

Noklus PATient Median (NOPAM) via SKML

How Patient Based Real Time QC can be part of
integral analytical quality management,
alongside classical EQA

Disclosure belangen Marcel van Borren

Geen (potentiële) belangenverstrengeling	Marcel van Borren
Voor bijeenkomst mogelijk relevante relaties	Geen
Sponsoring of onderzoeksgeld	Geen
Honorarium of andere (financiële) vergoeding	Geen
Aandeelhouder	Geen
Andere relatie, namelijk ...	Geen



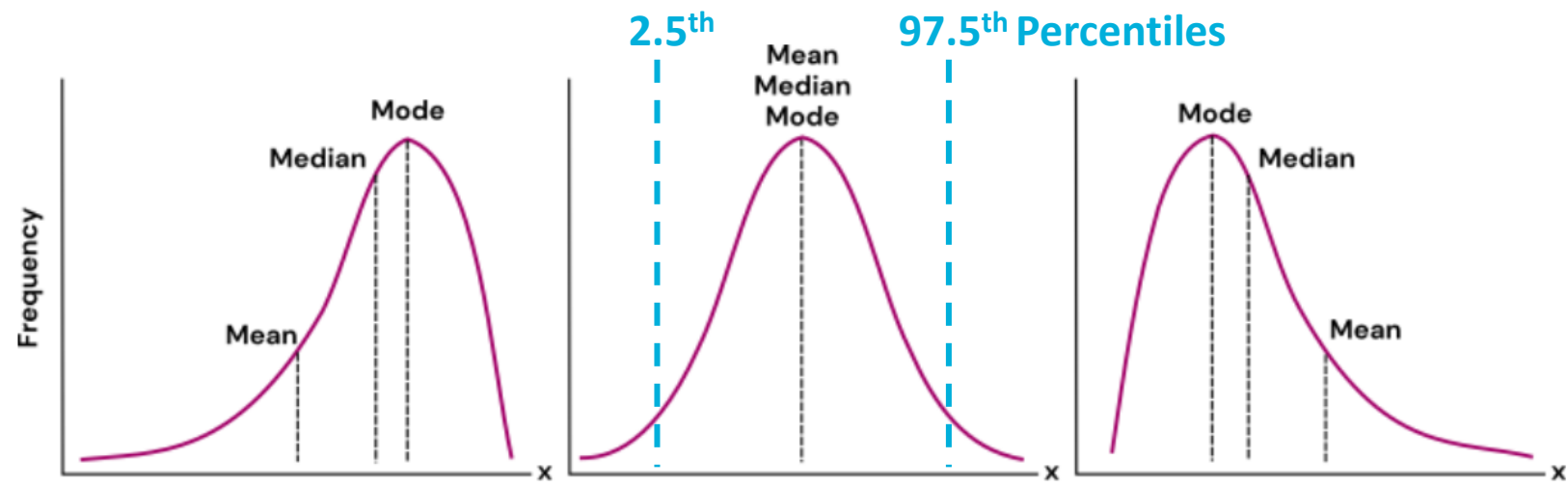
Stichting Kwaliteitsbewaking
Medische Laboratoriumdiagnostiek

Sectie Algemene Chemie Gebruikersdag 2025



The concept for the program:

Patient medians and flagging rates are normally stable over time, and any change is usually due to pre-analytical or analytical instability or error.



EMPOWER (2016): 20 assays

- The Percentiler/Program was a part of a project called *The Empower project* where patient medians and frozen single-donation samples were analyzed and compared

The Empower project – a new way of assessing and monitoring test comparability and stability, De Grande, L.A., Goossens, K., Van Uytfanghe, K., Stockl, D., Thienpont, L.M., Clin Chem Lab Med 2015; 53(8):1197-1204)

EMPOWER IVD GLOBE

General Flagger Report

02/05/2017

Project status (May 2017)

Number of instruments for the clinical chemistry analytes

Peer Group	Instruments per peer group	
	Percentiler	Flagger
Abbott Architect	23	7
Beckman AU	12	11
Beckman DxC	6	2
Ortho Vitros	22	3
Roche Cobas	162	89
Roche Integra	3	3
Roche Modular	8	6
Siemens Advia	16	4
Siemens Dimension	10	3
Total	262	128

Number of instruments for FT4 and TSH

Peer Group	Instruments per peer group	
	Percentiler	Flagger
Abbott Architect	23	7
Beckman Dxl	11	10
Roche Cobas ElecSys	78	32
Ortho Vitros	11	2
Siemens Advia Centaur	25	14
Siemens Dimension	7	3
Total	155	38

Geographical distribution of the Percentiler and Flagger participants worldwide:



The Percentiler

Quality Samples Demo Labs Devices Analytes Units Mails

Lab: DEMOLAB Device model: All device models Device: All devices

Start date: Stop date: Include weekend data: No

Range: 3M 6M 1Y All Moving median: 5 8 16 Filter

ALT AST
ALB ALP
CRP Ca
CI CRE
GGT GLU
PHOS LDH
Mg K
Na UREA
UAC BIL
CHOL PROT

ALT - GPT

	Value	Bias (%)	Robust CV(%)
Range: all			
Your	19.00	-3.3	7.8
Peer/All	19.65	-6.4	12.4
Target	21.00	9.5	NA
Range: period			
Your	19.00	-3.3	7.8
Peer/All	19.65	-6.4	12.4
Target	21.00	9.5	NA

