Best Practices to Recover from an Out-of-Control Event

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1

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2

Learning Objectives

1. Identify the first steps to take after an out-of-control event
2. Discuss how to evaluate patient results after an out-of-control event
3. Outline approaches to not only correct patient results but also to implement preventative actions

3

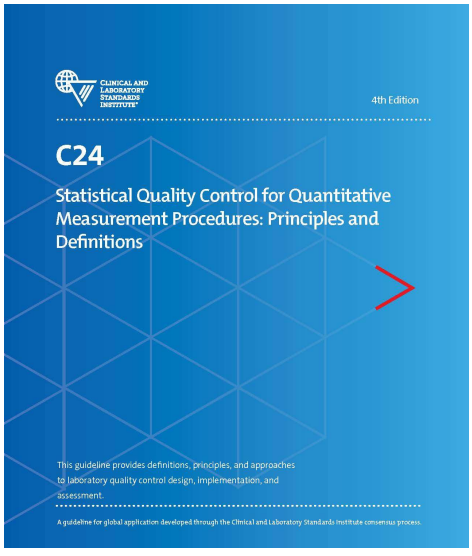
3

Primary reference

www.clsi.org

CLSI C24
Statistical Quality Control for Quantitative Measurement Procedures: Principles and Definitions, 4th Edition, 2016

- Design an effective QC strategy
- Select QC materials and QC frequency
- Establish QC target means and SDs
- Troubleshooting
- Recovery from out-of-control events



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4

Laboratory errors cause harm to patients and increase cost

Mistakes in a stat laboratory: types and frequency

Mario Plebani* and Paolo Carraro

Clin Chem 1997; 43(8): 1348-1351

40,490 laboratory results = 0.47% error rate [1/200 results]

6.4% → wrong care or inappropriate treatment
19.0% → unnecessary work-up, increased cost

5

5

Types of laboratory errors

Categories of Laboratory Errors

Phases of testing		Analytical error types	
Pre-analytical:	46-68%	Instrument:	14.2%
Analytical:	7-13%	Calibration:	9.0%
Post-analytical:	19-47%	Reagent:	3.3%

Laboratory Medicine 2012; 43(2): 41–44

Arch of Pathol Lab Med Dec 1996; 120: 1094-1101

Routine QC evaluates the analytical phase of testing

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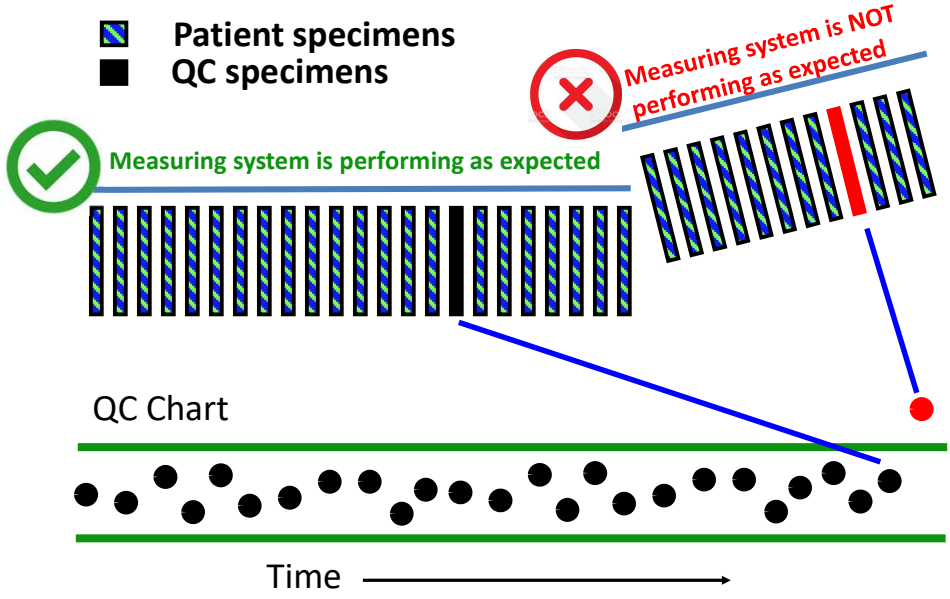


Slide courtesy of Greg Miller

7

7

Common causes of QC failures

- **Problem with the QC material itself** – improperly reconstituted, improperly stored, wrong QC material analyzed, inappropriate QC target mean or SD
- **Problem with reagents** – improper formulation or preparation, onboard degradation, altered shelf life, improperly stored, inappropriate QC target mean for a new reagent lot
- **Problem with calibrator** – improper formulation or target value assignment, improperly prepared or reconstituted, improper calibration frequency
- **Instrument problem** – lamp degradation, leak in tubing or damaged pipettor seals, mixer failure, pump failure
- **Inadequate maintenance** – inadequate cleaning or decontamination, wearing of parts
- **Improper procedure** – failure to follow SOP, inadequate SOPs or training program

8

8

QC Material	QC Value	Alert	SDI	Date/Time
Calcium LV1 QC	**4.95**	**LO**	**-3.6**	2/16/2021 8:16
Calcium LV1 QC	5.20		**-1.1**	2/15/2021 16:24
Calcium LV1 QC	5.31		**0.0**	2/15/2021 8:44
Calcium LV1 QC	5.33		**0.2**	2/14/2021 16:36
Calcium LV1 QC	5.35		**0.4**	2/14/2021 8:29
Calcium LV1 QC	5.40		**0.9**	2/13/2021 16:03
Calcium LV1 QC	5.45		**1.4**	2/13/2021 8:51

What steps should be taken when a QC out-of-control event occurs?

