Analytics: Real-Time Patient-Based Quality Control, Rapid Detection of Analytical Errors

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General QC Questions

- Why do we run QC?
  1. We want to provide accurate results for our patients
  2. Because our regulations tell us we have to
- How often do we have to run QC?
  1. Each day that patient samples are analyzed
     a) Not every 24 hours (CLIA certified laboratories)
- How often SHOULD we run QC?

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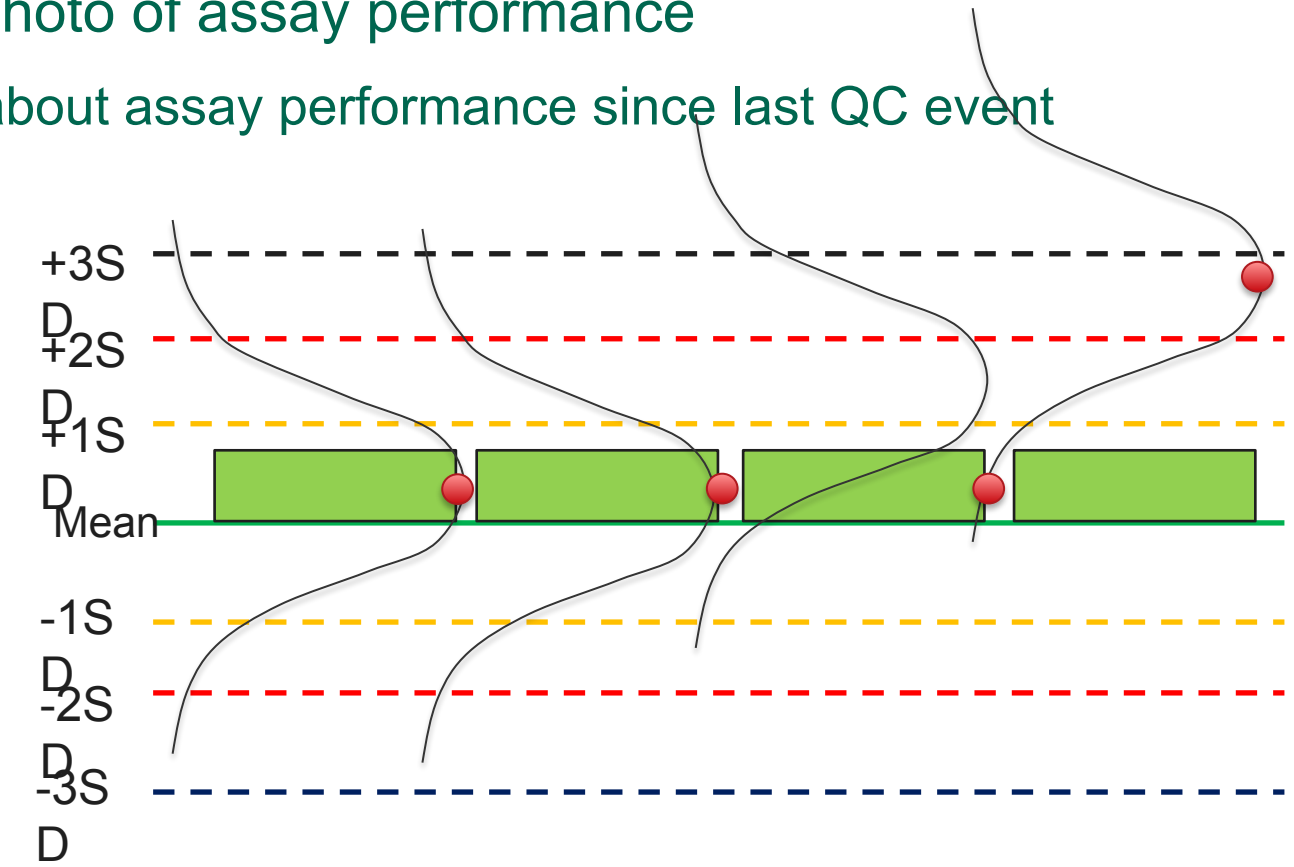
Traditional QC?

- Snapshot/photo of assay performance
  - Tells you about assay performance since last QC event



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Traditional QC: Other Limitations

- Snapshot/photo of assay performance
  - Tells you about assay performance since last QC event
- Cost
  - Monetary/financial: QC materials are expensive
  - Time: Technologist time in running and coordinating
- Non-commutability of QC material

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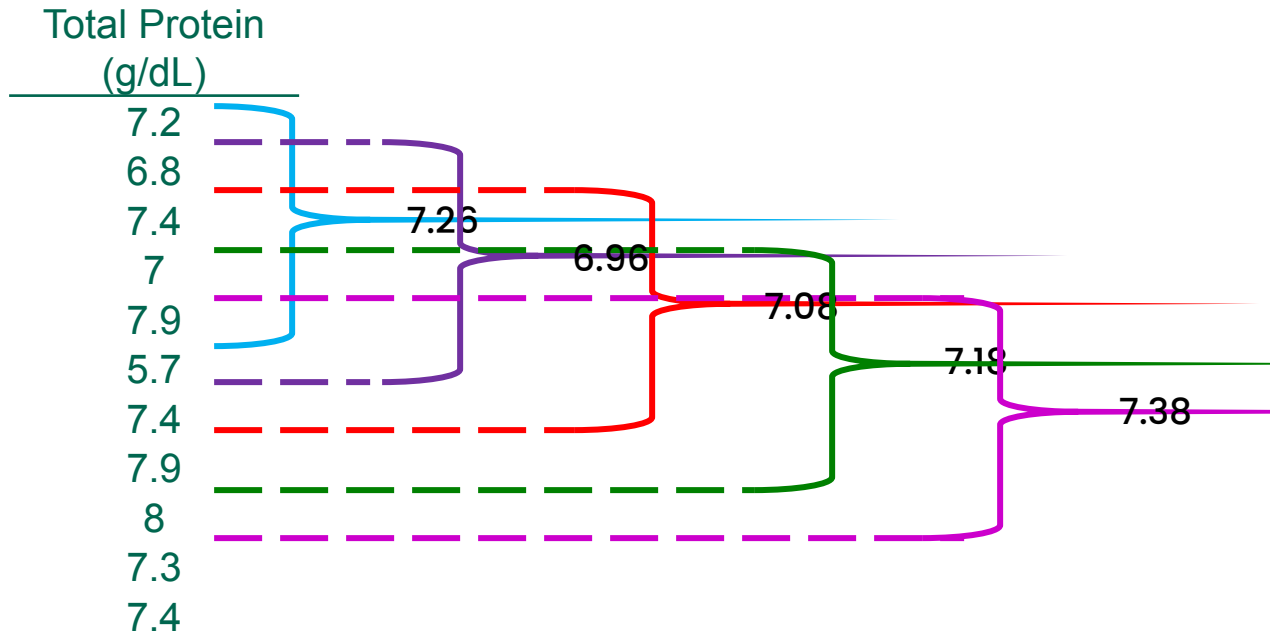
Patient-Based Real-Time QC (PBRTQC)

Continuous Patient-Based QC

- Using patient data to test the analytic process/assay

How?

- Monitor the mean/median of a fixed number of patient results
  - Moving Average or Moving Median



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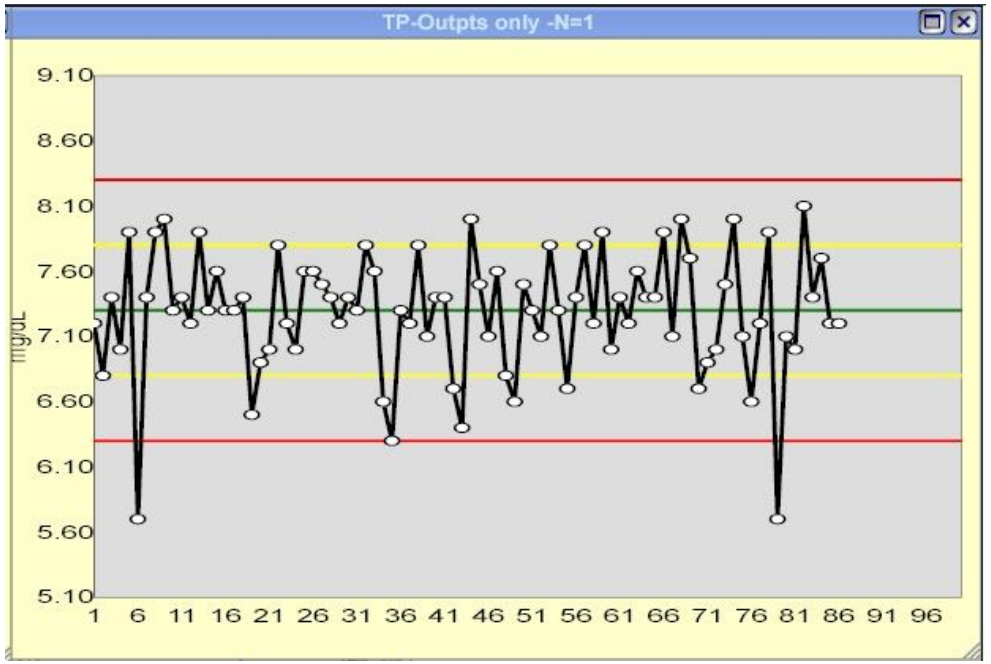
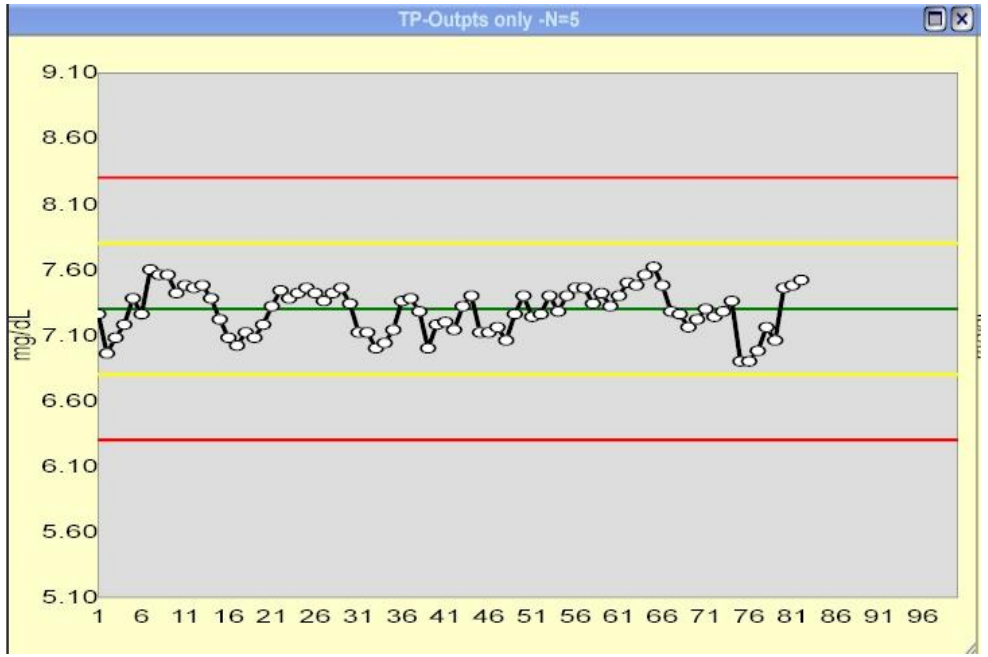
Moving Averages Example



- N = 1
- Each patient = 1 point
- NOT a moving average



- N = 5
- Each point = mean of 5 pt results
- Goal:
  - Monitor the process, Not the patients

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Moving Averages: Benefits and Challenges

Benefits

- No additional cost
- Continuous assessment
- Avoids non-commutability of QC materials
- Detection of error prior to IQC

Challenges

- Software/fees
- Establishing PBRTQC
  - Which tests?
  - How many data points?
  - Truncation limits?
  - Which calculation?
- Maintaining protocols

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How did we establish MA?

- Two phased process
- Phase I:
  - Used published literature as a guide
  - Tested protocols with historical data
- Phase II:
  - Optimized MA using algorithm in MatLab
  - Tested protocols via modeling of historical data

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Optimization Via Modeling

- Recreate MA process using laboratory data
- Simulated Annealing Software decides the ideal:
  - N (Filter Length)
  - Truncation Limits

$$min_{N,TLH,TLL} = ANP_{ed} + \beta \, x \, FP_{rate}$$

  - ANP_{ed} = average number of patients affected until error detected
- Possible that better parameters exist, not an exhaustive enumeration of all possible combos
  - PMID 27540031 : Ng D., Polito FA., Cervinski, MA. Clin Chem 2016;62:10 1361-1371

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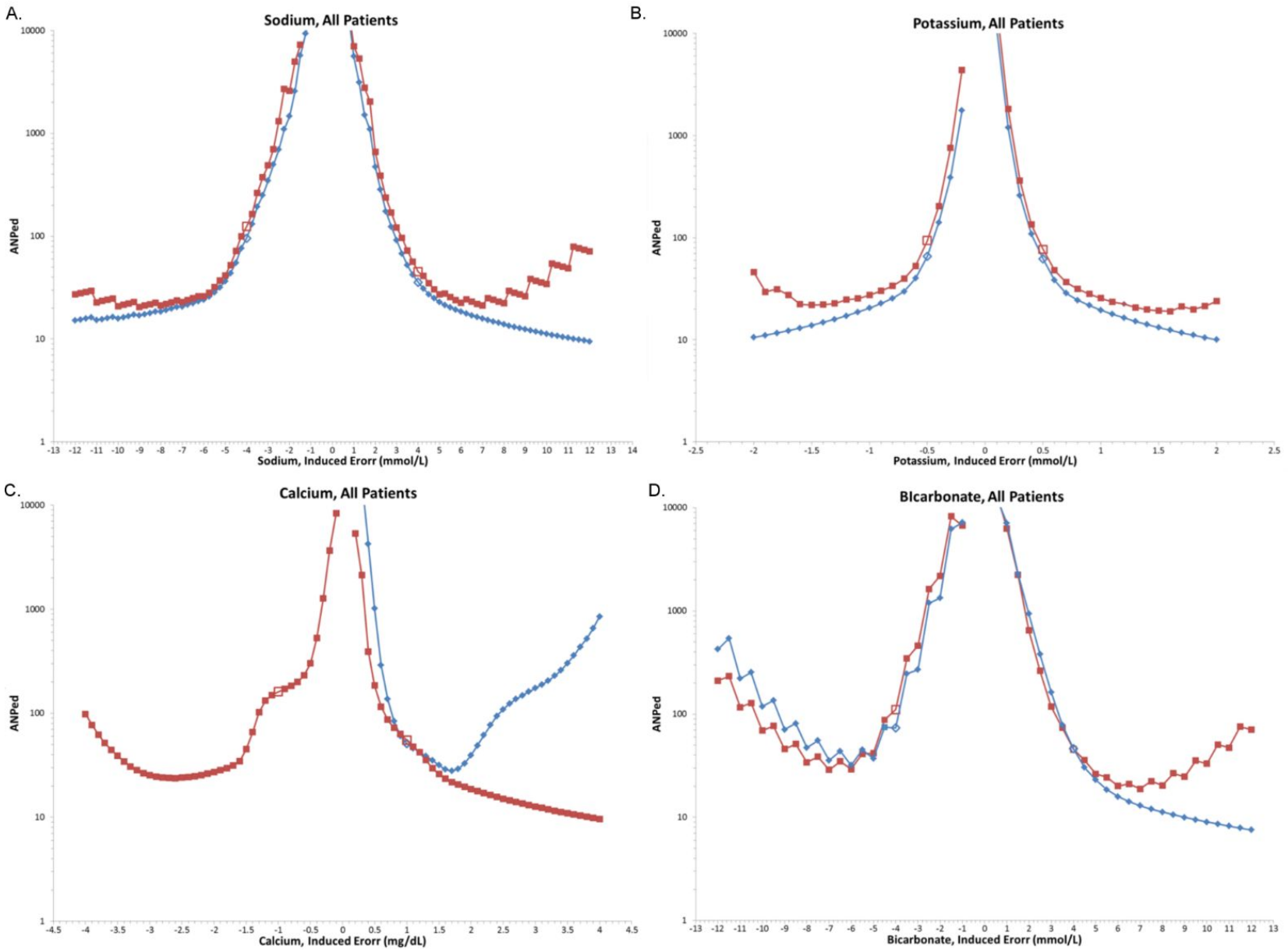

