The Delta Check in Action: *Causes and consequences of discrepant laboratory results*

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Outline: The Delta Check in Action

- Definitions
- Causes
- Institution
- Implications & Investigation Tips

Outline: The Delta Check in Action

Initiation of a Discrepant Results Policy:

<u>One hospital's experience: A Sentinel Event</u>

- Delta check alert occurred on several chemistry and hematology results for an individual patient
  - "Delta MCV" called to RN on floor; RN acknowledged receipt; heme results released to the patient chart
  - Delta chemistry results were confirmed; results released to the patient chart
- Type and cross was performed for transfusion
  - Patient had no previous ABO history for comparison
- Patient was given 2 units of blood and experienced a transfusion reaction

<u>What happened</u>?

The wrong patient was drawn…

Delta Check: Definition

- Difference between a patient's *present* laboratory result and their *previous* result exceeds a predefined limit within a predefined length of time
  - First described by Nosanchuk and Gottmann in 1974
  - Computers first used for delta check identification in 1975
  - Addresses errors that are not detectable with other methods of quality control; assesses preanalytical, analytical, postanalytical errors
- Two main goals…identify:

Changes in patient condition

Sample quality issues / patient misidentification

Am J Clin Pathol 65:707 (1974); Clin Chem 21:1648 (1975)

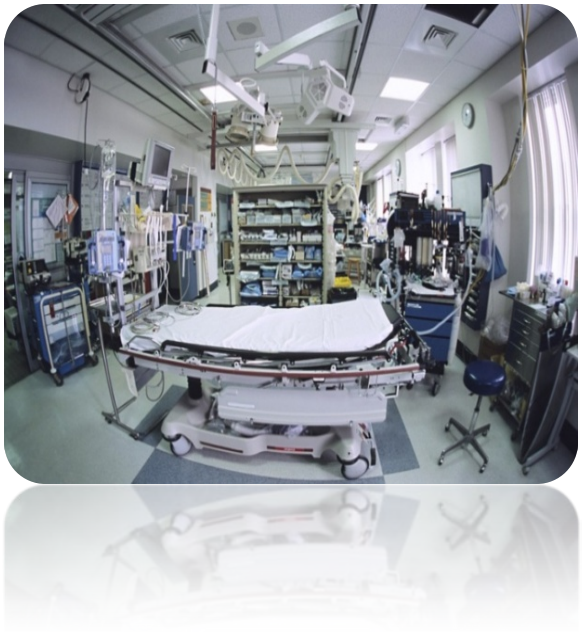
Delta Check: Examples

Test	Result	Absolute Difference	# of Days b/t Results
Urea Nitrogen	< 50 mg/dL	10 mg/dL	2
	> 50 mg/dL	20%	2
Sodium	All	13 mEq/L	3
Calcium	< 8 mg/dL	0.8 mg/dL	2
	> 8 mg/dL	1.0 mg/dL	2
MCV	All	5 fL	0

- *Actual limits will vary by analyte and institution*

Why bother using Delta Checks?

- Identify possible patient-specific errors
- Predictive value for detecting true specimen errors: between 0.4 and 6% [1,2]
  - >75% can be attributed to true changes in the patient's medical condition [2-5]
  - Therefore, goal is to minimize false positives
- Early error identification: patient care and safety [2]
  - Errors: incorrect drug dosing, anticoagulation therapy, cardiac intervention, blood transfusion, etc.
- Alert providers; fluctuations may indicate need for medical intervention



[1] Kim et al., J Korean Med Sci 5:189 (1990); [2] Dufour et al., Am J Clin Pathol 110: 531 (1998); [3] Ladenson, Clin Chem 27:1648 (1975); [4] Sher, Clin Chem 25:870 (1979); [5] Iizuka et al., Clin Chem 28:2244 (1982)

Outline: The Delta Check in Action

Causes of Discrepant Results:

Pre-analytical variation	Analytical variation	Biological variation
• Patient identification • Specimen collection • Post-collection	• Instrument • Method	• Rhythmic changes • Lifespan • Treatment

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Pre-Analytical Variation: Identification

- **Definition: "Mislabeled"**
  - Joint Commission National Patient Safety Goals:
    - Minimum two unique patient identifiers
    - Label samples in front of patient
  - Mislabeled: One or more identifiers are incorrect
    - Wrong patient label; tube label does not match paperwork or electronic order; contradictory labels on one tube
  - Major issue in transfusion medicine
  - Difficult to detect and assess—often go unreported

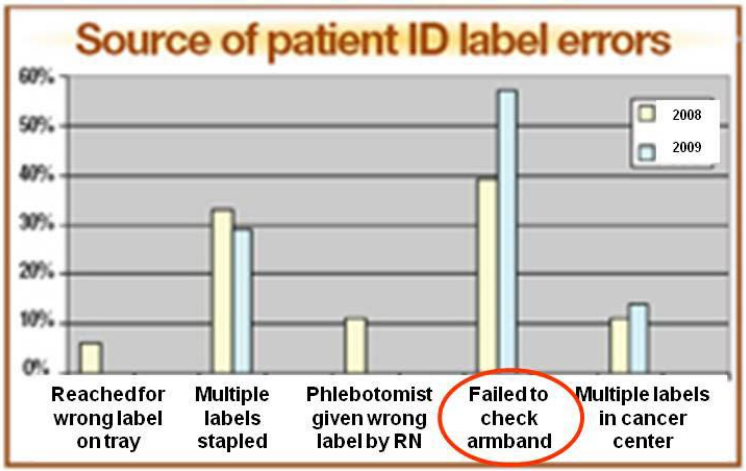
Pre-Analytical Variation: Identification

- **Definition: "Misidentified"**
  - WBIT = Wrong Blood in Tube
  - Possible causes:
    - NICU, ER, geriatric populations
    - Sleeping, uncommunicative patients
    - Language barriers
    - Fraud
    - Identical names
    - Multiple births
- Majority of errors (10/17) associated with invasive procedures are due to patient misidentification
  (Howanitz et al., Arch Pathol Lab Med 2002)

Table 1 Prevailing causes of misidentification in laboratory diagnostics.

1.	Physician ordering laboratory tests on the wrong patient
2.	Incorrect or incomplete entry of patient's data in the Laboratory Information System
3.	Collection of specimens from the wrong patient
4.	Inappropriate labeling of the specimens
5.	Lost identification (label) on the specimens
6.	Incorrect entry of patient's results in the database of the Laboratory Information System

Lippi et al., Clin Chem Lab Med 47:143(2009)



Titus, K. CAP Today Apr 2010

Pre-Analytical Variation: Identification

- Patient identification error statistics:
  - In transfusion medicine = 0.05% of specimens
  - In general laboratory = 1% - 7.4% of specimens
  - In stat laboratory = 8.8% of specimens
- WBIT rate = 0.03-0.04%, up to 8.8%
- Smaller hospitals have higher error rates
- Extrapolated data: 160,000 adverse events/yr due to misidentification
- Pre-verification error rate = 85.5%

Post-verification error rate = 14.5%

Important! Laboratorians are catching the majority of these errors.

Grimm, E. Clin Lab News, Oct 2008; Valenstein et al., Clin Lab Med 24:976(2004); Valenstein et al., Arch Pathol Lab Med 130:1106(2006); Renner et al., Arch Pathol Lab Med 117:573(1993); Carraro et al., Clin Chem 53:1338(2007); Grimm, E et al., APLM 134:1108(2010)

