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

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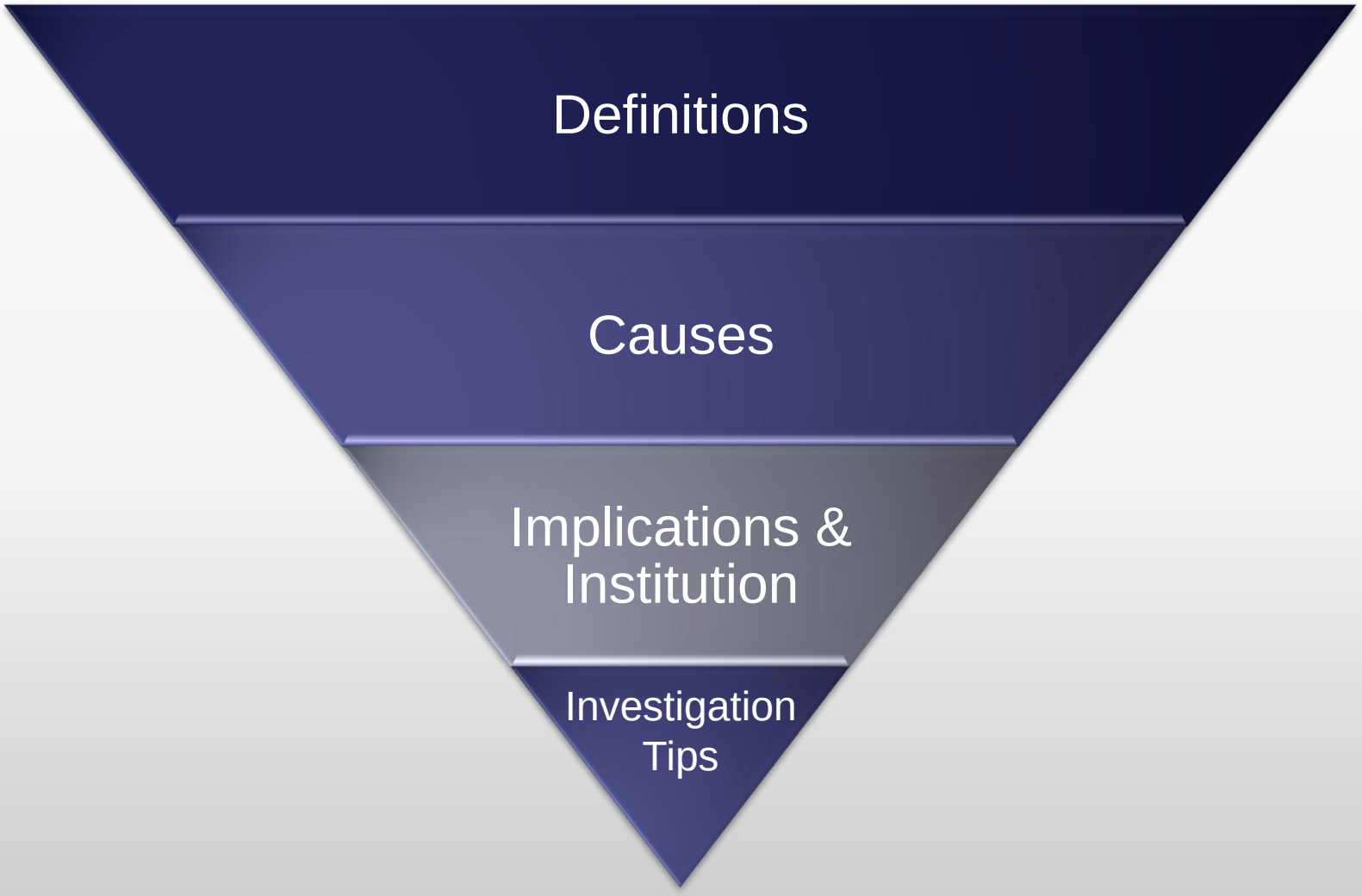
Outline: The Delta Check in Action