PMID: 27540031 Ng D., Polito FA., Cervinski, MA. Clin Chem 2016;62:10 1361-1371

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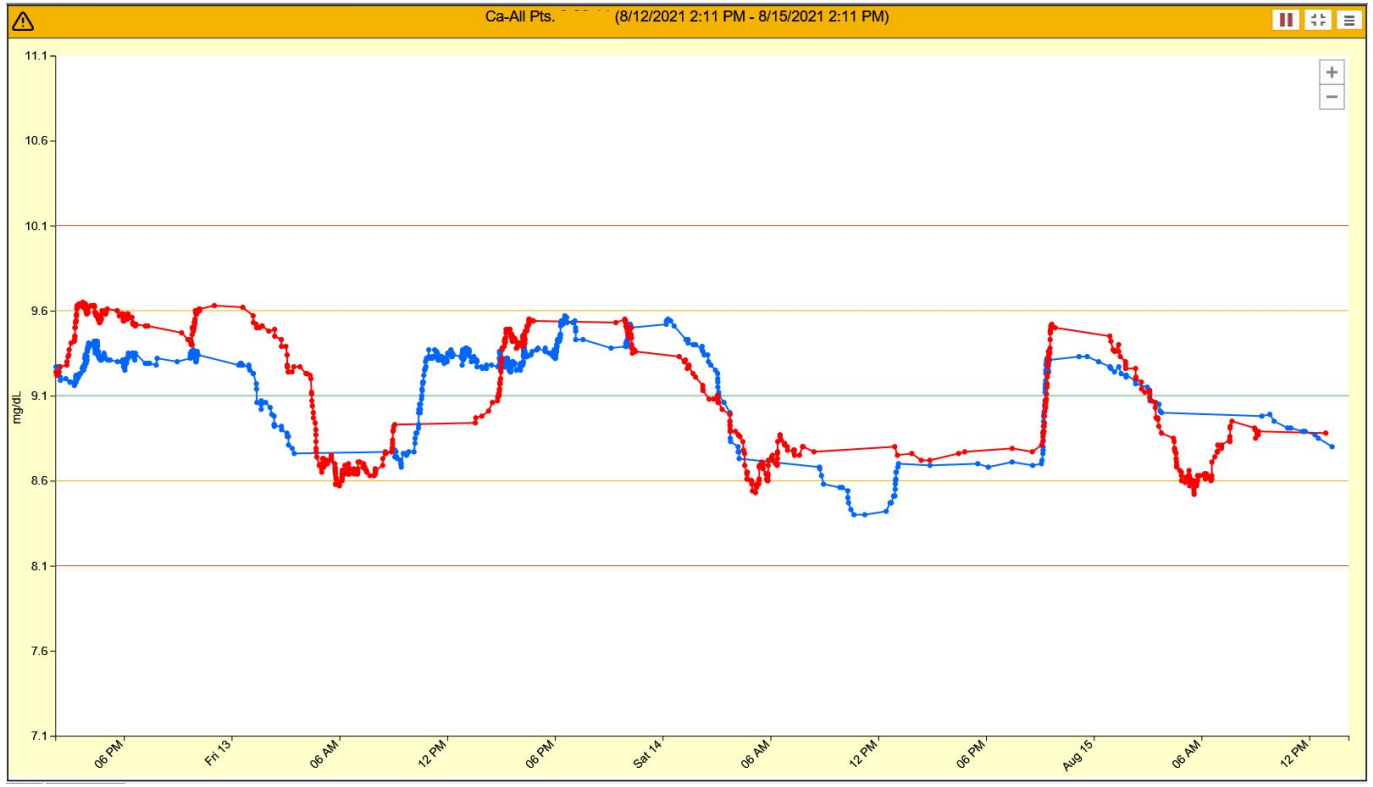
Problematic Analytes

- Albumin, Calcium, Total Protein,
  - Shift every day 04:00 – 07:00
  - More significant shift on weekend mornings



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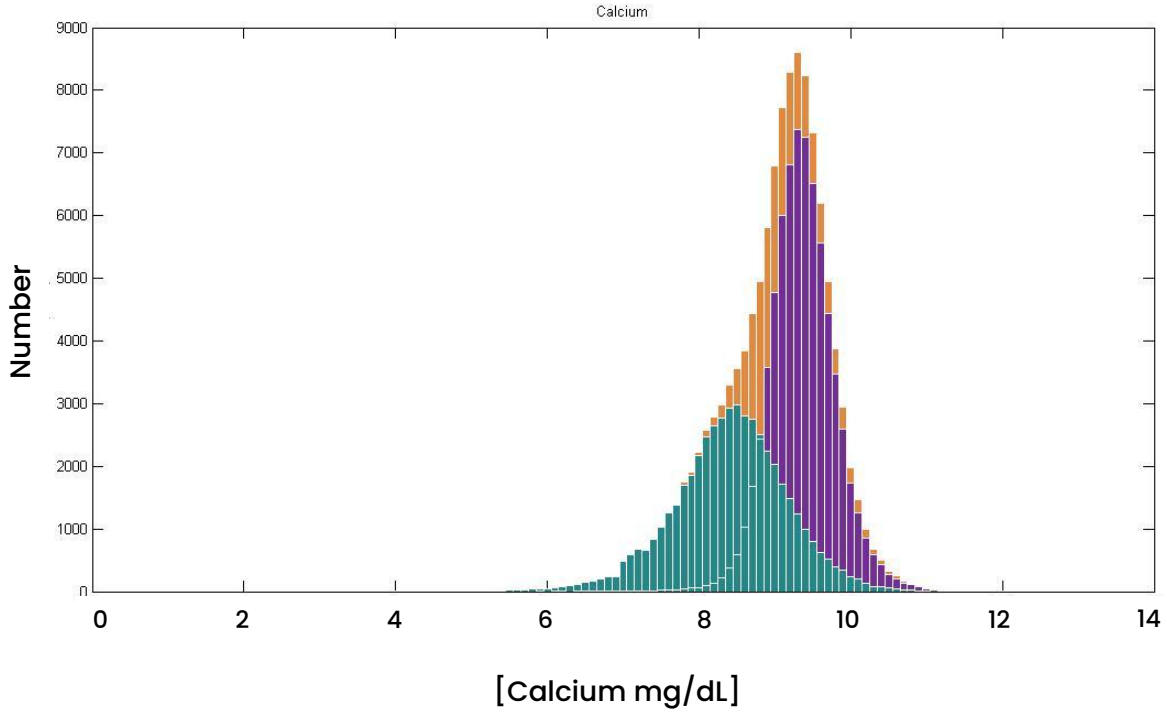
Ambulatory vs. Inpatient Populations

- Frequency distribution of plasma calcium
  - Orange=all patients
  - Purple=Ambulatory
  - Teal=Inpatients
- Two Distinct Populations
  - Overall distribution skewed
  - Individual distributions less-skewed



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Ambulatory vs. Inpatient Populations

- Frequency distribution of plasma calcium
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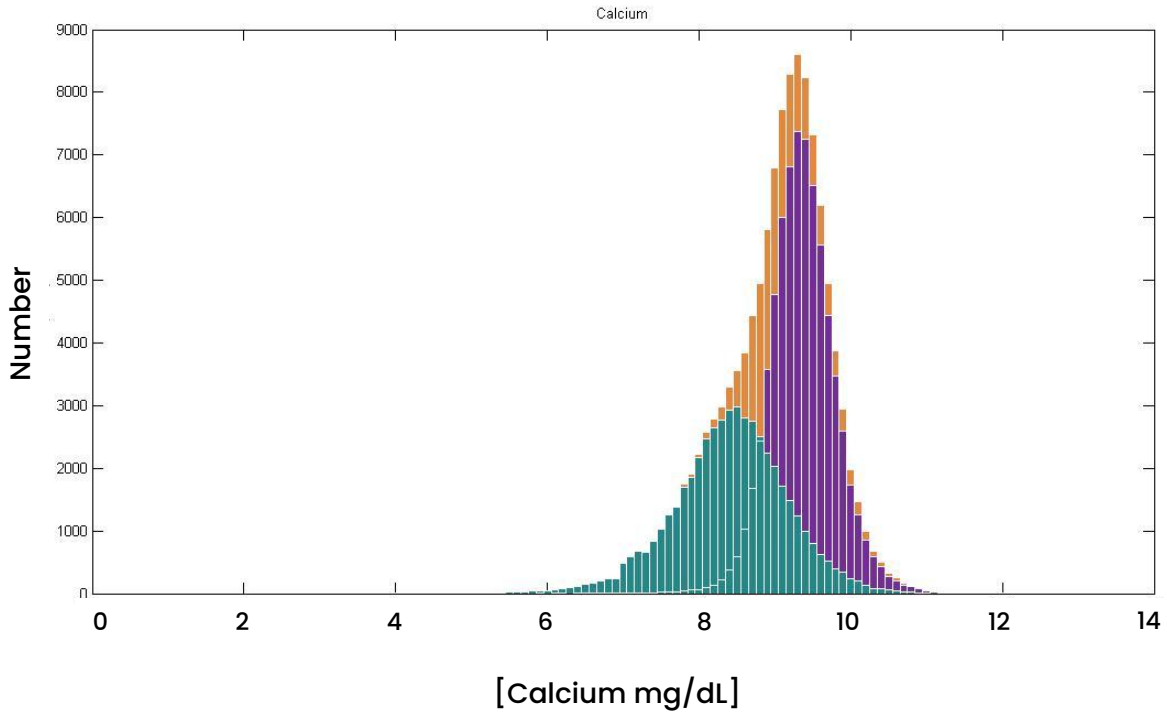
- Two Distinct Populations
  - Overall distribution skewed
  - Individual distributions less-skewed
- Improve error detection by monitoring populations separately?



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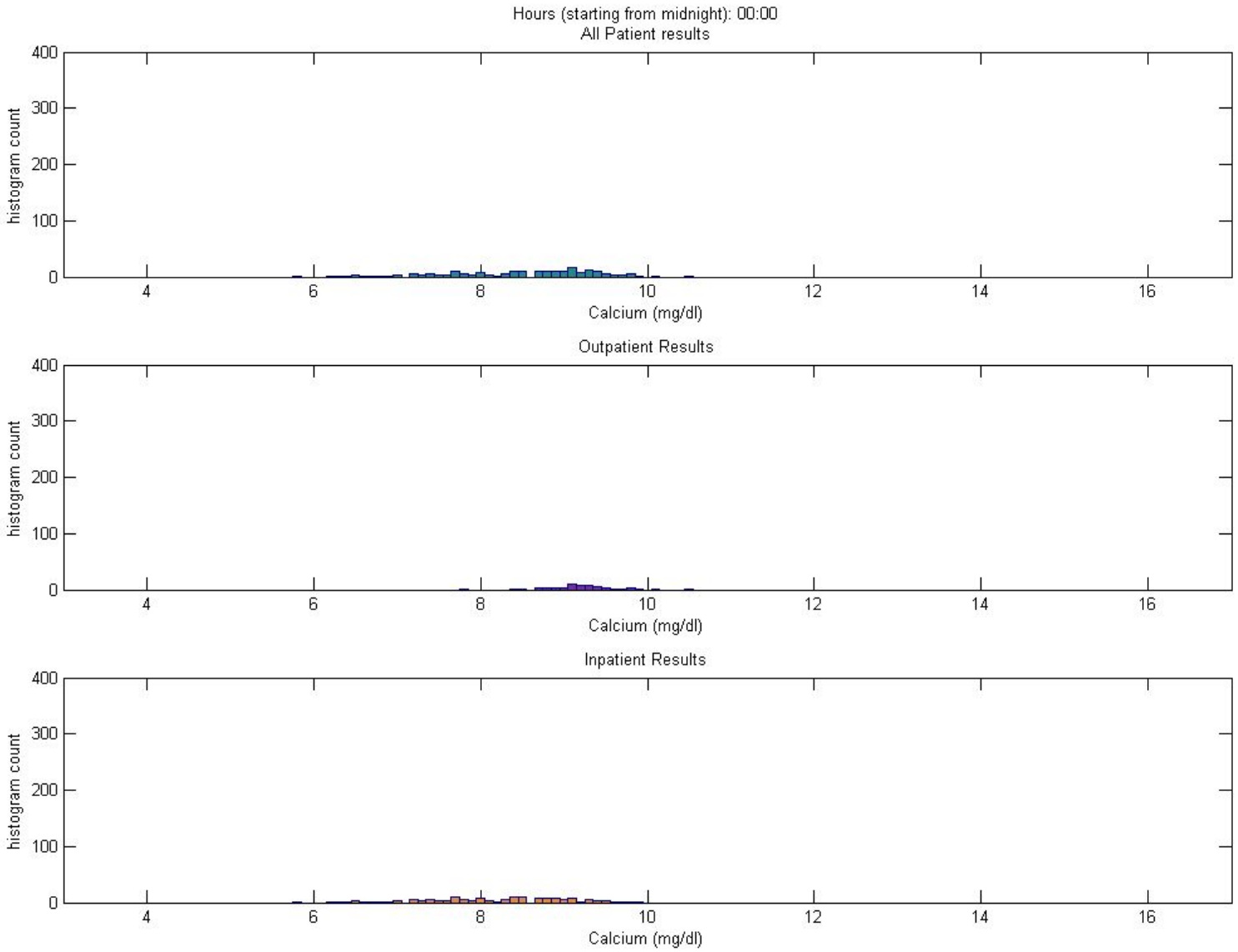
Variation:
A function of time & patient status

24 h cycle of serum calcium

Average of 400 days

Ca^{2+} low in AM (Inpts)

Ca^{2+} higher in PM (Outpts)



