Weqas
Unit 6, Parc Tŷ Glas
Llanishen, Cardiff, CF14 5DU

Tel: 02920 314750
Email: contact@weqas.com

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Analytical performance specifications (APS) - are they clinically appropriate?

Annette Thomas

Director

www.weqas.com

What is APS?

APS is defined as a range of values around the target which is considered acceptable for the performance of that test. A result outside the acceptable range should alert the laboratory that that their assay may produce results that are at risk of detrimentally affecting clinical decision making. It provides a simple tool to allow a rapid, standardized assessment of IQC and EQA results in both numerical and graphical report formats. Laboratories and Point of Care (POCT) users must ensure that the analytical quality attained for that test is appropriate for the needs of the clinical service and the clinical utility of the test. It is therefore essential that EQA performance specification also reflect the clinical need and utility of the test. Various strategies have been proposed over the last 25 years, including the Consensus hierarchy from the Stockholm Conference in 1999, and the simpler EFLM Milan strategy in 2014.

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EFLM
EUROPEAN FEDERATION OF CLINICAL CHEMISTRY AND LABORATORY MEDICINE

European Commission
Joint Research Centre
IRMM
Institute for Reference Materials and Measurements

CIRME

1st EFLM Strategic Conference

Defining analytical performance goals 15 years after the Stockholm Conference

8th CIRME International Scientific Meeting

Milan (IT)
24-25 November 2014

with the auspices of IFCC

Defining APS

Model 1. Based on the effect of analytical performance on clinical outcomes. This model is the most rationale since it is based on the actual clinical outcome; however, in practice it is applicable only to a few tests since it is difficult to show the direct effect of laboratory tests on medical outcome.

Model 2. Based on components of biological variation of the measurand. This model seeks to minimize the ratio of the analytical noise to the biological signal. Its applicability can however be limited by the validity and robustness of the data on biological variation.

Model 3. Based on the state of the art. This model is the one where data is most easily available. It is linked to the highest level of analytical quality achievable with the currently available techniques**.**

Clinically Relevant Performance Specification

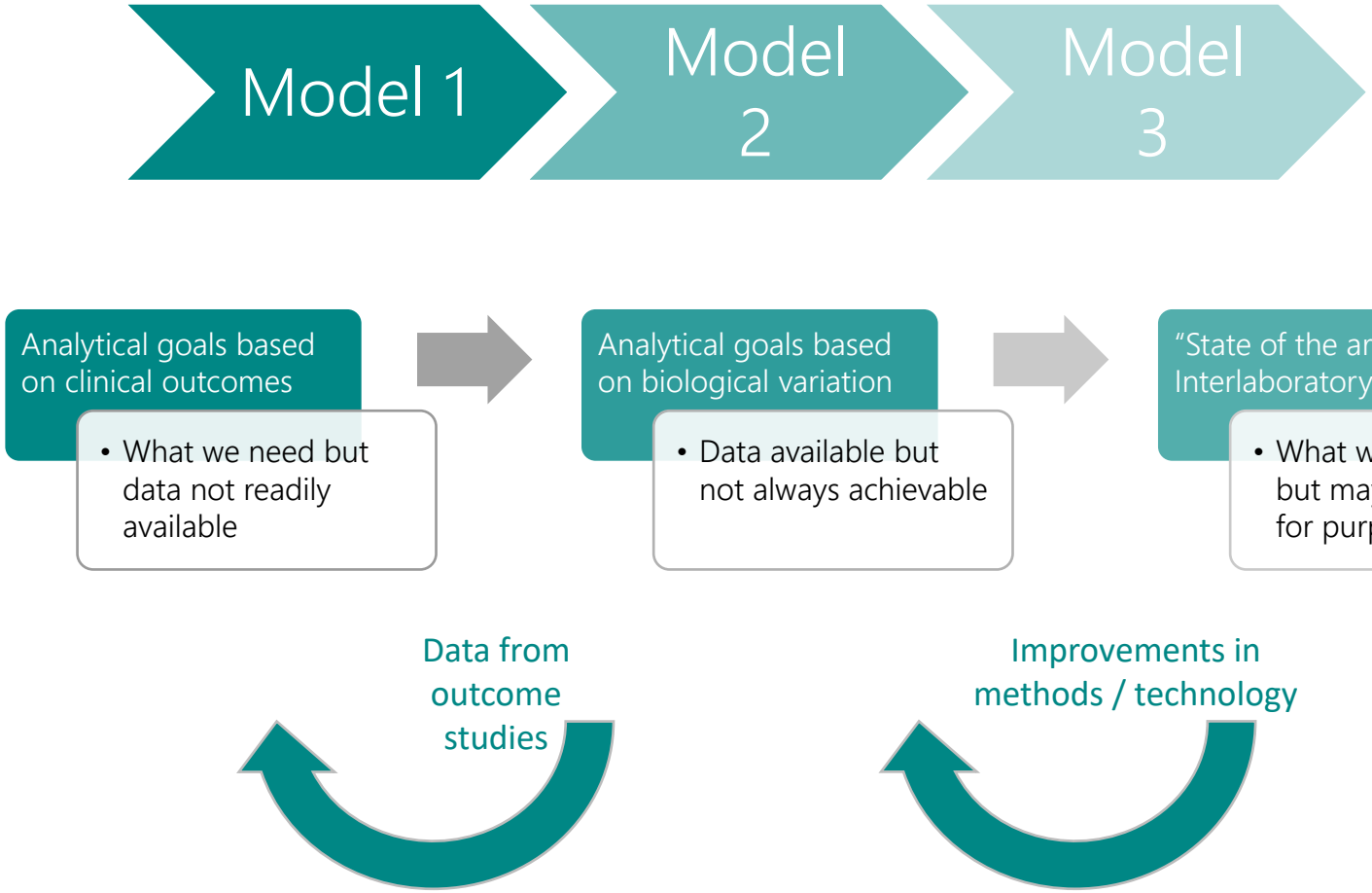

Table 1: Examples of current variation in models used to assign analytical performance specifications (APS) to External Quality Assurance (EQA) schemes.

EQA Program	Models
CSCQ Switzerland	Governmental regulations (combination of BV and state of the art) and Combination of limits given by scientific societies and Z-score
CTCB France	Z-score/state of the art/limits given by scientific societies or other/limits based on clinical impact
DEKS Denmark	Combination of BV, state of the art and expert opinion
NOKLUS Norway	Fixed percentage limits and based on a combination of BV, state of the art and expert opinion
RCPAQAP Australia	Combination of BV and state of the art
SEHH Spain	Statistical/state of the art/BV
SEQC Spain	Combination of BV and statistical results
SKML The Netherlands	Combination of BV and state of the art
WEQAS UK	Combination of BV and state of the art
CMCEQAS	Combination of state of the art and statistical considerations

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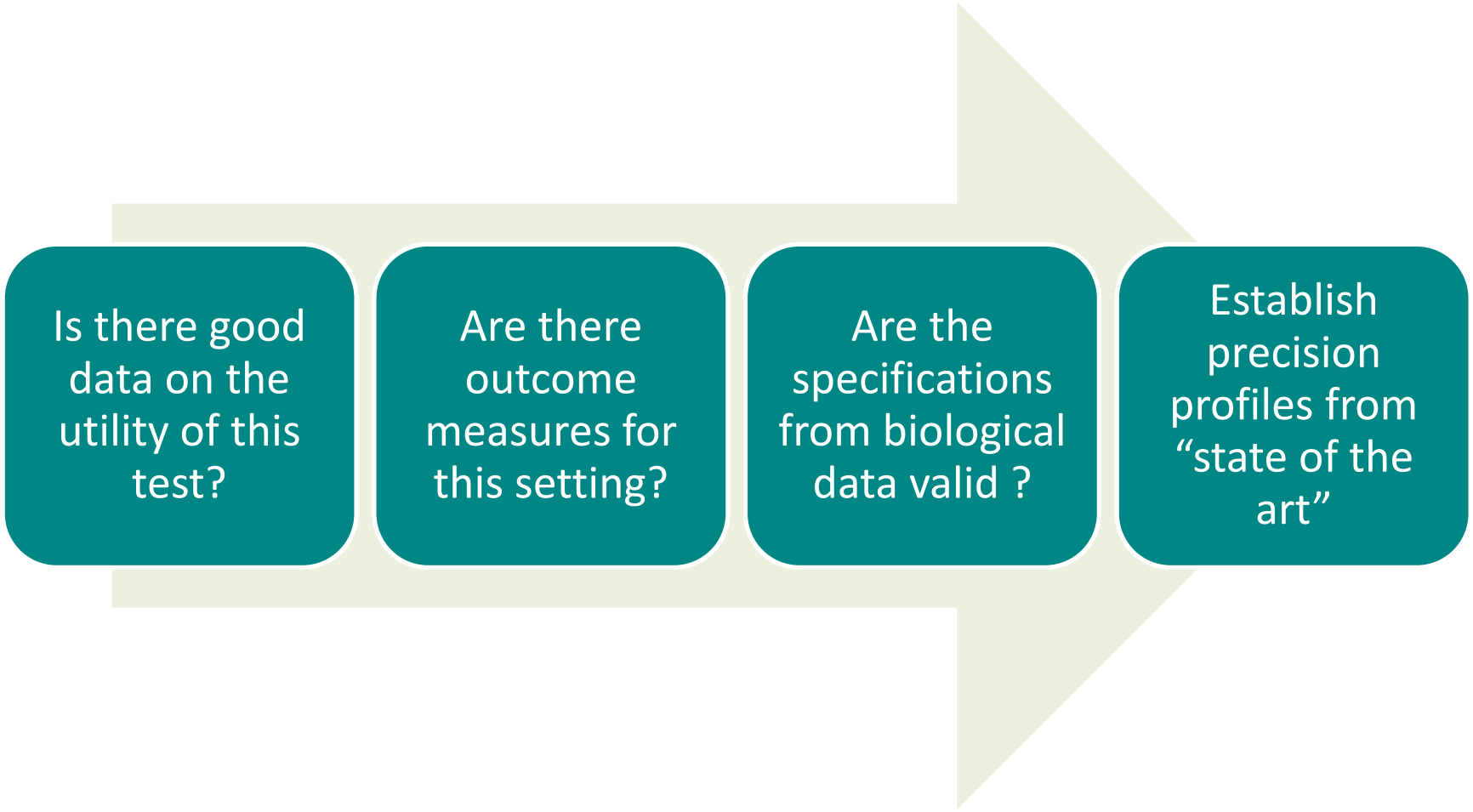
How to choose analytical specification



Are the specifications from biological data valid ?

The EFLM Biological Variation Database

Aarsand AK, Fernandez-Calle P, Webster C, Coskun A, Gonzales-Lao E, Diaz-Garzon J, Jonker N, Simon M, Braga F, Perich C, Boned B, Marques-Garcia F, Carobene A, Aslan B, Sezer E, Bartlett WA, Sandberg S. https://biologicalvariation.eu/ [03/10/2024]

Are the specifications from biological data achievable?

This paper attempts to address these 2 questions

Is the “state of the art” appropriate?

Method

Laboratory method performance data from Weqas in the UK was collected over the last five years across a wide clinical concentration for the common analytes in Clinical Biochemistry. The data covered 60 distributions using up to 240 samples, assayed by up to 200 laboratories using a range of analysers. Precision profiles were calculated for each sample for the overall data and for each of the major methods and analysers used for that analyte. The minimum number of data points for each analyser for each sample distribution was set at 5. The interlaboratory variation was represented as Standard Deviation, (SD), and/or Coefficient of variation, (CV), and plotted against analyte concentration. For certain analytes the data was also assessed according to whether the analyte was used for laboratory diagnosis or POCT monitoring.

APS based on Biological variation

	Intervention target	EFLM TEa (%)			Weqas TEa (SI units)		Weqas TEa (%)
Analyte	Conc.	Min	Des	Opt	1 SD	TEa	TEa (%)
Na	135 mmol/L	0.9	0.6	0.3	1.066	2.13	1.6 best fit
K	3.5 mmol/L	7.3	4.9	2.4	0.06	0.12	3.0 best fit
Ca	2.2 mmol/L	3.4	2.3	1.1	0.05	0.1	4.3 best fit
Creat	90 µmol/L	11.7	7.8	3.9	3.2	6.4	7.1 best fit
Glucose	2.0 / 6.5 mmol/L	9.2	6.1	3.1	0.16	0.32	
Urate	360 µmol/L	19	12.6	6.3	20	40	12.6 des
Cholesterol	5.0 mmol/L	12.5	8.3	4.2	0.21	0.42	8.3 des
HDL	1.0 mmol/L	14.9	9.9	5.0			
HbA1c	48 mmol/mol	4.7	3.1	1.6	0.35	0.7	

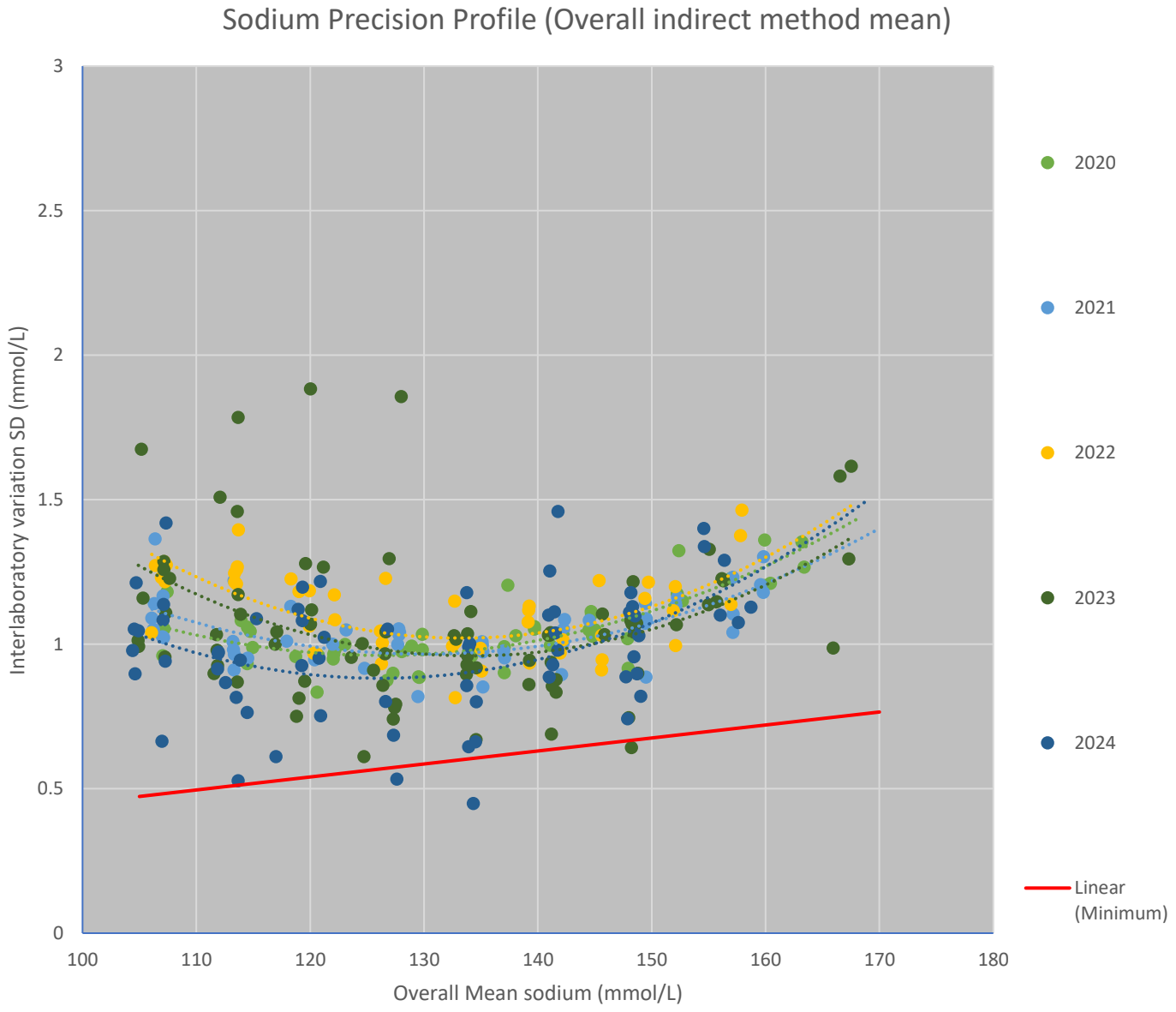
Sodium Precision Profile

Relationship of performance against concentration polynomial not linear

Minimum APS based on biological variation rarely achieved – some improvement in 2024 but not consistent