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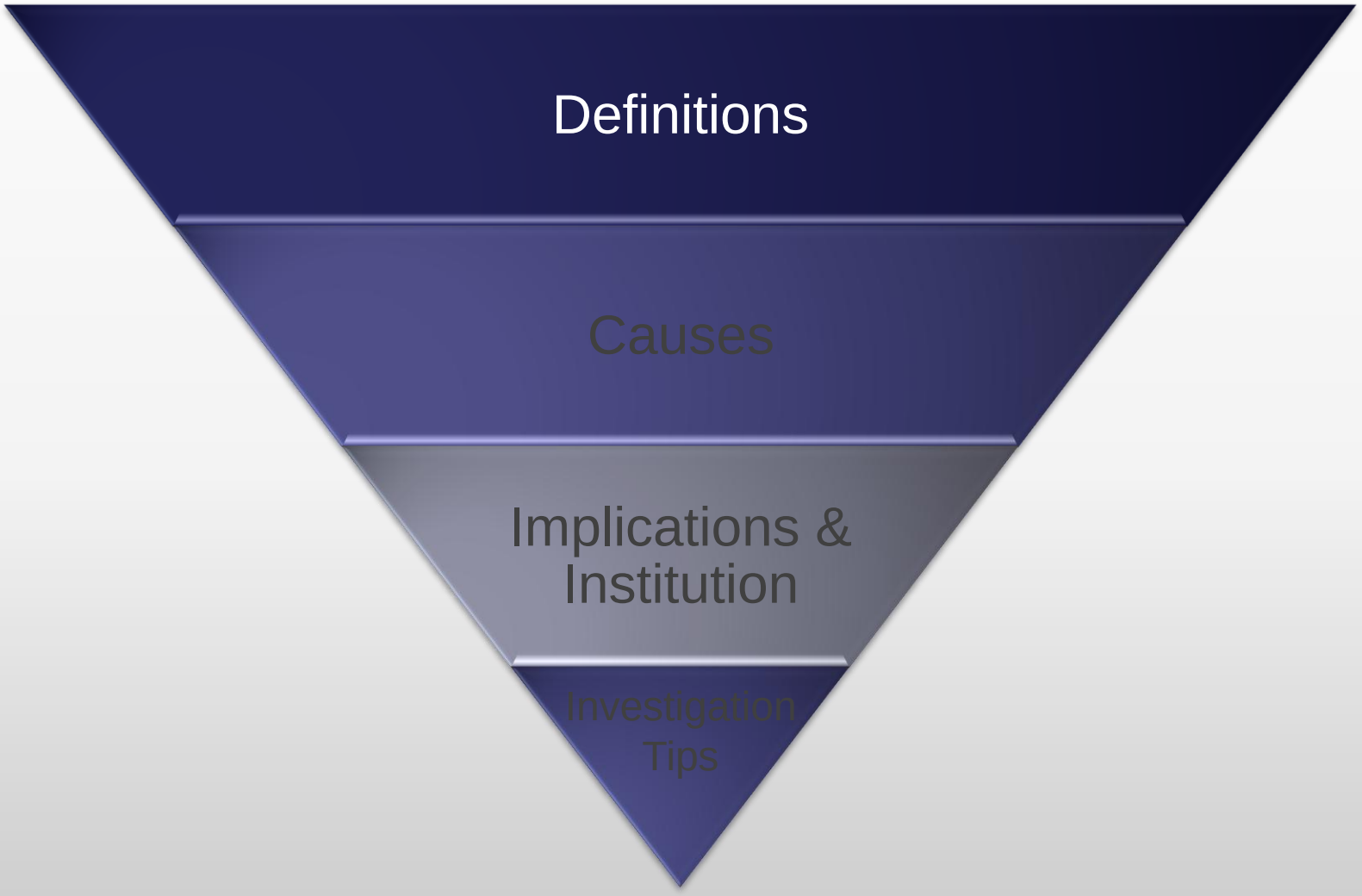


Initiation of a Discrepant Results Policy: One hospital's experience

Sentinel Event:

- Delta check alert occurred on several chemistry and hematology results for an individual patient
  - "Delta MCV" called to RN on floor, RN acknowledged receipt and results were released to the patient chart
  - Delta chemistry results were confirmed, results released to the 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

What happened?