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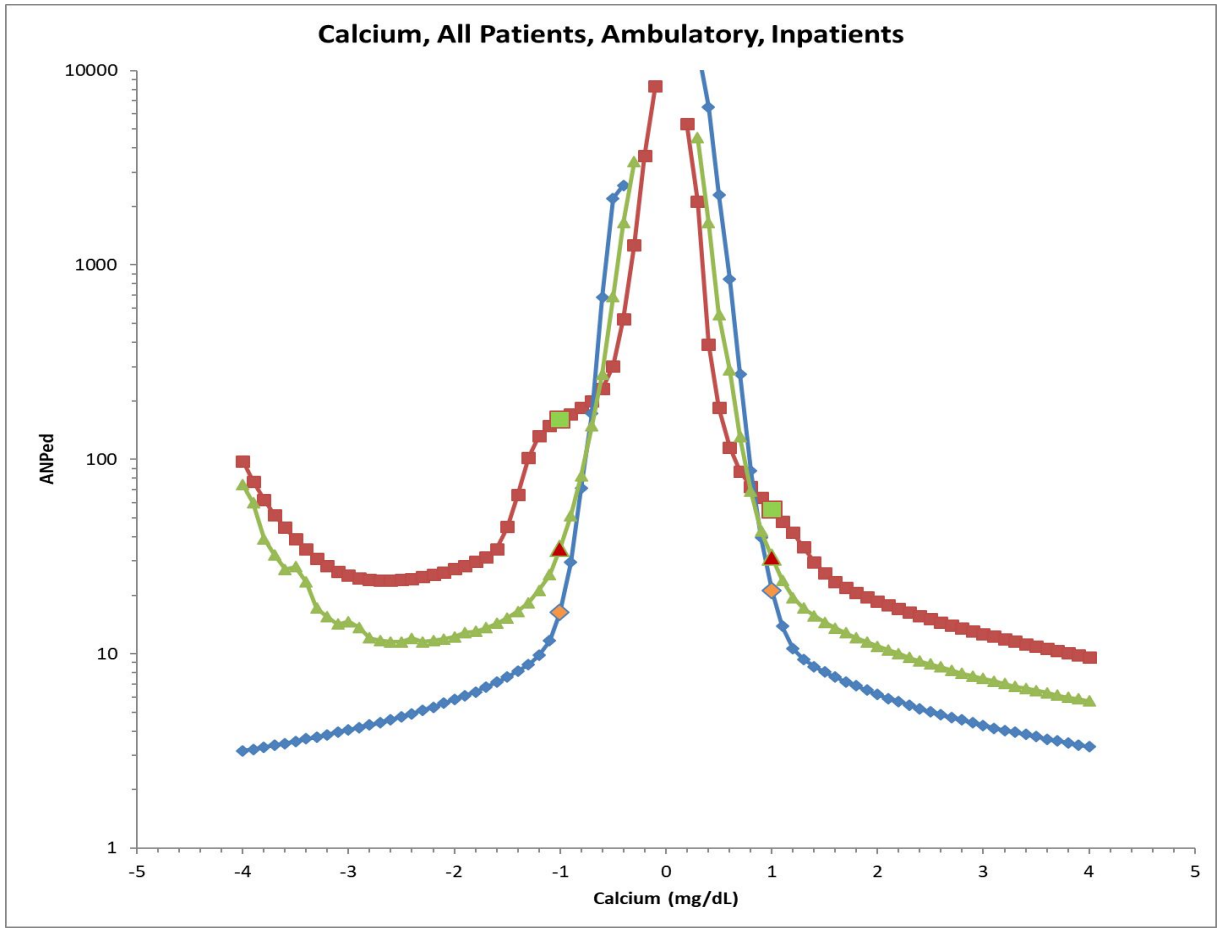
Ambulatory vs. Inpatient + Optimization



Calcium All

	ANP_{ed}	SD
-1.0 g/dL	161	134
+1.0 g/dL	51	55

Calcium Outpatient

	ANP_{ed}	SD
-1.0 g/dL	35	65
+1.0 g/dL	21	24

Calcium Inpatient

	ANP_{ed}	SD
-1.0 g/dL	31	22
+1.0 g/dL	35	28

PMID: 27540031 Ng D., Polito FA., Cervinski, MA. Clin Chem 2016;62:10 1361-1371

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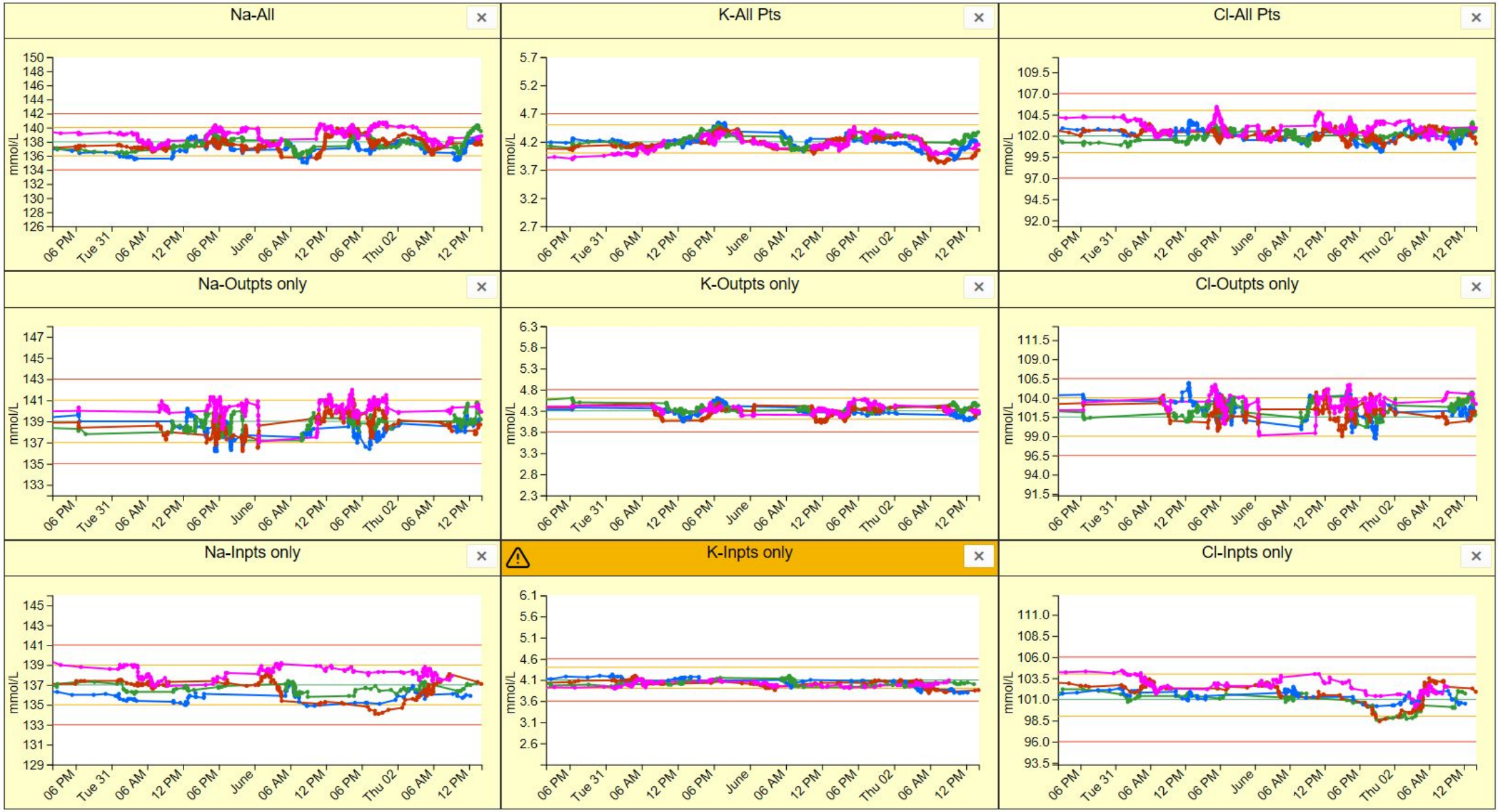
Example of Dashboard Display



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So Does it Work?

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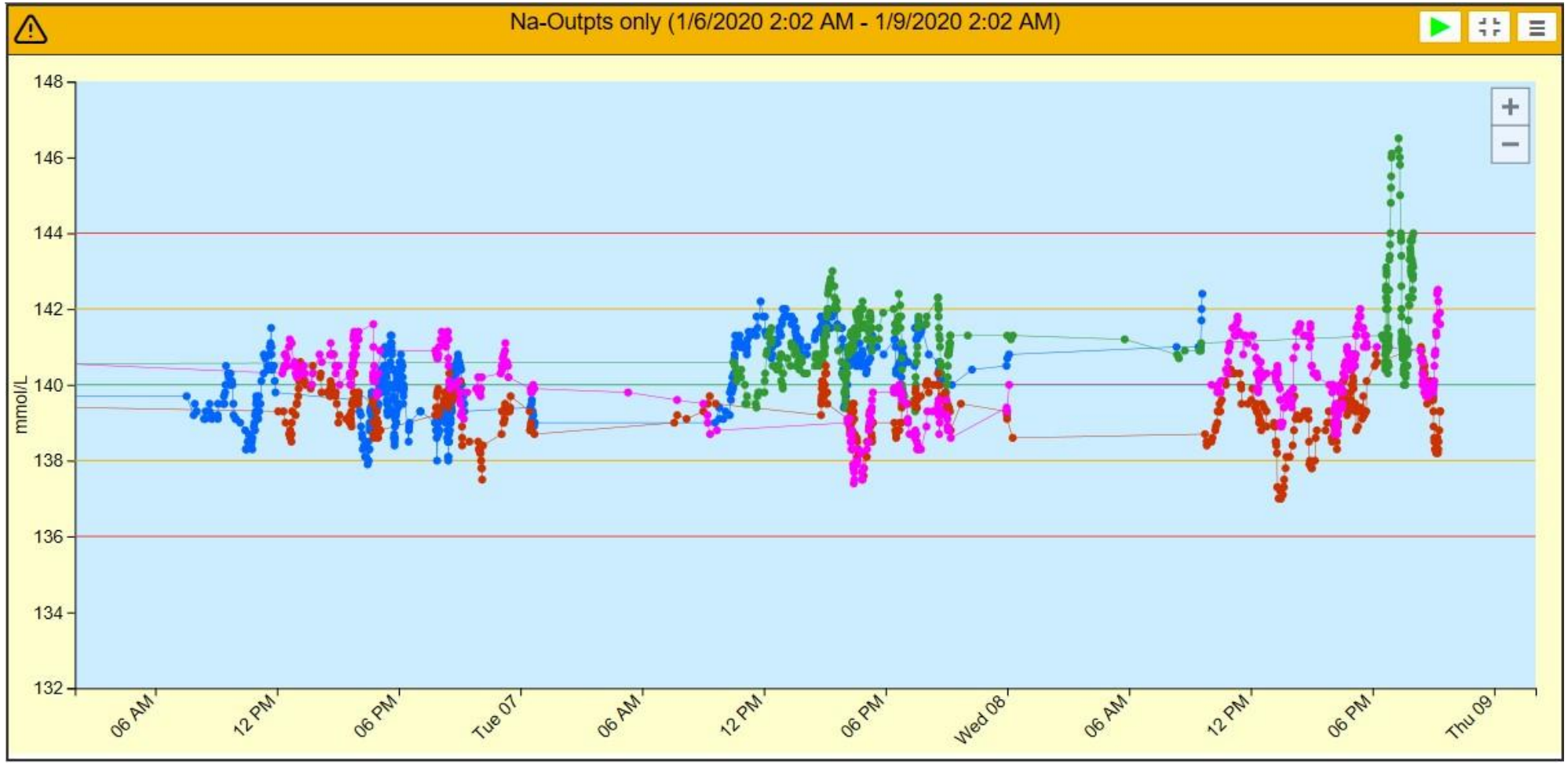
Error Detection: Sodium Ion-Selective Electrode



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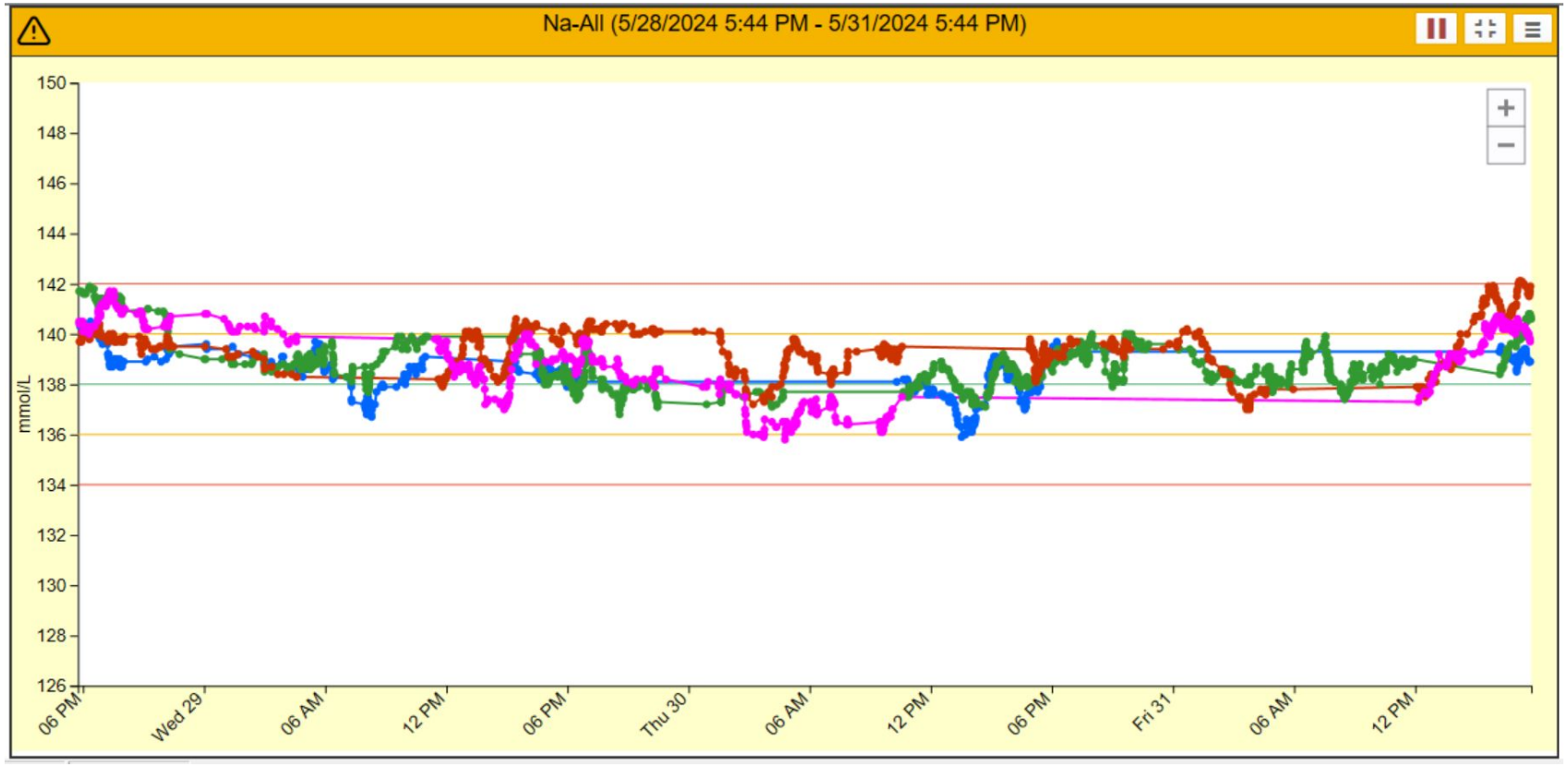
Positive Bias in Sodium Electrode?
“Na-All” protocol