Pre-Analytical Variation: Collection

Source of Variation:	Effect on Laboratory Result(s):
IV fluid dilution	False increase in corresponding analytes, dilution of other analytes
Serum vs. plasma	Fibrinogen causes differences in total protein levels; clot formation causes release of K^+ from platelets; extremely high WBC counts increase K^+ from cell leakage
Order of blood tube collection	Contamination of subsequent tubes with anticoagulant, preservatives or other additives. Red top (non-additive) tube should be used as waste/discard tube.
Improper anticoagulant	EDTA: increased K^+, decreased Ca^{2+}, Mg^{2+}, alk phos
	Sodium citrate: increased Na^+, anion gap
	Heparin: Inhibits PCR reactions
	Others: Increase in predominant anticoagulant component
Long tourniquet time	Concentration of analytes, false increase in K^+, ammonia, lactate
Contrast agents	Some gadolinium agents falsely decrease Ca^{2+}
Serum separator tubes (SST)	Serum separator gel may absorb small molecules such as drugs. Red top tubes recommended for therapeutic drug monitoring and other drug levels.

Pre-Analytical Variation: Post-collection

- Sample transport:
  - Timing: off-site blood drawing, delayed centrifugation, WBC glucose utilization, leakage of RBC contents
  - Temperature: Arterial blood gases, cryoglobulin, K^+, lactic acid, ammonia
  - Light exposure: bilirubin, vitamins, porphyrins
  - Tube closure: pH, pCO_2, iCa^{2+}, acid phos, ethanol
  - Pneumatic tubes: may cause RBC damage
  - Note: hemolysis is masked in whole blood samples—spin to confirm
- Centrifugation: Timely separation of serum and cells (w/i 2 hrs)
  - Delayed separation affects glucose, K^+, LD, ammonia, phosphate
  - Excessive spins: hemolysis due to RBC membrane damage; K^+, enzymes affected
- Storage
  - Labile analytes must be frozen, avoid excessive freeze-thaw cycles

Laboratory Mistakes:

Hospital study:

46% preanalytical

7% analytical

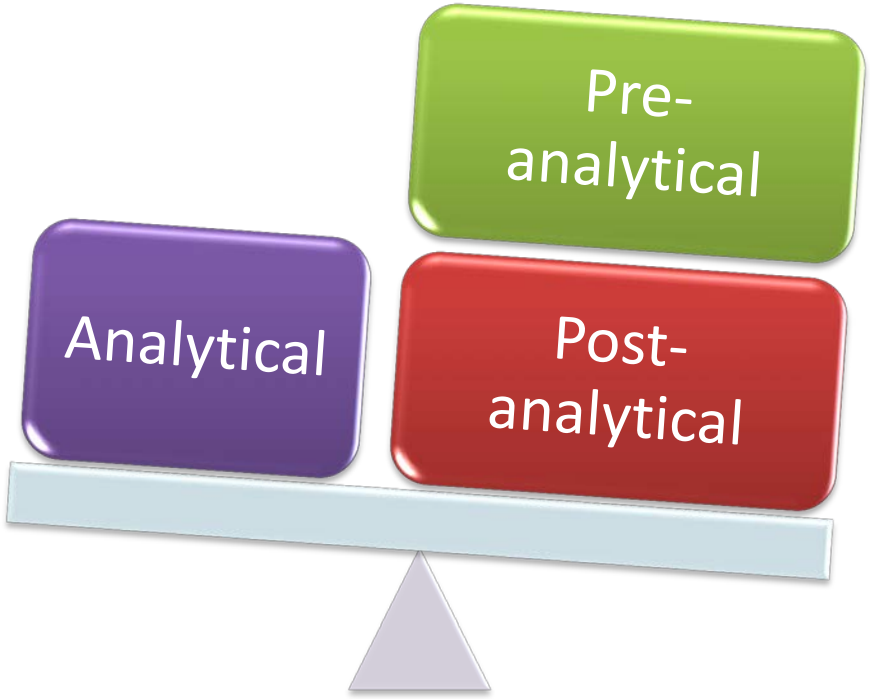
47% postanalytical

Blood bank study:

41% preanalytical

4% analytical

55% postanalytical



Ross, JW, Boone DJ. Abstract, in: 1989 Institute of Critical Issues in Health Laboratory Practice, DuPont Press (1991); Boone, DJ et al., Arch Pathol Lab Med 119:999 (1995)

The Laboratory's Role:

The majority of handling errors take place outside of the laboratory.