The wrong patient was drawn…

Delta Check: Definition

- A “delta check” failure or alert is caused by a discrepancy in patient results:
  - It occurs when the 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, Ladenson was the first to use computers for delta check identification (Am J Clin Pathol 65:707 (1974); Clin Chem 21:1648 (1975))
  - Addresses errors that are not detectable with other methods of quality control
- Two main goals:

Identify changes in patient condition or disease state	Identify sample quality issues or patient misidentification

Delta Check: Examples

- Examples of delta check parameters (will vary by analyte and by institution):

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

Delta Check: Implications for the Patient

- Small delta value, or difference, in serial measurements?
  - Patient is stable (for that analyte)

- Large delta value (one or many) in serial measurements?

Both situations are important to detect!

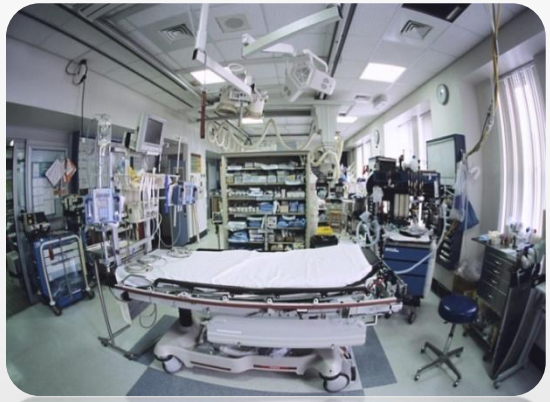
- True physiological change in the patient

  --- OR ---

- Possible error
  - Pre-analytical
  - Analytical
  - Biological

Why bother using Delta Checks?

- Delta checks are useful quality improvement measures that can help the laboratory identify possible patient-specific errors
- Predictive value for detecting true specimen errors is between 0.4 and 6%[1,2]
  - However, studies have found that the majority of delta check failures (>75%) can be attributed to true changes in the patient's medical condition[2-5]
- Early error identification may have considerable implications for patient care and safety[2]
  - Deadly errors due to incorrect drug dosing, anticoagulation therapy, cardiac intervention, blood transfusion, etc. may result from erroneous lab results



- Providers need to be alerted to large biological fluctuations in their patients, may indicate need for 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)

How are delta check limits derived?

A. Population distribution
   - Identify individuals representative of the patient group in question, gather serial results from each person for each analyte
   - Determine delta values between serial specimens and determine frequencies (similar to reference interval determinations)
   - Beneficial to establish institute-specific limits, to best serve unique patient populations

B. Biological variation
   - Includes multiple sources of variation: Preanalytical, analytical, postanalytical, biological
   - Reference change value (RCV) may be used to determine significance of differences between serial measurements *(discussed later)*