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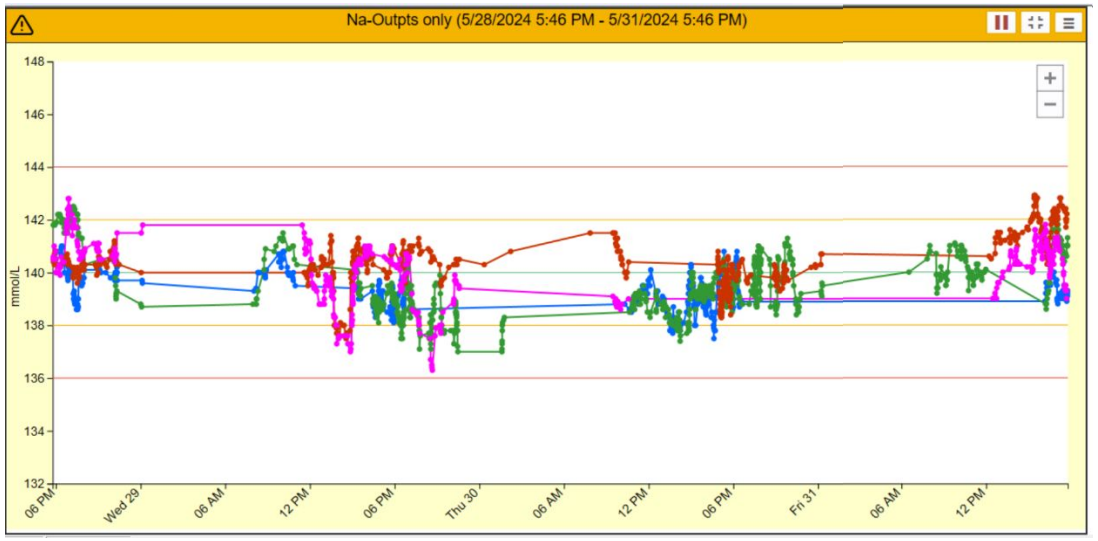
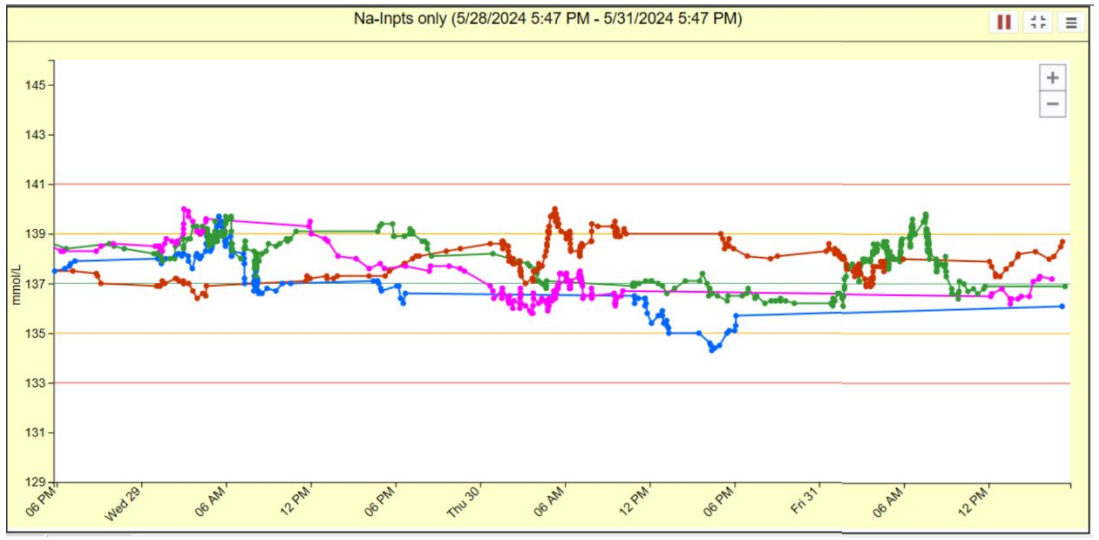
Shift in “All” not replicated in subset protocols





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False Rejections (Flags) do Occur

This “flag” did not indicate a shift in assay performance

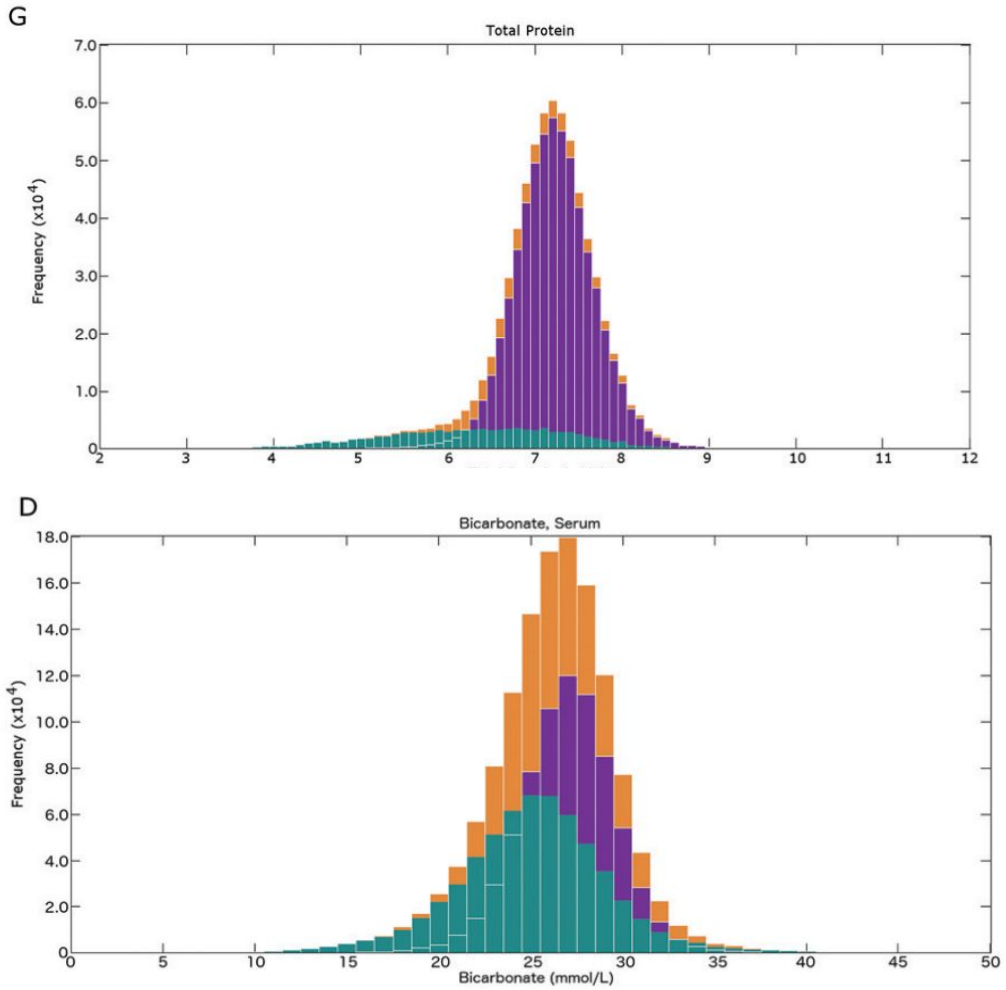
- Indications that this isn’t a real shift
  - All four electrodes are trending up together in the “All” protocol
  - No shift in the Outpatient or Inpatient protocols

- How do we tell if a shift is real?
  - We run internal QC/liquid QC
  - We repeat some samples on another module

Limitation of Moving Average: Error Detection for Inpatients

ANPed higher for inpatients vs ambulatory

- **Likely consequence of wider distributions**
- **Are there opportunities for improving error detection?**



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Average of Delta: Improving Error Detection Using Inpatient Data

- Hospitalized patients: Routinely have daily lab tests
  - Values vary due to:
    - Treatment, diurnal variation, improving or worsening status, etc.
  - Analyte conc does not vary greatly w/in an ind., particularly if collected at same time of day
    - Concept of Delta Check

- However, Delta Check is a relatively weak tool for analytical error
  - Ovens K, Naugler C. How useful are delta checks in the 21st century? A stochastic-dynamic model of specimen mix-up and detection. J Pathol Inform. 2011;3:5 **PMID: 22439125**
  - Strathmann FG, Baird GS, Hoffman NG, Simulations of delta check rule performance to detect specimen mislabeling using historical laboratory data. Clin Chem Acta 2011;412:1973-1977 **PMID: 21782806**

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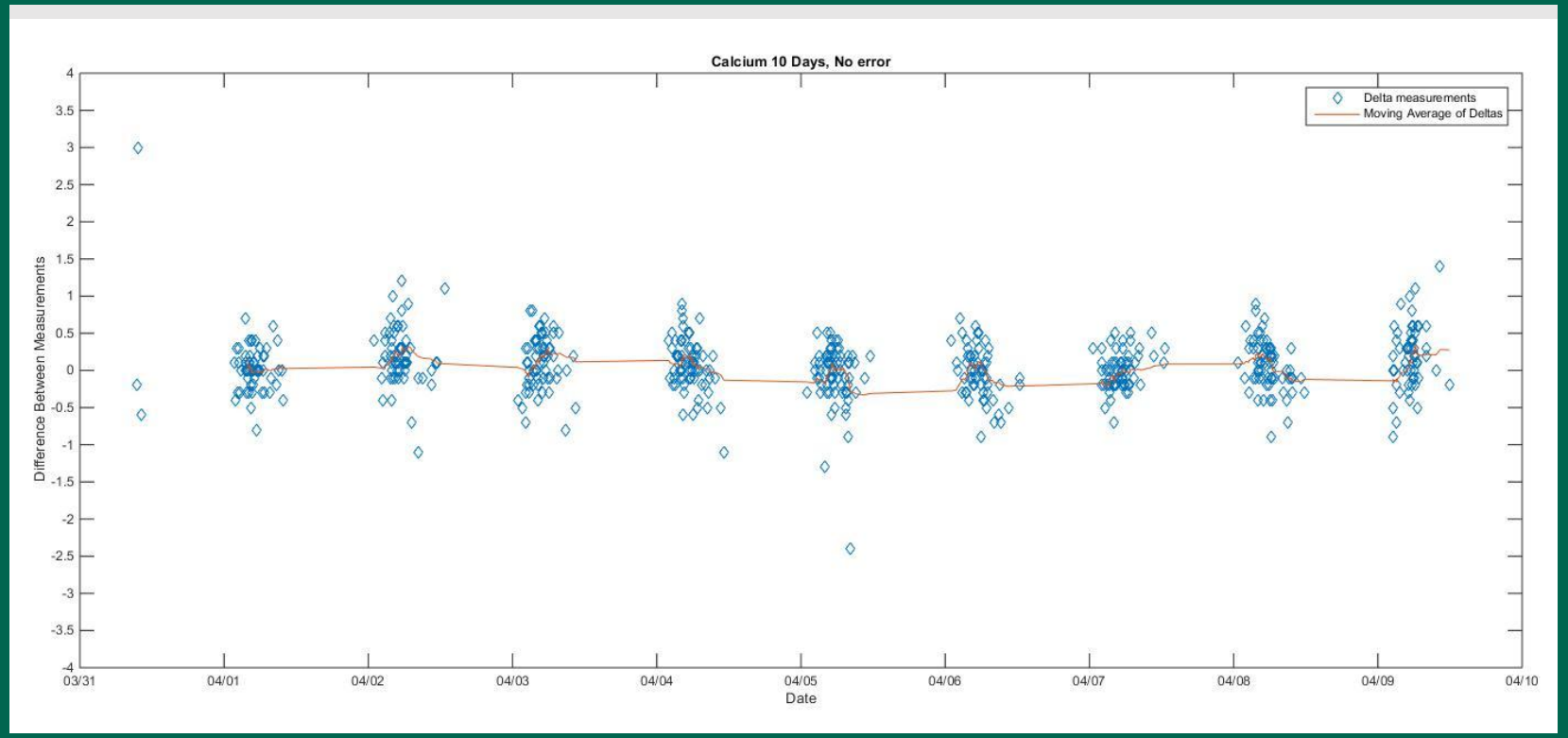
Ten Days of Calcium AoD Data

- Individual Δ's distributed around a mean Δ ~ 0 mg/dL
- AoD - surrogate for assay performance
- Allows detection of day-to-day bias
- Δ values are clustered together = daily morning phlebotomy



Cembrowski GS, Xu Q, Cervinski MA. Clin Chem 2021;67 (7): 1019-1029
PMID: 33993233

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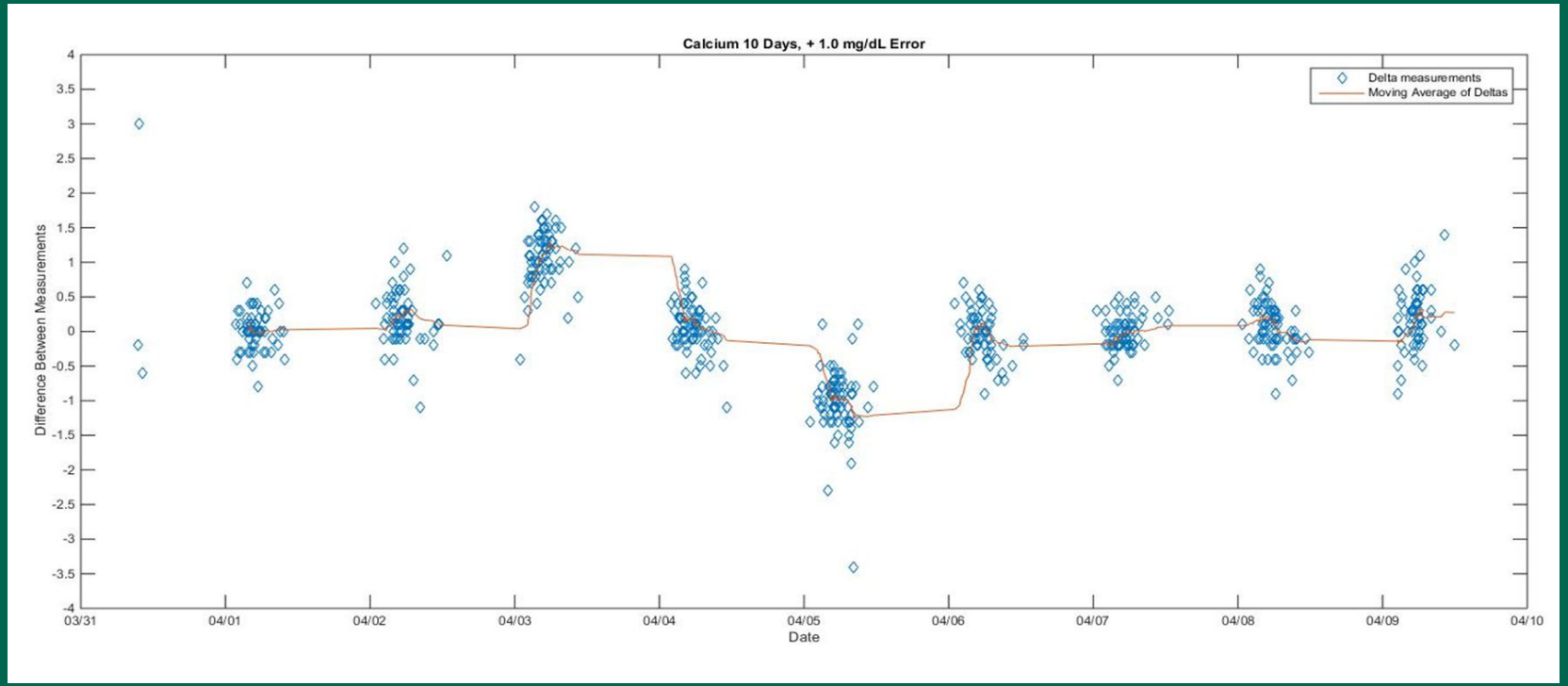
Calcium AoD + 1.0 mg/dL Systematic Error (SE)