Therefore, laboratory-specific quality indicators and flags are even more important to ensure patient safety.

Causes of Discrepant Results:

Pre-analytical variation	Analytical variation	Biological variation
• Patient identification • Specimen collection • Post-collection	• Instrument • Method	• Rhythmic changes • Lifespan • Treatment

Analytical Variation:

- Instrument-specific issues:
  - Probe or pipettor errors
  - Variation in reagent volumes, delivery
  - Air bubbles
  - Calibration
- Operator- or method-specific issues:
  - Dilution errors, improper mixing
  - pH, temperature
  - Reagent, lot changes
- *This is where the majority of our investigative power lies (QC, imprecision, bias, etc.).*

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Biological Variation: Overview

- Main goal of the human body = Homeostasis!
  - Avoid fluctuations
- Tightly regulated:
  - Alkaline phosphatase, sodium, calcium, RBC indices (MCV, RDW), hemoglobin, pH
- Less stringently regulated:
  - Iron, bicarbonate, lactate, albumin

Biological Variation: Sources

Physiological Sources of Variation

Controllable	Uncontrollable
Posture	Gender, age, and race
Immobilization	Rhythmic influences, such as circadian, circannual, and menstrual
Exercise	Fever
Diet	
Transfusion	
Environment (altitude, geographical location)	

Grenache, D. Clin Lab News Mar 2004

Type of Change	Timeframe	Examples
Circadian	Once per day	Hormones (cortisol, growth hormone)
Ultradian	> Once per day	Pituitary and hypothalamic hormones
Infradian	> One day	Menstrual cycle (FSH, LH)
Circannual	Yearly; seasonally	Vitamin D, LD, cholesterol

Biological Variation: Changes Over the Lifespan

- Delta check limits may change with patient age
  - MCV elevations in neonates
  - Creatinine decreases with age, urea increases
- Lifestyle changes cause variation
  - Nutritional status
  - Activity level

Biological Variation: Treatment

Treatment Examples:
IV fluids
Total parenteral nutrition (TPN; feeding via IV)
Chemotherapeutics
Dialysis
Surgery
Organ transplantation
Other medications

Outline: The Delta Check in Action

How are delta check limits derived?

A. Population distribution
   - Identify representative individuals; gather serial results
   - Determine delta values between serial specimens
   - Determine frequencies (similar to reference interval determinations)
   - Establish institute-specific limits

B. Biological variation
   - Preanalytical, analytical, postanalytical, biological
   - Use reference change value (RCV) to assess significance

C. Experience and adjustment over time

D. *Combination of the above approaches*

Choosing Delta Check Limits (1):

- Identify “goal” of a detected failure
  - What are you trying to identify?
    - Sample integrity issues, misidentified samples, changes in patient condition
  - Balance between proper error identification and excessive alerts/investigations

- Some analytes are more useful as delta checks than others:
  - Little day-to-day variation
  - Low Reference Change Value
  - Low Index of Individuality
    - Creatinine, alk phos, urea, bilirubin, MCV

Choosing Delta Check Limits (2):

- Different rules for different populations
  - Neonates, oncology, transplant, outpatients…
- Absolute, percentage, and/or rate change
  - May vary by analyte concentration
  - Increases in values may have different implications than decreases
  - Rate changes (Lacher and Connelly, Clin Chem 34:1966(1988))
    - Delta rate change = Delta difference ÷ Delta time interval

A question of timing…

General Rule: Correlation between results decreases as time intervals increase

Time Adjusted Sensitivity Analysis: A New Statistical Test for the Optimization of Delta Check Rules