9

9

Steps to recover from an out-of-control event: PHASE 1

1. **DETECT** the analytical measuring system error (QC alert)
2. **STOP reporting patient results**
3. **INVESTIGATE** to determine the **ROOT CAUSE** of the problem
4. **IMPLEMENT CORRECTIVE ACTION** to correct the problem

10

10

Steps to take after an out-of-control event: PHASE 2

5 **EVALUATE IMPACT** on previously reported **PATIENT RESULTS**

6 **Take steps to MITIGATE PATIENT HARM**

7 **IMPLEMENT PREVENTATIVE ACTION** to prevent recurrence of the problem

Be sure to **Document** the entire process

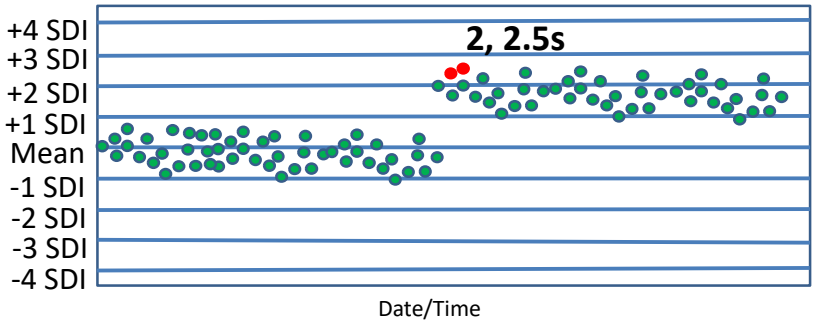
11

11

DETECT the analytical measuring system error

Establish an effective QC program

- Set QC target means (20 days) and target SDs (several months)
- Establish automated QC multi-rules (ex: 1,3s; 2,2.5s (within and across control), $8_{1.5m}$s, R4s)
- Routinely review Levey-Jennings charts



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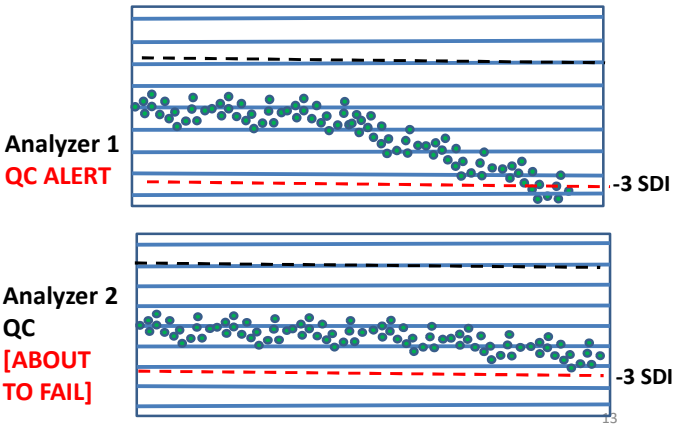
STOP patient result reporting

Immediately take measuring system (or assay) out of service, turn off auto-verification

Check other levels of QC

Check QC on other analyzers performing the same assay

Check QC for other analytes



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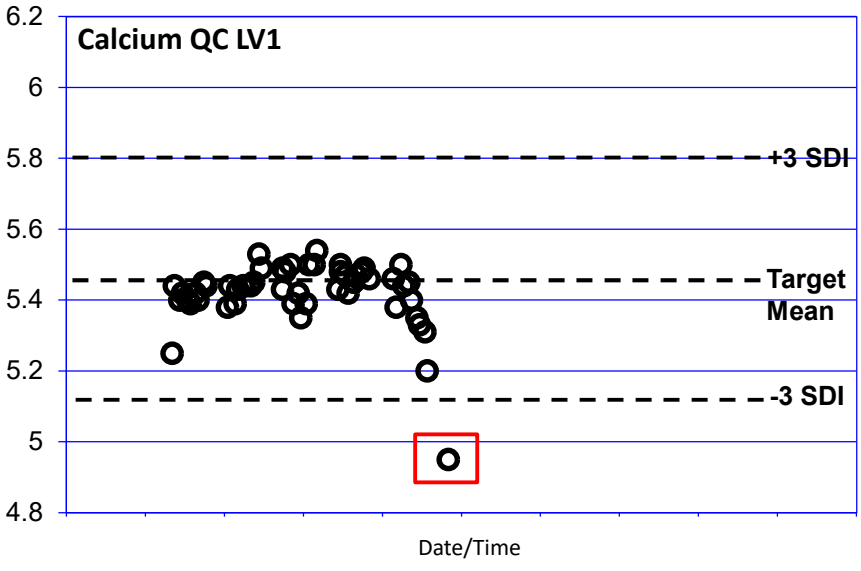
13

INVESTIGATE to determine the ROOT CAUSE



Review Records to get started

Any developing QC trends?

Any recent changes to the assay – ex: new reagent lot, new calibrator lot?

Any recent maintenance issues or parts replaced?

14

14

Tools to evaluate recent assay performance

Levey-Jennings charts and QC multi-rules - daily, weekly, monthly

Routine laboratory records – calibration records, lot changes, maintenance logs, temperature charts

Other laboratory QA records – 6 mo linearity checks, among-instrument comparisons

Peer Group QC data

Patient Based Real Time QC (PBRTQC) monitoring

15

15

Steps to recover from an out-of-control event: PHASE 1

1 **DETECT** the analytical measuring system error (QC alert)

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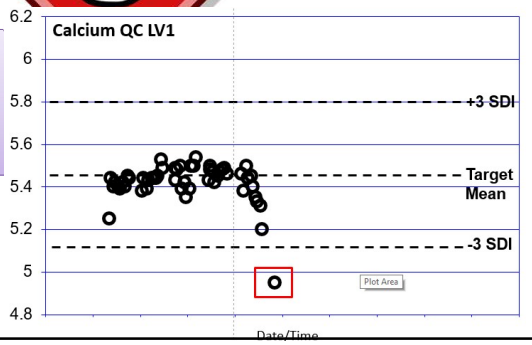
STOP reporting patient results