- AoD Shift due to Systematic Error
  - SE =1.0 mg/dL induced on day 4
  - AoD rapidly deviates from mean



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Optimization Via Modeling

- Recreate MA process using laboratory data
- Simulated Annealing Software decides the ideal:
  - Np (Number of pairs or Filter Length)
  - Truncation Limits

  - $min_{Np,TLH,TLL} = AND_{ED} + \beta \, x \, FP_{rate}$

- ANDED = average number of deltas to detection

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Average Number of Deltas to Detection (AND_{ED})

Graphs of AND_{ED} vs. induced error

- Orange symbols = assay TEa

AND_{ED} about ten-fold lower than ANP_{ed}

- Not a perfect comparison
- Number of deltas vs. number of results

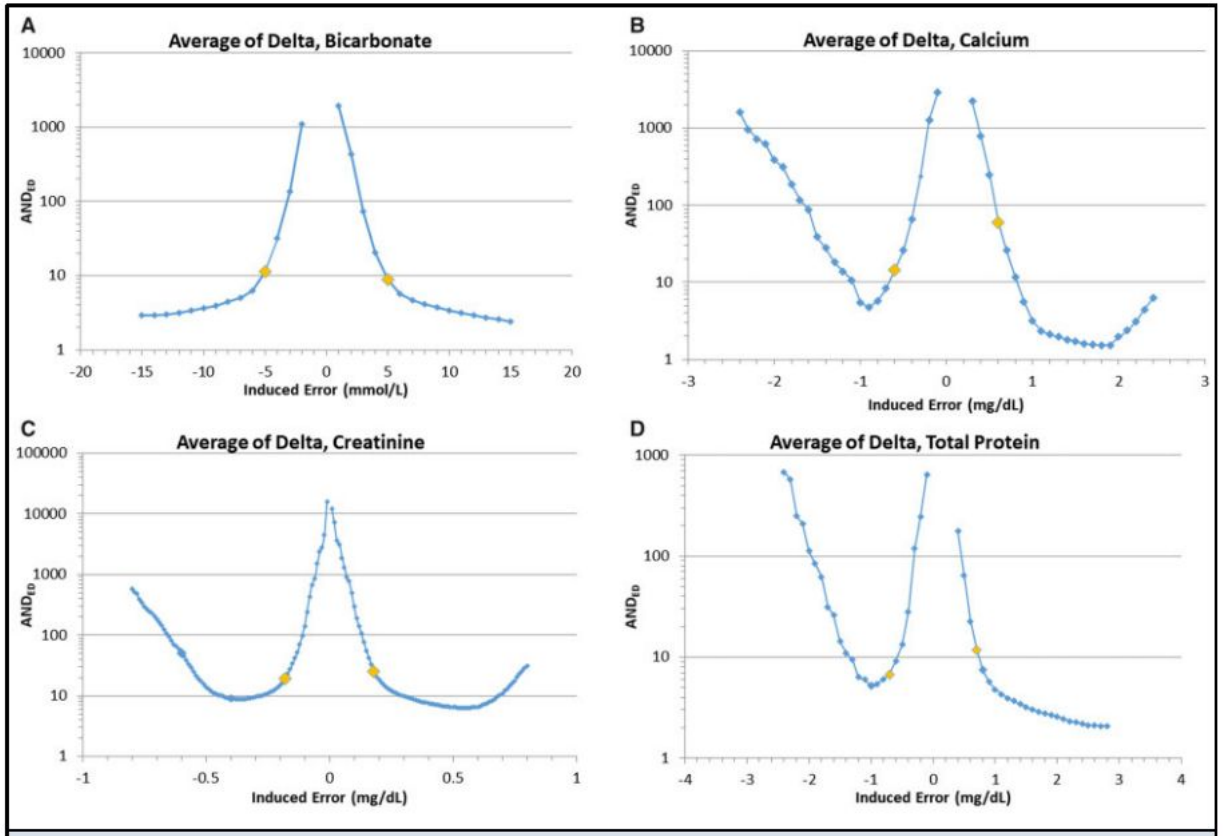

Fig. 2. AoD charts for bicarbonate (A), calcium (B), creatinine (C), and total protein (D). Each graph plots the AND_{ED} vs systematic error (±3 times control limits). Because the systematic error magnitude (negative and positive) is increased to 3 times the assay's control limits, AND_{ED} values decrease to a minimum value before again increasing, as large delta values are truncated from the AoD metrics. The orange (larger) diamonds correspond to the analyte-specific control limits (±2.5 times $SDD_{22\text{-}26\ h}$).

Cembrowski GS, Xu Q, Cervinski MA. Clin Chem 2021;67 (7): 1019-1029
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Average of Delta vs. Moving Average

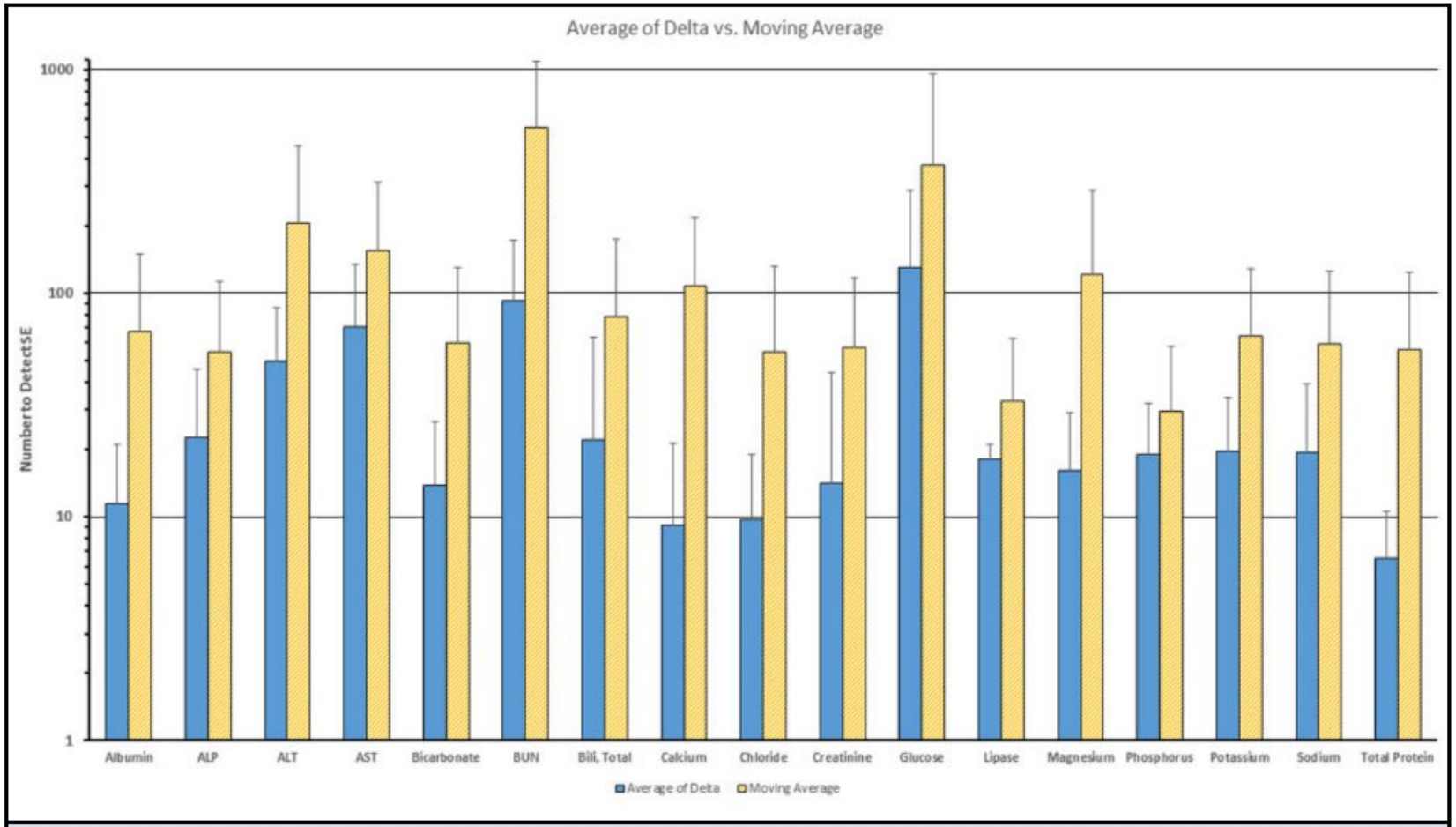

Fig. 4. Number of specimens required to detect systematic error using AoD (solid blue bars) and MA (hashed orange bars). Error bars represent SD.

PMID: 33993233

Strengths & Weaknesses of Moving Averages

- Able to detect systematic error (bias) with relatively few samples
  - Caveat – best performance on analytes with little between individual variability and those with low degree of skewedness
    - Compare ANP_{ed} for inpatient vs. outpatient populations
    - Transformation of data is an option I've not yet to explore
  - Mitigates the risk of erroneous result reporting
- Need higher volume analytes
- What about random error?

Increased Imprecision/Random Error

- Earlier this year we had an instrument issue affecting HbA1c results
  - Root cause was a pinprick sized hole in a vacuum line
  - Intermittently caused falsely high HbA1c values
  - Error was NOT caught by a simple moving average

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Moving SD and Moving Sum of Outliers: Detection of Increased Imprecision

- Liu et. al. developed movSD and movSO
- Imprecision monitored via the moving mean SD.
- Control limits dependent on pop. SD & block size
- Increased imprecision readily detected for assays with a small ratio $\frac{CV_I{}^2 + CV_g{}^2}{CV_a{}^2}$
  - Na^+ ratio = 1: ANP_{ed} = 43 samples with 2X CV_a
  - Cl^- ratio = 850: ANP_{ed} = 3411 samples with 2X CV_a

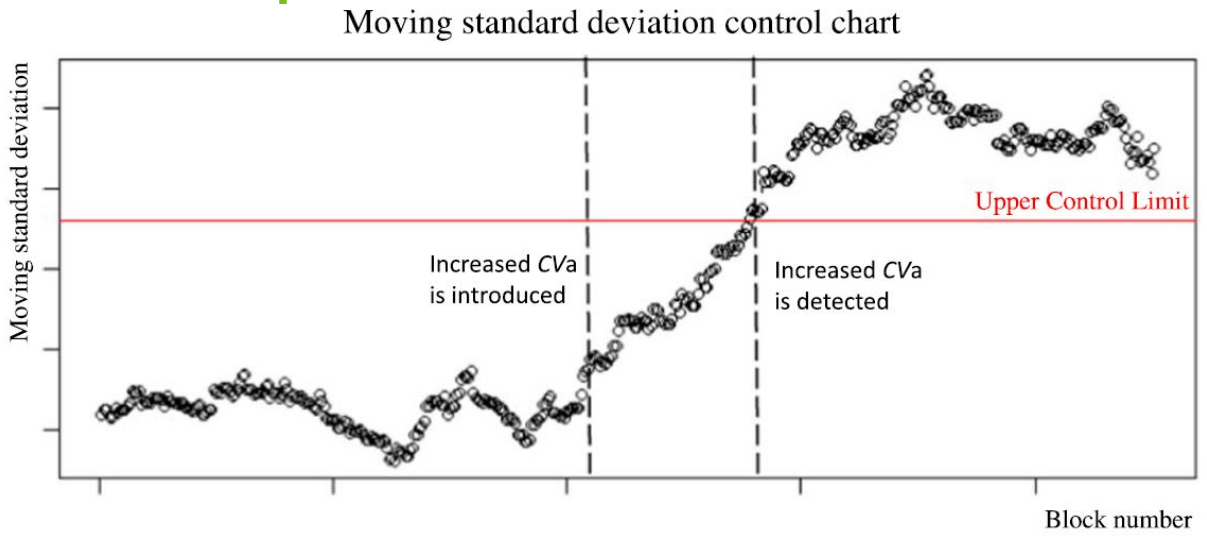


Fig. 1. A graphical representation of the moving standard deviation (SD) control chart detecting an increased analytical imprecision CV_a.

Clinical Biochemistry 52 (2018) 112–116 **PMID: 29107011**

Moving SD and Moving Sum of Outliers: Detection of Increased Imprecision

- MovSO performance virtually the same as MovSD
  - Values inside a threshold = 0
  - Values outside a threshold = 1
- MovSO also useful for detection of increased bias
  - Thyroglobulin in post-thyroidectomy
  - PSA in post-prostatectomy

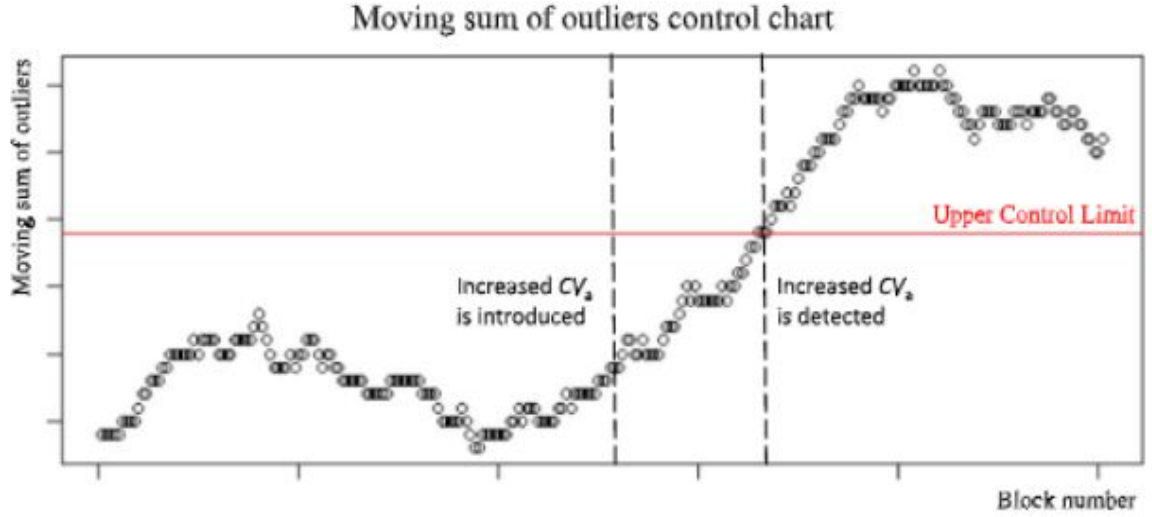
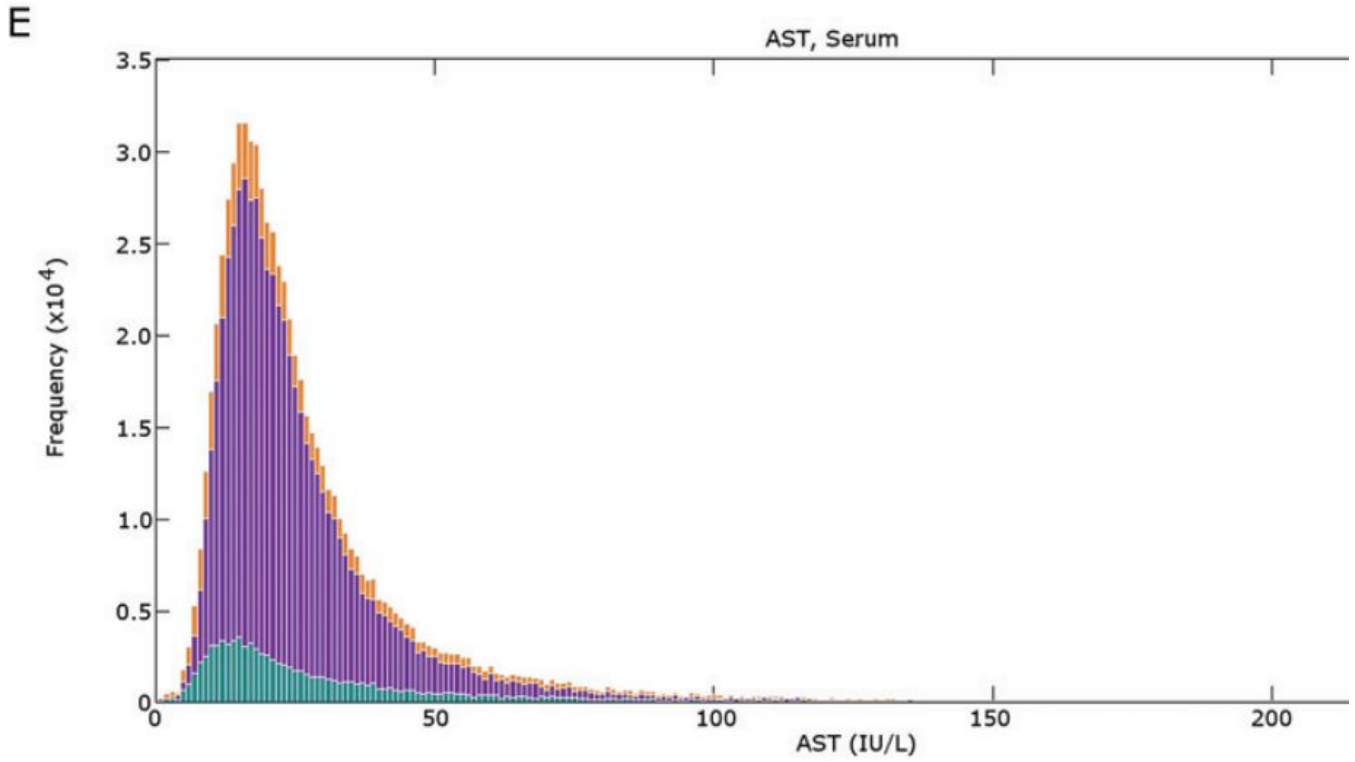