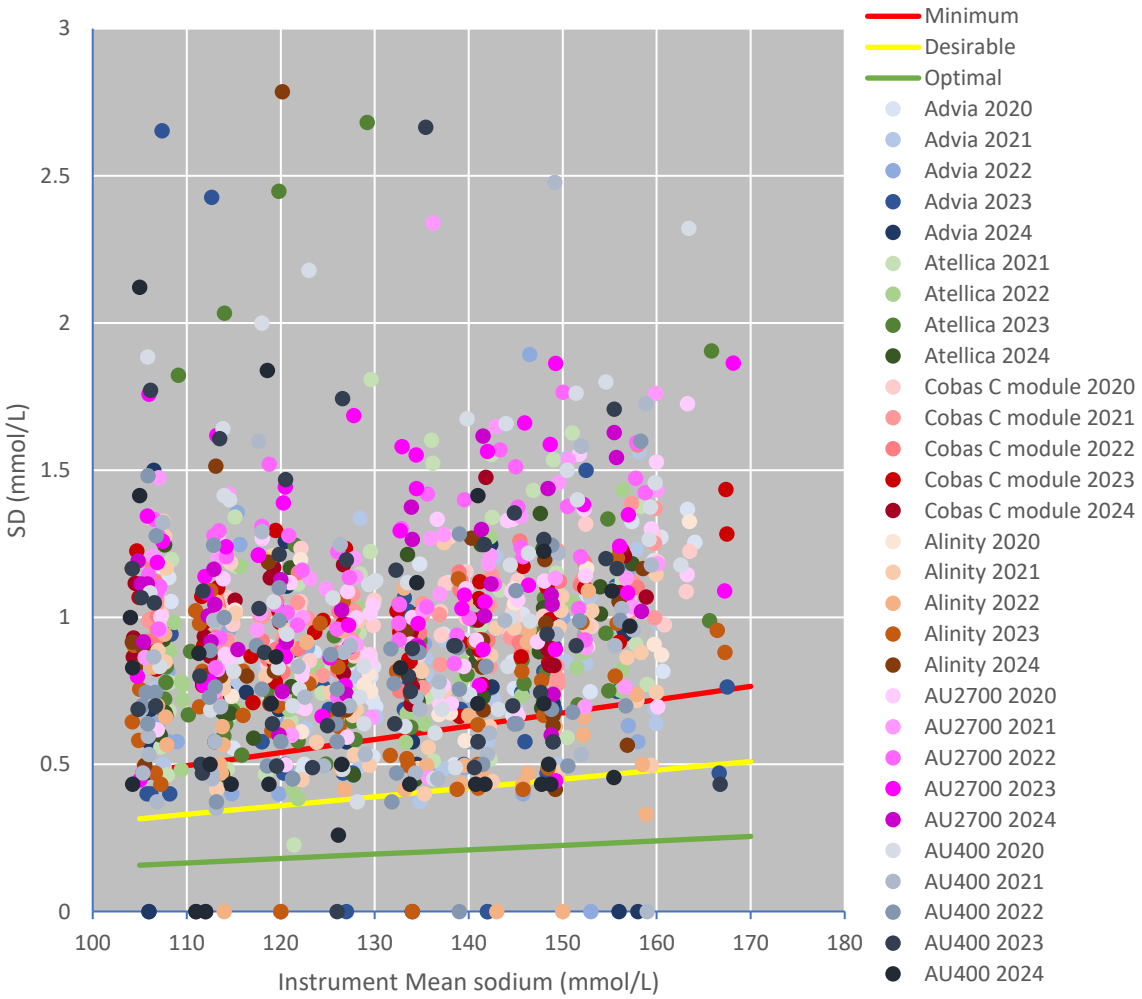
Can we use APS based on biological variation? – **NO**

Can we determine the APS based on best analytical method available?

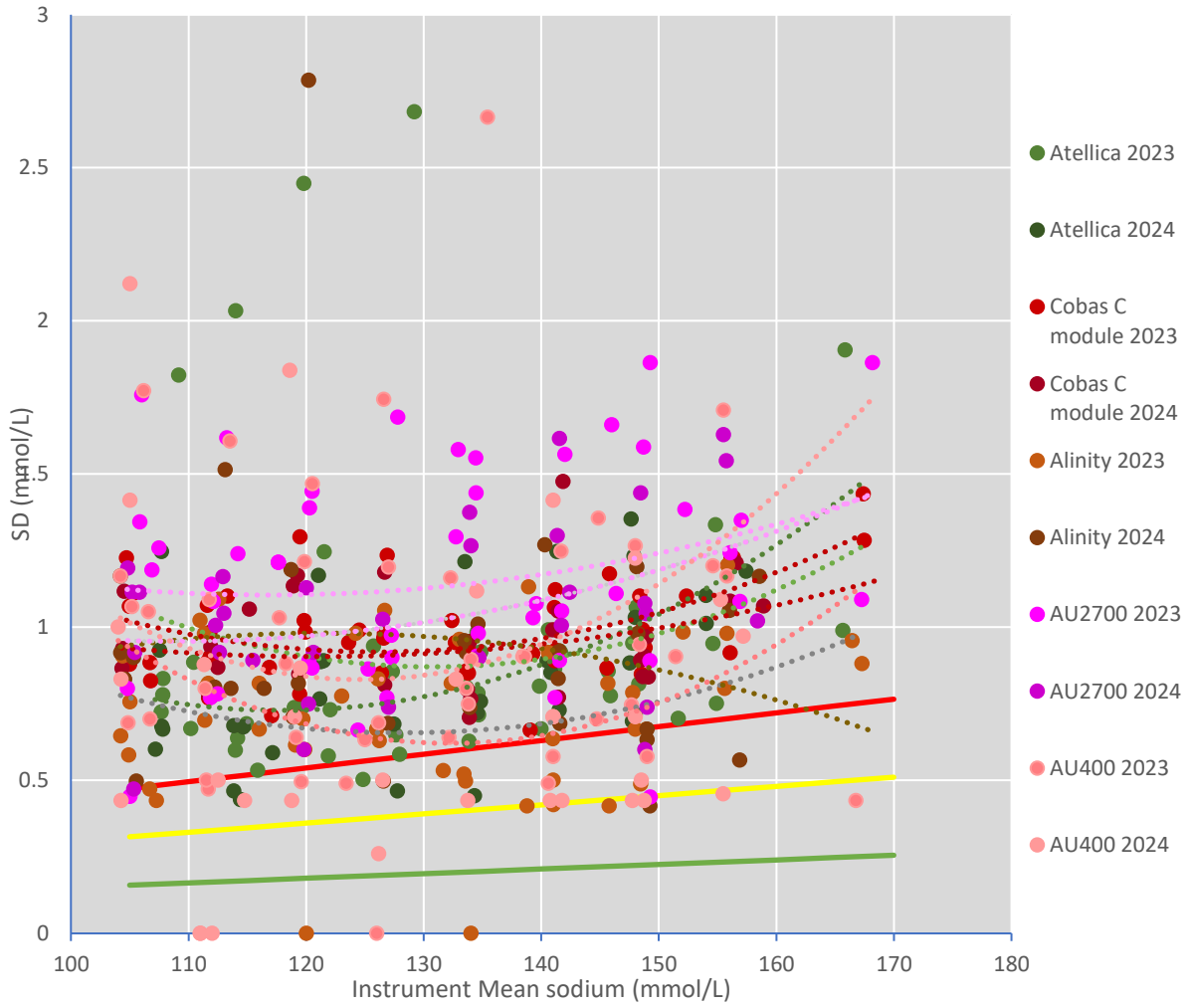


Sodium precision profile – State of the art of methods

All data 5 years



Current analysers from 2023



Sodium Precision Profile

APS based on highest level of quality with current technology

Best fit of the current “best method” TEa = 1.4mmol/L now close to minimum TEa of 0.9% @135-160 mmol/L

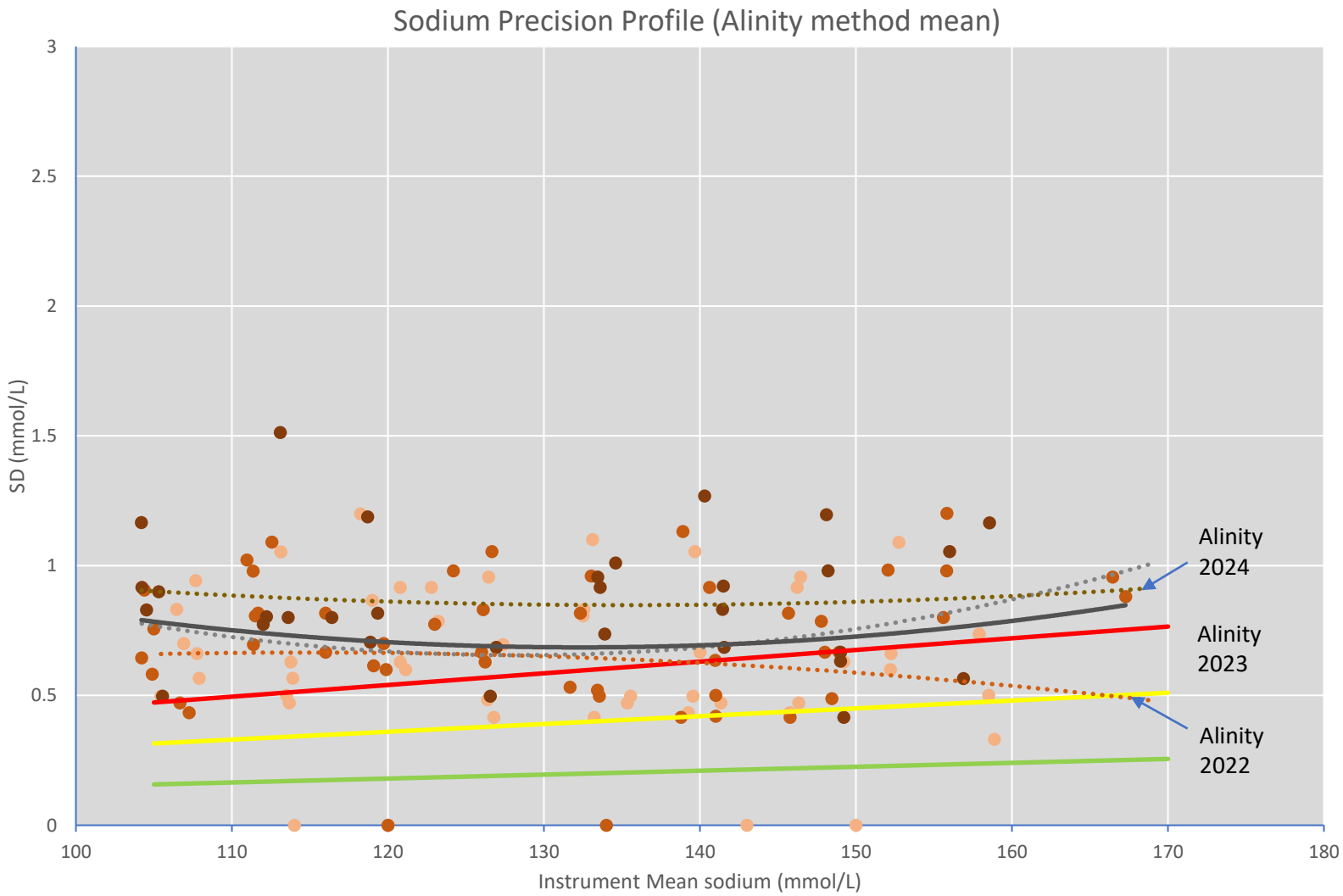
Wide variation around the best fit line – use TEa = 1.8 mmol/L

