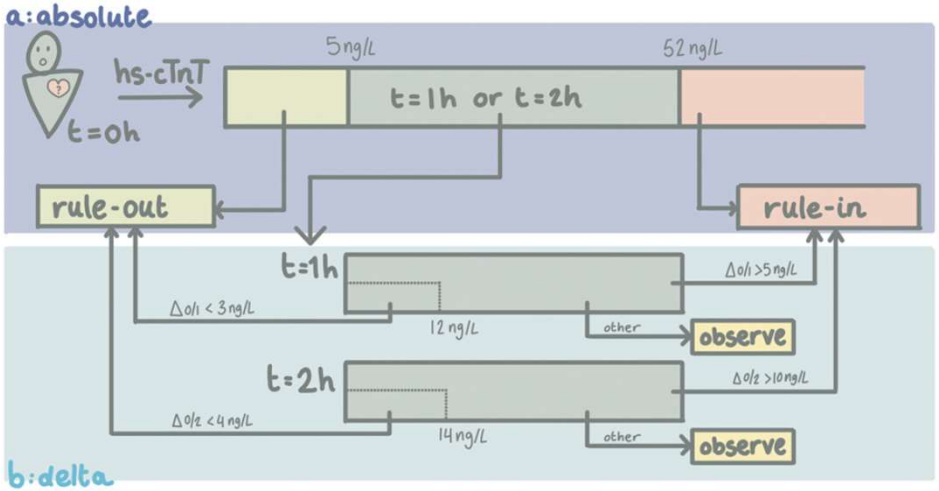
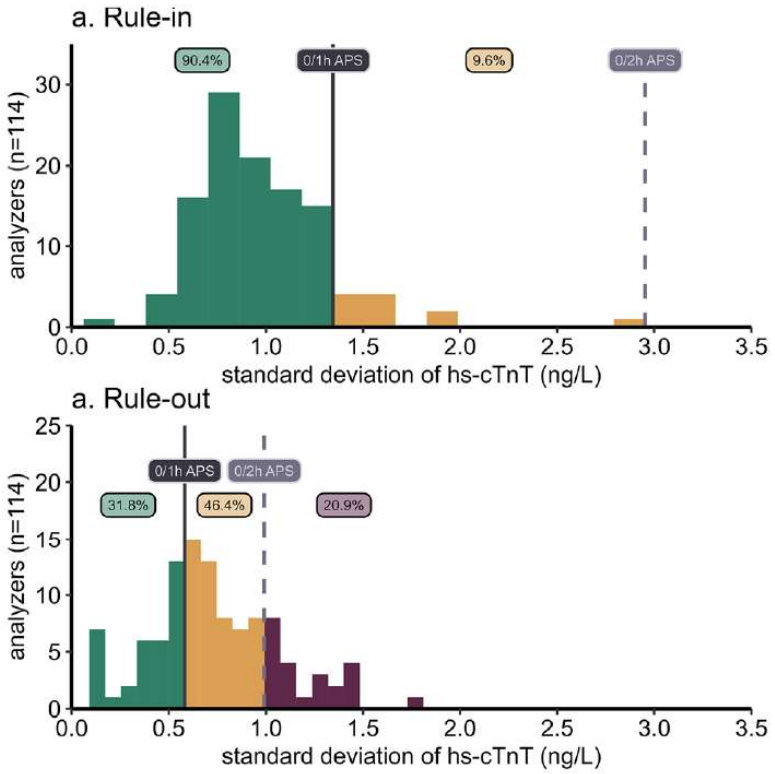
Marith van Schrojenstein Lantman*, Remco Grobben, Antonius E. van Herwaarden, Miranda van Berkel, Jeroen Schaap and Marc Thelen

To rule-in, or not to falsely rule-out, that is the question: evaluation of hs-cTnT EQA performance in light of the ESC-2020 guideline

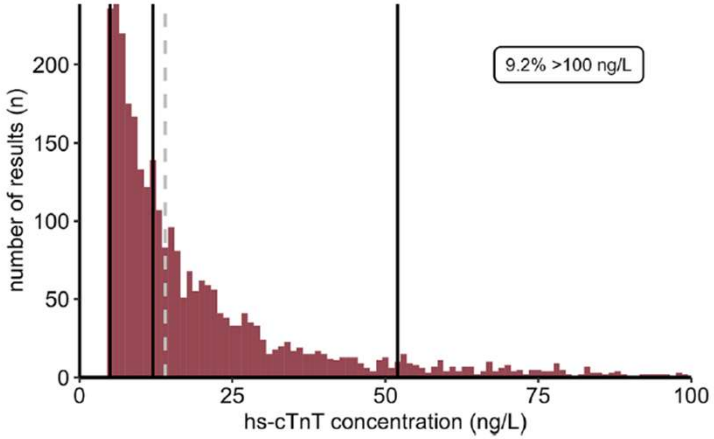


Multi point EQA for analysis of imprecision
Is RCV<delta?