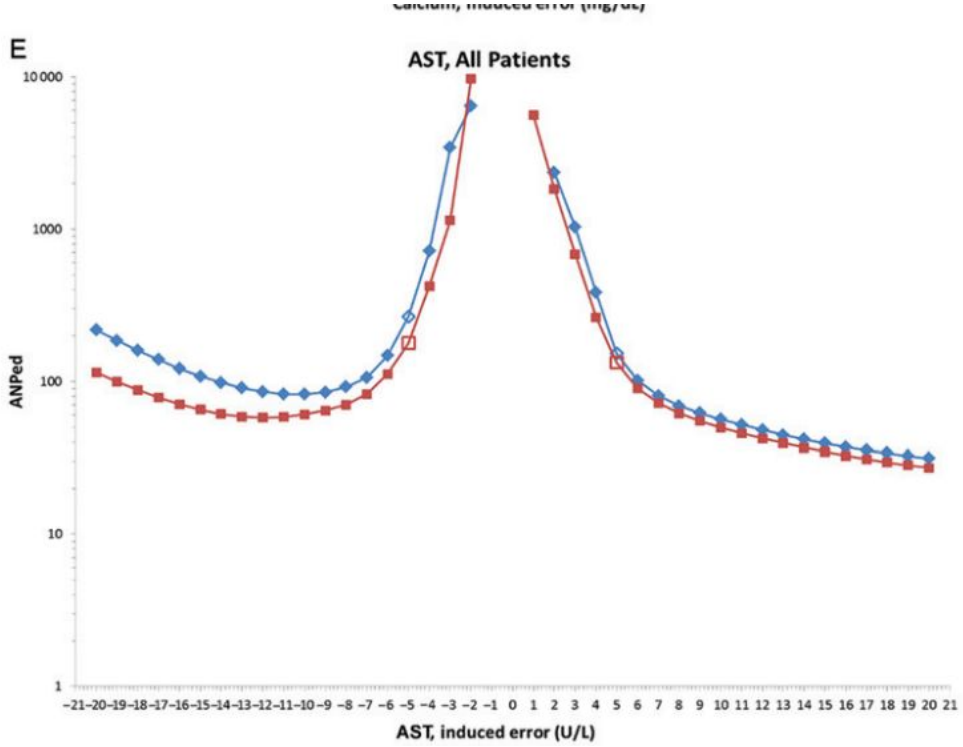
Fig. 2. A graphical representation of the moving sum of outliers control chart detecting an increase in analytical imprecision (CV_a).

Clin Biochem: 52; 112-116, 2018 **PMID: 29107011**

Clin Chem Lab Med 55; 1709-1724, 2017 **PMID:28328525**

Detection of Error in Skewed Distributions





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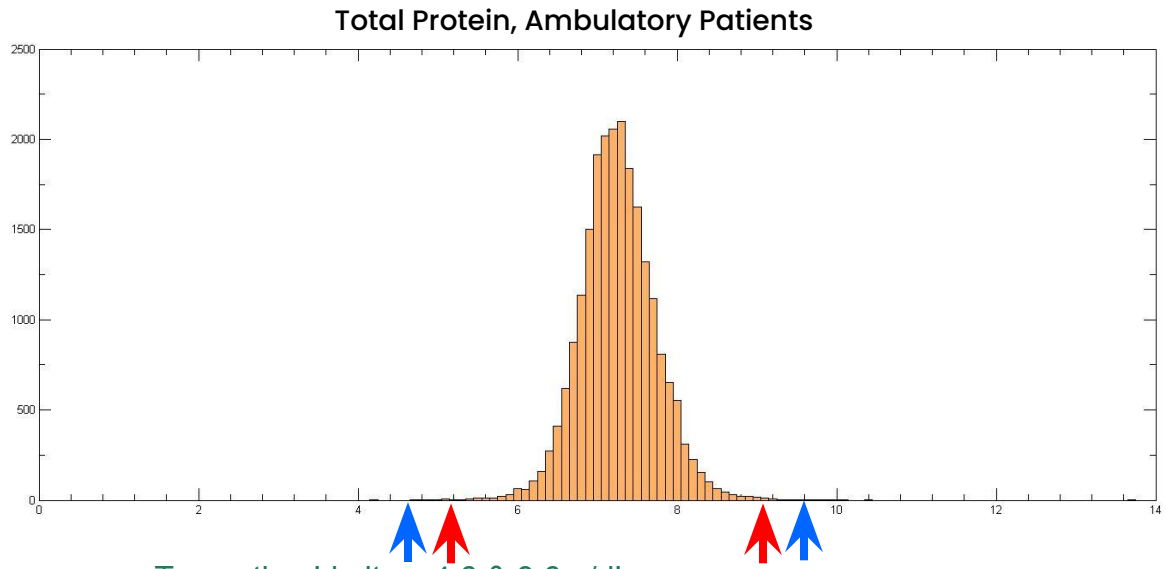
Effect of Data Truncation



Truncation Limits = 4.6 & 9.6 g/dL;

	ANPed	SD
+0.8 g/dL	22.00	16.48
-0.8 g/dL	15.32	9.79

ANPed = Ave. number of patients affected prior to error detection.

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Improving Error Detection of Skewed Distributions.

- Novel proposed solution, “Regression-Adjusted Real-Time Quality Control”
  - Duan X, Wang B, Zhu J, Zhang C, et al. *Clin Chem*, 67 (2021) 1342–1350 **PMID: 34355737**
  - Authors use multiple regression model (Age, sex, outpatient/inpatient, diagnosis, ordering dept.)
  - Residual = Actual observation – fitted value; Monitored the residual via exponentially weighed MA

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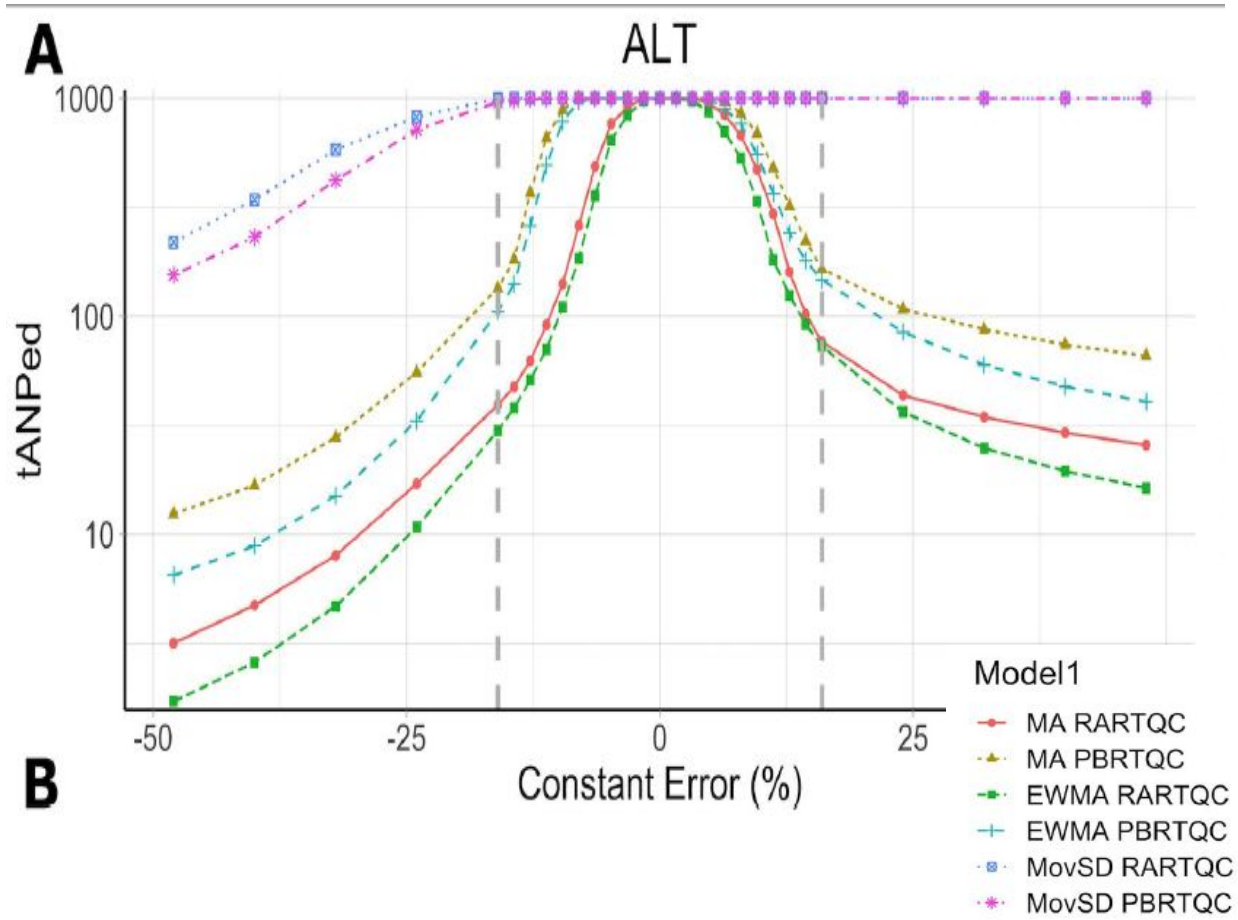
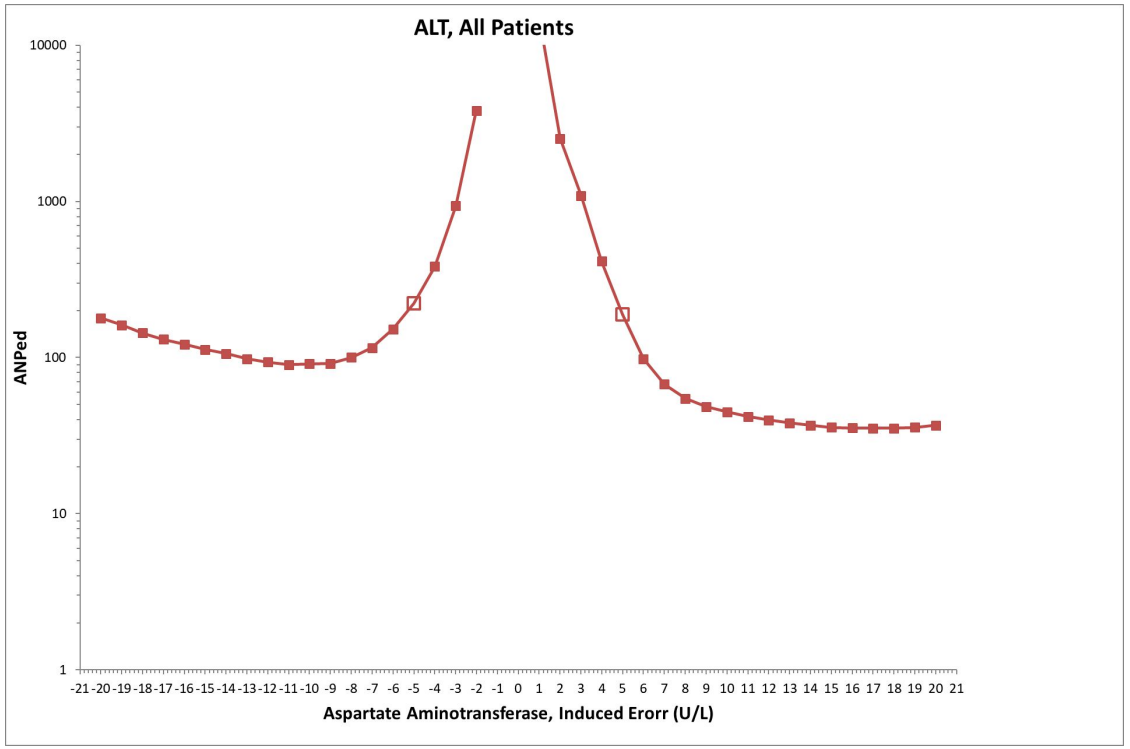
Regression Adjusted PBRTQC





"Regression-Adjusted Real-Time Quality Control"
PMID: 34355737

Remaining Challenges for PBRTQC #2

- PBRTQC – very interesting manuscripts
  - How many are actually being implemented?
- Lack of widely available software
  - Some software programs very limited
- Modeling of data needed for worthwhile error detection for many analytes
  - We need a better system

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Summary

- PBRTQC can detect error in advance of internal QC event
- Optimization method(s) are needed to establish sensitive protocols
  - Separation of inpatient and ambulatory pop improved error detection
  - Monitoring residual between measured and regression predicted value
- Moving standard deviation (movSD), Moving sum of outliers (movSO)
  - Clinical Biochemistry 52 (2018) 112–116 PMID: 29107011
- AoD improves SE detection on inpatients
  - Can be implemented with off-the-shelf software