3 **INVESTIGATE** to determine the **ROOT CAUSE** of the problem



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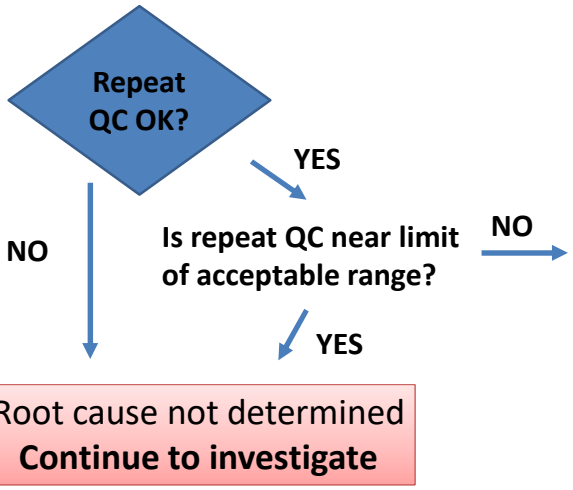
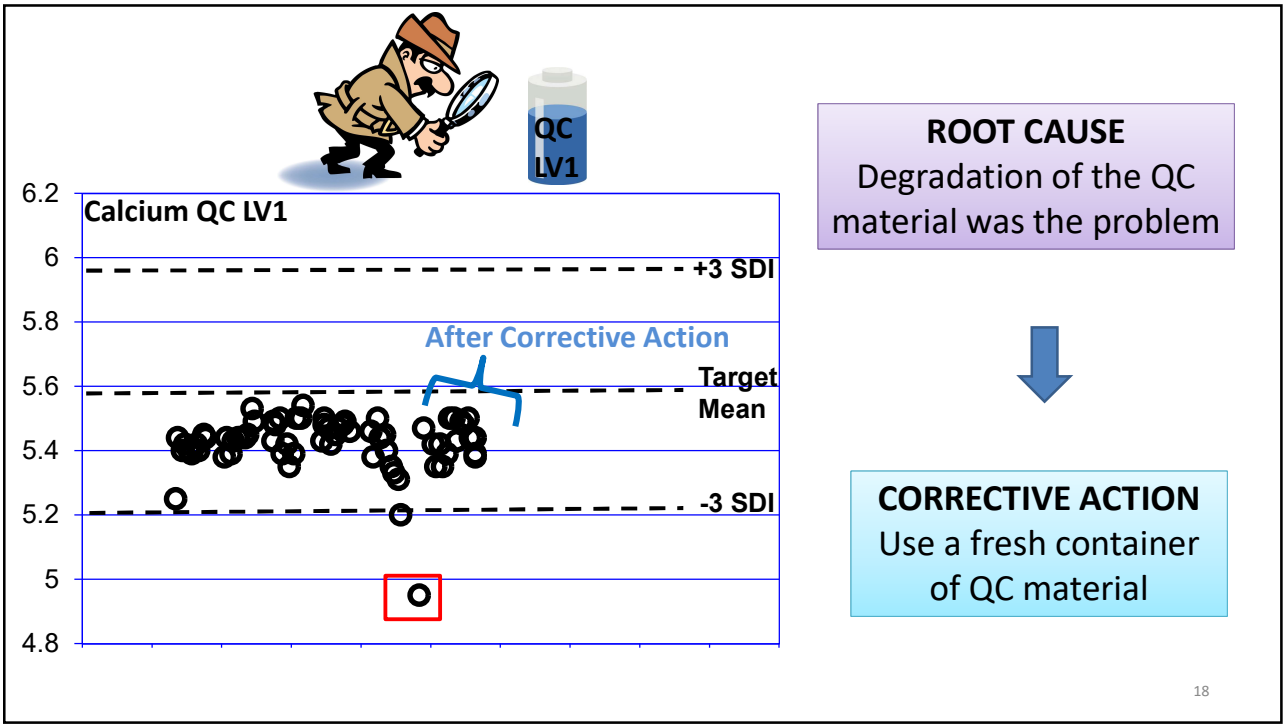
Repeat QC analysis using a fresh container of control material



ROOT CAUSE
Problem with **QC material itself** (or QC acceptance criteria)

- QC material evaporated or improperly stored
- QC material nearing expiration
- Wrong QC level analyzed
- Damaged shipment of QC material
- Using incorrect target mean for a new lot of QC material

17



ROOT CAUSE
Degradation of the QC material was the problem

CORRECTIVE ACTION
Use a fresh container of QC material

18

18

Steps to recover from an out-of-control event: PHASE 1

1. **DETECT** the analytical measuring system error (QC alert)
2.  **STOP reporting patient results**
3. **INVESTIGATE** to determine the **ROOT CAUSE** of the problem
4. **IMPLEMENT CORRECTIVE ACTION** to correct the problem

19

19

Implementation of corrective action is NOT THE END of the recovery process!!

Steps to take after an out-of-control event: PHASE 2

5. **EVALUATE IMPACT** on **previously reported PATIENT RESULTS**
6. **Take steps to MITIGATE PATIENT HARM**

7. **IMPLEMENT PREVENTATIVE ACTION** to prevent recurrence of the problem

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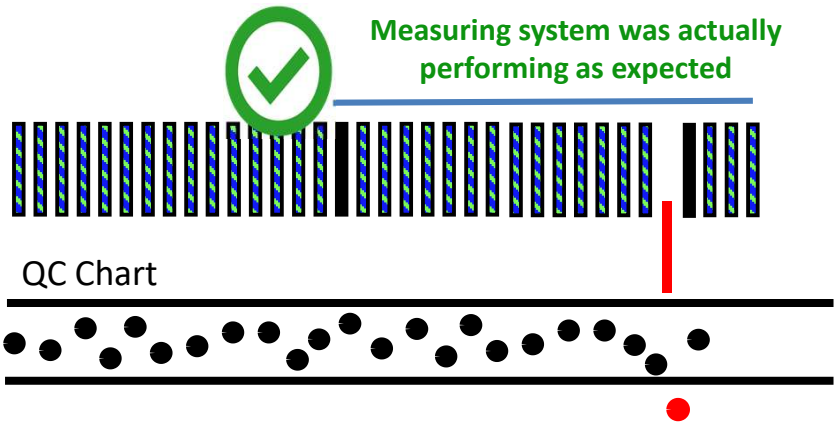
20

EVALUATE IMPACT on patient results



Measuring system was actually performing as expected

ROOT CAUSE:
Problem with QC material itself

No need to repeat patient samples

PREVENTATIVE ACTION
Modify QC material open-vial stability

21

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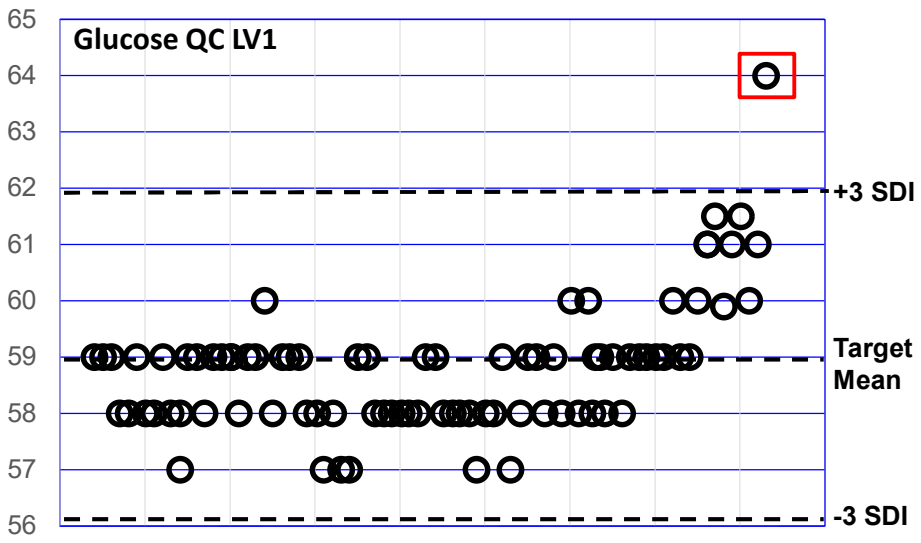