Application of performance on real life patient results in a data simulation

1. Precision profile of fail and pass
2. Simulate alternative results 3300 patients
3. Check opportunity for other decision



intended decision		decision made	0/1h CDL Δ	0/1h CDL PASS	0/1h CDL FAIL	0/2h CDL Δ	0/2h CDL PASS	0/2h CDL FAIL
rule-in	→	rule-out	6	0.0001%	2.1%	11	0%	0.01%
rule-in	→	observe	6	6.7%	25.0%	11	7.8%	27.8%
observe	→	rule-out	4	1.1%	10.4%	9	0%	0.28%
observe	→	rule-in	4	28.0%	39.5%	9	29.7%	39.7%
observe	→	rule-out	0'	1.8%	3.3%	0''	1.4%	3.4%
observe	→	rule-in	0'	0.07%	6.5%	0''	0%	0.09%
rule-out	→	observe	0'	1.7%	24.2%	0''	1.4%	13.7%
rule-out	→	rule-in	0'	0%	3.4%	0''	0%	0.001%

' hs-cTnT(t0) <12 ng/L
'' hs-cTnT(t0) <14 ng/L

CPS is <1%

Misclassification due to
1. Analytical performance: imprecision

As long as PS does not meet APS
Changing to 0/2h CDL can save the day

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Marith van Schrojenstein Lantman*, Remco Grobben, Antonius E. van Herwaarden, Miranda van Berkel, Jeroen Schaap and Marc Thelen

And finally the decision limits

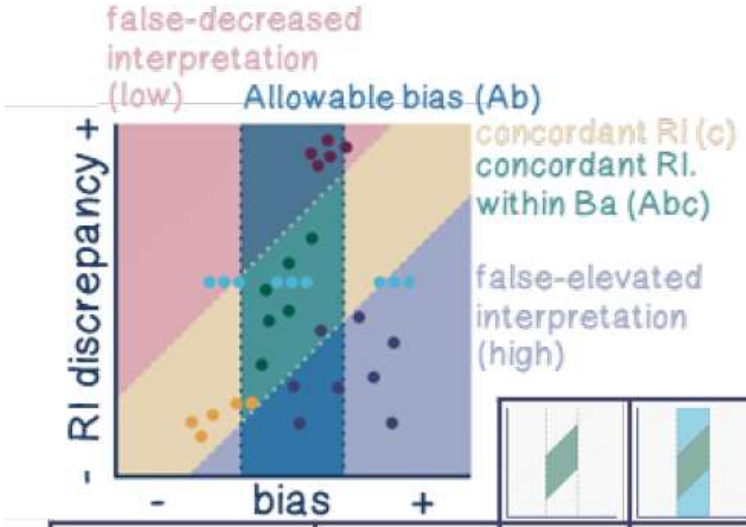
- Rationale:
- If results are standardised

For equivalent decision making

- Decision limits need to be standardised

- Disclaimer: RI are only transferable if:
  - Patient groups are comparable, if not: multiple RI (not: one size fits none!)

Do differences in RI compensate for bias? For methods and for laboratories???



Method	n of labs	Abc	Ab	c	low	high
ideal method	6	100%	100%	100%	0%	0%
method A	5	20%	20%	100%	0%	0%
method B	5	0%	80%	0%	100%	0%
method C	8	12.5%	50%	12.5%	0%	87.5%
method D	9	33.3%	33.3%	55.9%	22.2%	22.2%

Clinical Chemistry 00:0
1–10 (2024)

General Clinical Chemistry

Clinical Decision-Making Suffers from Inequivalent Measurement Results and Inadequate Reference Intervals