TEa at 135 mmol/L = 1.3%

TEa at 110 mmol/L = 1.6%

TEa at 160 mmol/L = 1.1%

Nonlinear



Potassium Precision Profile

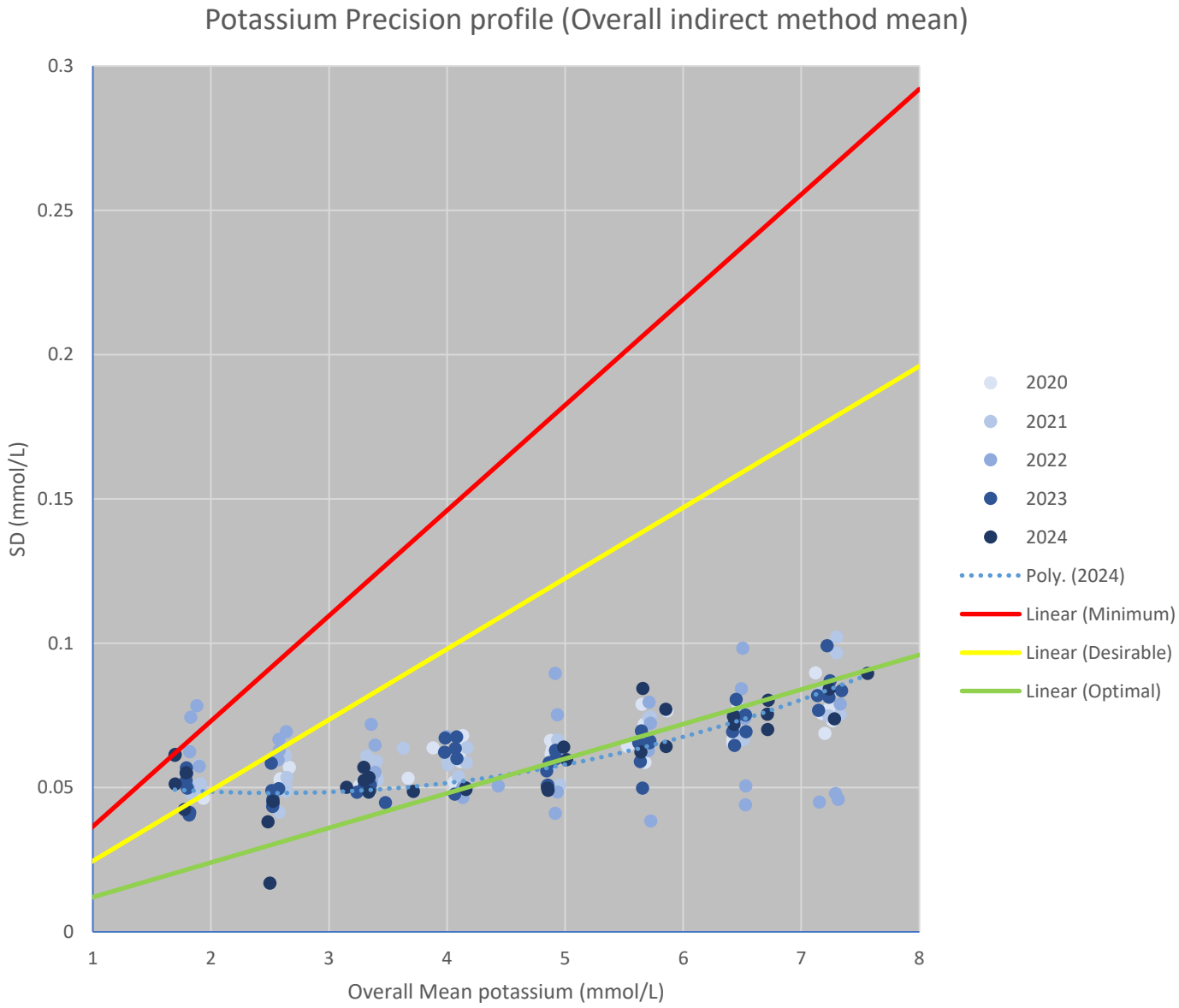
Can we use APS based on biological variation? – **YES**

Desirable APS based on biological variation achieved to 2.0 mmol/L

Optimal APS achieved @ > 4 mmol/L

Relationship of performance against concentration polynomial not linear.

Use best fit (optimal to 4 mmol/L)



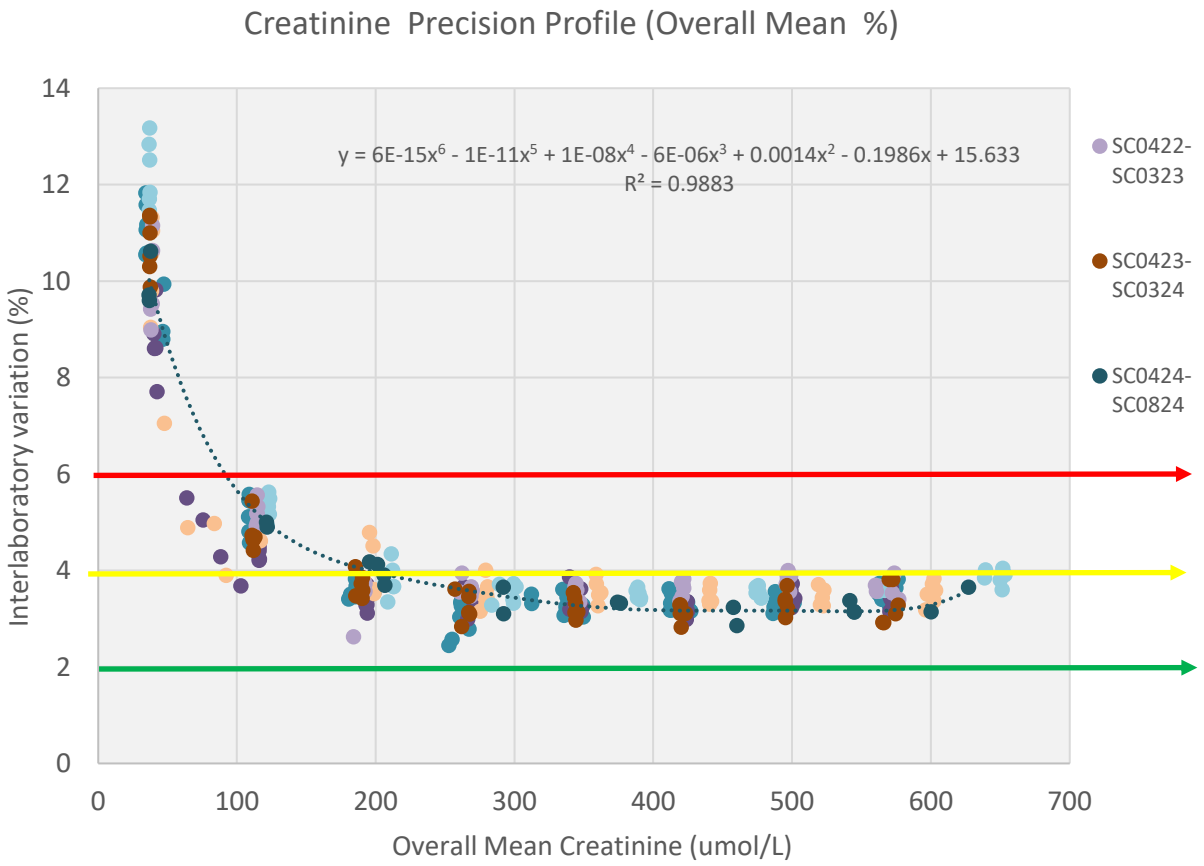
Creatinine Precision Profile

Can we use APS based on biological variation? – **YES**

Minimal APS based on biological variation achieved >70 µmol/L

Desirable APS achieved > 200 µmol/L

Variation includes method bias

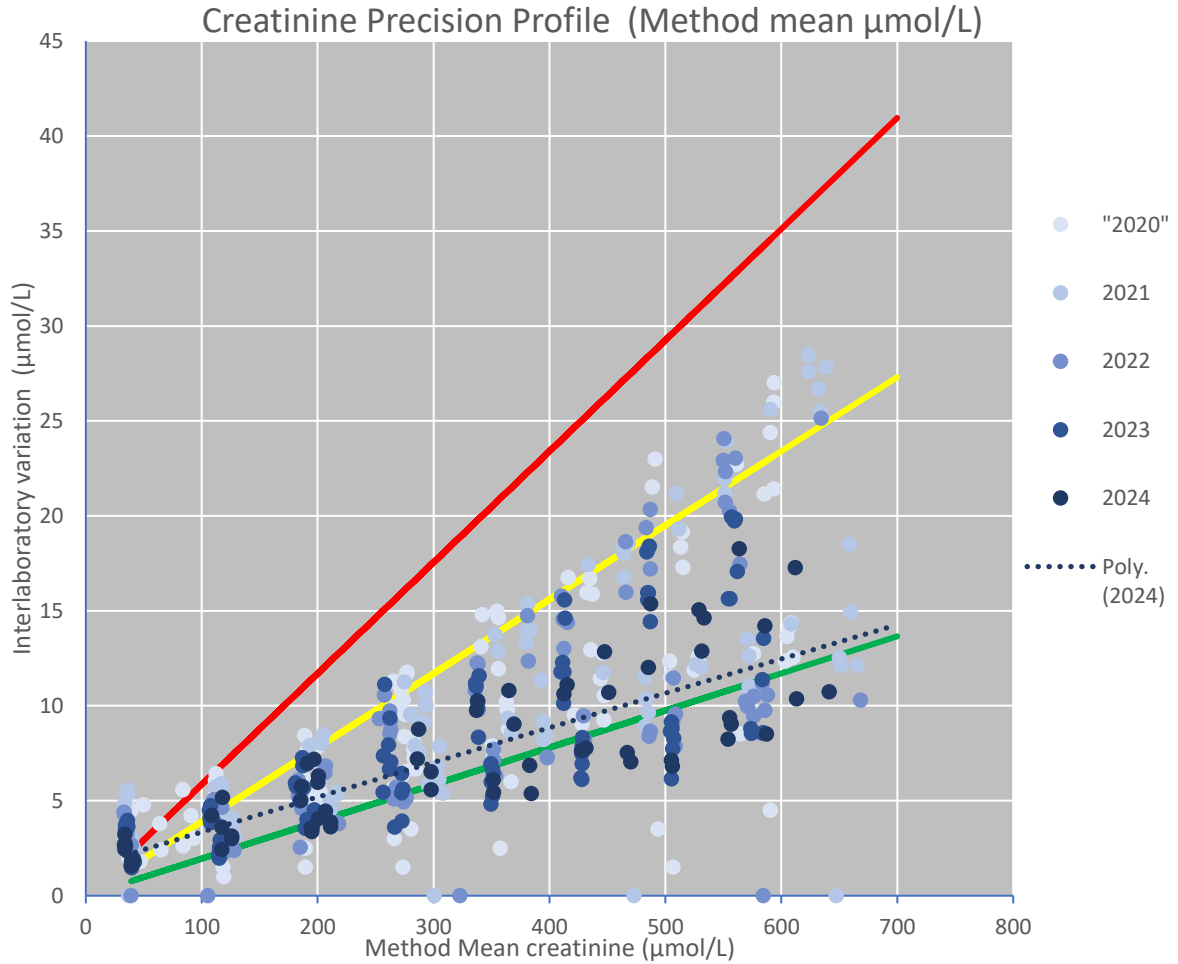


Are there methods that can achieve better? – **YES**

Desirable APS based on biological variation achieved to 100 µmol/L for all methods.

Optimal APS achieved for some methods

Use desirable or best method that can achieve optimal?



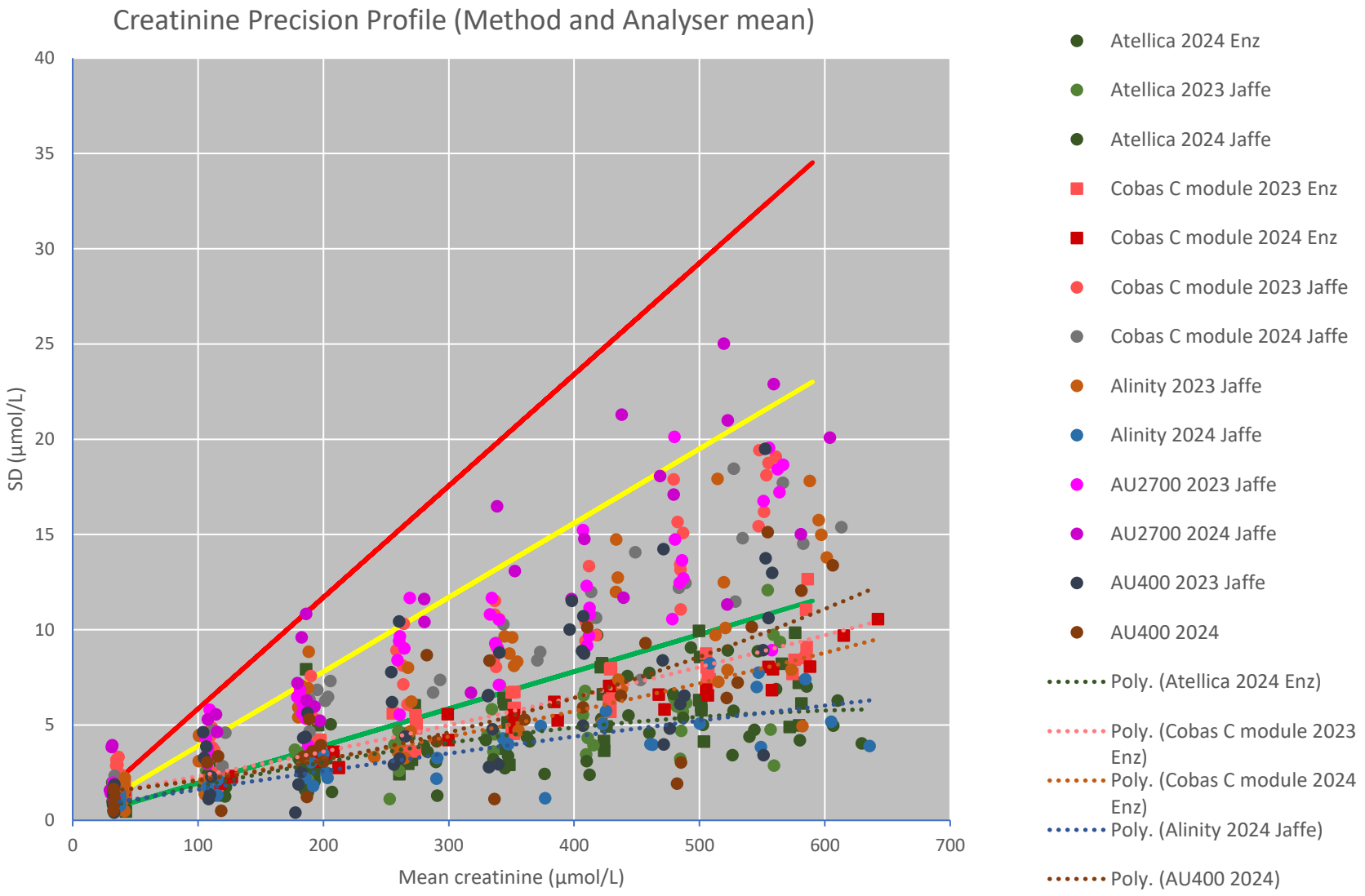
Creatinine Precision Profile

Determination of APS biological variation category based on highest level of quality with current technology

Optimal APS achieved for Alinity and Atellica analysers at all concentrations.

Optimal APS achieved for all other enzymatic methods as well as 2 Jaffe methods at a concentration > 100 µmol/L.

Target value consideration?