Maureen L. Sampson, BS Nadja N. Rehak, PhD Lori J. Sokoll, PhD Mark E. Ruddel, MS
Gregory A. Gerhardt, MS Alan T. Remaley, MD, PhD

VOLUME 30, NUMBER 1-2, SPRING-SUMMER 2007 *JOURNAL OF CLINICAL LIGAND ASSAY*

- Goal: optimizing delta check rules, to increase sensitivity and specificity
- 20 general chemistry analytes
- 1-28 days apart; total n (2 sites) = 62,640

A question of timing…

- Time-Adjusted-Sensitivity Score (TAS) =

  Sensitivity * relative cumulative frequency
  (repeat ordering frequency)

- Peak TAS determines optimal time interval between measurements
- Findings:
  - Creatinine: high R^2 over time, slow ordering pattern, high TAS over time
  - Enzymes: peak TAS > 25%; prior to day 5
  - Electrolytes: lower peak TAS
  - Glucose, Mg: TAS < 2%; delta checks not helpful

Sampson et al., J Clin Ligand Assay 30:44(2007)

TABLE 2 Optimum TAS score parameters

			Site A					
Analyte	± Rule	Unit	Opt. Day	Day range*	Sens%	Spec%	RCF	Max TAS%
CK	0.50	log (IU/L)	1	1–3	48.6	99.0	0.882	42.8
DBIL	0.65	Log (μmol/L)	5	2–5	47.7	99.0	0.889	42.4
TBIL	0.54	Log (μmol/L)	3	2–10	37.8	99.0	0.907	34.3
ALT	0.71	log (IU/L)	4	2–17	35.4	98.9	0.943	33.3
LDH	0.27	log (IU/L)	1	1–3	54.8	98.8	0.524	7
ALP	0.43	log (IU/L)	5	2–10	28.9	99.0		
ALB	13.00	g/L	5	2–14	26.7			
BUN	125.00	percent	2	1–4				
TP	23.00	g/L	5					16.1
CREAT	47.00	percent log					0.959	14.1
AST	0.74	log (IU/L)				99.0	0.813	13.5
Cl	14.00				14.7	98.9	0.907	13.4
Na				2–3	9.4	98.8	0.948	8.9
Ca			2	2–5	8.0	99.0	0.909	7.3
PO_4		percent	2	2–5	7.7	99.0	0.825	6.3
K	2.10	mmol/L	2	2–3	5.0	99.0	0.910	4.6
CO_2	12.00	mmol/L	4	2–7	8.2	98.9	0.528	4.3
UA	0.50	mmol/L	2	1–2	3.2	99.0	0.852	2.7
Mg	1.20	mmol/L	21	4–28	1.8	98.9	1.000	1.8
GLU	14.20	mmol/L	7	2–28	1.3	99.0	0.997	1.3

Ideal time range = 2-5 days

Sampson et al., J Clin Ligand Assay 30:44(2007)

Reference Change Value (RCV):

- "Is the difference between 2 values actually significant?"
- May use to determine delta check limits
  - Analytical and biological variation
  - Determines the allowable change in serial measurements
- "Significant Change Value"
  - 2010 convocation of experts on laboratory quality (Cooper et al., CCLM 49:793(2011))

Reference Change Value (RCV):

$$RCV = 2^{0.5} * Z * (CV_A^2 + CV_I^2)^{0.5}$$

Z = For 2 tailed analyses:
1.96 at 95% probability ("significant");
2.58 at 99% probability ("highly significant")

CV_A = analytical variation (from QC)

CV_I = intraindividual variation (from literature or http://www.westgard.com/biodatabase1.htm)

RCV: Hypothetical Example

Alkaline phosphatase internal QC has an SD of 0.56 U/L at a mean of 40 U/L. $CV_A = 0.56 / 40 * 100 = 1.4\%$

Within subject biological variation (CV_I) is 6.4%

Formula is: $RCV = 2^{0.5} * Z * (CV_A^2 + CV_I^2)^{0.5}$

RCV at 95% = $1.414 * 1.96 * (1.4^2 + 6.4^2)^{0.5} = 18\%$
RCV at 99% = $1.414 * 2.58 * (1.4^2 + 6.4^2)^{0.5} = 24\%$

Therefore, if the laboratory is mainly interested in identifying large variations in this analyte ($P < 0.01$), a delta check limit of 24% change in serial results (or higher) could be established, or an absolute difference of 9.6 U/L at 40 U/L levels.