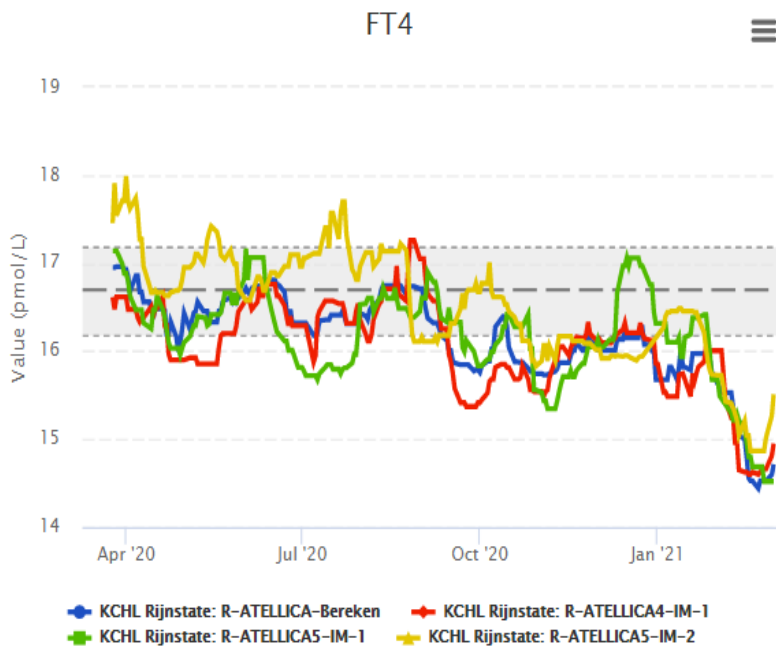
NOLKUS (2019): 33 assays

<https://thepercentiler.be/Login>

<https://theflagger.be/Login;jsessionid=72FB3EB9BE4A92080FD82636E2B651A8>

NOKLUS The Percentiler

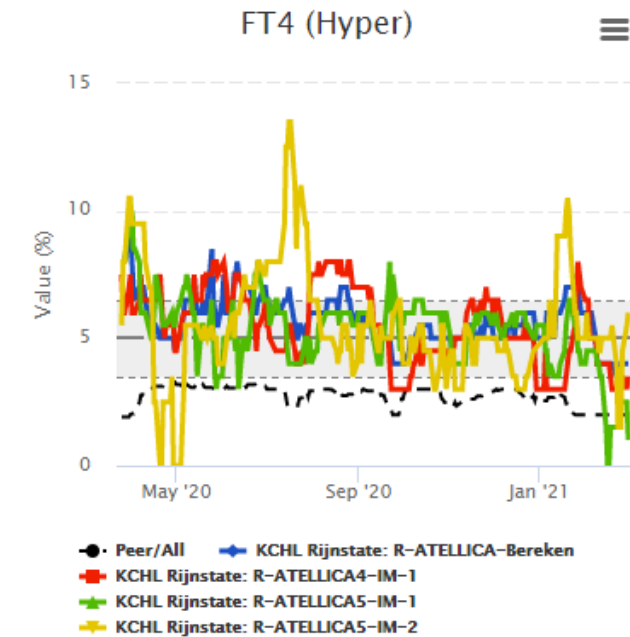
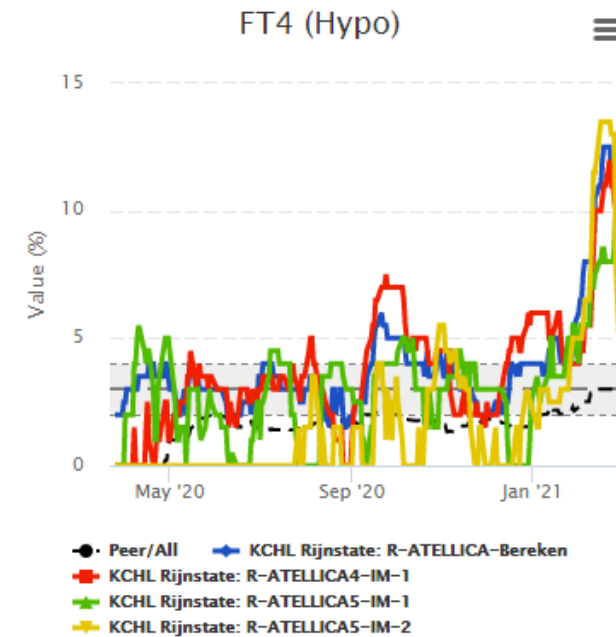
Login



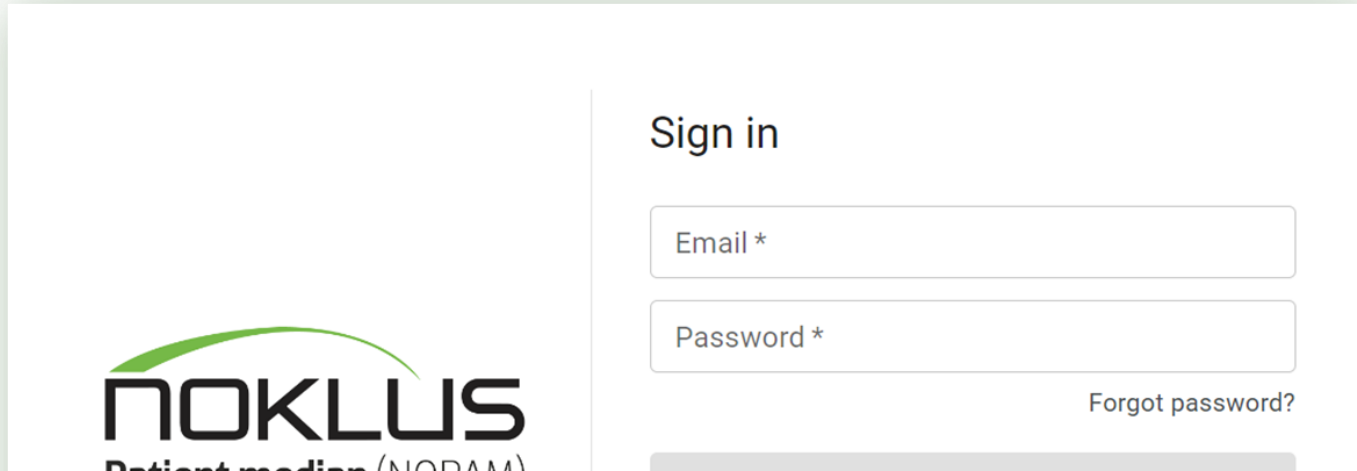
	Value	Bias (%)	Robust CV(%)
Range: all			
Your	16.69	0.0	6.3
Target	15.00	3.3	NA
Range: period			
Your	16.22	0.0	6.3
Target	15.00	3.3	NA

NOKLUS The Flagger

Login



NOPAM (2024): 45 assays



Percentiler & flagger => 1 programma

ALP	Glucose	Na	TSH	Antitrombin (research only)
ALT	HbA1c	K	FT4	APTT (research only)
AST	Albumin	Cl	Cortisol	D-dimer (research only)
GGT	Protein (total)	Ca	PTH	Fibrinogen (research only)
LDH	CRP	Mg	PSA	Protein C
LDH (reverse)	IgA	Phosphate		Protein S (research only)
Bilirubin (total)	IgG	Iron	Hb	INR(research only)
Amylase	IgM	Ferritin	RBC	
BUN	Cholesterol	active vitamin B12	WBC	
Creatinine	HDL-cholesterol	Vitamin B12	PLT	
Urea	LDL-cholesterol	Folate	MCV	
Uric acid	Triglycerides	25-Hydroxyvitamin D	MPV	

NOPAM vs Percentiler & Flagger

		NOPAM	Percentiler Flagger
Data	Country	Ja	-
	Patient population	Ja	-
	Sample material /condition	Ja	-
	Manufacturer	Ja	Ja
	Instrument model /type	Ja	Ja
	Reagent lot-number	Ja	-

Information
about
the participating
laboratory registered

Data:

Country

Patient population

Sample material

Fasting / all results

Method

Reagent lot-number

Manufacturer

Instrument model

Instrument type

Locally used factors

Daily results sent to NOPAM

Laboratory
informationsystem



NOKLUS
Patient median (NOPAM)

- instrument-specific medians (preferably outpatients)
- instrument-specific percentage of patient <LLN
- instrument-specific percentage of patient >ULN
- total number of patient results
- Reagent lot-numbers (or manually)

A daily result report example

Lab.	Execution day	Instrument	Requester ward	Test	Unit	Median	Number	% < REF	% > REF	Assay lot id
Laboratory ID	01.07.2023	ARC-T3	External	S_ALAT	U/L	25.46	43	0.00 %	33.33 %	50159UD00
Laboratory ID	01.07.2023	ARC-T3	External	S_ALB	g/L	29.81	39	100.00 %	0.00 %	46167UD00
Laboratory ID	01.07.2023	ARC-T3	External	S_ALP	U/L	77.06	13	0.00 %	33.33 %	53995UN22
Laboratory ID	01.07.2023	ARC-T3	External	S_ASAT	U/L	91.99	41	0.00 %	100.00 %	49192UD00
Laboratory ID	01.07.2023	ARC-T3	External	S_BIL	umol/L	7.87	21	0.00 %	0.00 %	62807UQ09
Laboratory ID	01.07.2023	ARC-T3	External	S_CA	mmol/L	2.33	45	0.00 %	0.00 %	35579UN22
Laboratory ID	01.07.2023	ARC-T3	External	S_CRP	mg/L	5.56	34	0.00 %	0.00 %	30197Y600
Laboratory ID	01.07.2023	ARC-T3	External	S_GGT	U/L	47.66	27	0.00 %	33.33 %	47518UD00

Sample type

Instrument model/type/manufacturer etc

factoren

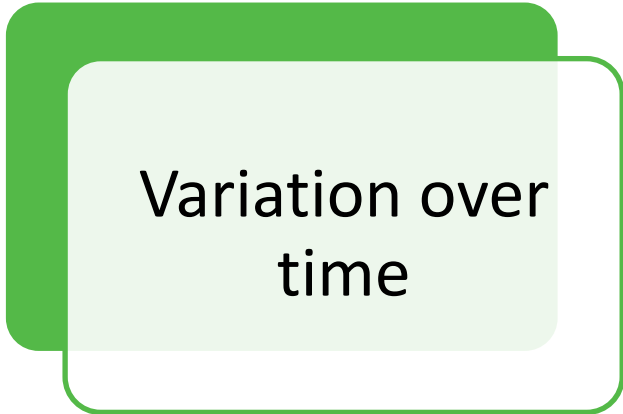
Participants get analyte specific warnings



Alerts per instrument

1. Median_day > threshold X for 3 consecutive days
2. Median_Month > X% Median_Year.
3. Median_Month > X% Median_peer group.
4. Results < X% LLN & Results > X% ULN (% outside ref range)

How can the results be used?