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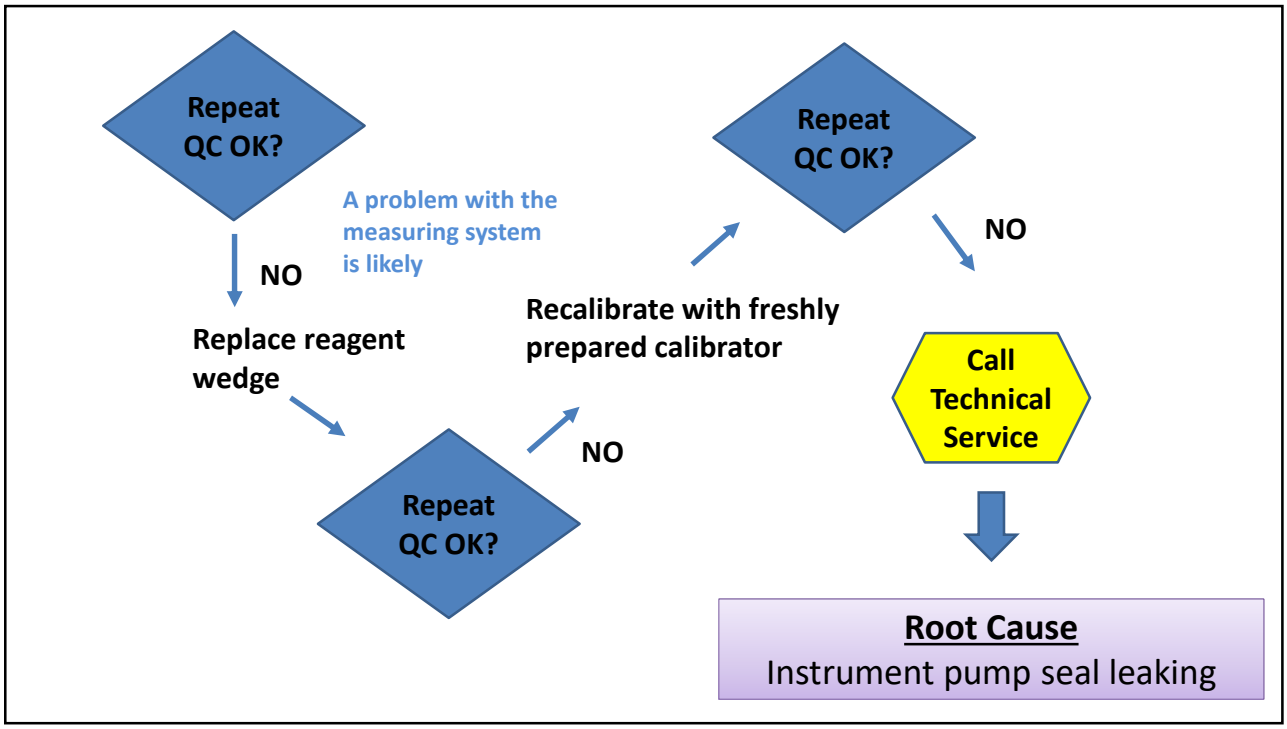
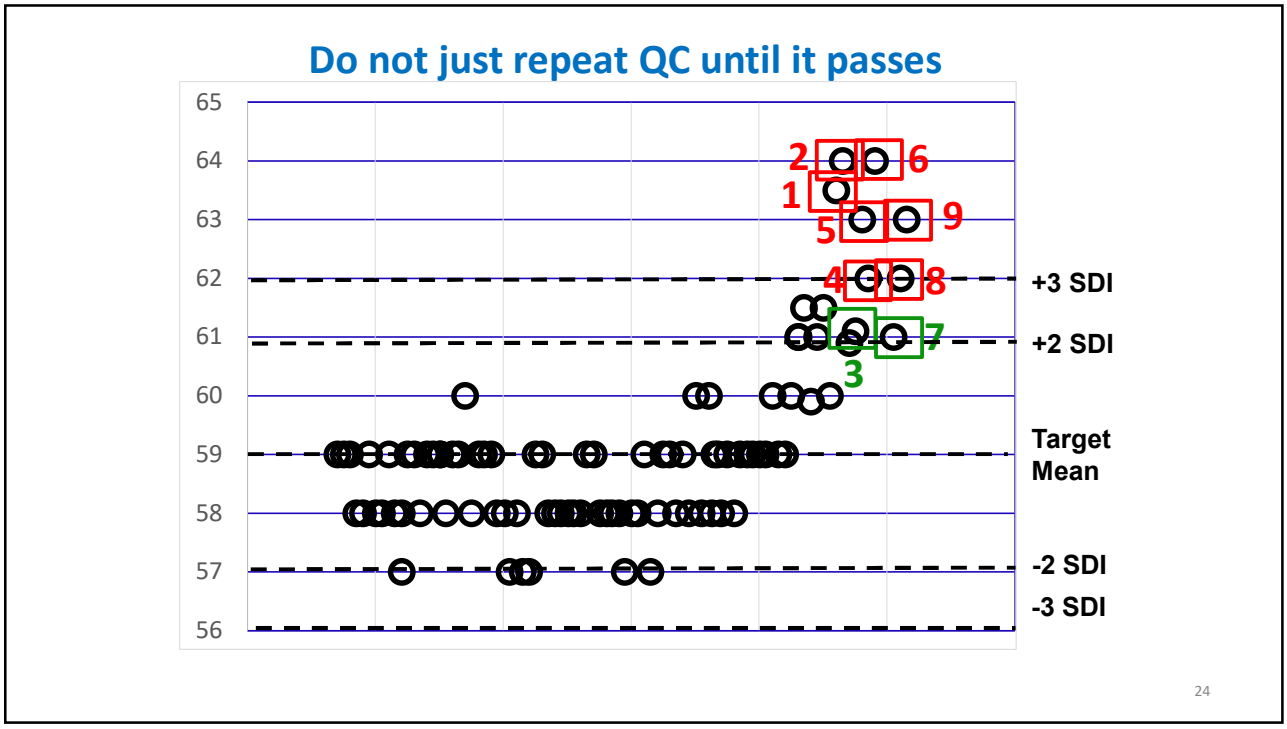