C. Experience and adjustment over time

D. *Combination of the above approaches*

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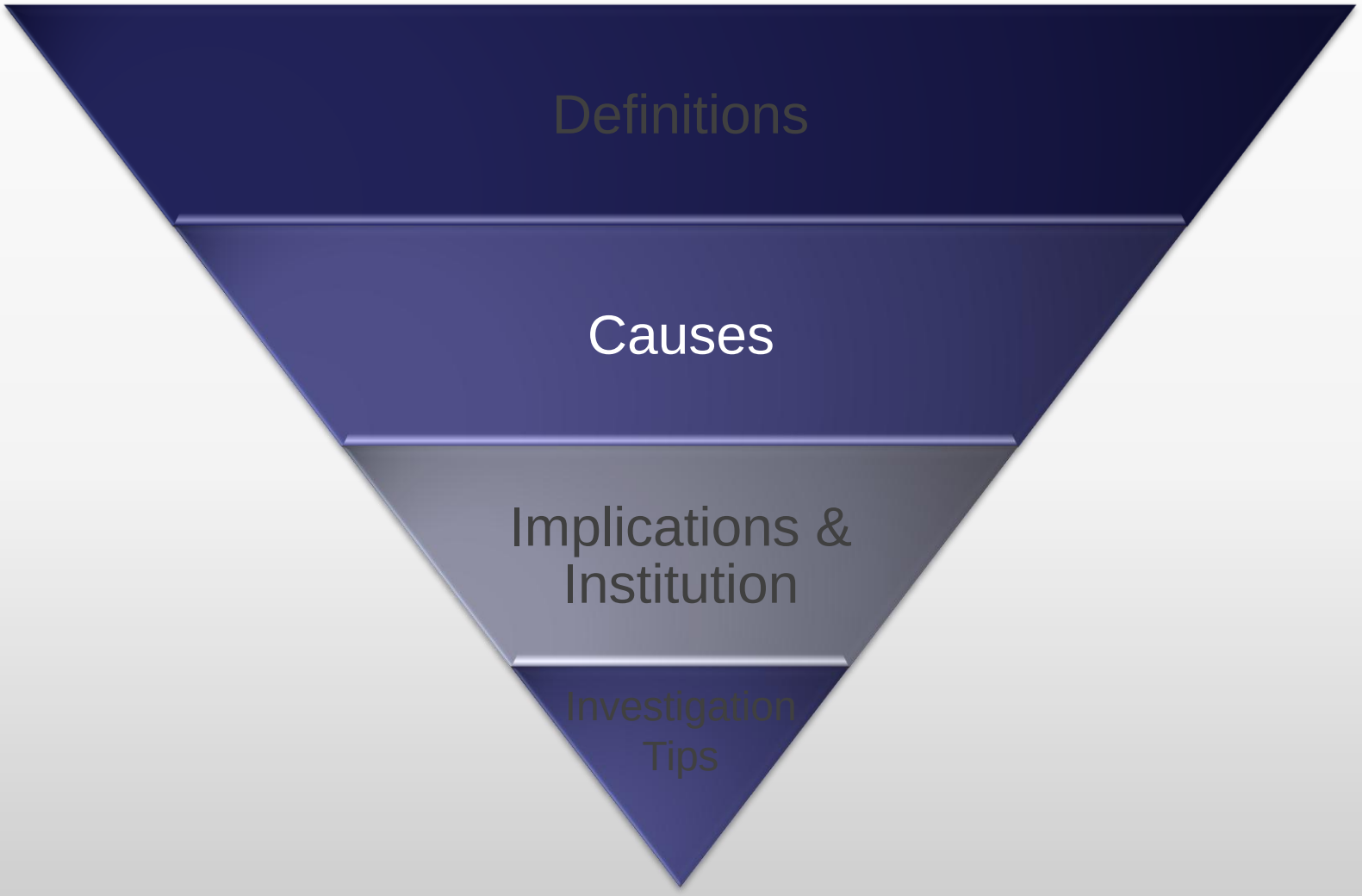

Causes of Discrepant Results:

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:
    - Use at least two unique patient identifiers (other than patient’s location)
    - Label sample collection containers in the presence of the patient
  - Mislabeled specimens have one or more identifiers that are incorrect
    - Wrong patient label; tube label does not match paperwork or electronic order; contradictory labels on one tube
  - Major issue in transfusion medicine
  - These errors can be difficult to detect and assess—they often go unreported