Variation over
time

Past bij iQC?

Betreft meerdere modules?

Results

Statistics

- Monthly overview of laboratory instruments
- Differences between instrument groups
- Daily median values of instruments
- Group overview - variation over time

1. Monthly overview of laboratory instruments

2. Differences between instrument groups

3. Daily median values of instruments

4. Group overview – variation over time

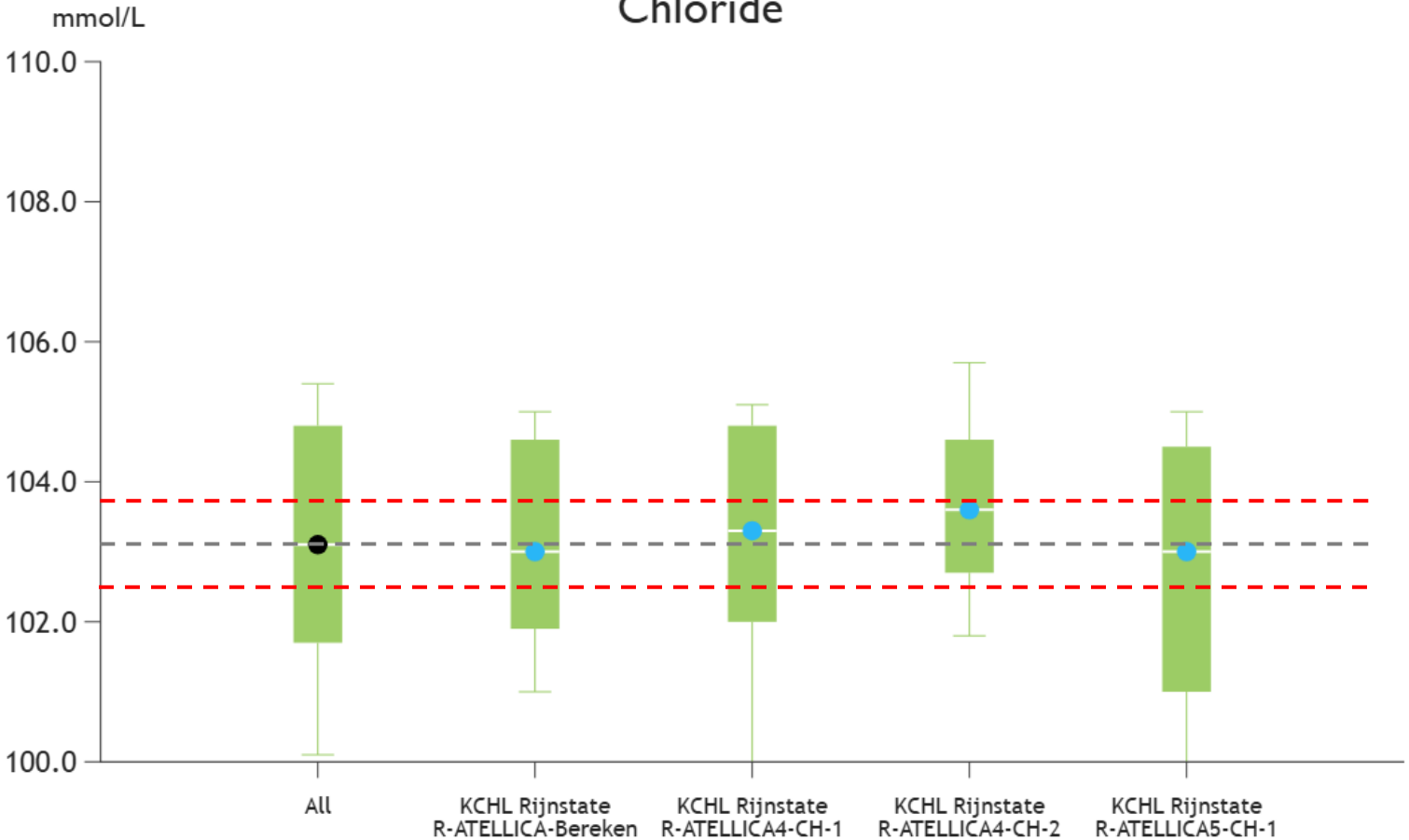
Monthly overview of laboratory instruments

Analyte* Chloride
Year and month* 2025/10
 Include weekends

FILTER

mmol/L

Chloride



$$\text{Bias}_{\max} = 0,375 * \sqrt{CV_i^2 + CV_g^2} = 0,6\%$$

+Bias_{max}
-Bias_{max}



Specific alert

Onderlinge apparatenvergelijk

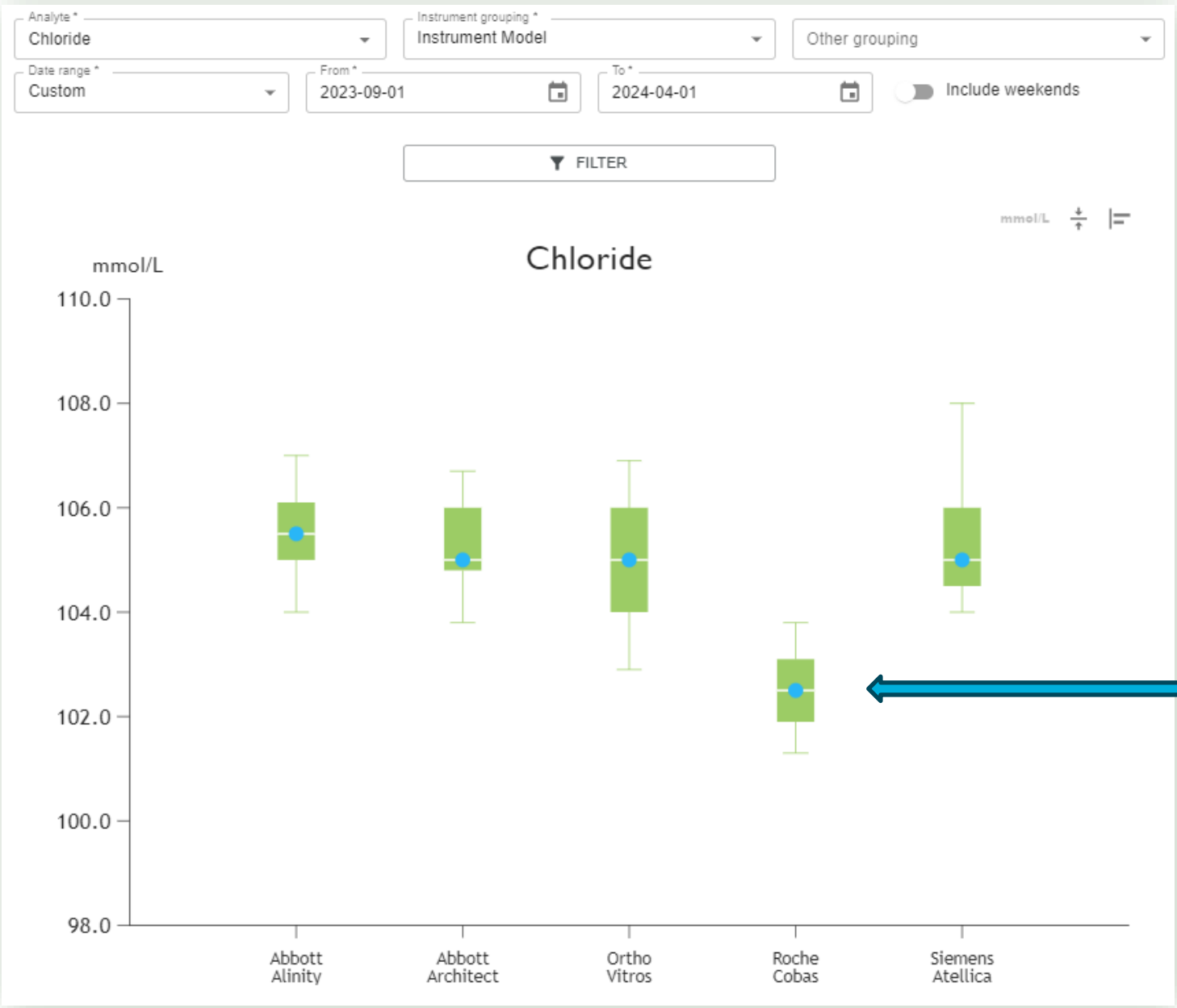
Monthly overview of laboratory instruments