Calcium Precision Profile

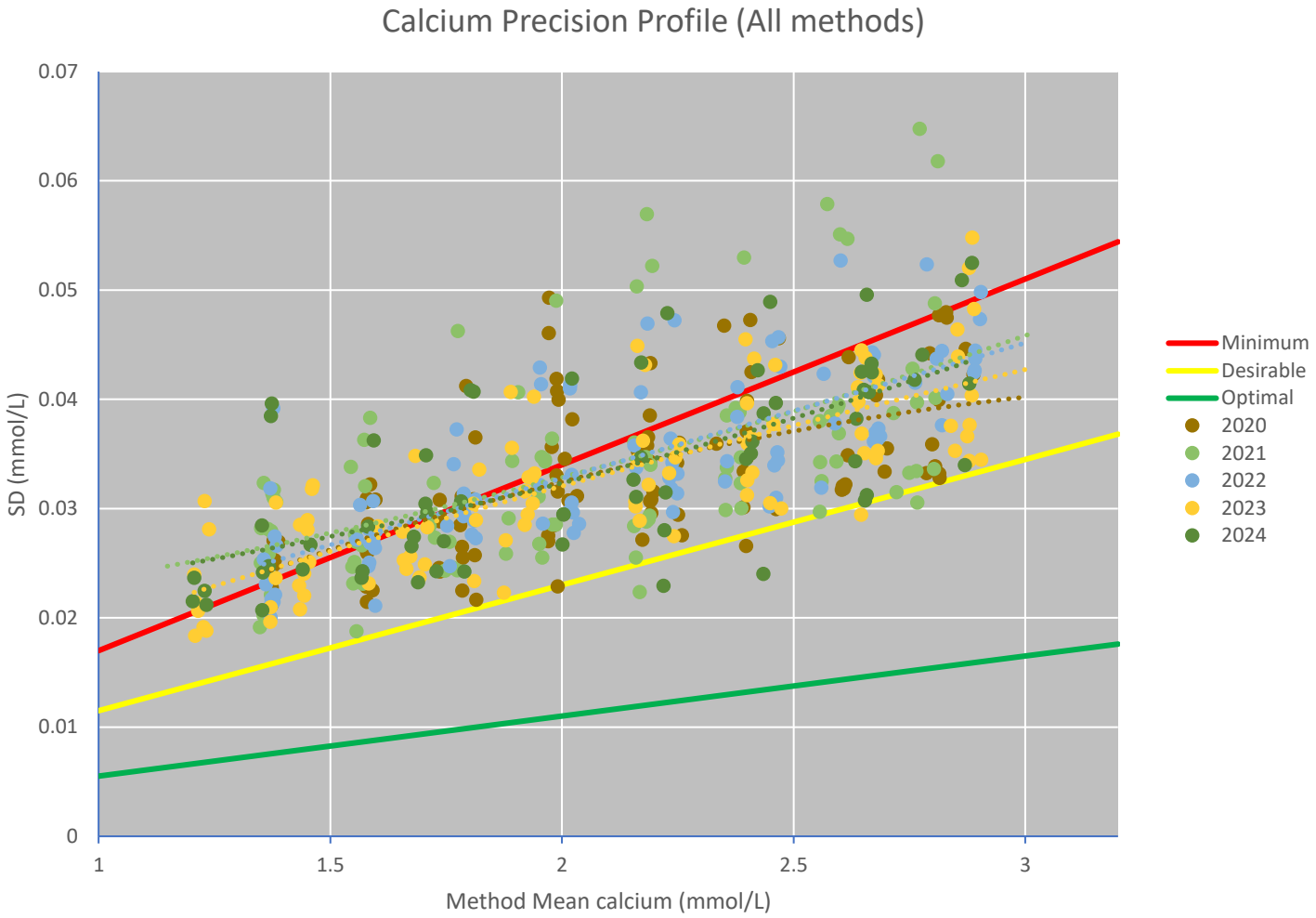
Can we use APS based on biological variation? – **Yes (partly)**

Minimum APS based on biological variation achieved > 1.8 mmol/L for most methods.

Relationship of performance against concentration close to linear

Use minimum to 1.8 mmol/L and then best fit.

Are then any methods that can achieve desirable?



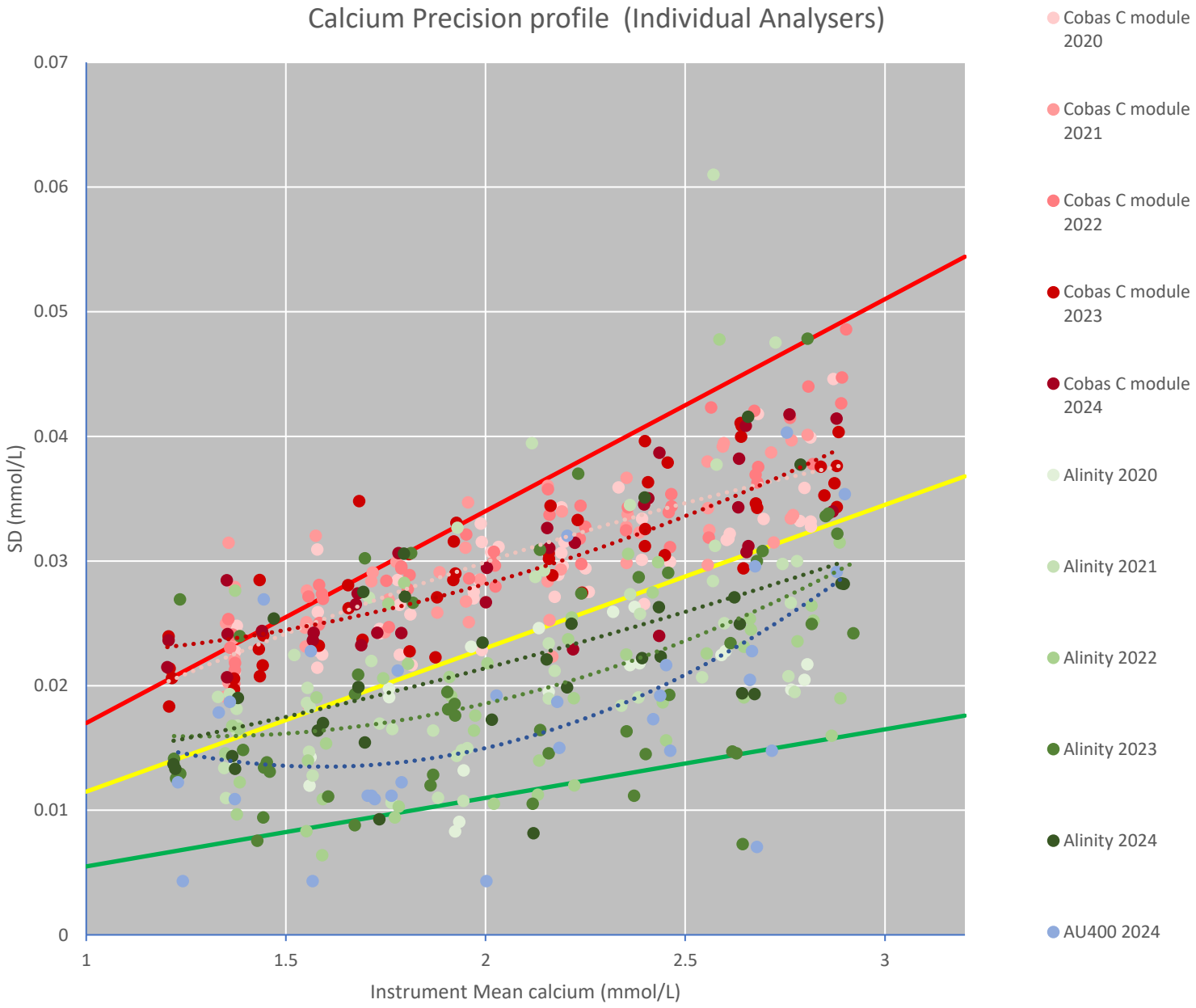
Calcium Precision Profile

Are then any methods that can achieve desirable? YES

Cobas C at concentration > 1.7mmol/L achieves performance between **minimal** and **desirable**

Alinity > 1.4 mmol/L achieves performance between **desirable** and **optimum**

AU400 mostly achieves performance between **desirable** and **optimum**

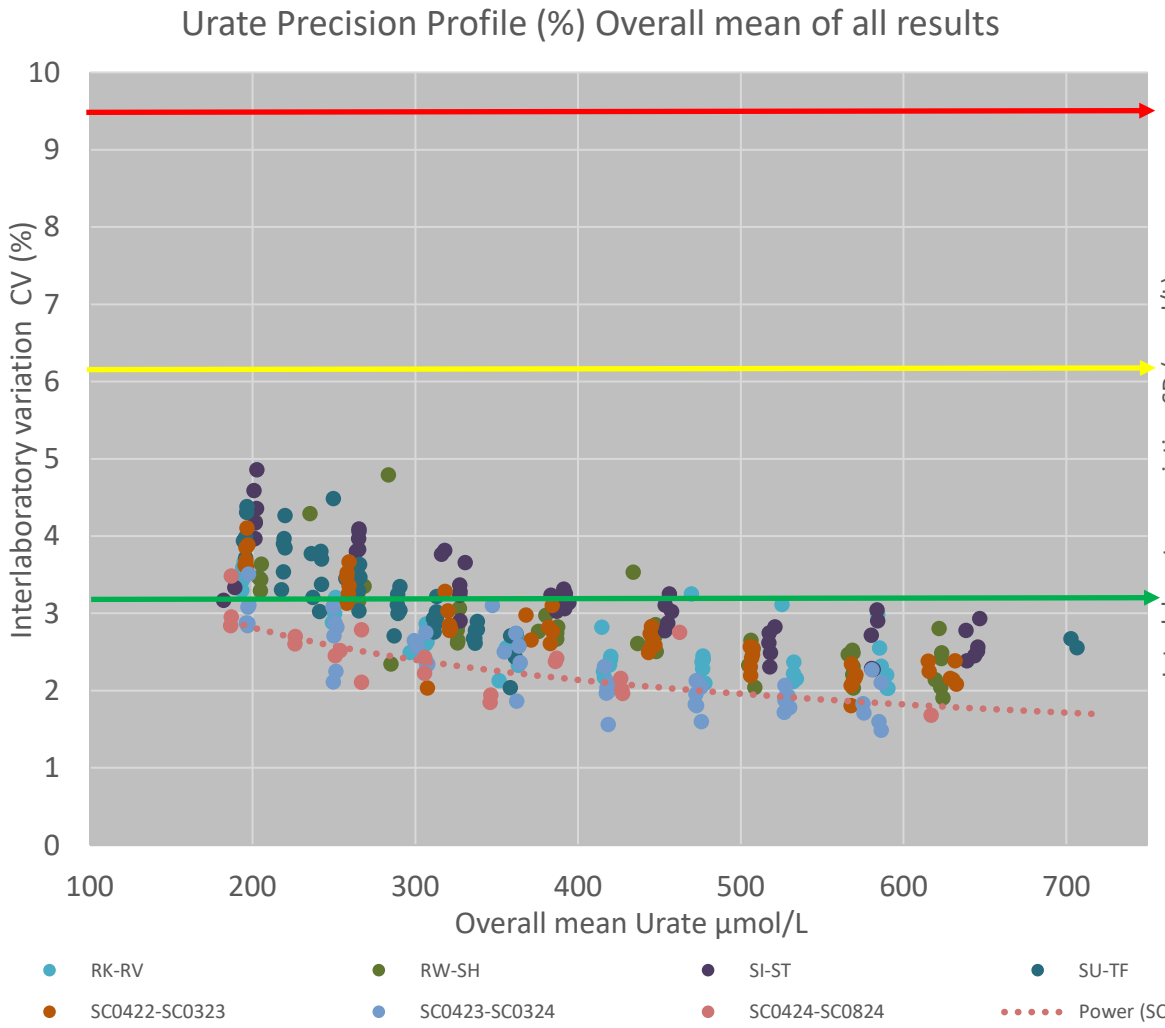


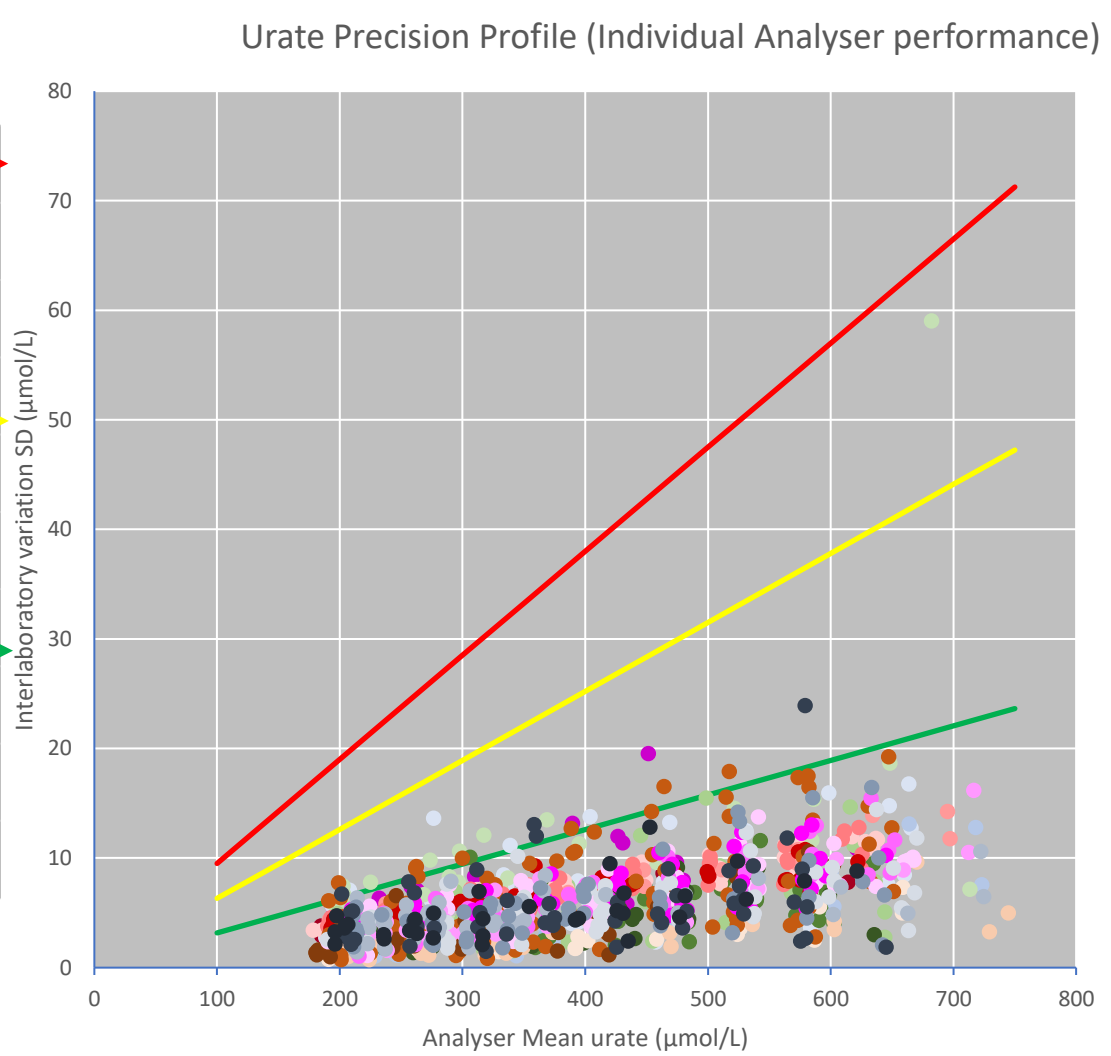
Urate Precision Profile

Can we use APS based on biological variation? – **YES**

Desirable APS based on biological variation achieved at all concentrations.