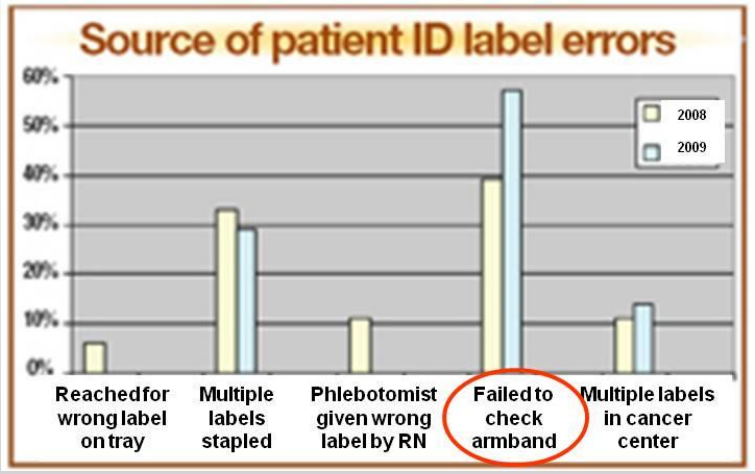
Pre-analytical Variation: Identification

- Definition: “Misidentified”
  - WBIT = Wrong Blood in Tube
  - Possible causes of patient misidentification:
    - NICU, ER, geriatric populations often cannot actively participate in identification process
    - 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
- Adverse events = 1 in 18 identification errors
- 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)

Pre-analytical Variation: Identification

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.

Pre-analytical Variation: Specimen 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: Issues that may affect analyte levels
  - 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
  - Short spins keep cellular components in the serum: K^+, enzymes affected
  - Excessive spins may cause hemolysis due to RBC membrane damage
- Storage
  - Labile analytes must be frozen, avoid excessive freeze-thaw cycles

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 may include:
  - Probe or pipettor errors
  - Variation in reagent volumes, delivery
  - Air bubbles
  - Calibration
- Operator- or method-specific issues may include:
  - 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!
  - The body attempts to keep essential analytes from fluctuating on a daily basis
- Examples of tightly regulated analytes:
  - Alkaline phosphatase, sodium, calcium, RBC indices (MCV, RDW), hemoglobin, pH
- Examples of less stringently controlled analytes:
  - Iron, bicarbonate, lactate, albumin

Biological Variation: A variety of 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

Biological Variation: Rhythmic changes

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
- Discrepant results may make sense if the patient age is considered
  - MCV is elevated in neonates
  - Creatinine decreases with age, urea increases
- Lifestyle changes cause variation as well
  - Change in nutritional status
  - Change in activity level

Biological Variation: Treatment

- Treatments and medical intervention may cause large fluctuations in overall patient biology, affecting a variety of test results