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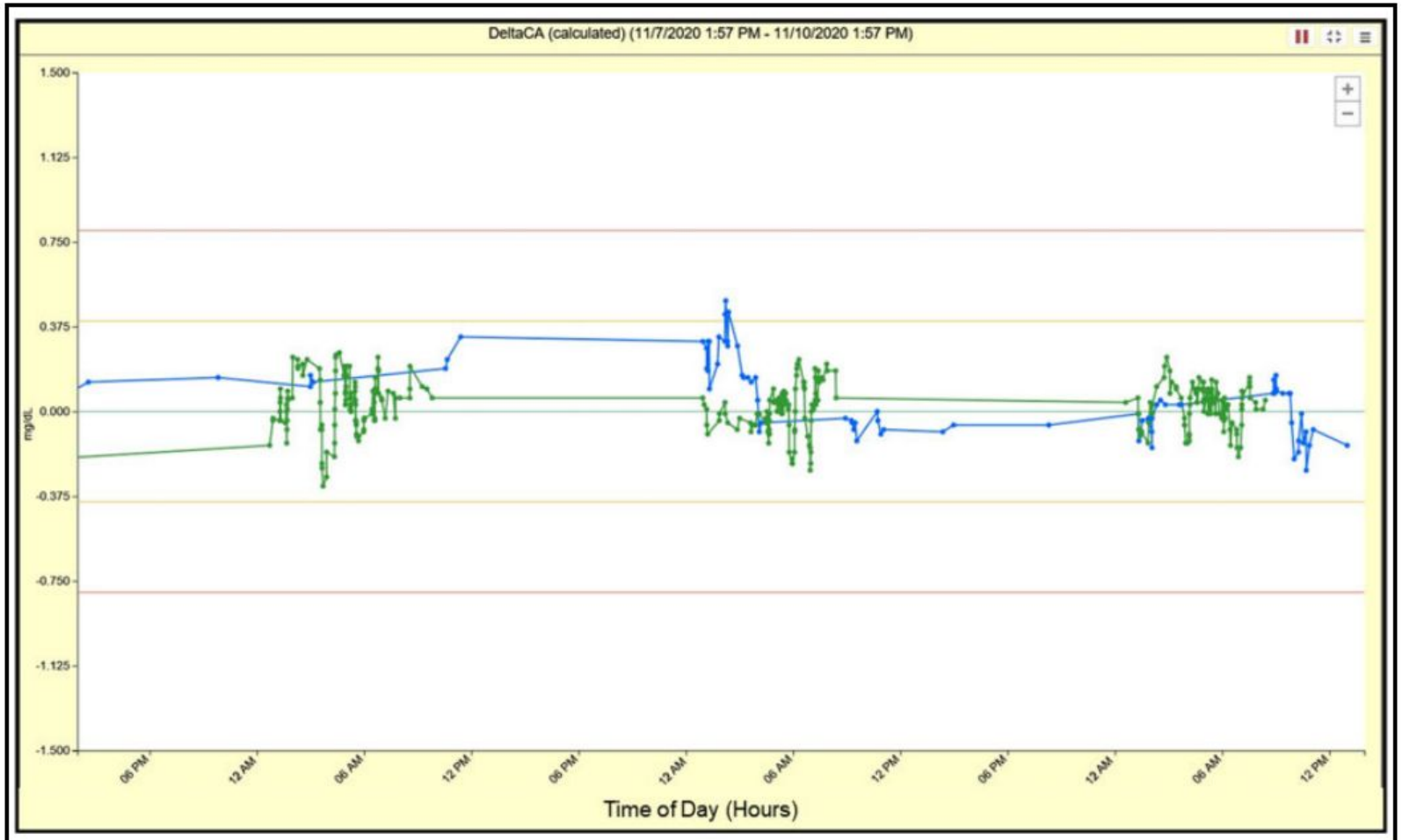
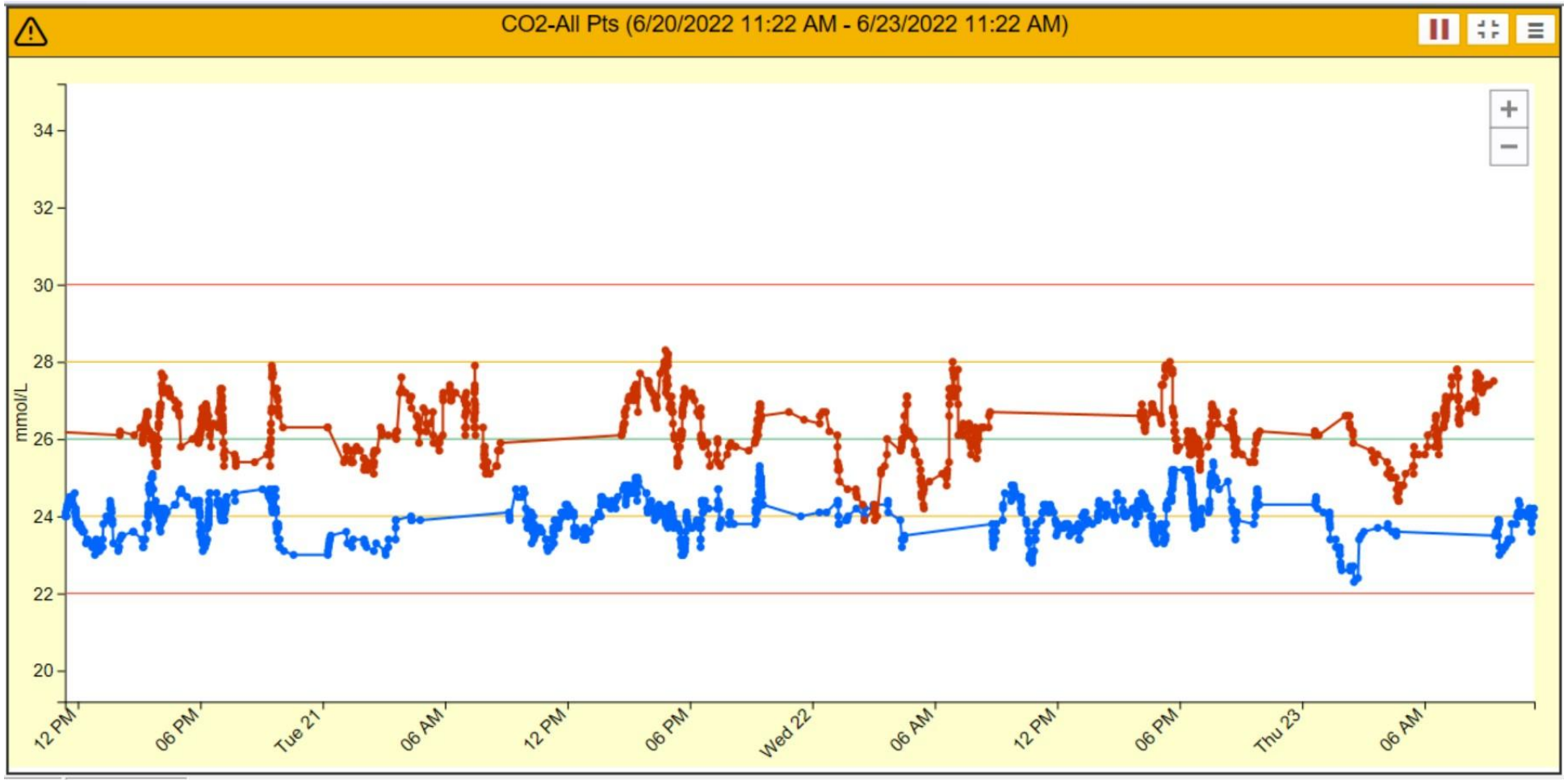


Fig. 3. Three-day AoD chart for calcium performed on 2 different chemistry analyzers. The horizontal axis represents the time of day. The green middle line represents a delta of 0, the inner yellow lines represent an average bias of ±0.375 mg/dL, and the outer red lines represent an average bias of ±0.75 mg/dL. There are 2 separate colored traces (green and blue), each representing a separate chemistry analyzer.

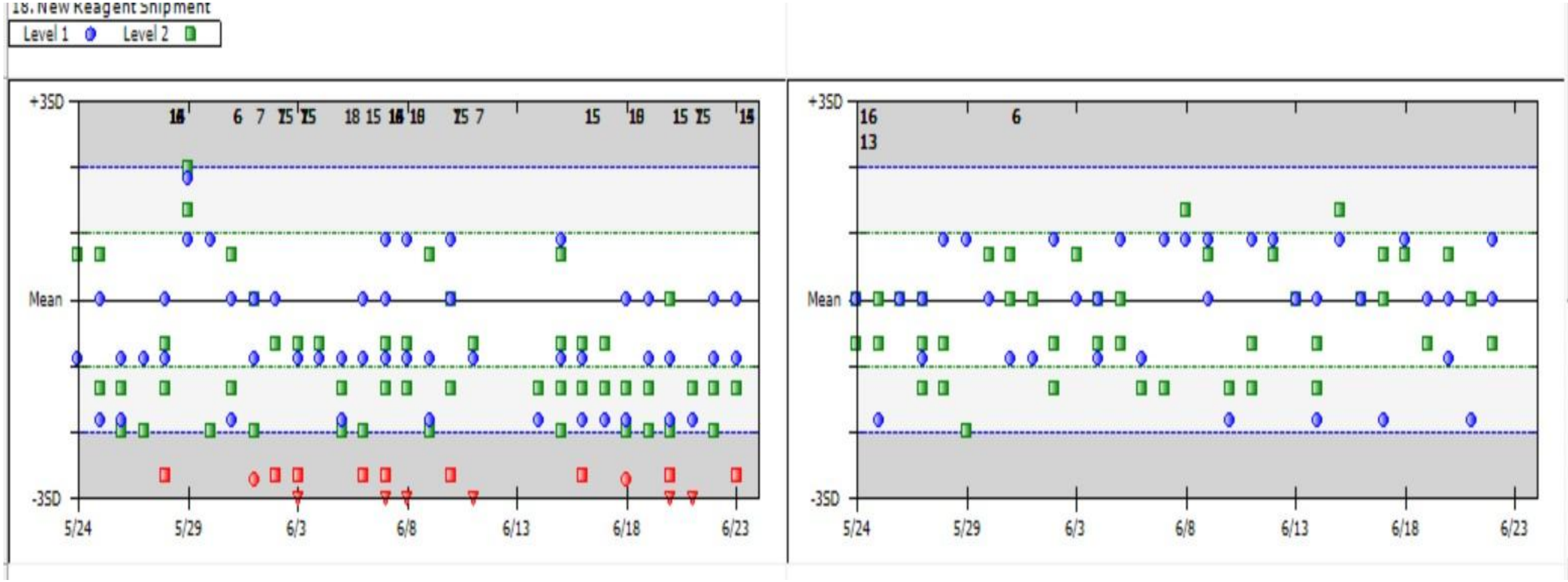
Cembrowski GS, Xu Q, Cervinski MA. Clin Chem 2021;67 (7): 1019-1029
PMID: 33993233

What Else Can Moving Averages Tell Me?

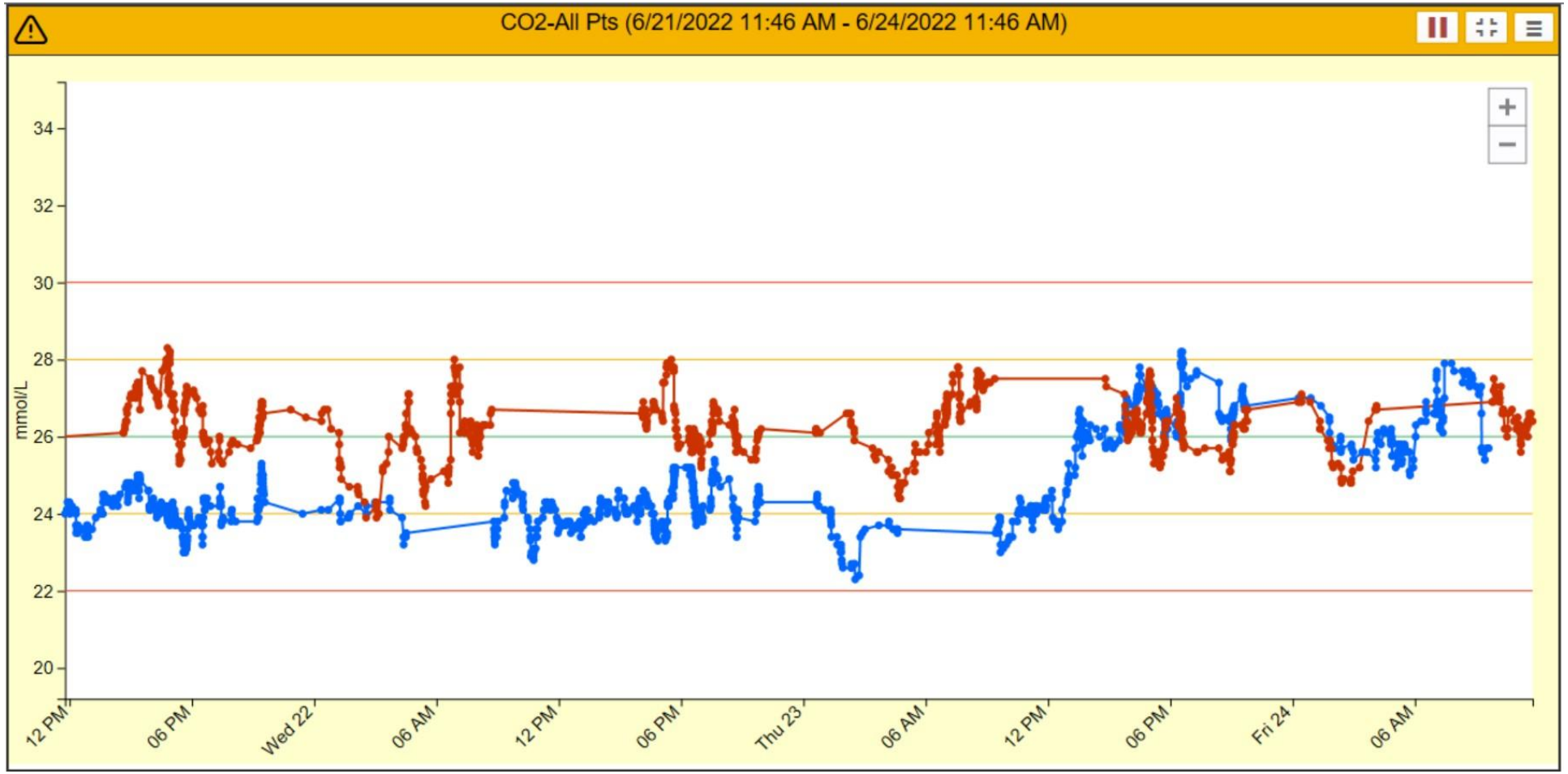
Detection of Inter-Instrument Bias Prior to Error