Optimal APS achieved for current performance.





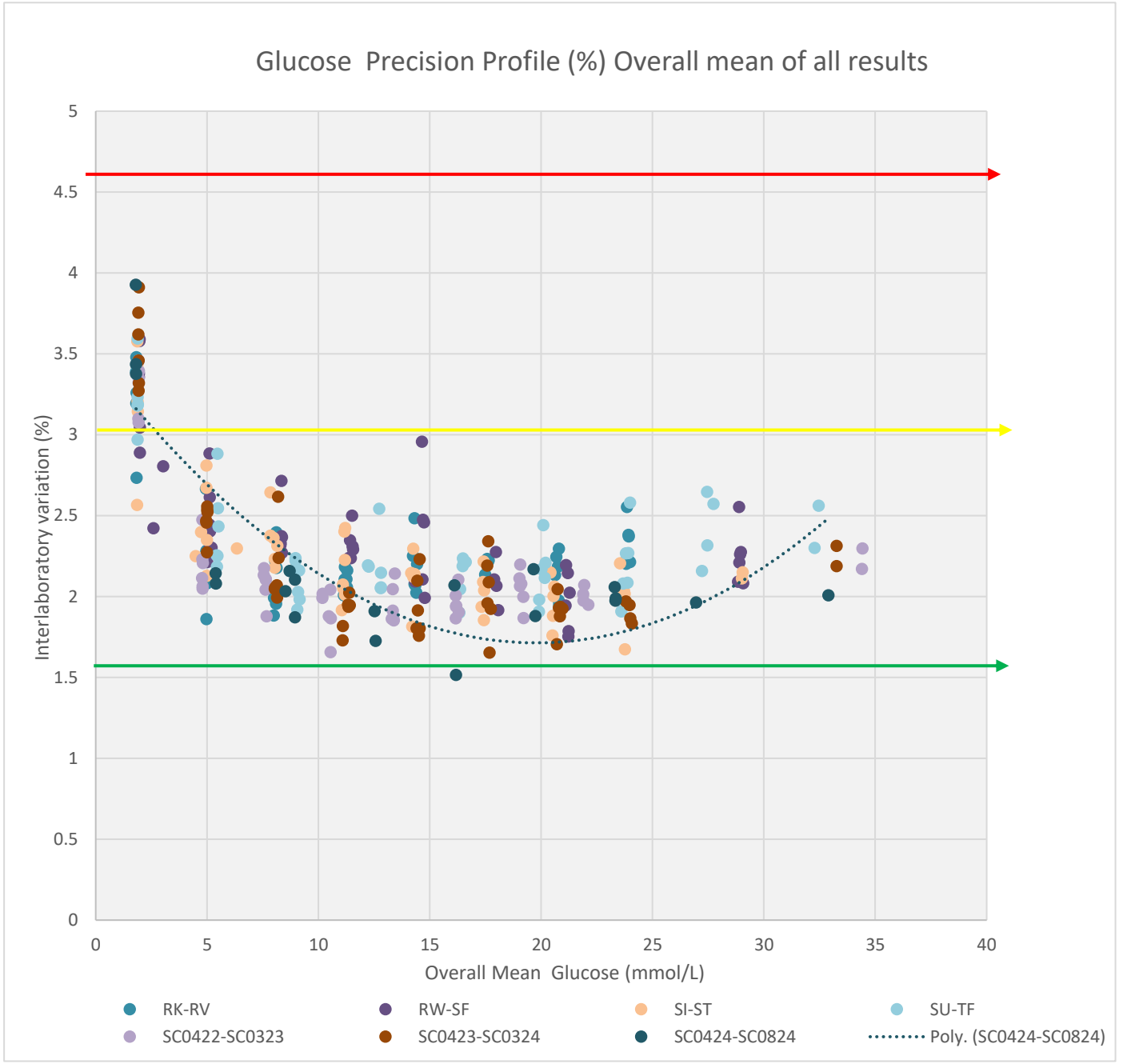
Glucose Precision Profile

Can we use APS based on biological variation? – **YES**

Desirable APS based on biological variation achieved >3.0 mmol/L for all methods.

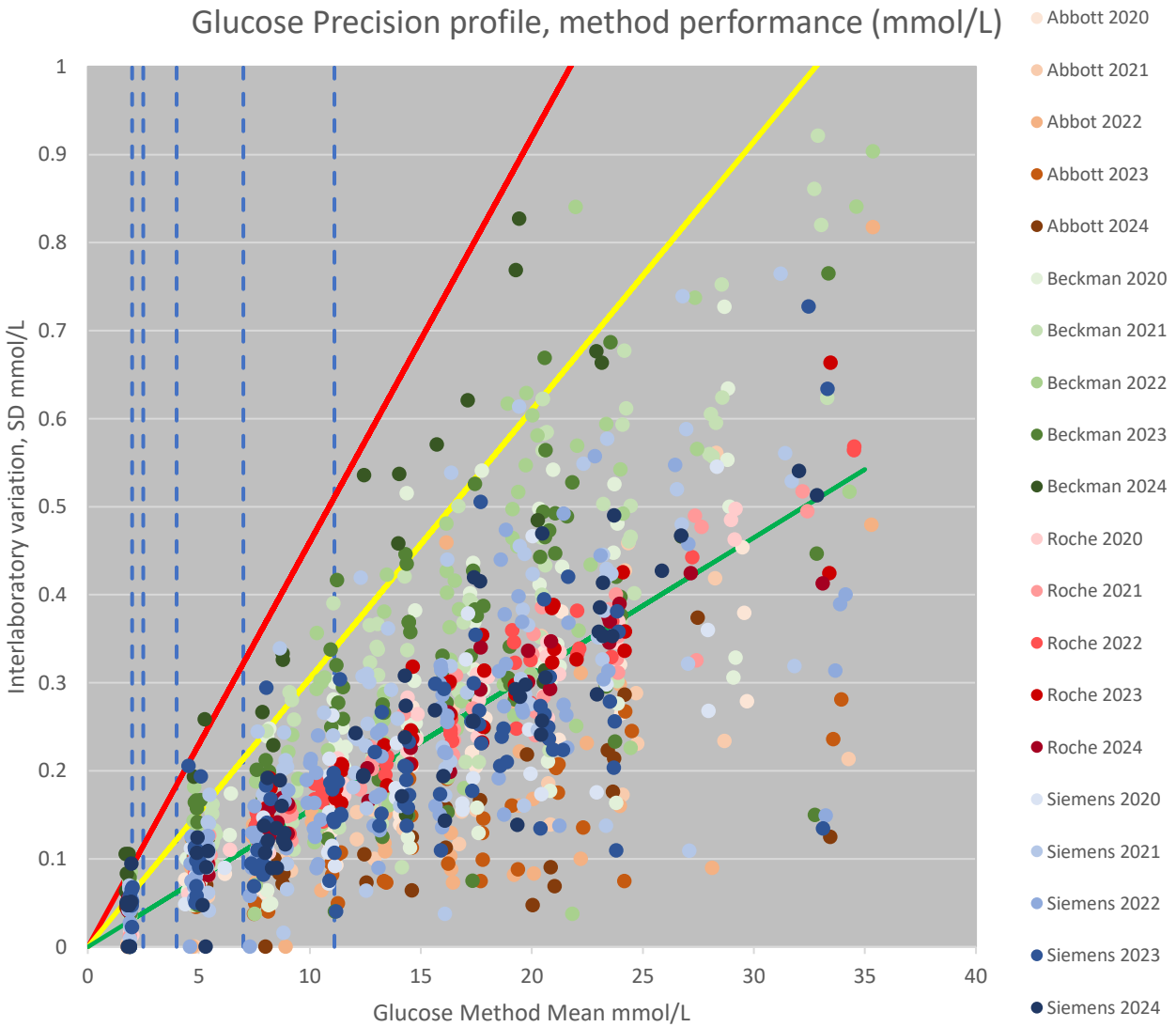
Relationship of performance against concentration polynomial not linear.

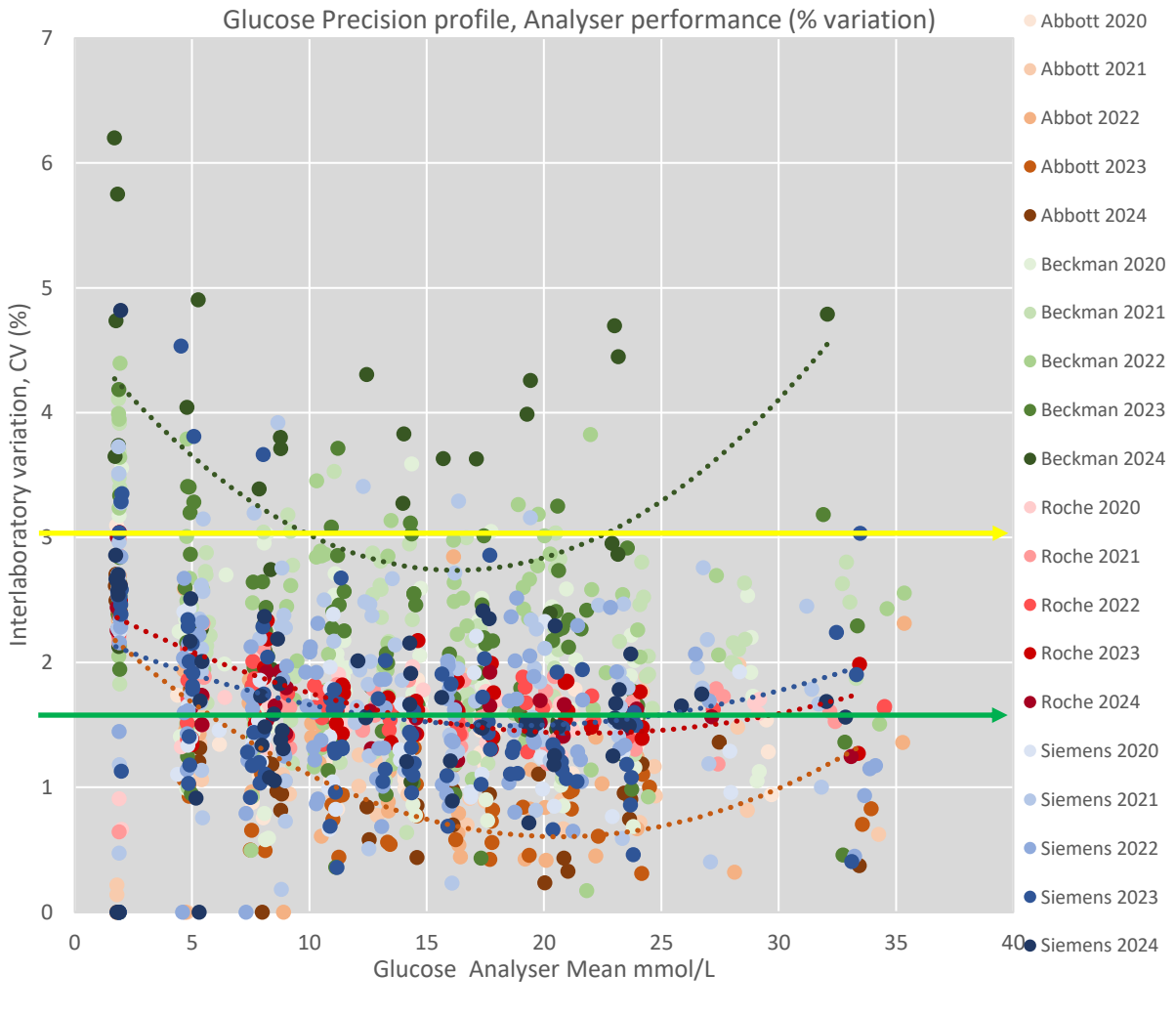
Can we do better at critical decision points for individual analysers?



Glucose intervention thresholds include:

2 mmol/L – hypoglycaemia for neonates with no clinical signs. Most difficult to achieve
2.5mmol/L – hypoglycaemia for neonates with clinical signs
4.0 mmol/L – adult hypoglycaemia
7.0 mmol/L - fasting glucose DM diagnosis



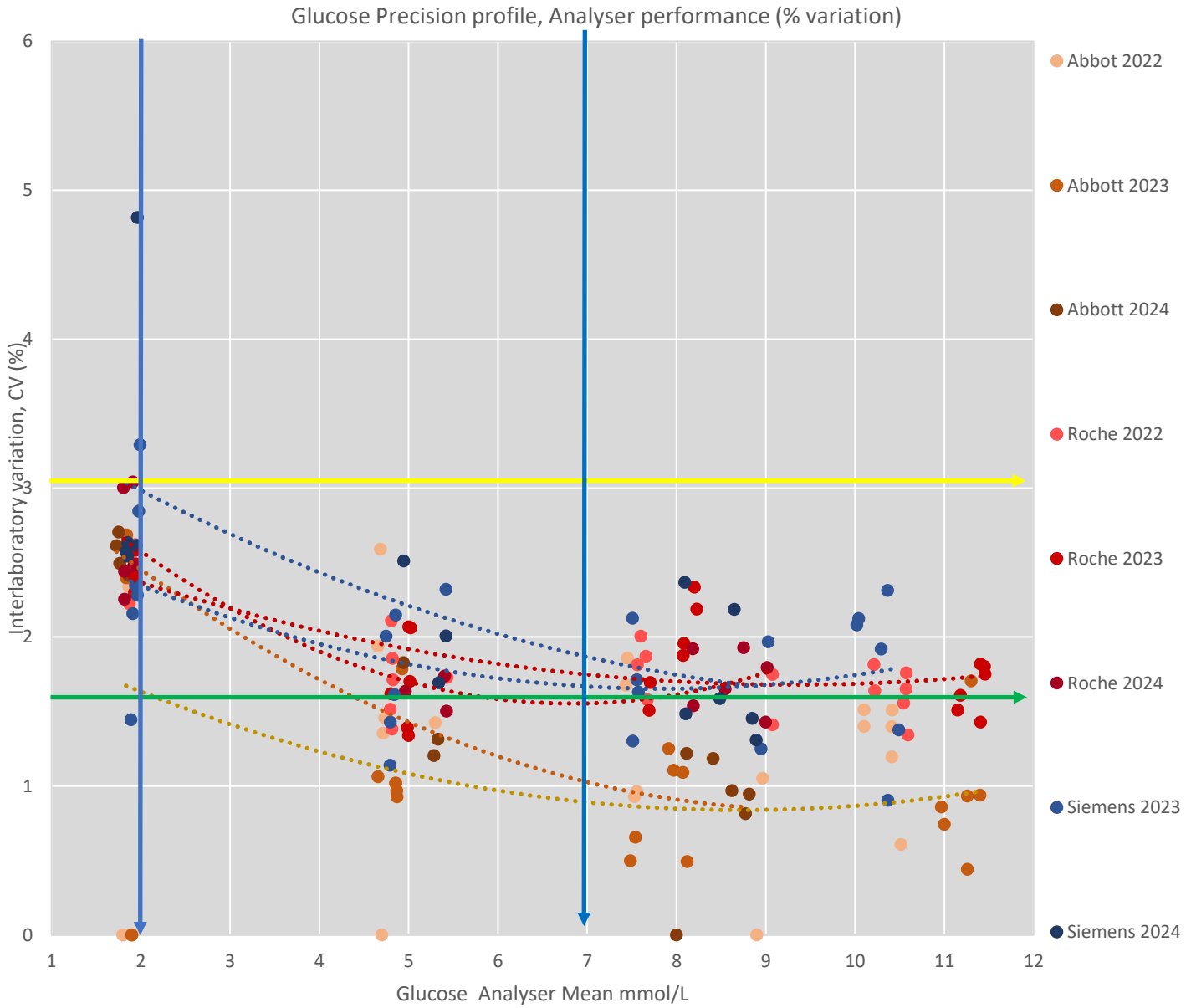


Glucose Precision Profile

Can we do better at critical thresholds?