Index of Individuality (II):

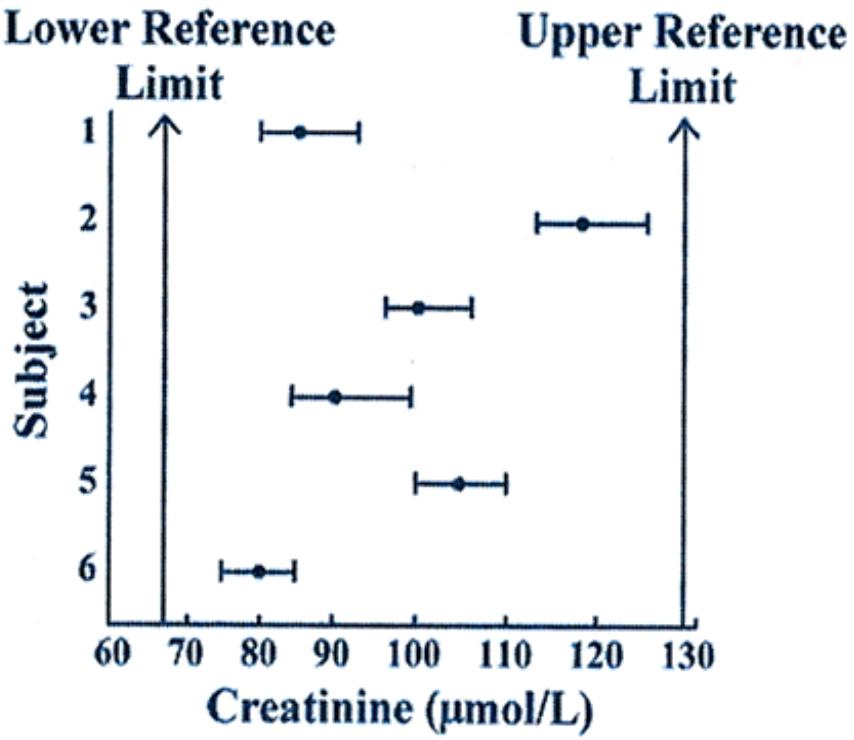
- Fluctuation within an individual
  - Within-individual variation (CV_I)
  - Between-individual variation (CV_G)

$$II = \frac{CV_I}{CV_G}$$

- Low values (< 0.6):
  - Tightly regulated *within* an individual
  - Variation may exist *between* people

Index of Individuality (II):