Repeat QC OK?
NO
Replace reagent wedge
Repeat QC OK?
NO
A problem with the measuring system is likely
Recalibrate with freshly prepared calibrator
Repeat QC OK?
NO
Call Technical Service
Root Cause
Instrument pump seal leaking

23


Do not just repeat QC until it passes
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58
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56
+3 SDI
+2 SDI
Target Mean
-2 SDI
-3 SDI
1
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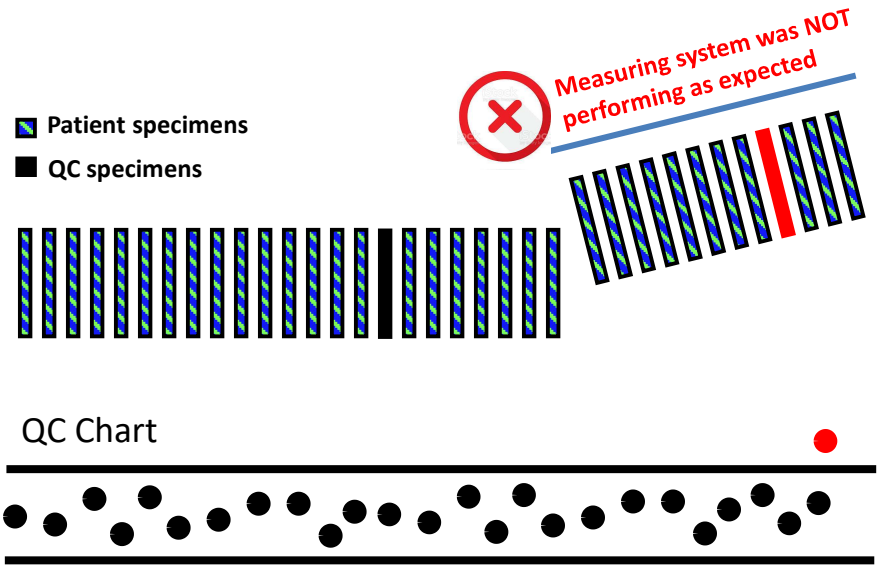
EVALUATE IMPACT on patient results



ROOT CAUSE
Problem is measuring system related

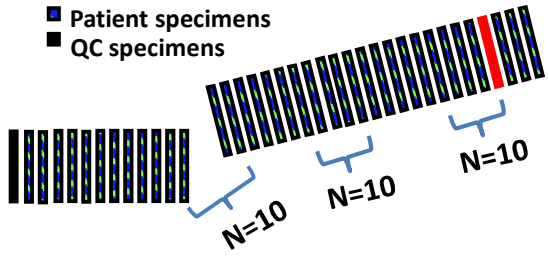
Patient results may be erroneous

Patient samples must be repeated

25

EVALUATE IMPACT on previously reported patient results

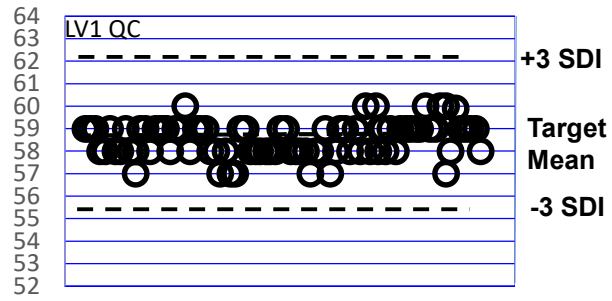
Determine the date/time of the last acceptable QC
Determine number of samples analyzed since the last acceptable QC

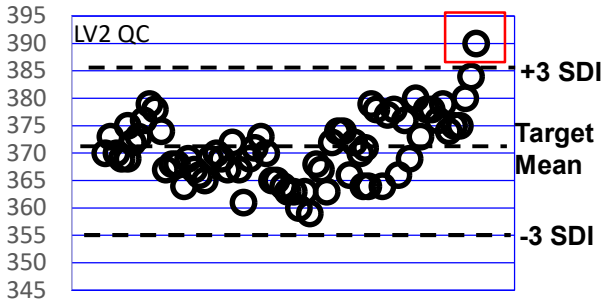


Repeat ALL patient samples
or
Repeat SUBSETS of patient samples

26

26





May not need to repeat all patient sample concentrations if only a single level of QC fails

ROOT CAUSE
Error due to calibration drift - calibration frequency inadequate, corrected by recalibration

QC LV1 had no effect,
Only repeat patient samples with original result > 59 mg/dL

27

27

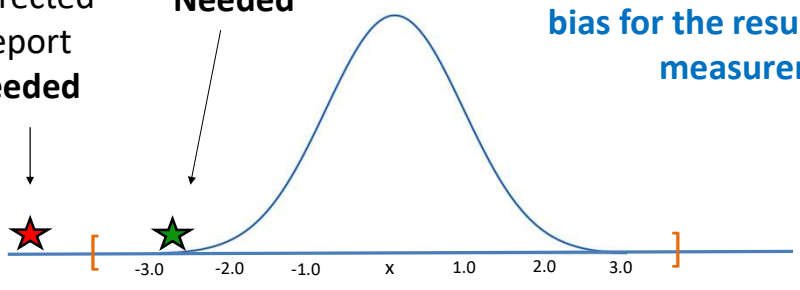
Do corrected reports for patient result repeats need to be issued?