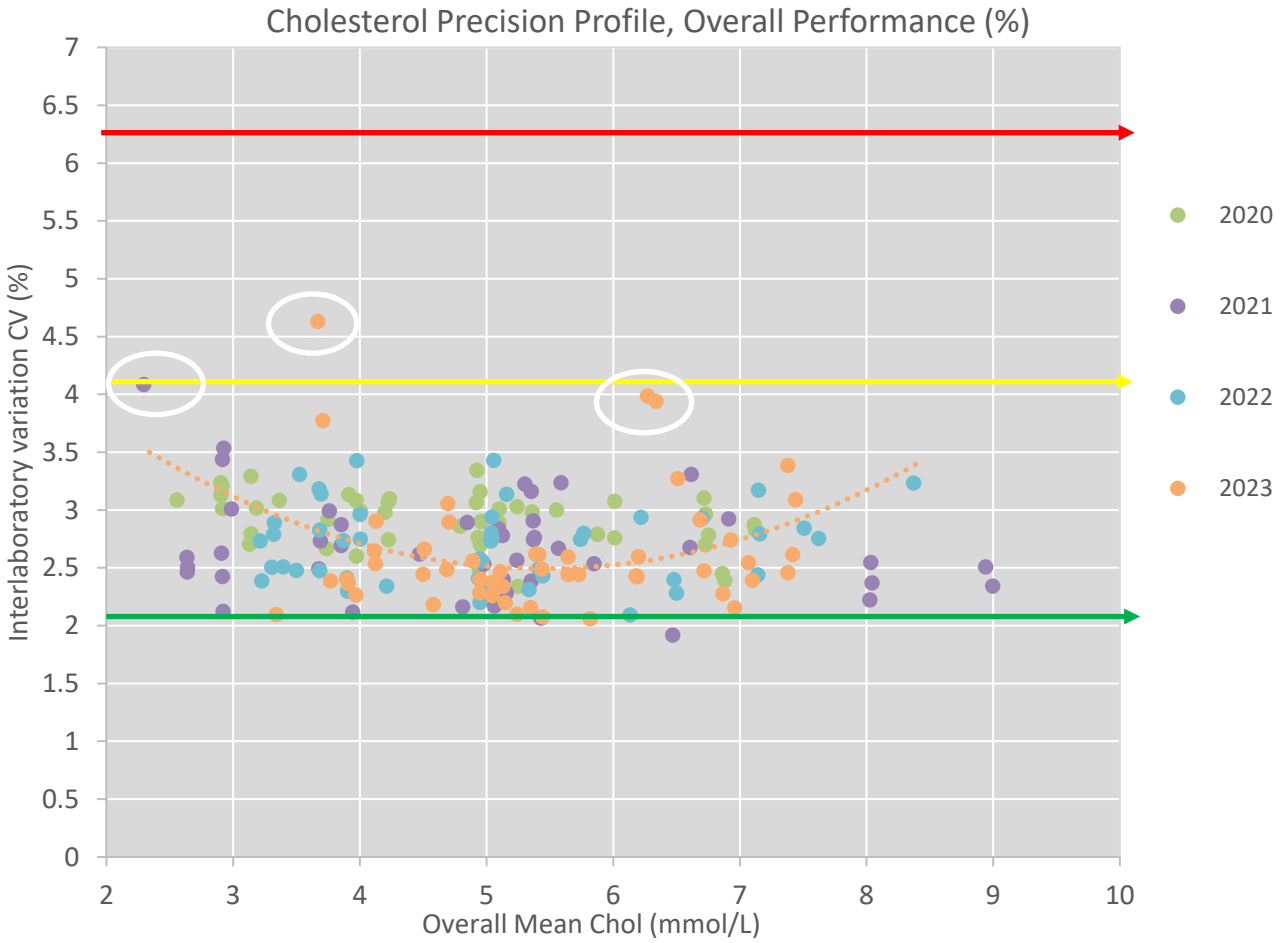
Desirable APS based on biological variation achieved < 2 mmol/L for Abbott, Roche and Siemens methods.

Optimum APS achieved for Abbott method at 2.5, 4.0 and 7.0 mmol/L and close to optimum at 2 mmol/L.

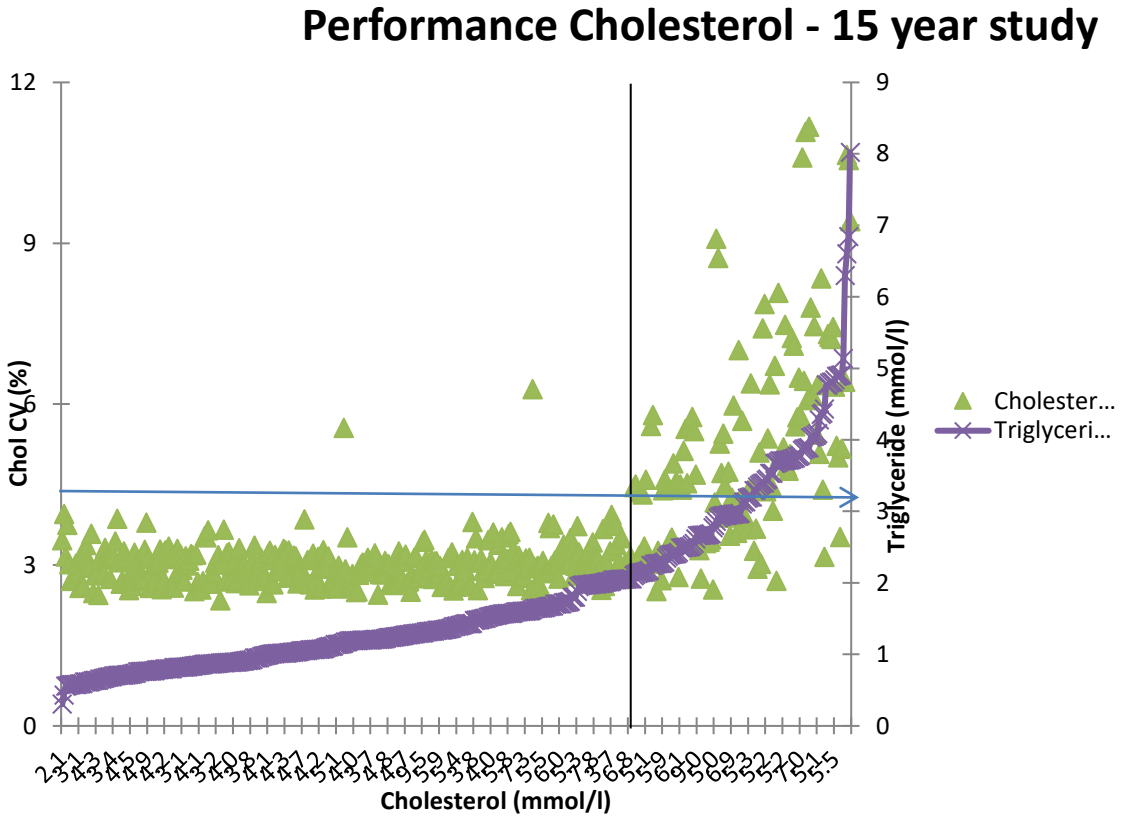


Cholesterol Precision Profile

Can we use APS based on biological variation? – **YES**
Desirable APS based on biological variation achieved at all concentrations.

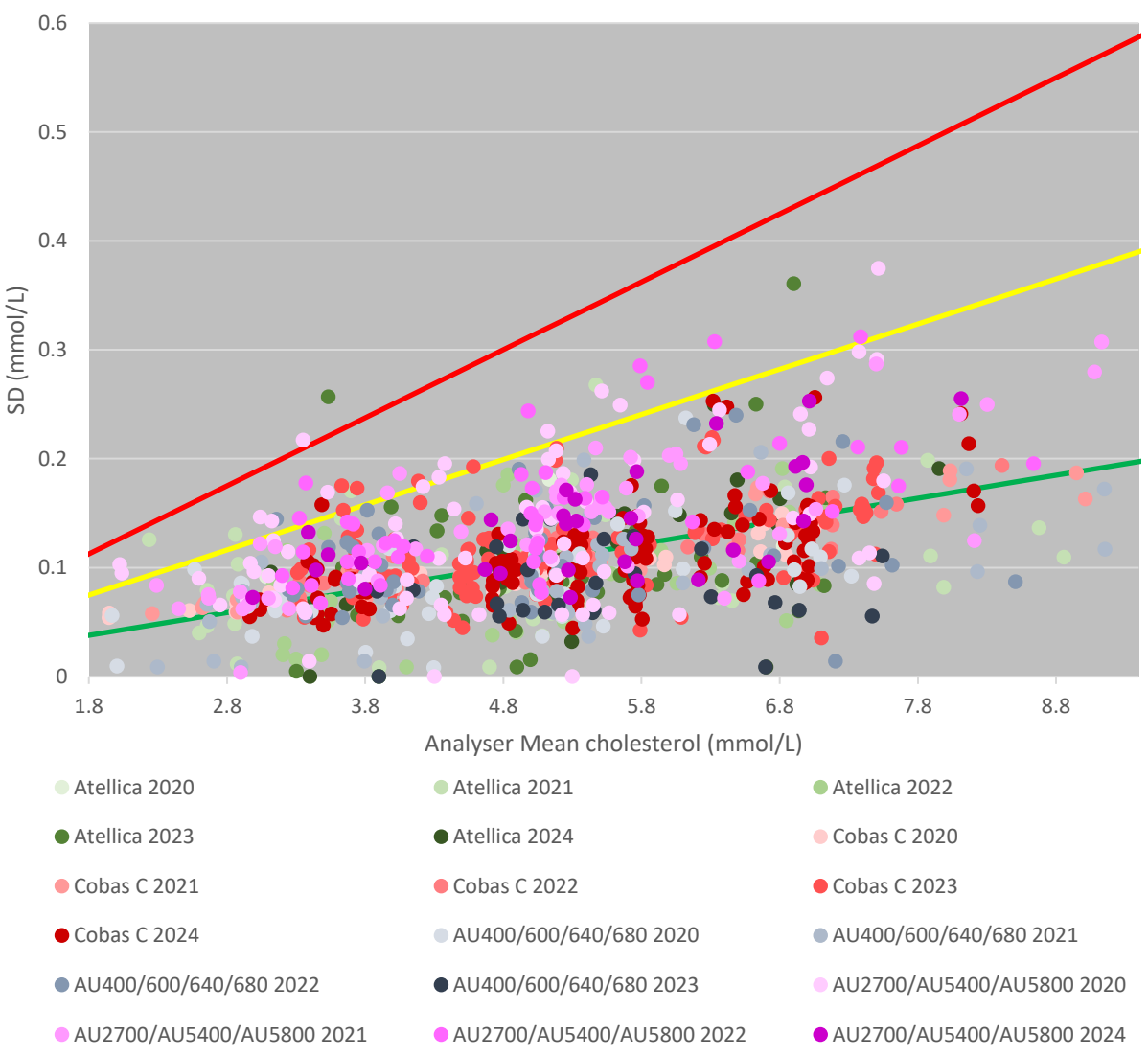


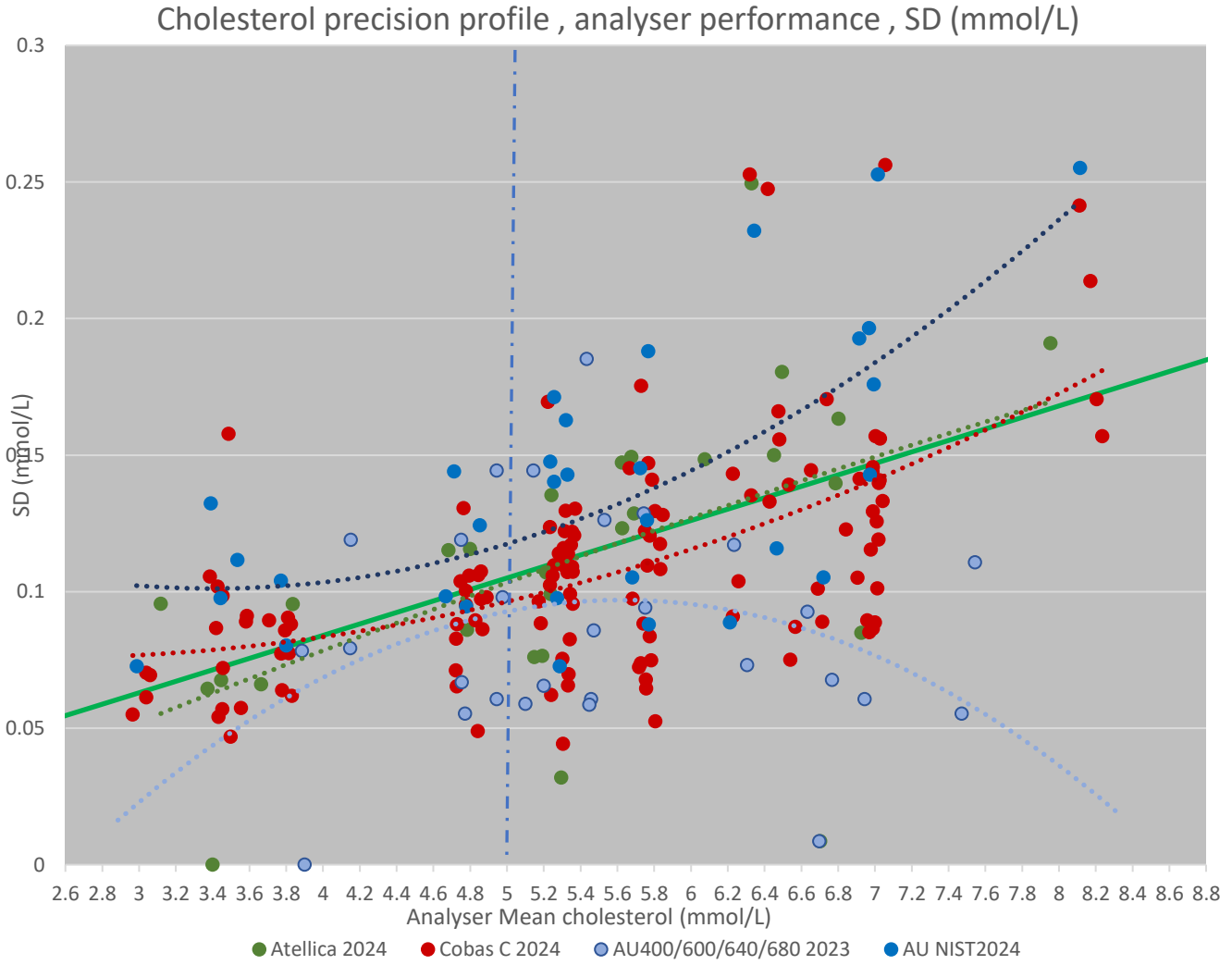
"state of the art "performance compares well with biological APS up to triglyceride concentration of 3 mmol/L.