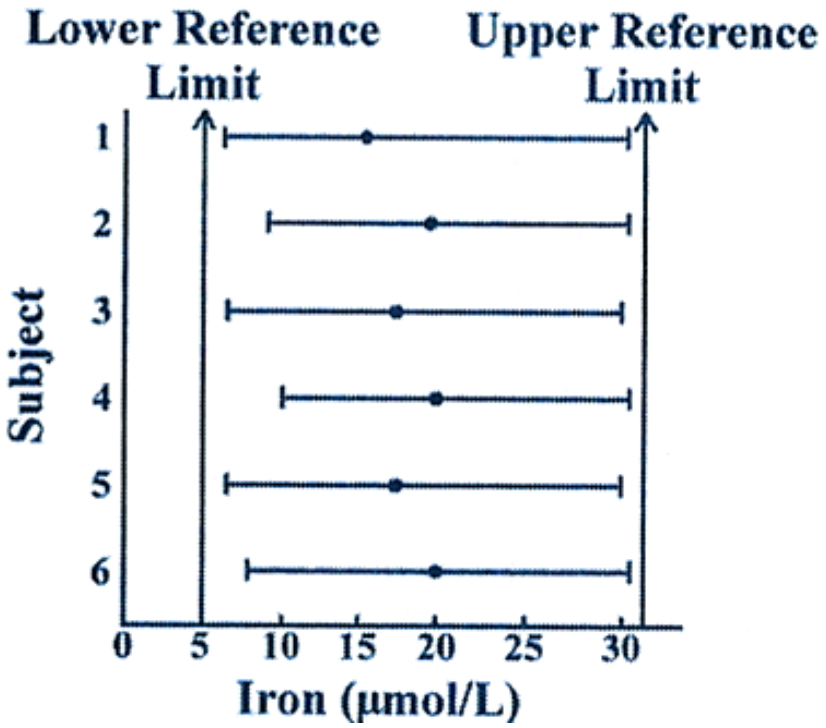
- Analytes with low II:
  - Maintained within a small interval for each person
    - Only a small portion of the actual reference interval
  - Large change in analyte? Good chance that value is still within the reference interval
    - ❖ Thus—reference interval not as helpful to indicate a change in patient status
    - ❖ Delta check may be beneficial



Fraser, Biological Variation, AACC Press 2001

Index of Individuality (II):

- Analytes with high II:
  - Individual values found anywhere within the reference interval
  - Large change in analyte? Good chance the value will fall outside the reference interval



- ❖ Thus—the reference interval itself indicates a biologically relevant change

Fraser, Biological Variation, AACC Press 2001

Institution of the Delta Check: Recent Examples

- Troponin:
  - 20 or (30%) change in baseline values may help delineate acute from chronic causes of elevation, identification of risk
  - Assay-dependent delta check limits
    - Lower imprecision = smaller changes required for significance
- Determining criteria for significant change
  - Monoclonal gammopathy
  - Dehydration
  - Creatinine for AKI detection

Fraser CG, www.westgard.com/troponin-interpretations.htm; Katzmann et al., Clin Chem 57:12(2011); Cheuvront et al., CCLM 49:1033(2011); Garner et al., Annals Clin Biochem 49:59(2012)

Questioning Utility:

- Computer modeling approach: identify mislabeled specimens?
- Two inpatient populations
  - Trauma/critical care center
  - Cancer/transplant population
- Findings:
  - Sodium, potassium = unlikely to identify mislabeling events
  - MCV = best predictor, fewest false-positives
  - Performance varied between patient populations

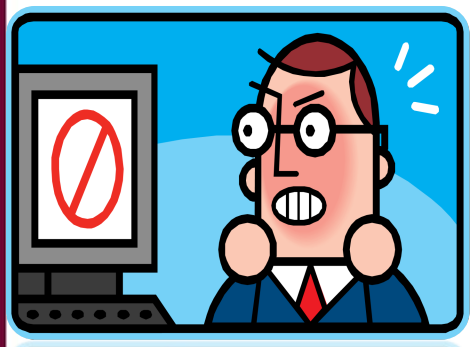
Strathmann et al., Clin Chem Acta 412:1973(2011)

Multiple tests can reveal multiple things…

- Examination of multiple test results
  - You SHOULD NOT see…
    - Direct bilirubin > total bilirubin
    - Albumin > total protein
    - RBC morphology that doesn't correlate with measured indices
    - Extreme elevation of only one liver enzyme (AST, ALT)
    - Extremely elevated creatinine with normal BUN
- If *multiple* delta check limits fail, the likelihood of sample misidentification is increased

Kazmierczak, Clin Chem Lab Med 41:617(2003); Lacher, Clin Chem 36:21364(1990);
Rheem and Lee, Stud Health Technol Inform 9:859(1998)