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

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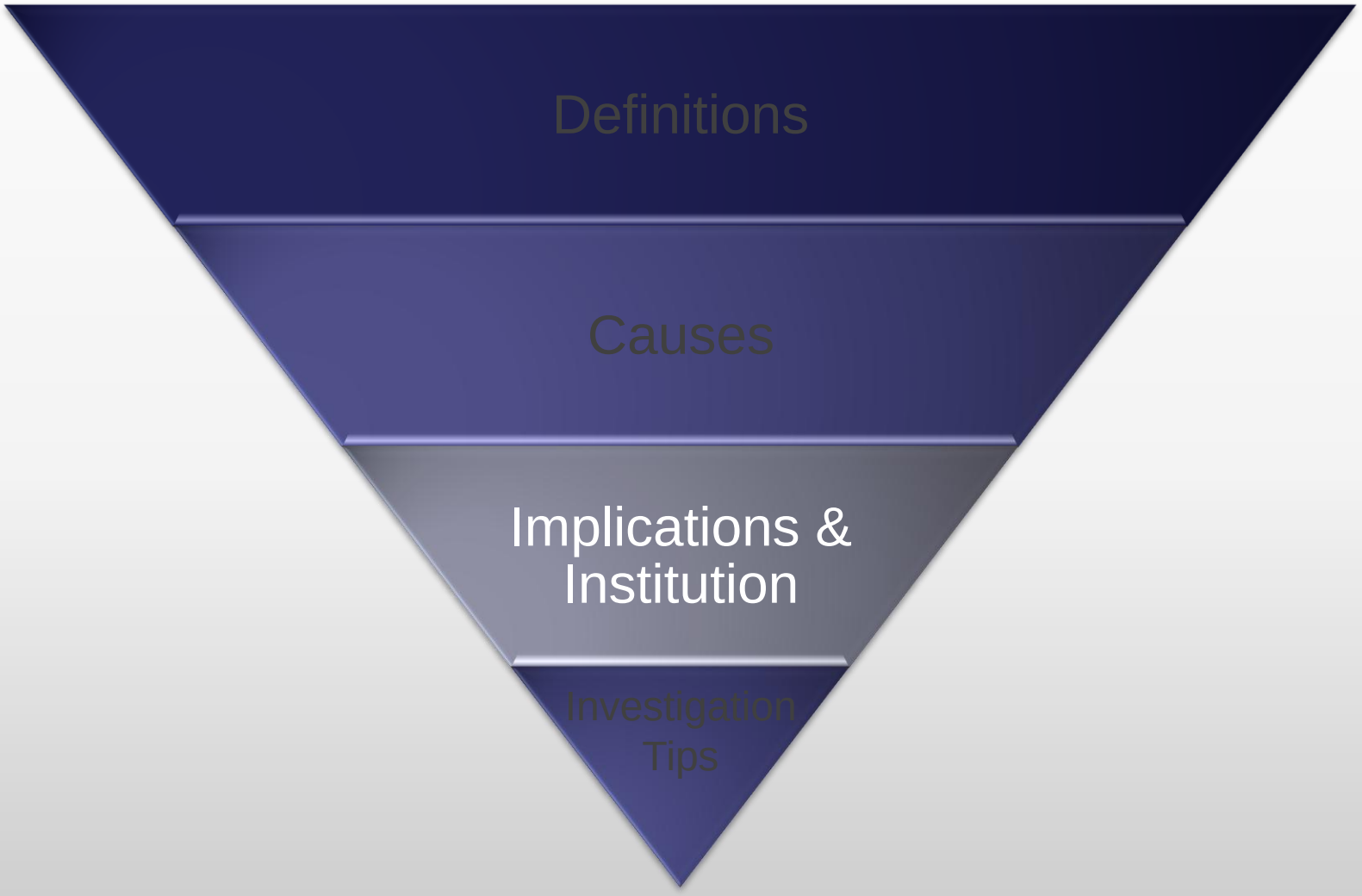


To report or not to report:

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
  - Consider implications beyond chemistry and hematology
    - Transfusion Services
    - Immunology
    - Infectious Diseases
    - Genetic and Molecular Testing
  - Harm may not be realized for hours, days or years, depending on the nature of the result

How to choose delta check limits (1)

- Important to know “goal” of a detected failure
  - What are you trying to identify? Delta check limits may be set differently if you are trying to identify sample integrity issues, misidentified samples, or changes in patient condition
  - Must balance between proper error identification and excessive alerts and investigations by staff
- Some analytes are more useful as delta checks than others
  - Ideally, analytes for delta checks will have:
    - Little day-to-day variation
    - Low Reference Change Value *(discussed shortly)*
    - Low Index of Individuality *(discussed shortly)*
      - Examples: creatinine, alk phos, urea, bilirubin, MCV

How to choose delta check limits (2)

- Absolute, percentage, and/or rate change
  - May vary by analyte concentration (e.g., absolute changes at lower concentrations, percent change at higher concentrations)
  - Increases in values may have different implications than decreases
  - Use of rate changes may increase positive predictive values of delta check alerts (Lacher and Connelly, Clin Chem 34:1966(1988))
    - Delta rate change = Delta difference ÷ Delta time interval
- Different delta check rules may be applied to different populations (e.g., neonates, oncology, transplant, outpatients)

Reference Change Value (RCV):

- RCV can be used to determine delta check limits
  - Takes into account analytical and biological variation
  - Determines the allowable change in serial measurements

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

Z score = 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)

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):