Corrected Report **Needed**

Corrected Report **NOT Needed**

Allowable Total Analytical Error (TEa)

Limit for acceptable imprecision and bias for the result of a single measurement



28

28

Establishing TEa

European Federation of Clinical Chemistry and Laboratory Medicine (EFLM) Conference Recommendations

Clinical outcomes – allowable TEa based on change of analyte concentration in disease or for therapy; professional practice guidelines, clinical trials studies

Biological variation – biological variation studies; databases (EFLM, Westgard QC)

State-of-the art (assay performance) – manufacturer's package insert, laboratory's validation data

Clin Chem Lab Med 2015; 53(6): 833–835

29

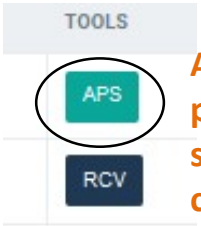
29

EFLM Biological Variation Database: https://biologicalvariation.eu/

Glucose (serum/plasma)

Between-individual (CV_g): 8.1%

Within-individual (CV_i): 5.0%



Analytical performance specifications calculator

References

LINK	ESTIMATE OF CVI	ESTIMATE OF CVG
Short-term, within-person variability in clinical chemistry test results, Eckfeldt J,Chambless LI and Shen Y, 1994, Arch Pathol Lab Med, 118, 496-500	4.2	10.8
Within subject biological variation of glucose and HbA1c in healthy persons and in type 1 diabetes patients, Carlsen S, Petersen PH, Skeie S, Skadberg O and Sandberg S, 2011, Clin Chem Lab Med, 49, 1501-7	4.5	5.8
The EuBIVAS: within- and between-subject biological variation data for electrolytes, lipids, urea, uric acid, total protein, total bilirubin, direct bilirubin and glucose, Aarsand AK, Diaz-Garzón J, Fernández-Calle P, et al, 2018, Clin Chem, 64(9), 1380-93	4.7	8.1
Within subject biological variation of glucose and HbA1c in healthy persons and in type 1 diabetes patients, Carlsen S, Petersen PH, Skeie S, Skadberg O and Sandberg S, 2011, Clin Chem Lab Med, 49, 1501-7	5.4	5.6
Biological and analytic components of variation in long-term studies of serum constituents in normal subjects, Harris EK, Kanofsky P, Shakarji G and Cotlove E, 1970, Clin Chem, 16, 1022-7	5.6	7.8
Biological and analytic components of variation in long-term studies of serum constituents in normal subjects. IV. Results of a study designed to eliminate long-term analytic deviations., Young DS, Harris EK and Cotlove E, 1971, Clin Chem, 17, 403-10	6.6	2.7
La variabilidad biológica intraindividual como objeto de calidad analítica, Ricós C, Codina R, 1989, Rev Diag Biol, 38, 34-6	10.8	

30

Calculates TEa based on biological variation estimates

CV_g: 8.1%

CV_i: 5.0%

Submit

$$TEa = 1.65 \times 0.5\ CV_i + 0.25\ (CV_i^2 + CV_g^2)^{1/2}$$

%Total Error Specifications

Minimum Specification	Desirable Specification	Optimum Specification
9.8	6.5	3.3

https://biologicalvariation.eu/search?q=glucose

31

31

TAKE STEPS TO MITIGATE HARM – issue corrected reports to providers

Original Result Glucose	Repeat Result TEa = 10%	Unit Diff	% Diff	Issue Corrected Report?
102	91	-11	-10.8	YES
78	65	-13	-16.7	YES
225	221	-4	-1.8	NO
110	89	-21	-19.1	YES
68	56	-12	-17.6	YES
367	350	-17	-4.6	NO
98	90	-8	-8.2	NO
121	105	-22	-17.3	YES
280	266	-14	-5.0	NO
325	311	-14	-4.3	NO
97	85	-12	-12.4	YES
101	82	-19	-18.8	YES

Develop tools to enable expedited review and automated decisions

32

32

Approaches to mitigate patient harm

- Develop data entry templates to quickly identify patients that require corrected reports
- Call in extra staff to assist with patient sample repeats and provider phone calls
- Issue memos to clinical staff in real time
- Engage Risk Management or institutional Safety Teams

33

33

Steps to take after an out-of-control event: PHASE 2

5 **Evaluate Impact** on **previously reported patient results**

6 **Take steps to MITIGATE PATIENT HARM**

7 **Implement Preventative Action** to prevent recurrence of the problem

PREVENTATIVE ACTION

Implement more frequent preventative maintenance including pump seal replacements

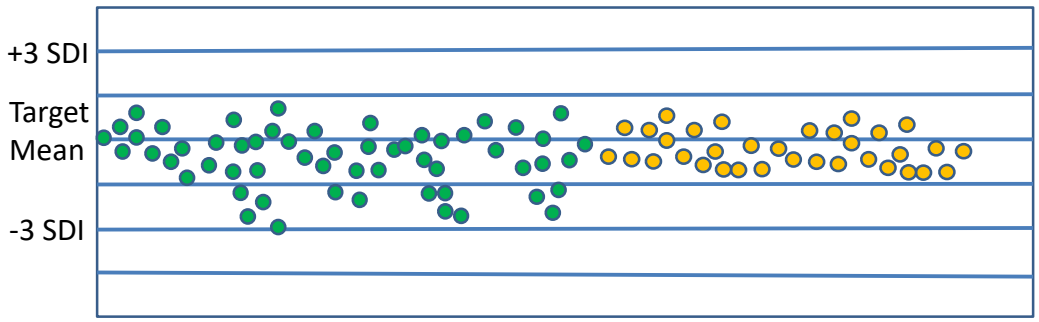
34

Approaches for PREVENTATIVE ACTION

35

35

Increased frequency of QC analysis



- ✓ If assay is unstable
- ✓ For large testing volumes
- ✓ For results with immediate clinical intervention

36

36

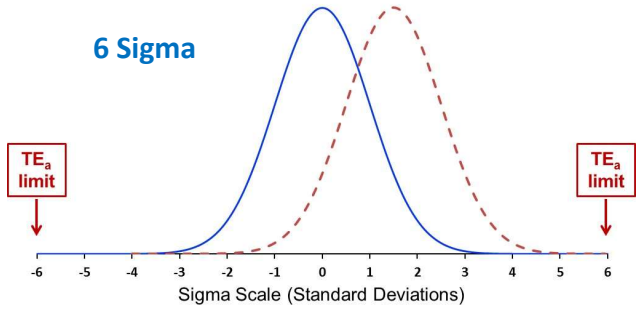
Establish QC rules based on method performance relative to TEa limits