Delta Checks: Issues and Shortcomings



- Balance error detection with false-positives
  - Cost of investigating rule failures
  - Remember: Majority of failures are due to changes in patient status
- Population in question
  - Inpatient vs. outpatient populations
  - Treatments and therapies (e.g., transfusions, chemotherapy, transplantation)
  - Population may dictate useful analytes (e.g., creatinine for renal patients)
- Many previously established delta check limits were determined in healthy populations

Outline: The Delta Check in Action

To Report or Not to Report:

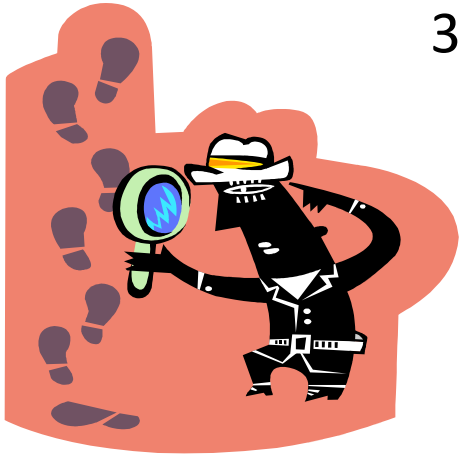
There is a fine balance between cancelling questionable results and reporting them:

- Implications of result cancellation:
  - Difficult to redraw
  - Neonate issues
  - Loss of blood volume
  - Delayed treatment
  - Delayed discharge

- Implications of reporting incorrect results:
  - Lengthened hospital stays, inappropriate medical care, economic, psychological and social issues
  - Implications beyond chemistry and hematology
    - Transfusion Services
    - Immunology
    - Infectious Diseases
    - Genetic and Molecular Testing
  - Harm may not be realized for hours, days or years

General Checklist: Starting the Investigation

1. Repeat analysis
   - Confirm correct patient was analyzed
   - Make new aliquot, if applicable
2. Investigate pre-analytical issues
   - Correct sample type (serum, plasma, whole blood)
   - Gross hemolysis, icterus, lipemia
     - Check for hemolysis of whole blood samples
   - Clots, air bubbles
3. Investigate analytical issues
   - QC, proper reagents, proper calculations
   - Isolated event, or others from same run



All check out?
Consider biological explanations…

General Tips to Confirm Discrepant Results:

- Do lab values match previous results?
  - Look at test history and overall trends
  - Look at > 2 results to confirm trends
- Were the previous results questionable?
- Look at patient location
  - NICU, Labor & Delivery, Oncology, etc.
  - Recent surgery?
- Was a type and screen ordered?
  - Suggests recent transfusion
- Were therapeutic drug monitoring tests ordered?
  - "None Detected" suggests possible misidentification

❖ *Think beyond the immediate lab area:*
Chemistry, hematology, blood bank, immunology, infectious diseases, molecular genetics, microbiology may ALL be affected.

Sentinel event: Wrap-up

- Multiple delta check failures
-Type and screen OK
- Transfusion reaction

Immunocompromised (HIV+) patient, thus reaction was not lethal.

Method of conveying laboratory alerts is critical.

Summary:

- Delta checks can be useful tools for detecting sample quality issues, sample misidentification and biologically relevant changes in patient status.
- Preanalytical error, analytical error and biological variation are possible causes of discrepant results.
- Delta check limits should be tailored to particular patient populations.
- Multiple sources of error must be considered when determining delta check limits.
- Consequences to patient care must be considered when deciding to cancel or report a discrepant laboratory result.

Additional Resources:

- Fraser, CG. Biological Variation: From Principles to Practice. AACC Press (2001).
- http://westgard.com/biodatabase1.htm
- Cembrowski and Carey. Laboratory Quality Management, QA and QC. ASCP Press (1989).
- CLSI. Procedures for the Handling and Processing of Blood Specimens for Common Laboratory Tests; Approved Guideline-Fourth Ed. CLSI Document H18-A4 (2010).
- Ricos, C et al. Current databases on biological variation: pros, cons and progress. Scan J Clin Lab Invest 59:491 (1999).

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