Statistics

Filter	Instrument code	Number of results ⁱ	Median ⁱ
<input type="checkbox"/>	All	56	103.1
<input type="checkbox"/>	KCHL Rijnstate - R-ATELLICA-Bereken	16	103.0
<input type="checkbox"/>	KCHL Rijnstate - R-ATELLICA4-CH-1	13	103.3
<input type="checkbox"/>	KCHL Rijnstate - R-ATELLICA4-CH-2	12	103.6
<input type="checkbox"/>	KCHL Rijnstate - R-ATELLICA5-CH-1	15	103.0

Differences between instrument groups



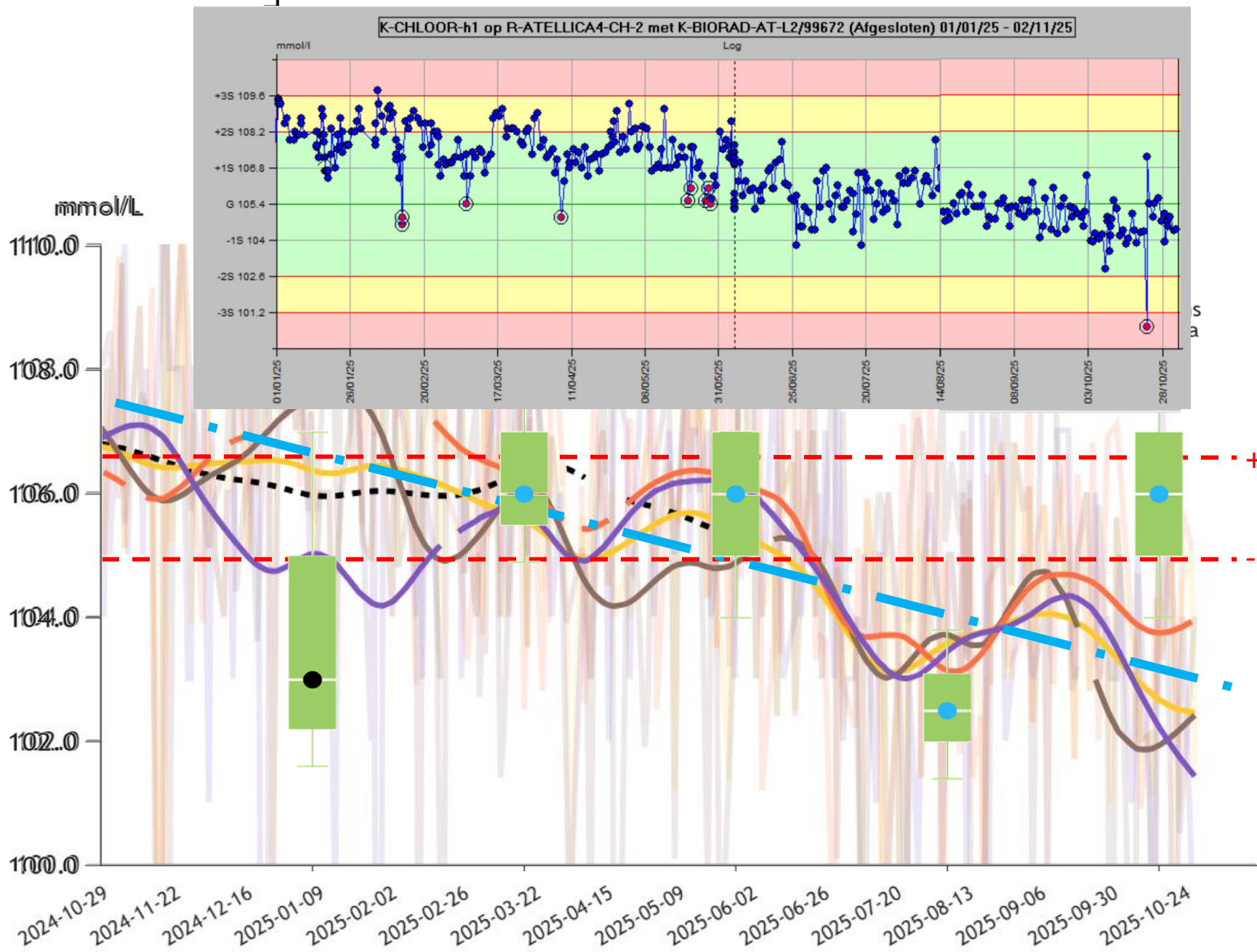
Here we see that the negative bias as found in SKML EQA is confirmed in patient samples



Differences between instrument groups – corresponding data

Instrument group name	Number of results	Median	Min - Max	10th - 90th percentile	Lower quartile	Upper quartile
Abbott - Alinity	2894	105.5	91.3 - 118	104 - 107	105	106.1
Abbott - Architect	5229	105	89 - 113	103.8 - 106.7	104.8	106
Ortho - Vitros	915	105	96.4 - 111.3	102.9 - 106.9	104	106
Roche - Cobas	32744	102.5	5 - 123.9	101.3 - 103.8	101.9	103.1
Siemens - Atellica	1777	105	84 - 125.4	104 - 108	104.5	106