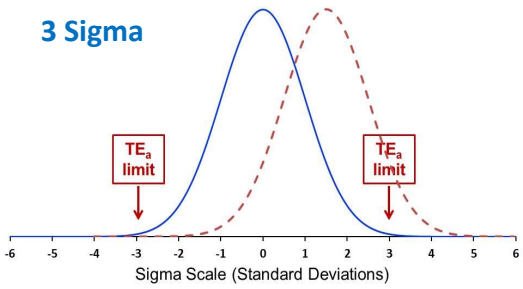
$$Sigma_{(x)} = \frac{(TEa_{(x)} - |Bias_{(x)}|)}{SD_{(x)}}$$

$$Sigma = \frac{TEa_{(x)}}{SD_{(x)}}$$

37

Using the Sigma metric to set QC rules





- A small bias can be tolerated
- Larger SDI criteria can be used (1, 5s)

- More conservative SDI criteria needed to keep assay in control
- Use QC Multi-rules (1, 3s; 2, 2.5s within and across, 8, 1.5s, R4s)

Slide courtesy of Greg Miller

38

38

Peer Group QC programs

		Assay Mean	Your Mean	Your SD	Group Mean	Group SD	Mean Diff	Delta %	SDI Range	Notes	SDI	Your CV	Group CV
RBC 10^6/µL	L1	2.360	2.358	.02	2.354	.03	.004	.2			.1	.8	1.4
	L2	4.400	4.382	.04	4.404	.05	-.022	-.5			-.5	.8	1.1
	L3	5.300	5.293	.04	5.328	.06	-.036	-.7			-.6	.8	1.1
HGB g/dL	L1	5.60	5.59	.06	5.60	.08	-.01	-.2			-.1	1.0	1.4
	L2	12.70	12.46	.08	12.54	.12	-.09	-.7			-.7	.6	1.0
	L3	16.60	16.37	.11	16.53	.15	-.16	-1.0			-1.1	.6	.9
HCT %	L1	16.90	16.82	.21	16.82	.33	.00	.0			.0	1.3	2.0
	L2	36.90	36.70	.45	37.00	.59	-.30	-.8			-.5	1.2	1.6
	L3	47.60	47.52	.53	47.92	.73	-.40	-.8			-.5	1.1	1.5
MCV fL	L1	71.30	71.32	.62	71.45	.91	-.13	-.2			-.1	.9	1.3
	L2	83.80	83.75	.69	84.01	.97	-.26	-.3			-.3	.8	1.2
	L3	89.80	89.77	.68	89.93	1.01	-.16	-.2			-.2	.8	1.1
MCH pg	L1	23.80	23.70	.27	23.79	.33	-.09	-.4			-.3	1.1	1.4
	L2	28.80	28.43	.28	28.49	.33	-.05	-.2			-.2	1.0	1.2
	L3	31.40	30.93	.27	31.03	.35	-.10	-.3			-.3	.9	1.1
MCHC g/dL	L1	33.40	33.23	.45	33.29	.60	-.06	-.2			-.1	1.4	1.8
	L2	34.30	33.95	.43	33.91	.53	.04	.1			.1	1.3	1.6
	L3	35.00	34.46	.39	34.51	.52	-.05	-.1			-.1	1.1	1.5
PLT 10^3/µL	L1	90	91	3.67	89	3.99	02	1.7			.4	4.0	4.5
	L2	250	248	6.14	249	7.79	00	.0			.0	2.5	3.1
	L3	549	549	7.58	546	12.14	03	.5			.2	1.4	2.2
RDW-SD fL	L1	47.60	47.03	.41	47.05	.50	-.02	.0			.0	.9	1.1
	L2	48.20	47.86	.53	47.99	.65	-.13	-.3			-.2	1.1	1.3
	L3	47.50	46.97	.39	47.14	.66	-.17	-.4			-.3	.8	1.4
RDW-CV %	L1	18.70	18.53	.18	18.51	.20	.02	.1			.1	.9	1.1
	L2	16.10	15.93	.10	15.95	.13	-.02	-.1			-.2	.7	.8
	L3	14.70	14.58	.08	14.62	.13	-.04	-.3			-.3	.6	.9
WBC 10^3/µL	L1	2.940	2.932	.06	2.966	.07	-.034	-1.1			-.5	2.2	2.5
	L2	6.720	6.615	.10	6.663	.13	-.049	-.7			-.4	1.6	1.9
	L3	15.840	15.802	.16	15.902	.25	-.100	-.6			-.4	1.0	1.5

Acceptability criteria: within ±3SDI and CV < 1.5x group CV

Lot 1088
Peer group size
L1 = 1367
L2 = 1368
L3 = 1370

Historical performance data for current lot and previous lots included

39

39

Peer Group QC programs

Peer Group Blood Gas
Program: O2HB **Reagent Lot#s: 15208016-7, 15208019-815208016-9**

	Lab Mean	Group Mean	Group SD	SDI	#of Labs
O2Hb LV1	81.8	82.3	0.46	1.08	20
O2Hb LV2	51.4	48.5	0.61	**4.75**	20
O2Hb LV3	22.7	20.4	0.80	**2.88**	21

- Results can be submitted in real time, peer group data provided
- Can review peer group QC values for new lots of reagent, calibrator, assay reformulations
- Can be used by manufacturers to assist with troubleshooting
- Can facilitate faster identification of the root cause of the issue

40

40

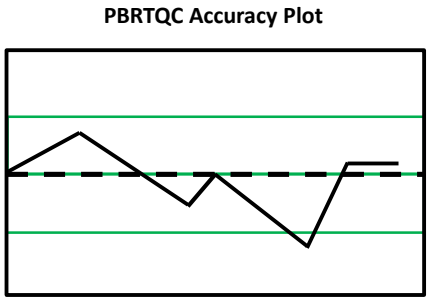
Patient-based real-time QC (PBRTQC)

Means, medians, exponentially weighted means, cumulative sums (or other metrics) are calculated every N patient sample results

Metrics compared against acceptability criteria limits (based on: SDI, RCV, TEa, modeling approaches) and alerts generated

Variables that influence effectiveness:

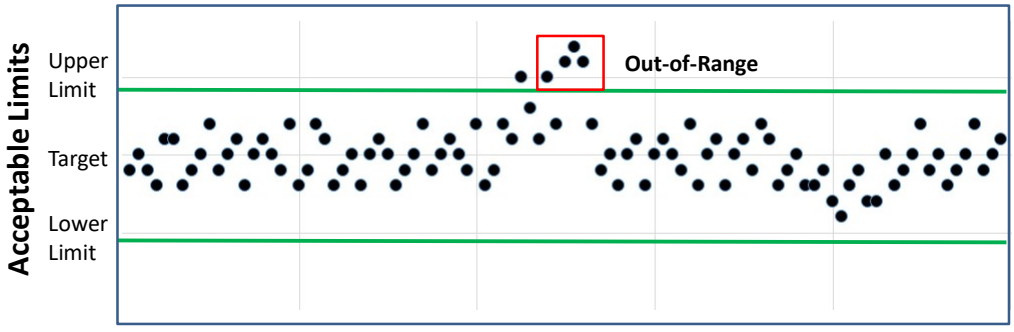
- **Number of patient results to average**
- **How to identify outliers and extreme values -subgroups needed, not useful for all analytes**
- **What magnitude of error should trigger an alert**



41

41

Patient-based real-time QC (PBRTQC) plot



Detection of a systematic error

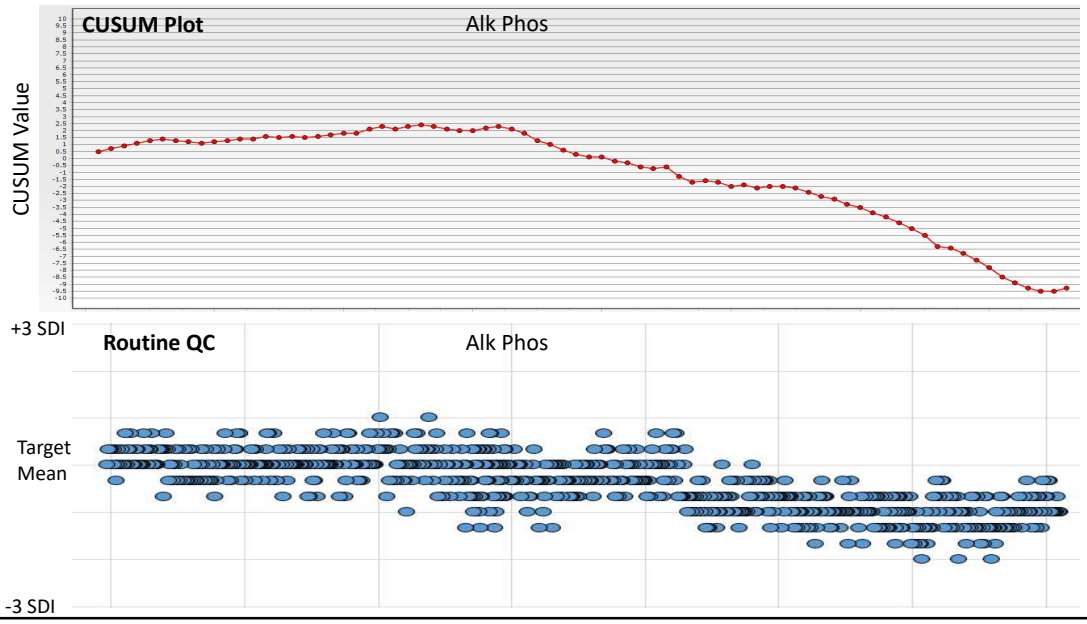
Responding to an out-of-control event:

- Review records
- Run assay QC immediately to confirm alert
- Run previously analyzed patient samples to confirm alert

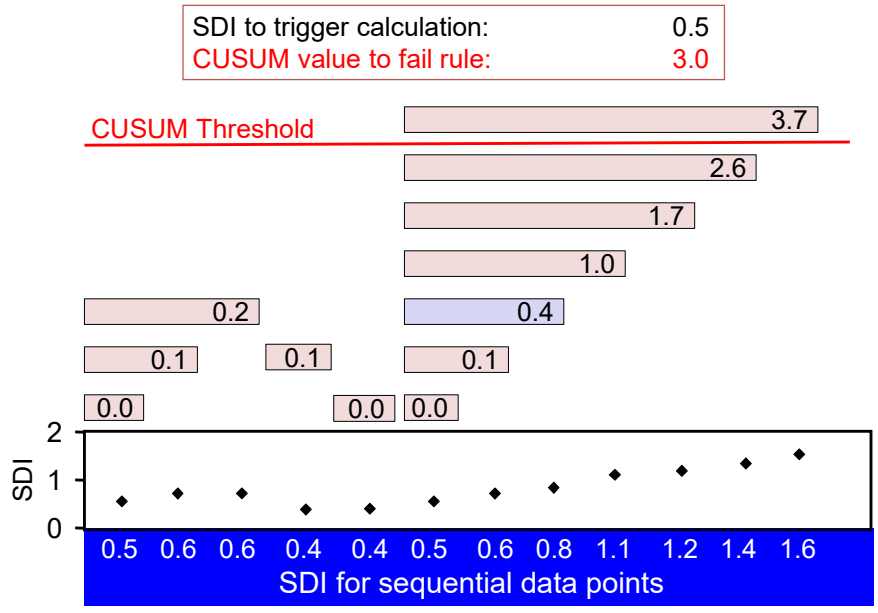
42

42

Cumulative Summation – can be used for QC or patient samples



43



Slide courtesy of
Greg Miller

44

Comparison of PBRTQC to standard statistical QC

Attribute	Standard QC	PBRTQC
Frequency	1-3x per day	After a defined # of patient samples
Phases Tested	Analytical	Pre-analytical, Analytical, Post-analytical
Commutability Characteristics	Not commutable (for most)	Commutable
Type of Error Detected	Systematic, Random	Systematic

Am J Clin Pathol 1984;81:492–9

45

45

Conclusions

Steps to respond to an out-of-control event:

- **PHASE 1:** **Detect Error, Stop Patient Testing, Investigate and Identify Root Cause, Implement Corrective Action**
- **PHASE 2:** **Evaluate Impact on Patient Results, Mitigate Patient Harm, Implement Preventative Action**

TEa should be used to evaluate the impact on patient results after an out-of-control event, and also for designing an effective QC program that will prevent errors

Additional tools are available that can improve ability to DETECT errors and PREVENT them from reaching clinical significance

46

46

47