Marith van Schrojenstein Lantman [a,b,*] Miranda van Berkel,[b] Philip Kuijper [c] Marloes Langelaan,[d] Nannette Brouwer,[e] and Marc Thelen[a]

https://doi.org/10.1093/clinchem/hvae129

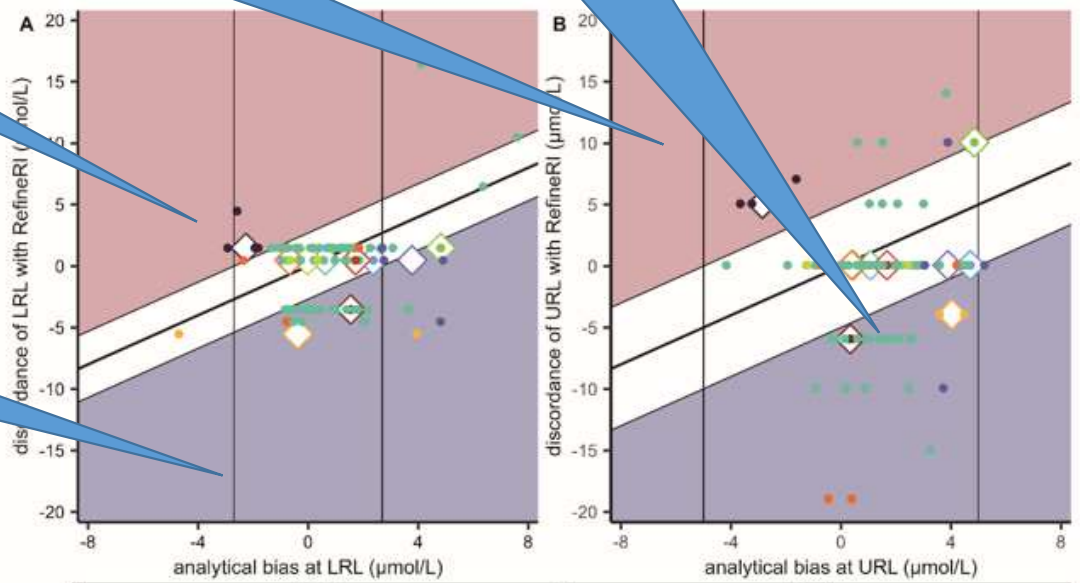
Creatinine

Overdiagnosis Cachecsia

Underdiagnosis Renal insufficiency

Overdiagnosis Renal insufficiency

Underdiagnosis Cachecsia



Misclassification due to

1. AP: method bias
2. AP: lab bias
3. DL: improper RI

Workflow should be

1. Abandon non selective methods
2. Assay standardisation
3. Correct local bias
4. Apply universal RI suitable for standardised method

Creatinine

		LRL					URL				
Method	N	Abc	Ab	c	Low	High	Abc	Ab	c	Low	High
Abbott enzymatic	4	0%	75.0%	0%	100%	0%	0%	100%	0%	100%	0%
Beckman Coulter AU enzymatic	6	33.3%	33.3%	50%	0%	50%	16.7%	66.7%	16.7%	33.3%	50%
Beckman Coulter DxC enzymatic	2	100%	100%	100%	0%	0%	100%	100%	100%	0%	0%
Roche enzymatic	70	55.7%	91.4%	60%	5.7%	34.3%	64.3%	100%	64.3%	4.3%	31.4%
Roche Jaffe	1	0%	0%	0%	0%	100%	0%	100%	0%	100%	0%
Siemens Advia enzymatic	4	100%	100%	100%	0%	0%	100%	100%	100%	0%	0%
Siemens Advia Jaffe	2	0%	0%	50%	0%	50%	0%	100%	0%	0%	100%
Siemens Atellica enzymatic	7	42.9%	100%	42.9%	14.3%	42.9%	57.1%	100%	57.1%	0%	42.9%
Siemens Dimension enzymatic	1	100%	100%	100%	0%	0%	100%	100%	100%	0%	0%
Siemens Dimension Jaffe	1	0%	100%	0%	0%	100%	0%	100%	0%	0%	100%
Total	98	52.0%	85.7%	57.1%	9.2%	33.7%	58.2%	98.0%	58.2%	10.2%	31.6%
Total enzymatic	94	54.2%	88.3%	58.5%	9.6%	31.9%	60.6%	97.9%	60.6%	9.6%	29.8%
Total Jaffe	4	0.0%	25.0%	25.0%	0.0%	75.0%	0.0%	100.0%	0.0%	25.0%	75.0%

Take home messages

- EQA with commutable samples can be used as proxy for analytical performance in clinical samples
- Data simulations can study the real life impact of AP from EQA
- Intended use matters
- The quality of your work matters