Daily median values of instruments

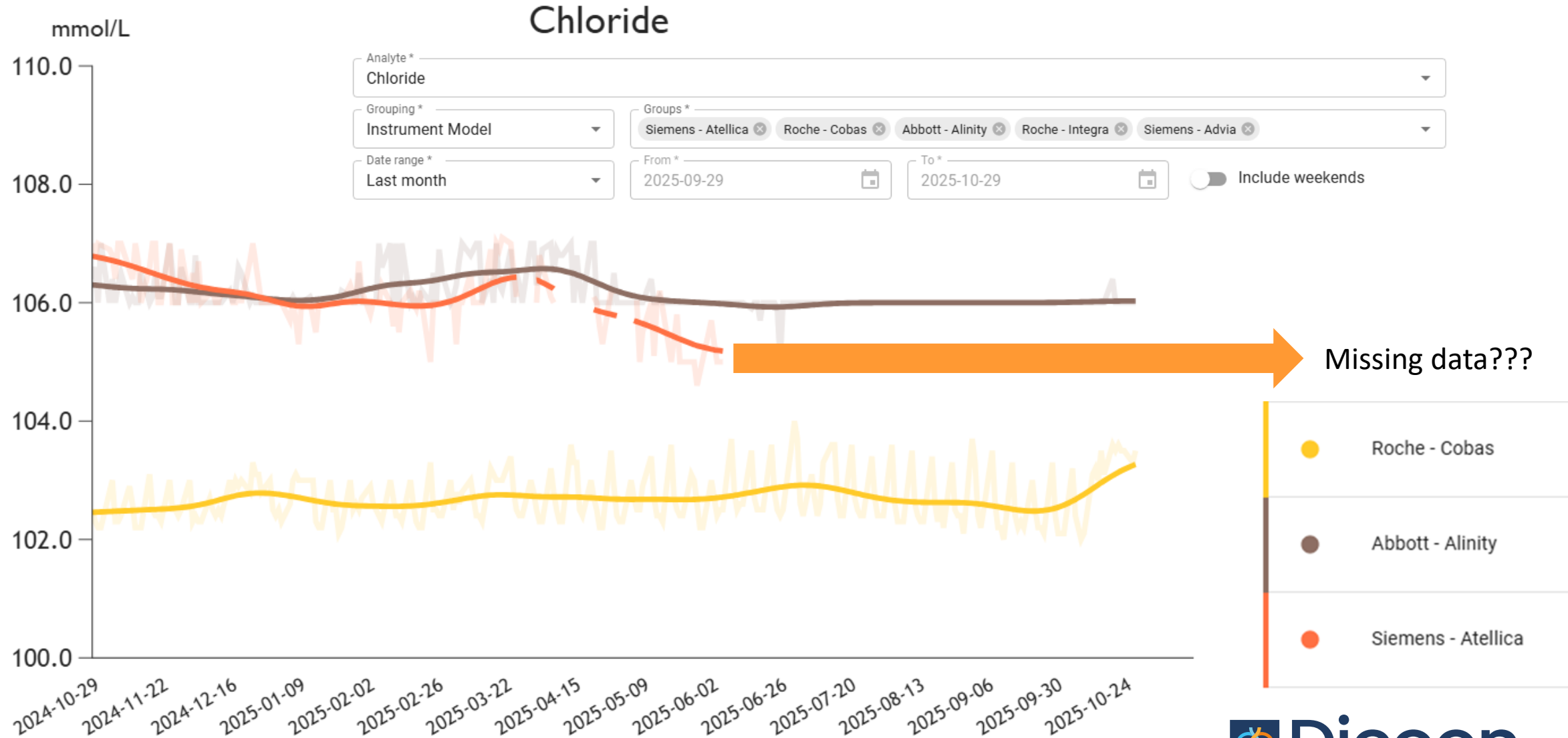


QC target adjustment
106,7 => 105,4 mmol/L

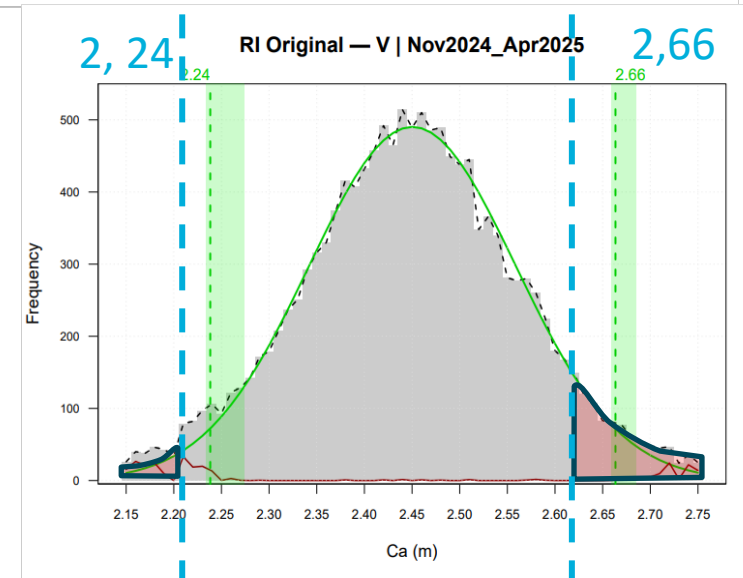
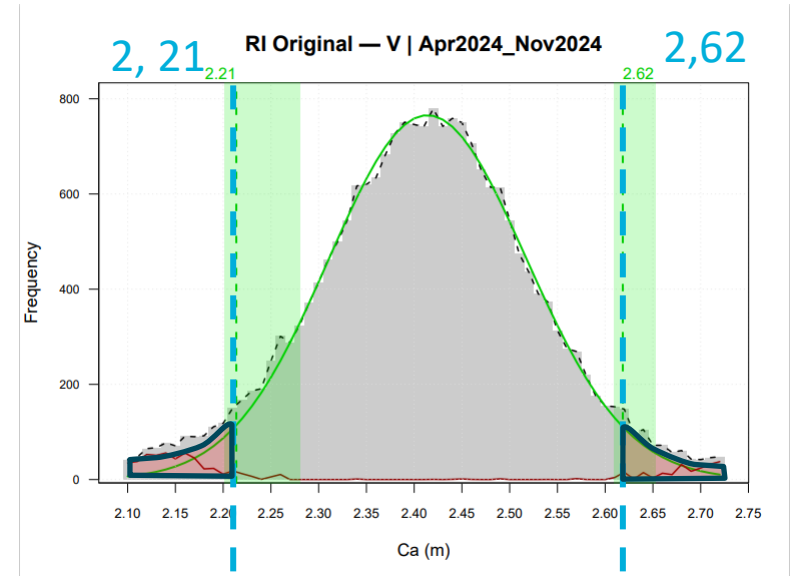
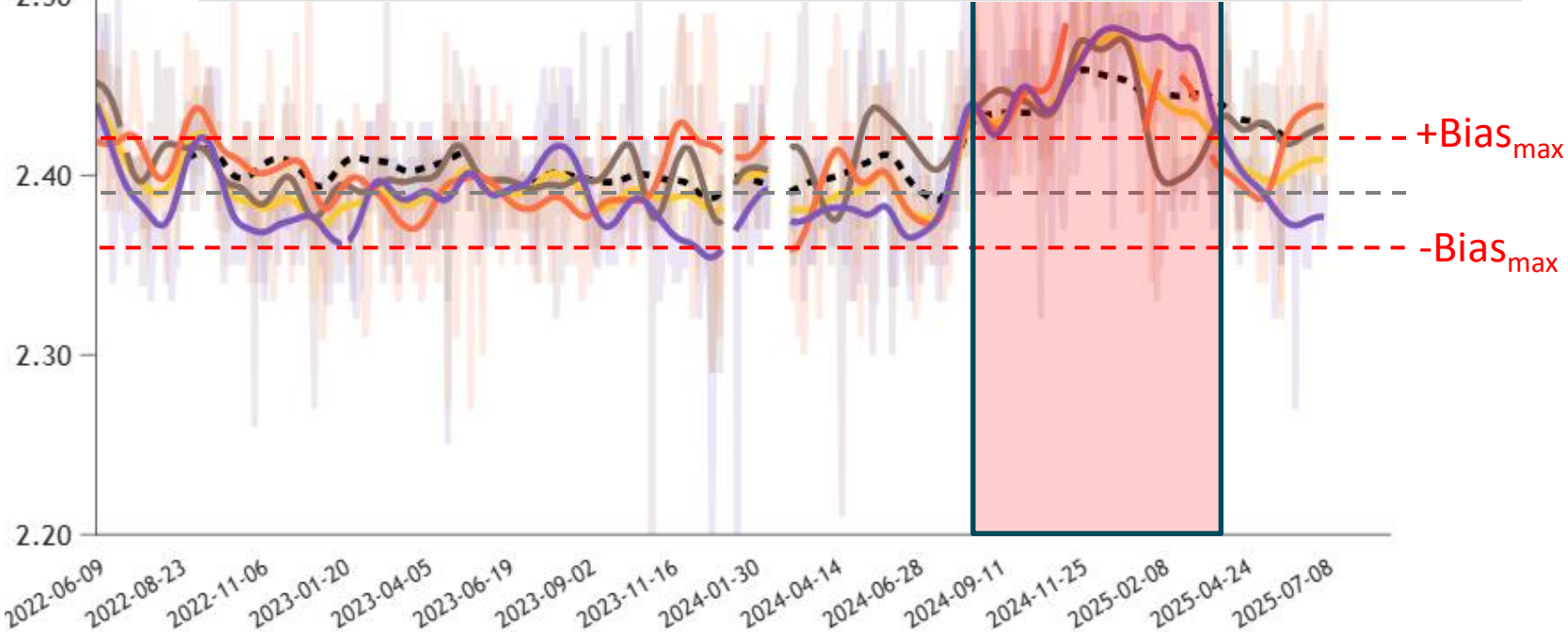
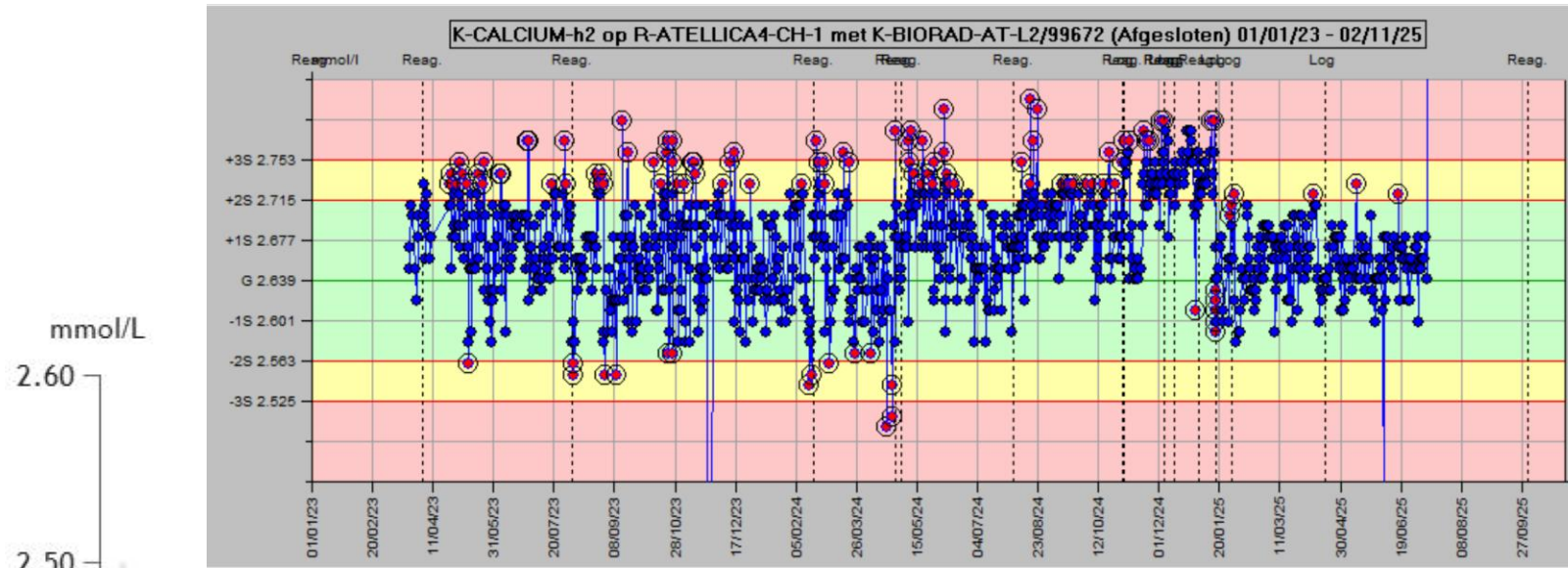
Assay problem??