Correction of Inter-Instrument Bias Prior to Error



Correction of Inter-Instrument Bias Following Calibration



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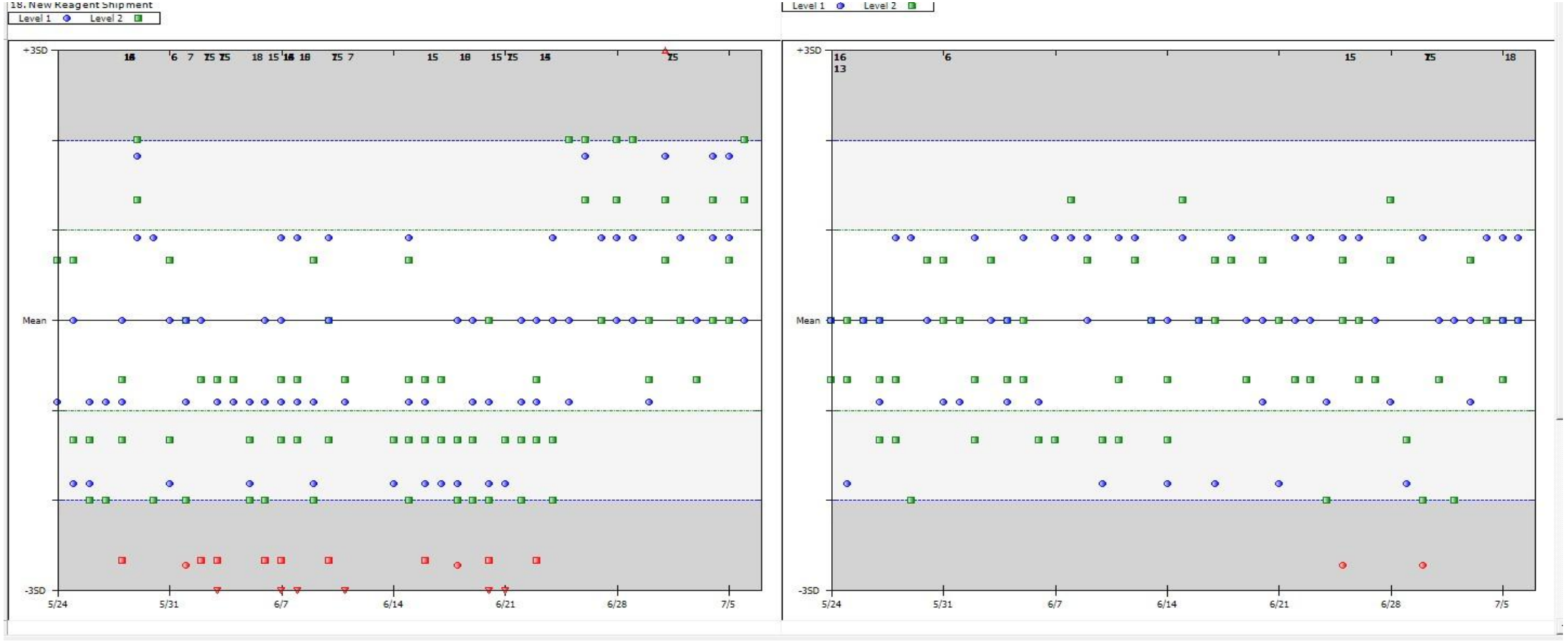

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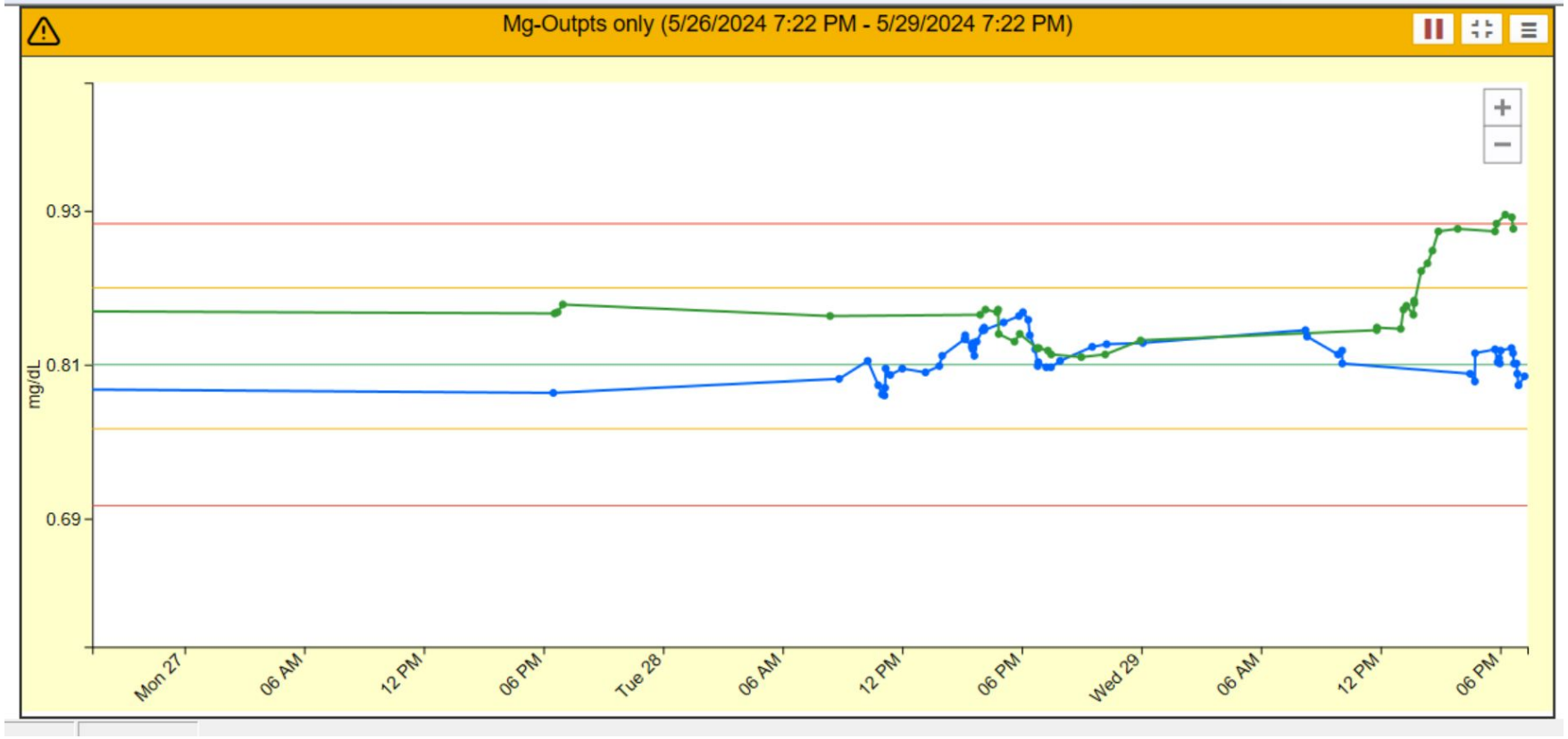
A Potential Shift in Serum Magnesium



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QC Data from same day

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Repeat Analysis of Patient Samples

Magnesium		TAE	0.1	mmol/L	8	Percent				
Tech	Date	Instrument/Module	Accession Number	Original Result	Repeat Result	Bias (Error)	Percent Error	Pass/Fail	TIC	Comments (Corrections made Y/N)
MM	5/11/2024	AU5		0.83	0.81	0.02	2.5	Pass	MM	
MM	5/11/2024	AU5		0.77	0.76	0.01	1.3	Pass	MM	
MM	5/11/2024	AU5		0.83	0.81	0.02	2.5	Pass	MM	
MM	5/11/2024	AU5		0.96	0.92	0.04	4.3	Pass	MM	
MM	5/11/2024	AU5		0.59	0.57	0.02	3.5	Pass	MM	
EWR	5/14/2024	AU5		1.03	1	0.03	3.0	Pass	JC	
EWR	5/14/2024	AU5		0.95	0.92	0.03	3.3	Pass	JC	
EWR	5/14/2024	AU5		0.88	0.84	0.04	4.8	Pass	JC	
EWR	5/14/2024	AU5		0.83	0.8	0.03	3.7	Pass	JC	
EWR	5/14/2024	AU5		0.94	0.88	0.06	6.8	Pass	JC	
RD	5/19/2024	AU1		0.92	0.85	0.07	8.2	Pass	JJ	
RD	5/19/2024	AU1		0.93	0.89	0.04	4.5	Pass	JJ	
RD	5/19/2024	AU1		0.89	0.86	0.03	3.5	Pass	JJ	
RD	5/19/2024	AU1		0.89	0.86	0.03	3.5	Pass	JJ	
RD	5/19/2024	AU1		0.91	0.89	0.02	2.2	Pass	JJ	
IMM	5/29/2024	7588/AU5		0.98	0.96	0.02	2.1	Pass	MM	
IMM	5/29/2024	7588/AU5		0.82	0.77	0.05	6.5	Pass	MM	
IMM	5/29/2024	7588/AU5		0.94	0.94	0	0.0	Pass	MM	
IMM	5/29/2024	7588/AU5		0.92	0.88	0.04	4.5	Pass	MM	
IMM	5/29/2024	7588/AU5		0.85	0.85	0	0.0	Pass	MM	
NB	6/12/2024	AU1		0.65	0.64	0.01	1.6	Pass	JC	

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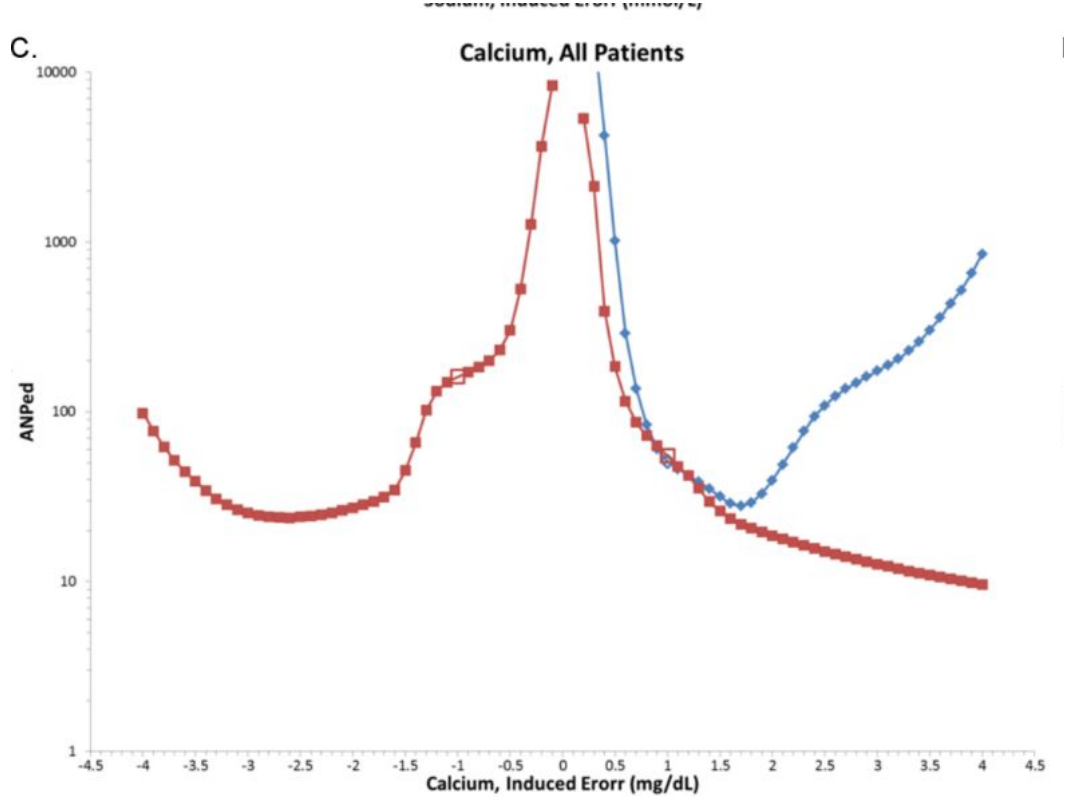
Detection of Error in Skewed Distributions

Albumin, Ca^{2+} & total protein = poor performance

- Particularly for negative bias



Calcium All

	ANP_{ed}	SD
-1.0 g/dL	∞	
+1.0 g/dL	51	55

Calcium Outpatient

	ANP_{ed}	SD
-1.0 g/dL	52	66
+1.0 g/dL	63	81

Calcium Inpatient

	ANP_{ed}	SD
-1.0 g/dL	109	104
+1.0 g/dL	75	66

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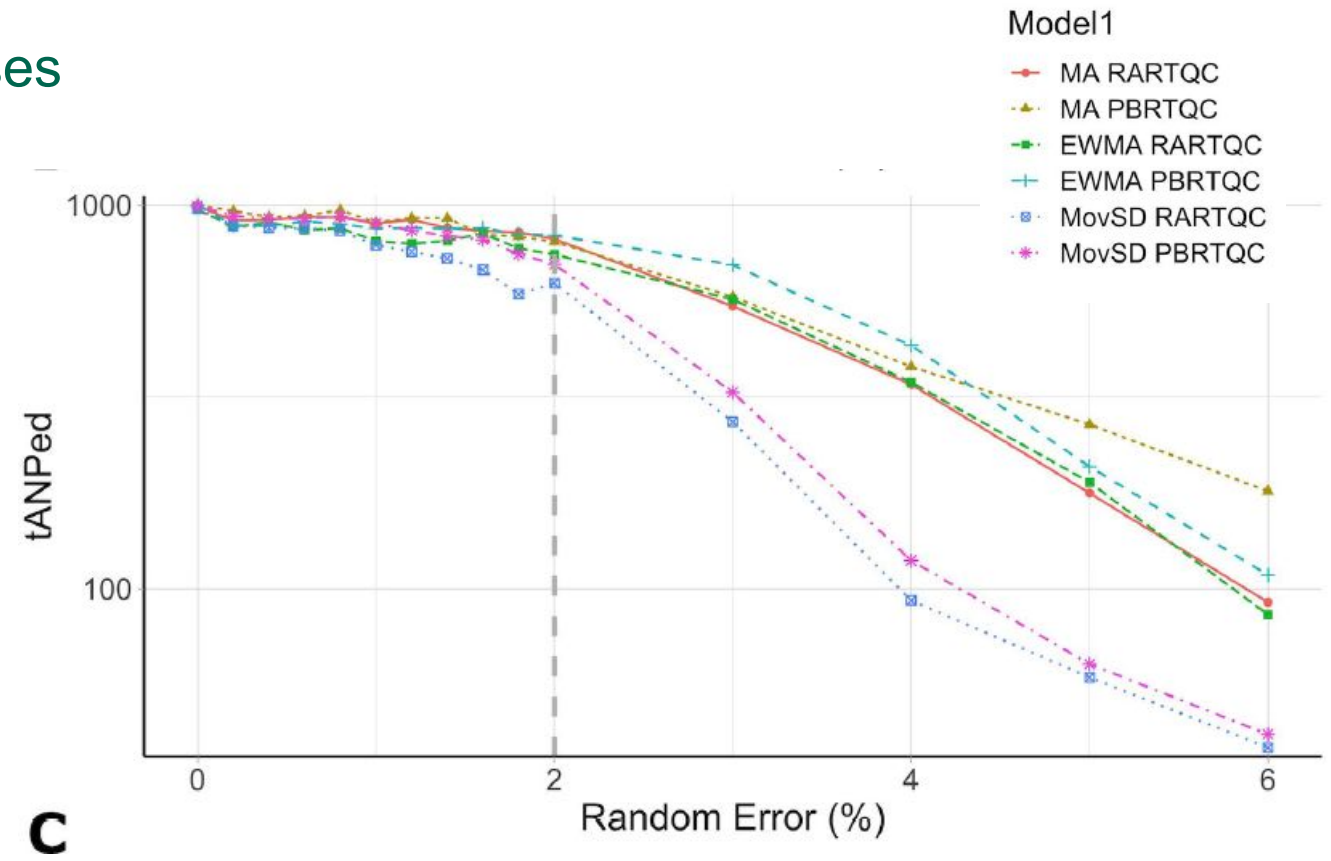
Regression Adjusted PBRTQC & Random Error

- Regression adjustment = only mild increases in random error detection
- Differences in ANP_{ed} between groups?



"Regression-Adjusted Real-Time Quality Control"
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