Cholesterol Precision Profile

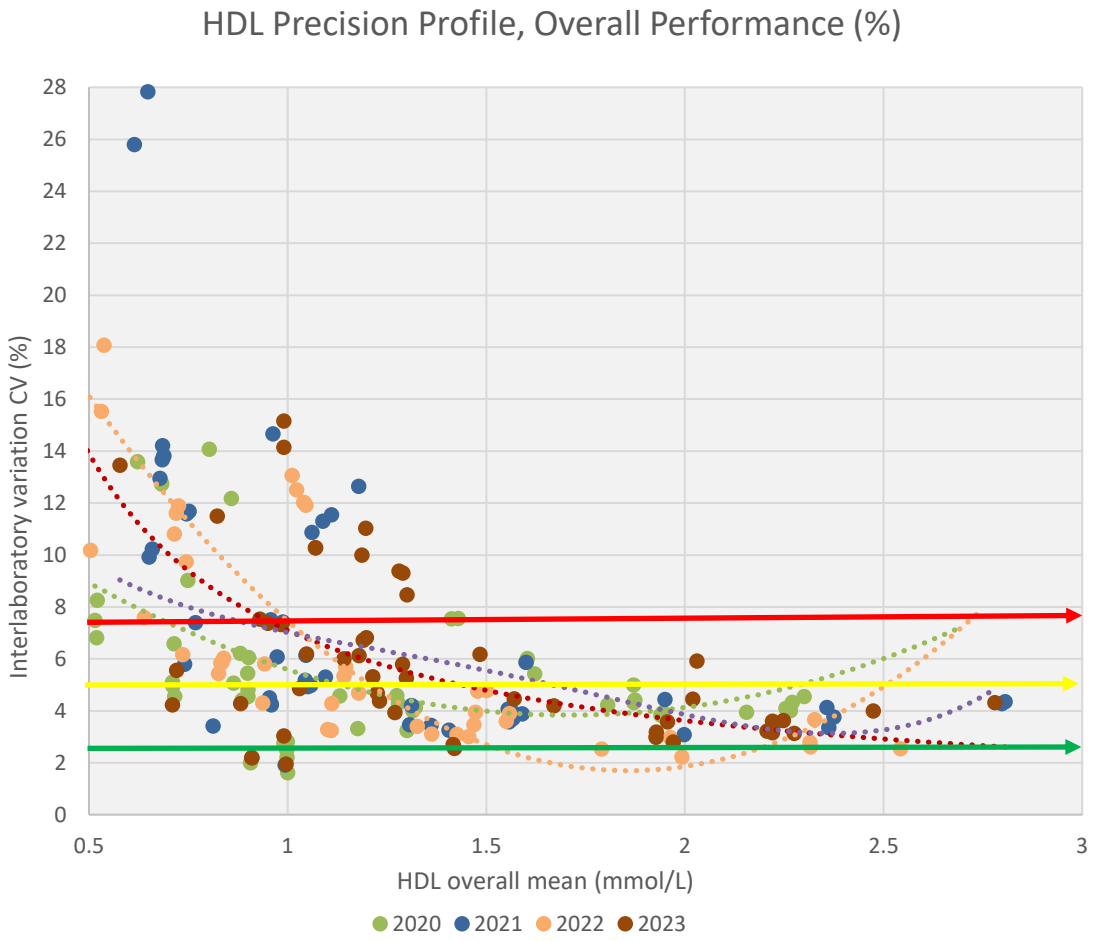
Are there methods that can achieve better? – **YES**
Could we do better at critical decision points?



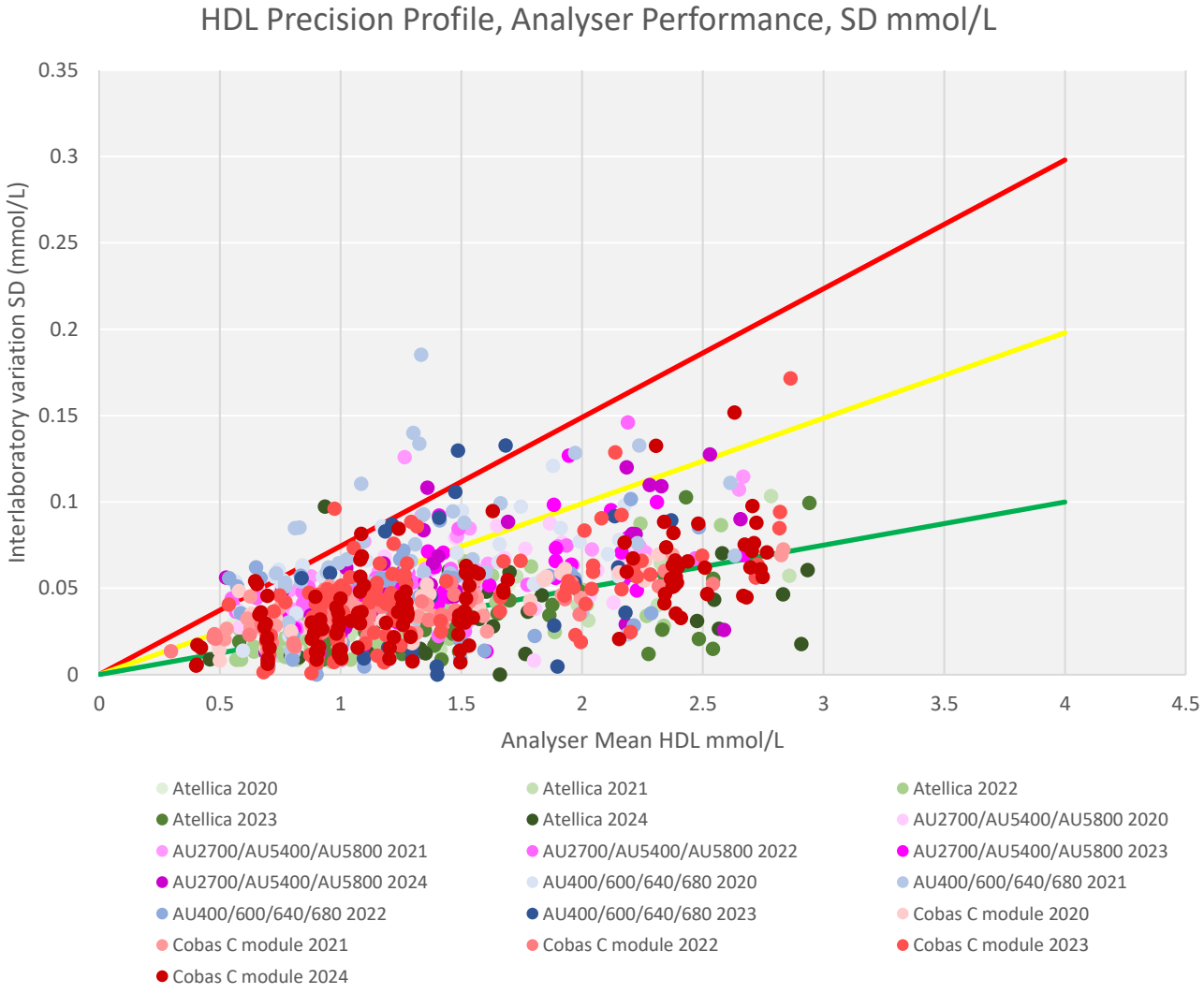


HDL Cholesterol Precision Profile

Can we use APS based on biological variation? – MAYBE
Minimum APS based on biological variation achieved at > 1.0 mmol/L concentration. Data also includes effect of bias.

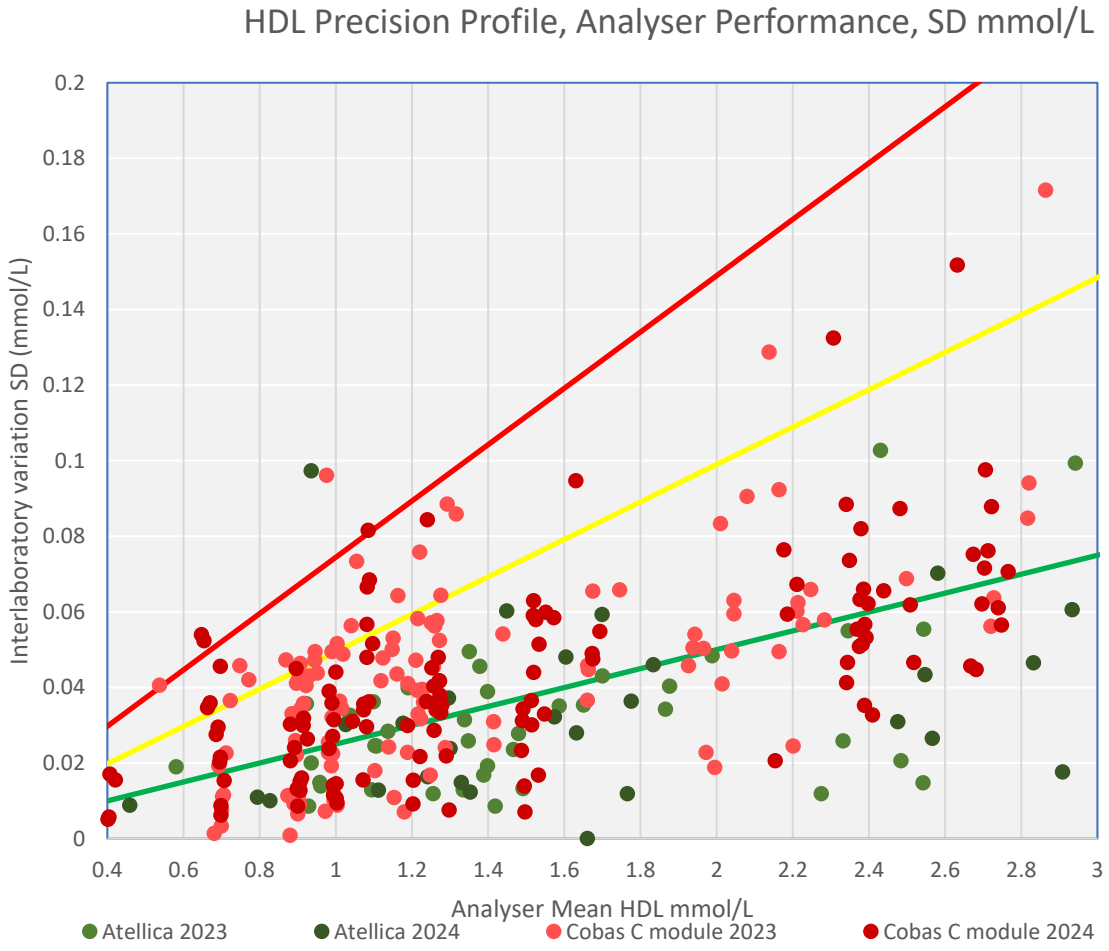


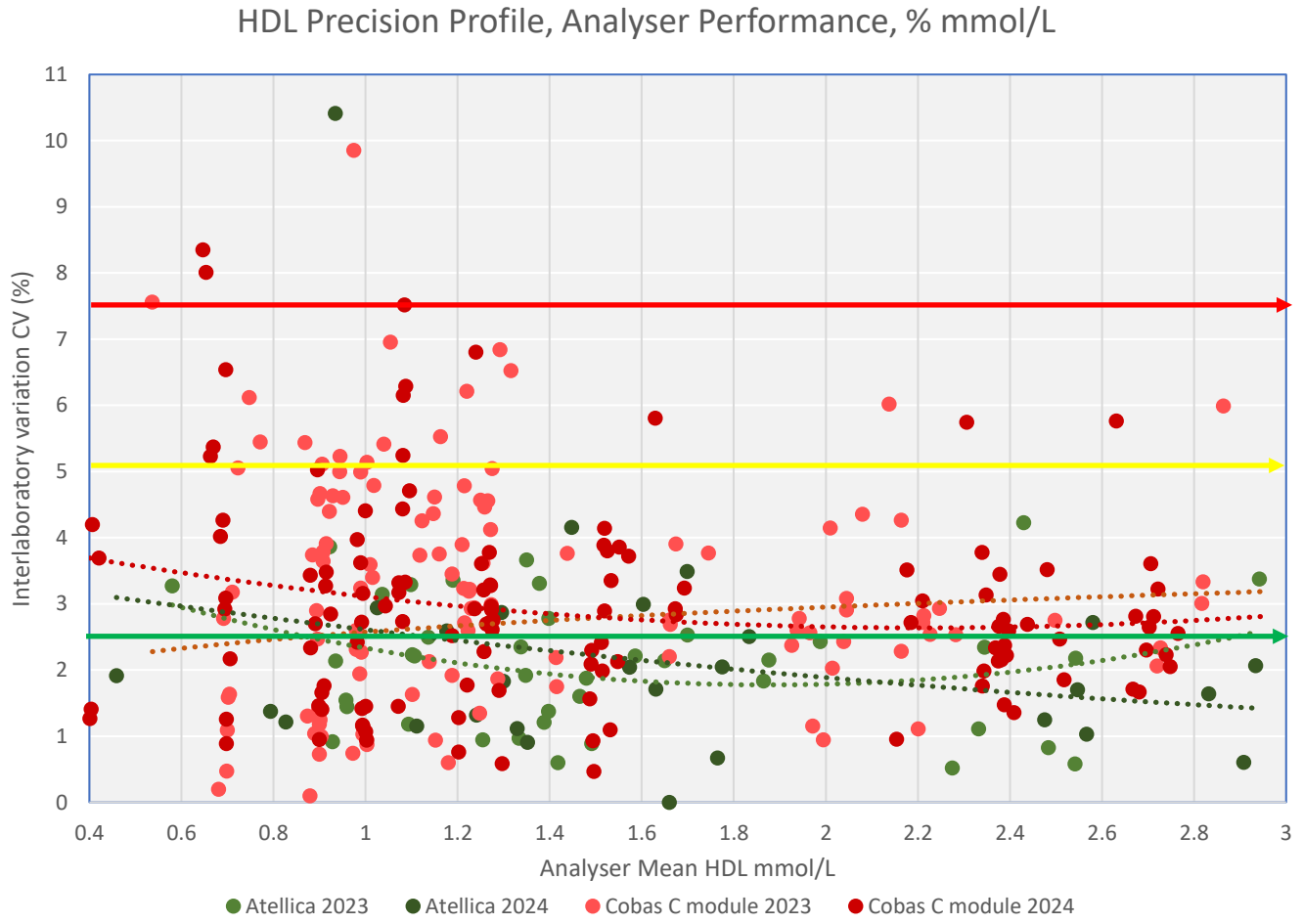
Can we use APS based on best technology?
Most can achieve **Desirable**