Group overview – variation over time

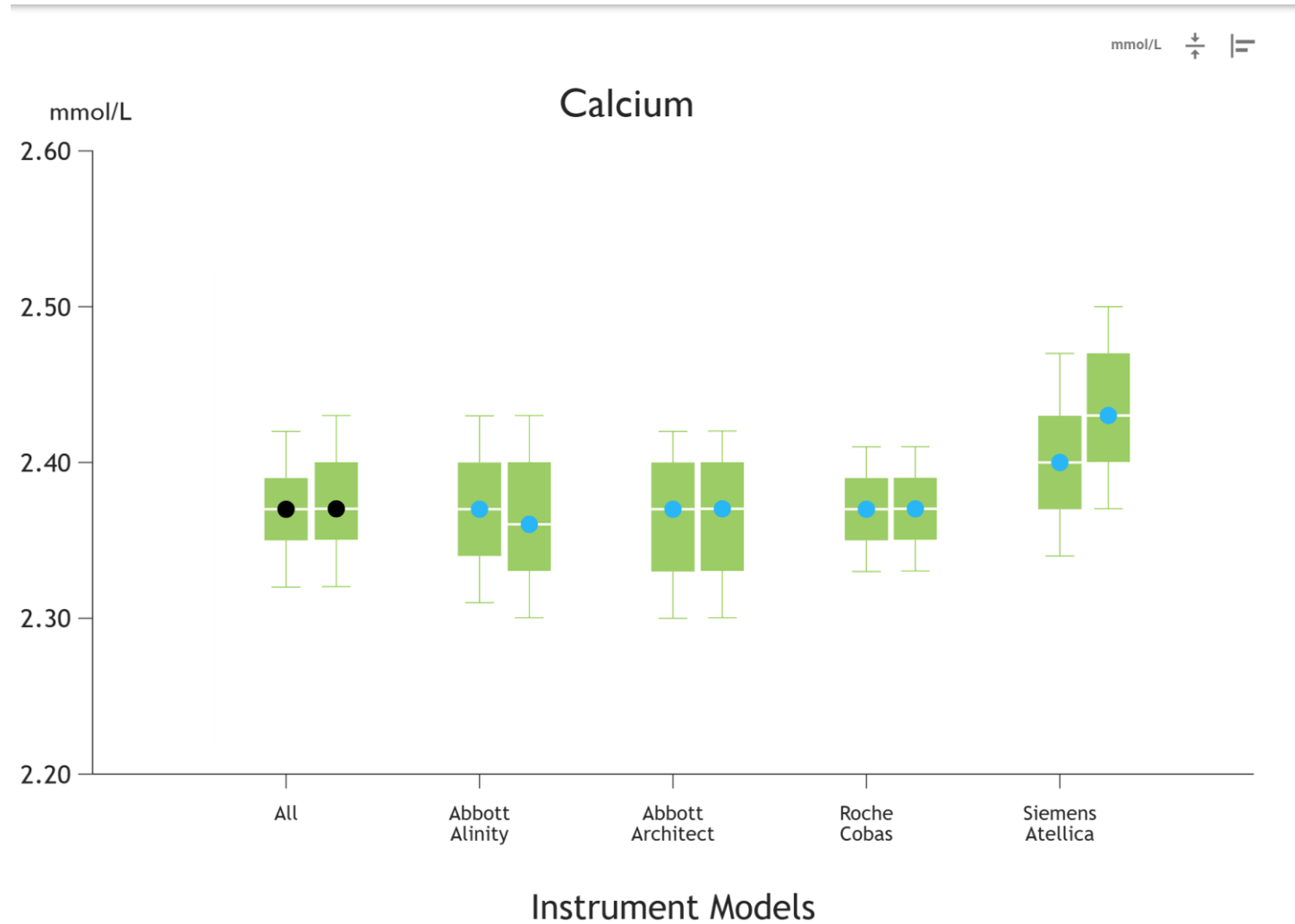


Case: calcium too high

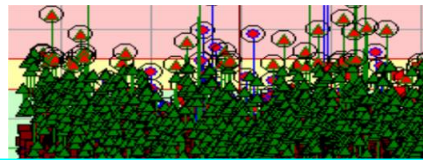


Clinical consequences!!

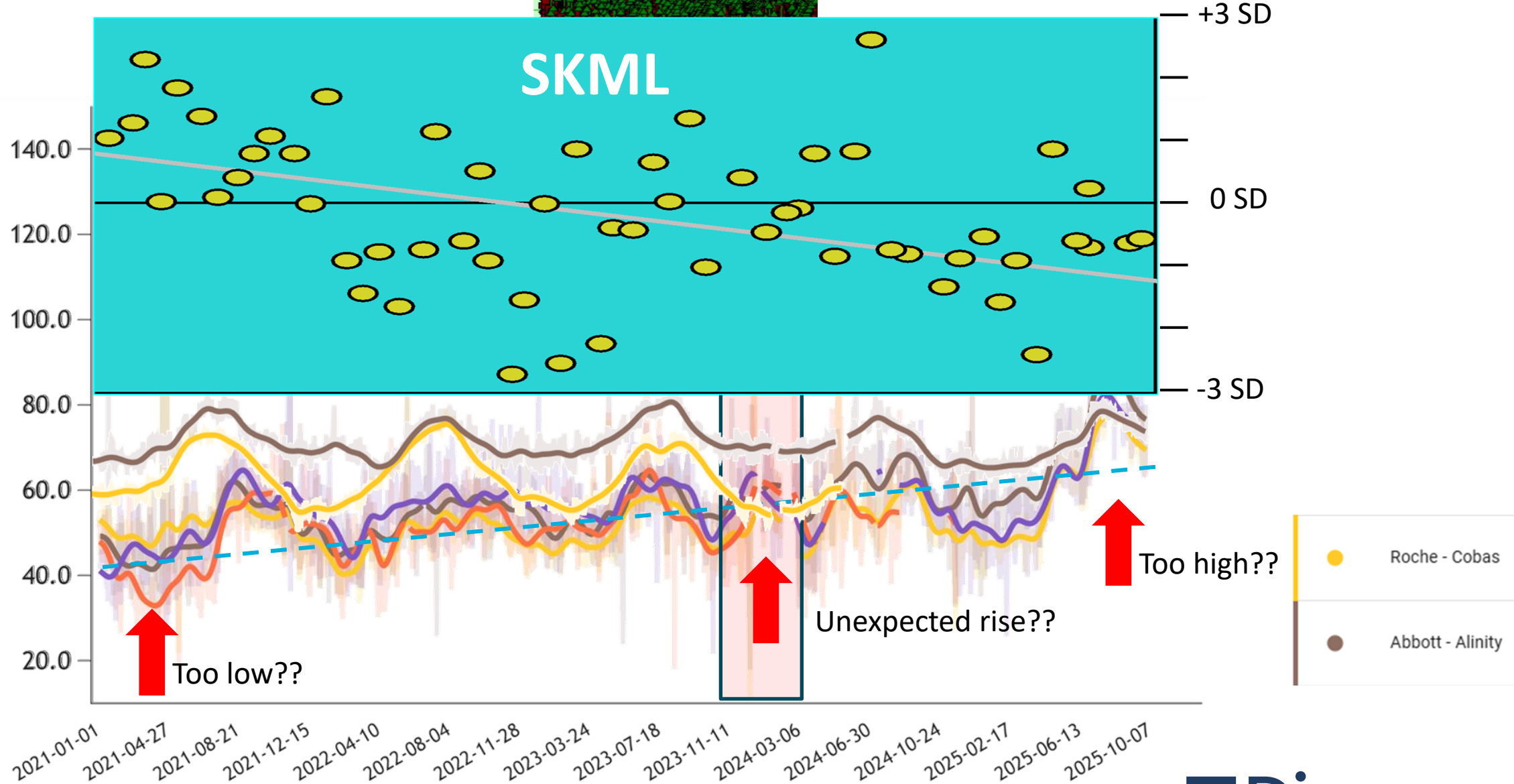
Case: calcium too high



Case: vitamin D drift



iQC

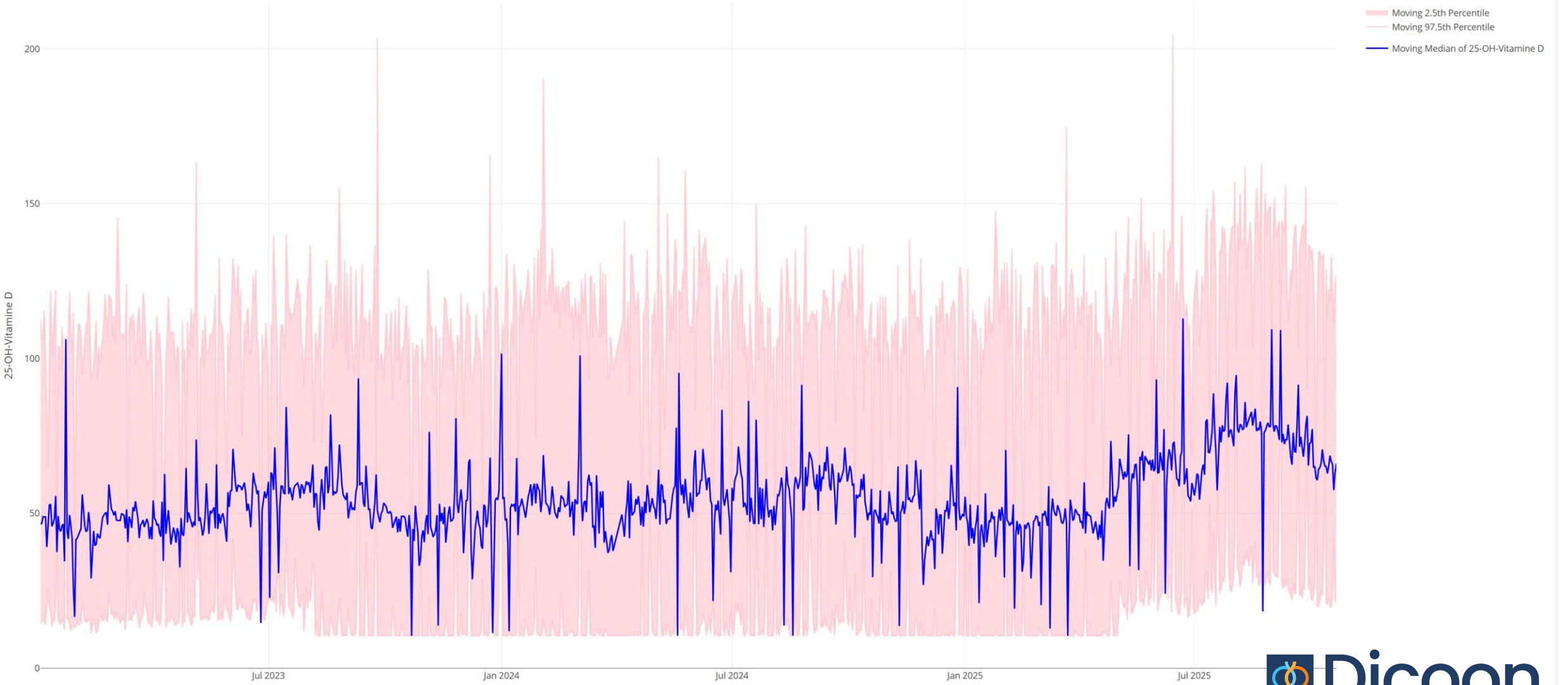


Case: vitamin D drift



Moving daily Median and percentiles for 25-OH-Vitamine D

- Moving 2.5th Percentile
- Moving 97.5th Percentile
- Moving Median of 25-OH-Vitamine D