Can we use APS based on best technology?
Some methods can achieve **optimum**
However relationship is non linear < 1.4 mmol/L

For peer review assessment – use **desirable**
Assessment of trueness – use **minimum**





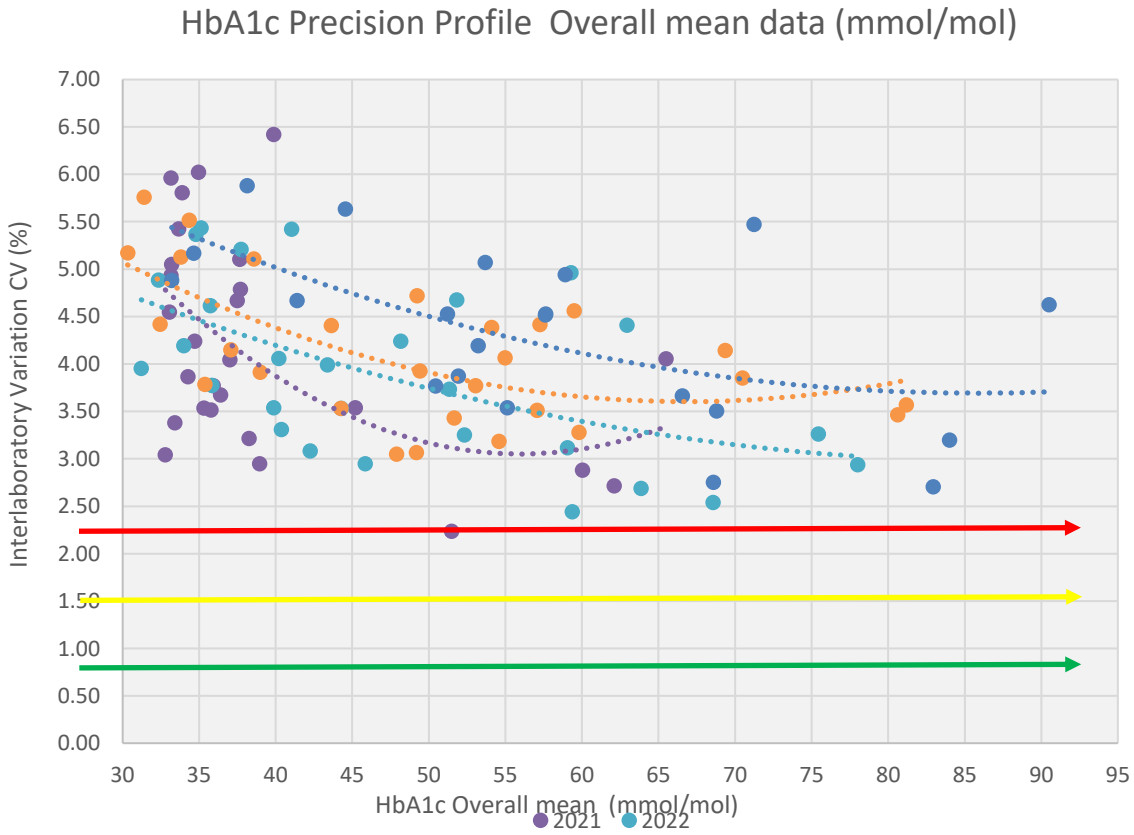
HbA1c Precision Profile

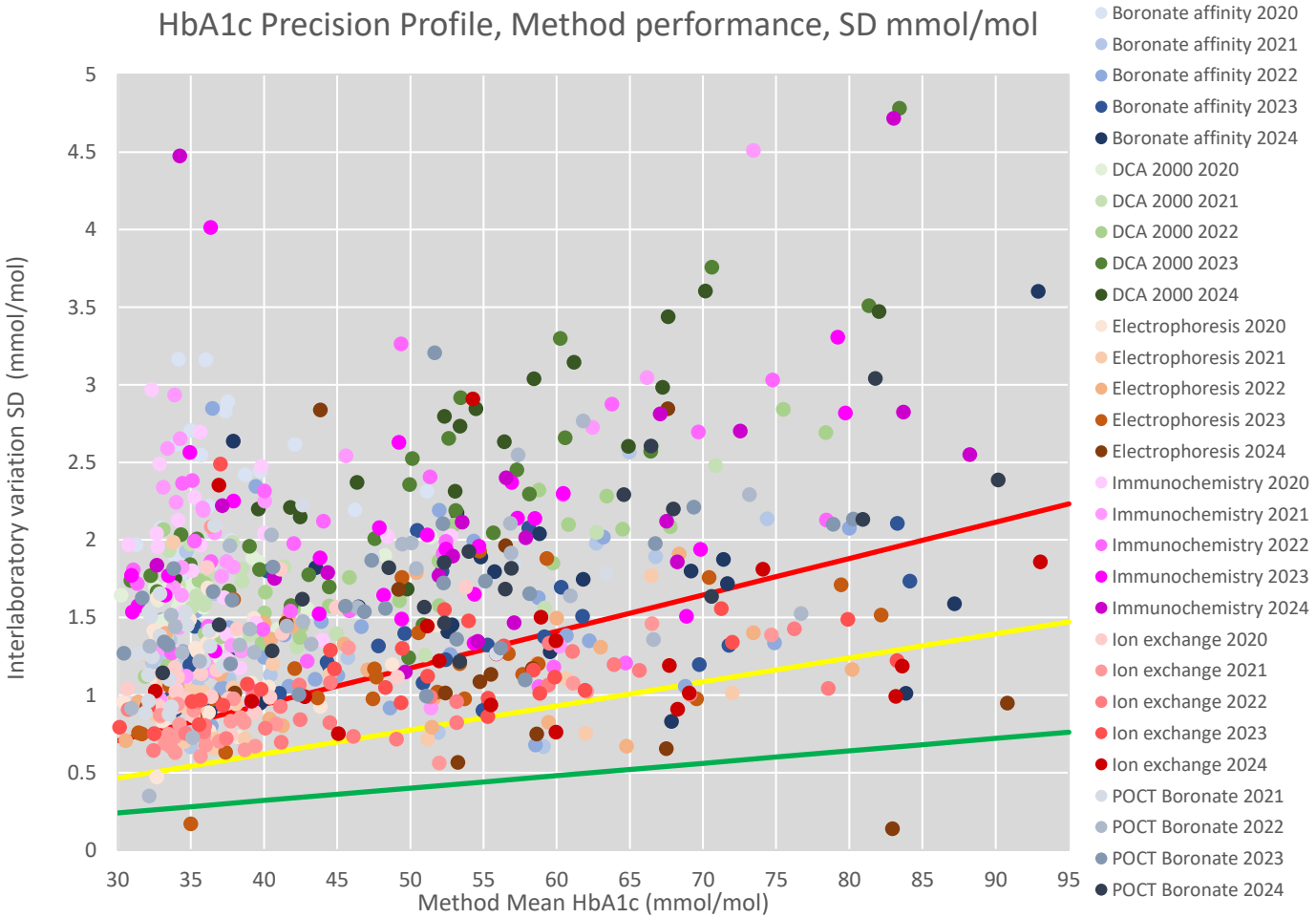
Overall data also includes affects of bias. Data includes laboratory and POCT methods

Can we use universal APS based on biological variation? – NO

Should we use different APS for laboratory and POCT methods? - **YES**

Most laboratory electrophoresis and Ion exchange methods can achieve **Minimum**





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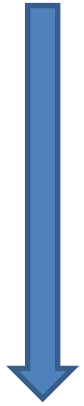
Analytical performance specification of Test related to disease process

- Specification should be designed to provide performance assessment that best meets the needs of the service.
- What laboratory service is being provided?
  - Diagnosis
  - Prognosis
  - Monitoring
  - Screening



Performance specification may be different for the same analyte used in different settings

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Strategy for HbA1c

- Monitoring - Need method that is stable over time. Monitor intralaboratory variation as well as interlaboratory variation.

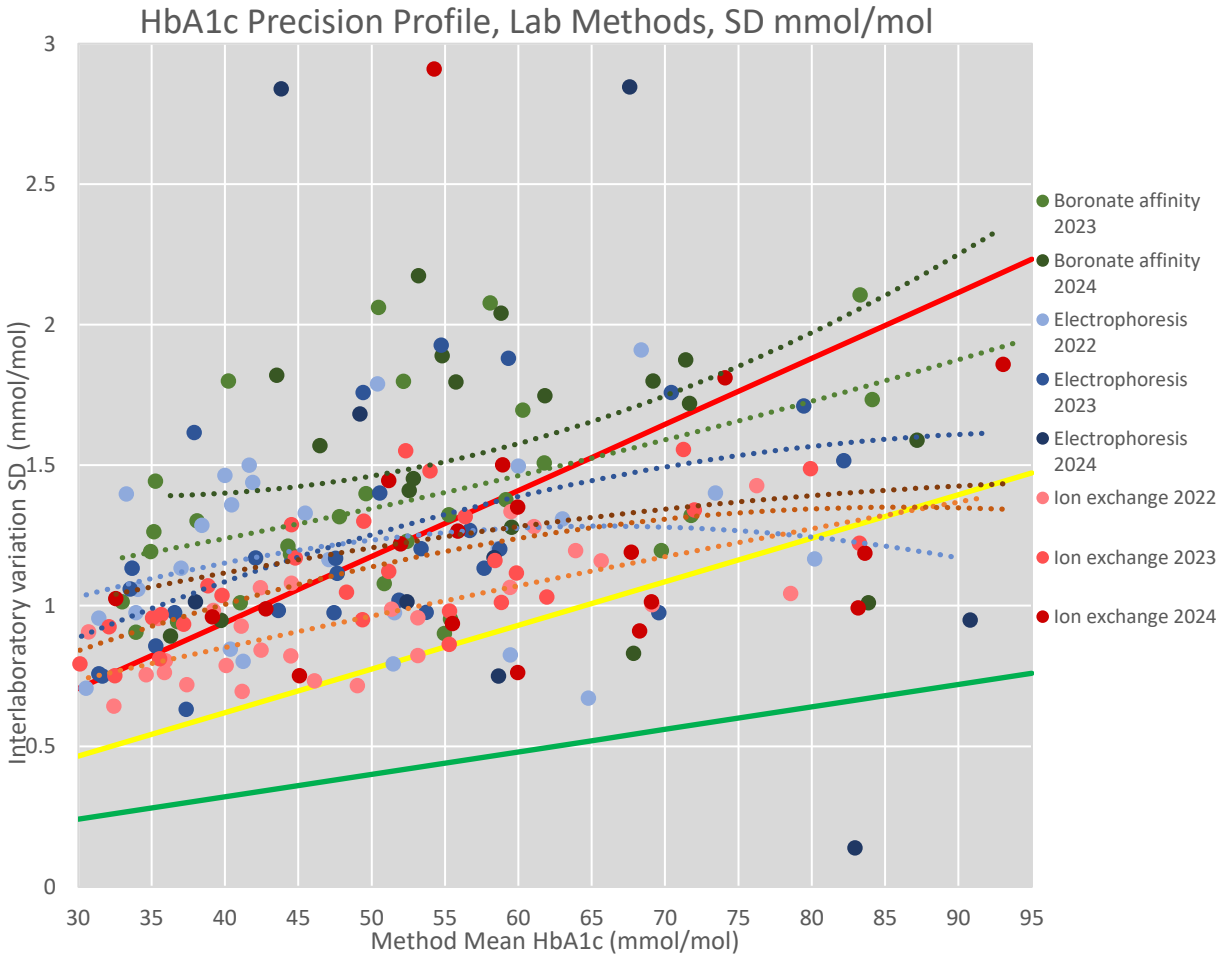
- Diagnosis - Need to ensure that WHO global target goals are valid. Monitor bias of method (lab performance) to standardised procedure (IFCC method).

WHO Recommendation

HbA1c can be used as a diagnostic test for diabetes providing that stringent quality assurance tests are in place and assays are standardised to criteria aligned to the international reference values, and there are no conditions present which preclude its accurate measurement.

An HbA1c of 48 mmol/mol (6.5%) is recommended as the cut point for diagnosing diabetes. A value of less than 48 mmol/mol does not exclude diabetes diagnosed using glucose tests.

Can we use APS based on best lab method?
Laboratory Ion Exchange close to desirable



APS based on Biological variation

	Intervention target	TEa (%)			Weqas TEa (SI units)		Weqas	
Analyte	Conc.	Min	Des	Opt	1 SD	TEa	TEa (%)	Recommendation APS (%)
Na	135 mmol/L	0.9	0.6	0.3	1.066	2.13	1.6 best fit	1.3
K	3.5 mmol/L	7.3	4.9	2.4	0.06	0.12	3.0 best fit	2.4 opt
Ca	2.2 mmol/L	3.4	2.3	1.1	0.05	0.1	4.3 best fit	3.4 min
Creat	90 µmol/L	11.7	7.8	3.9	3.2	6.4	7.1 best fit	7.0 hybrid
Glucose	2.0 / 6.5.2 mmol/L	9.2	6.1	3.1	0.16	0.32		
Urate	360 µmol/L	19	12.6	6.3	20	40	12.6 des	6.3 opt
Cholesterol	5.0 mmol/L	12.5	8.3	4.2	0.21	0.42	8.3 des	
HDL	1.0 mmol/L	14.9	9.9	5.0	0.08	0.16	16.0 des hybrid	
HbA1c	48 mmol/mol	4.7	3.1	1.6	0.35	0.7	7.0	
Troponin	10 µg/L							

Highlighted TEa where minimum Biological goals not achievable

Take home messages

This strategy can be used for all quantitative analytes.

Although Model 2 was achievable for a number of analytes, it was rarely achievable across the full pathological range. The relationship between performance (%) and analyte concentration was rarely linear, and a hybrid (mixed) model is proposed in this situation.

APS should be designed to provide performance assessment that best meets the needs of the service, whether used for screening, monitoring or diagnosis. Where clinical utility of the test includes 2 or more then the more stringent model is selected.

More stringent APS models should be considered at concentrations for critical intervention.

For their use in EQA, the choice of target value should be considered. Programmes that assess trueness need to take into account method bias and should select a less stringent APS than a programme that uses peer group assessment.

Choice of matrix needs to be considered including challenging samples.

Programme aims – regulatory / assessment of poor performance, quality improvement or educational role.