Personal opinion NOPAM



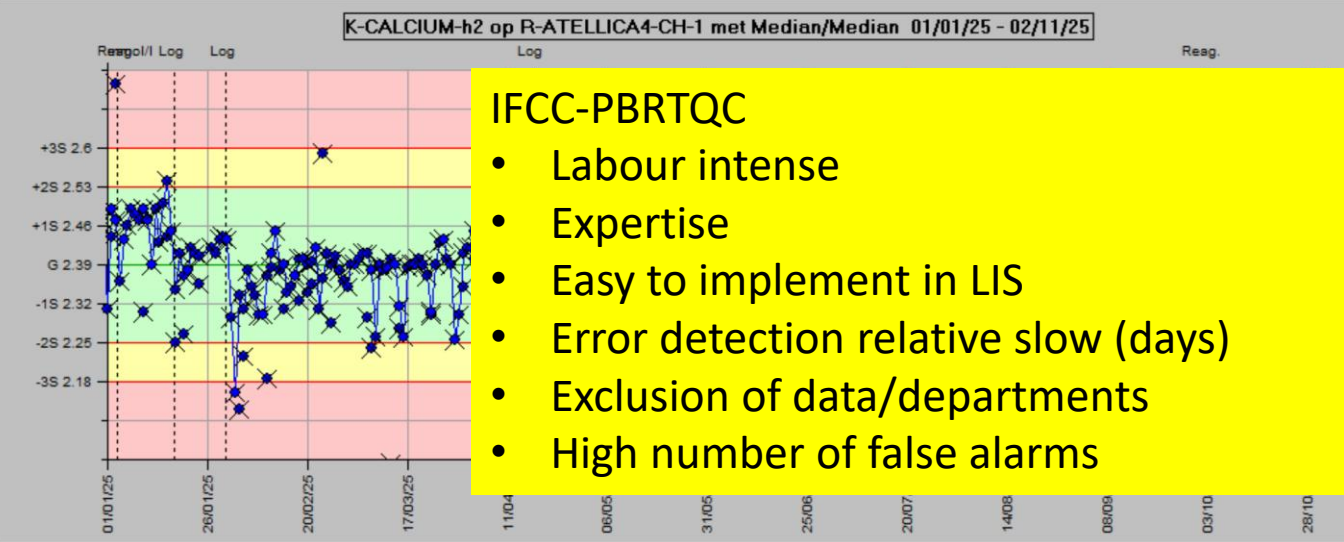
Easy to use /implement
No costs
Data is daily updated
Commutable samples
Overview own instruments
Overview instrument group
Overview between groups

Alarm feature not implemented??
Only 45 assays

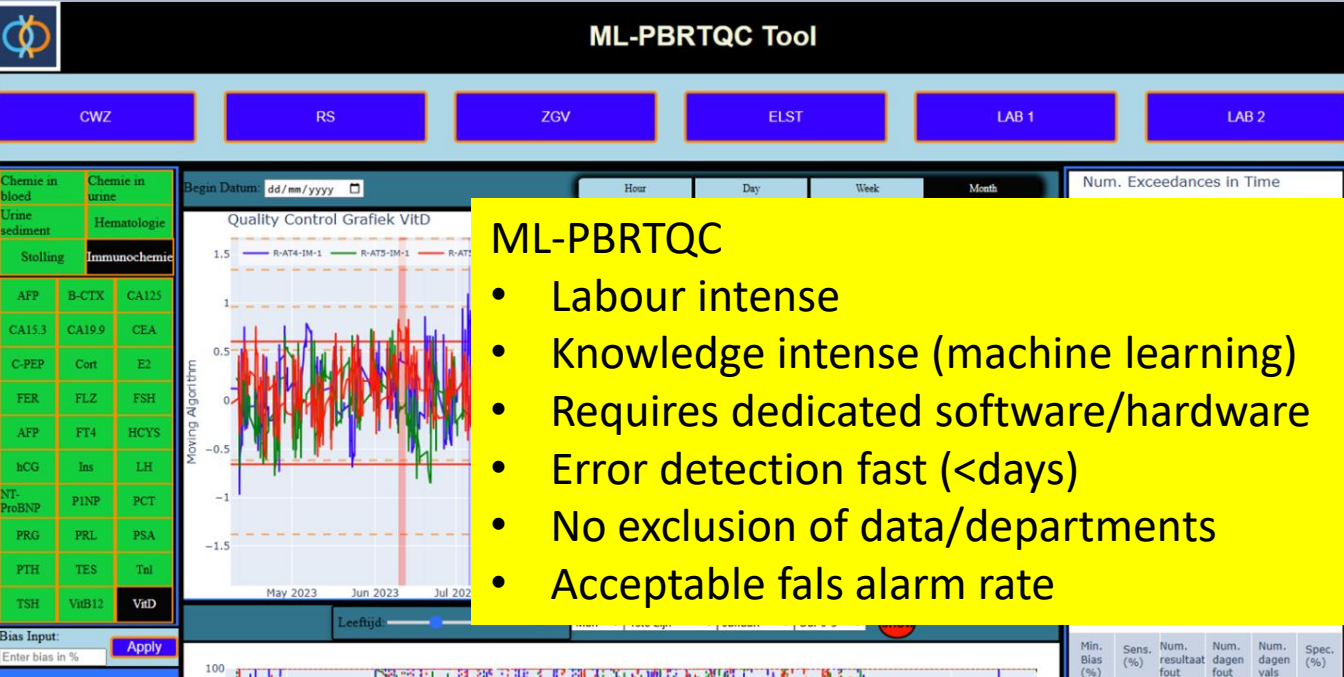
Data-loading is slow
Error detection takes days
Number Atellica users low
Missing data

Overall conclusion: usefull tool additonal to eQC en iQC

Other tools: IFCC-PBRTQC & ML-PBRTQC



- ### IFCC-PBRTQC
- Labour intense
 - Expertise
 - Easy to implement in LIS
 - Error detection relative slow (days)
 - Exclusion of data/departments
 - High number of false alarms



- ### ML-PBRTQC
- Labour intense
 - Knowledge intense (machine learning)
 - Requires dedicated software/hardware
 - Error detection fast (<days)
 - No exclusion of data/departments
 - Acceptable fals alarm rate

Steps	What & How	IFCC-PBRTQC	ML-PBRTQC
Data extraction	LIS	Yes	Yes
Stable period	remove	Yes	>Bias(Max)
All inclusive	ICU/ED/DIAL/PE D	No	Yes
Extreme values	Winsorization	Yes	Yes
Transformation	Box-Cox	Yes	Yes
Split data	50% training	Yes	Yes
Machine learning	Regression	No	nonlinear
Moving algorithm	MA/MM/EWMA	Yes	Yes
Control Limits	95-99 th percentile	Yes	Yes
Block size	N= 10, 20, 40	Yes	Yes
Error simulation	± 1-4 BiasMax	Yes	Yes
Error detection	Bias-ANPED plots	Yes	Yes
Performance	SPEC, SENS	Yes	Yes
False alarm rate	Optimization	No	Yes
Validation	50% test data	Yes	Yes

Can PBRTQC replace EQA?



	Classical EQA	PBRTQC	PBRTQC via NOPAM
Pre-analysis	Partly/Mostly out of scope	Per definition as in patient samples	←
Target value	Set by EQA	n.a.	←
Suitable for assessment of metrological traceability	Possible, if commutable and target value in RMP	not	←
Commutability	Challenging to achieve and to demonstrate	By definition	←
Method malperformance vs lab performance	If commutable	Not possible	yes
Confirmation of classical EQA	--	--	yes

NOPAM: What is in it for EQA organisations?

Frequent access to updated results

Evaluate reference limits in use for laboratories (NUMBER project)

verify method specific issues in their EQA program

Monitor outcome of harmonisation and standardisation efforts

Check if EQA program identifies issue signalled by NOPAM

On instrument level

On method level

On participant

Exclude that method specific bias is caused by non-commutability of EQA samples

EQA-providers are invited to contribute to the development of the program

NOPAM: Tips from Noklus

Start with a small number of laboratories.

Start with two different instruments

For the first report, it would be best to begin with a short time period, such as one week.

The biggest challenge for the labs is generating the report with the data required for import into NOPAM

Laboratories having the same LIS system should work together to prepare the result report

Support by SKML and NOKLUS

NOKLUS

instructions (webinar) for the data export files to NOPAM

help participants to test their report and give technical advice

Inform the users about the charts and how to interpret the results

SKML

Register interested Dutch SKML participants to NOPAM, without extra costs

Or asks labs to allow access to their NOPAM data by SKML

Study NOPAM performance of Dutch participants in relation to their SKML performance

NOKLUS and SKML will work together to document important differences between instruments and methods and make sure these differences also are known to manufacturers.

NOPAM support team

If you are interested in participating in the program,
please contact us:

Office SKML

office@skml.nl

Eva Rønneseth

eva.ronneseth@noklus.no

Program coordinator

Anne Elisabeth Solsvik

anne.elisabeth.solsvik@noklus.no

Program manager