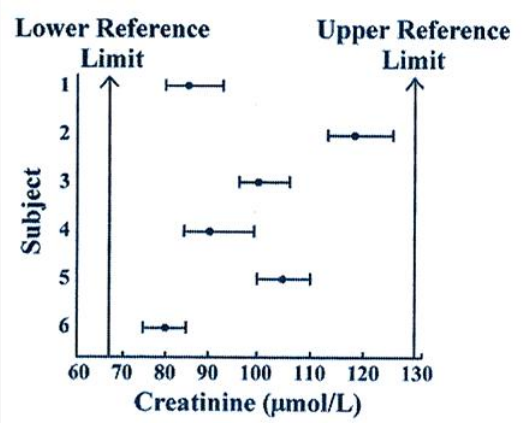
- The II indicates which analytes are more likely to fluctuate within an individual
- Ratio between inter-individual variation (CV_I) and between-individual variation (CV_G)

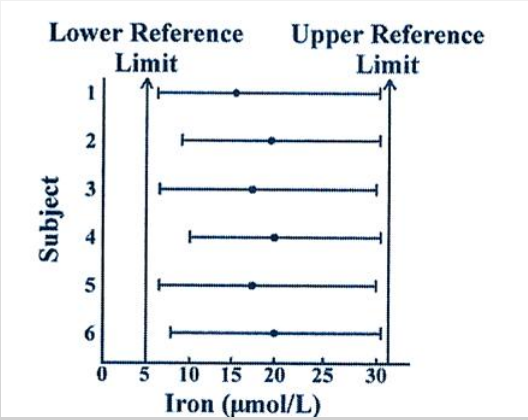
$$II = \frac{CV_I}{CV_G}$$

- Low values (< 0.6) indicate analyte values are tightly regulated *within* an individual, although variation may exist *between* people

Index of Individuality (II):

- Analytes with low II are usually maintained within a small interval for each person. That interval represents only a small portion of the actual reference interval (e.g. creatinine)
  - Therefore, if a person experiences a large change in analyte value, that value may still be within the reference interval
    - Thus—the reference interval is not as helpful to indicate a change in patient status and a delta check may be beneficial for analytes with a low II
- Analytes with high II are less tightly regulated, and thus, values for an individual may be found anywhere within the reference interval (e.g., iron)
  - Therefore, if a person experiences a large change in analyte value, there is a good chance that value will fall outside of the reference interval
    - Thus—the reference interval itself may adequately indicate a biologically relevant change has occurred in analytes with a high II





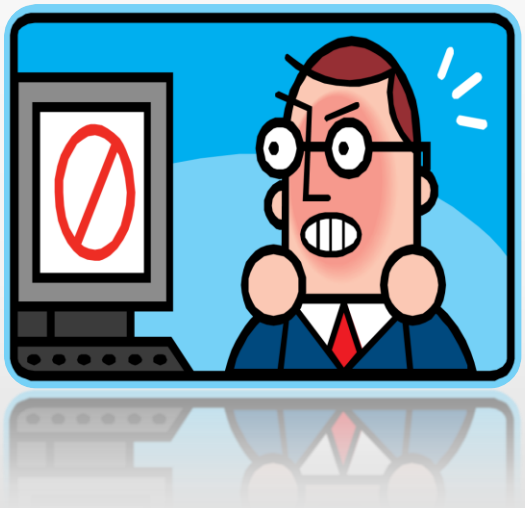
Fraser, Biological Variation, AACC Press 2001

Multiple tests can reveal multiple things…

- Simultaneous examination of multiple test results can provide additional clues to sample issues or patient misidentification
  - 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



- Must balance error detection with false-positives
  - Cost of investigating rule failures
  - Majority of failures are due to changes in patient status
- Population in question
  - Inpatient populations will experience large fluctuations in analyte concentrations that directly relate to their disease processes
  - Treatments and therapies for specific patient populations may skew appropriate delta check values (e.g., transfusions, chemotherapy, transplantation)
  - Population may dictate which analytes are appropriate to monitor (e.g., use of creatinine delta checks for renal patients)
- Many previously established delta check limits were determined in healthy populations

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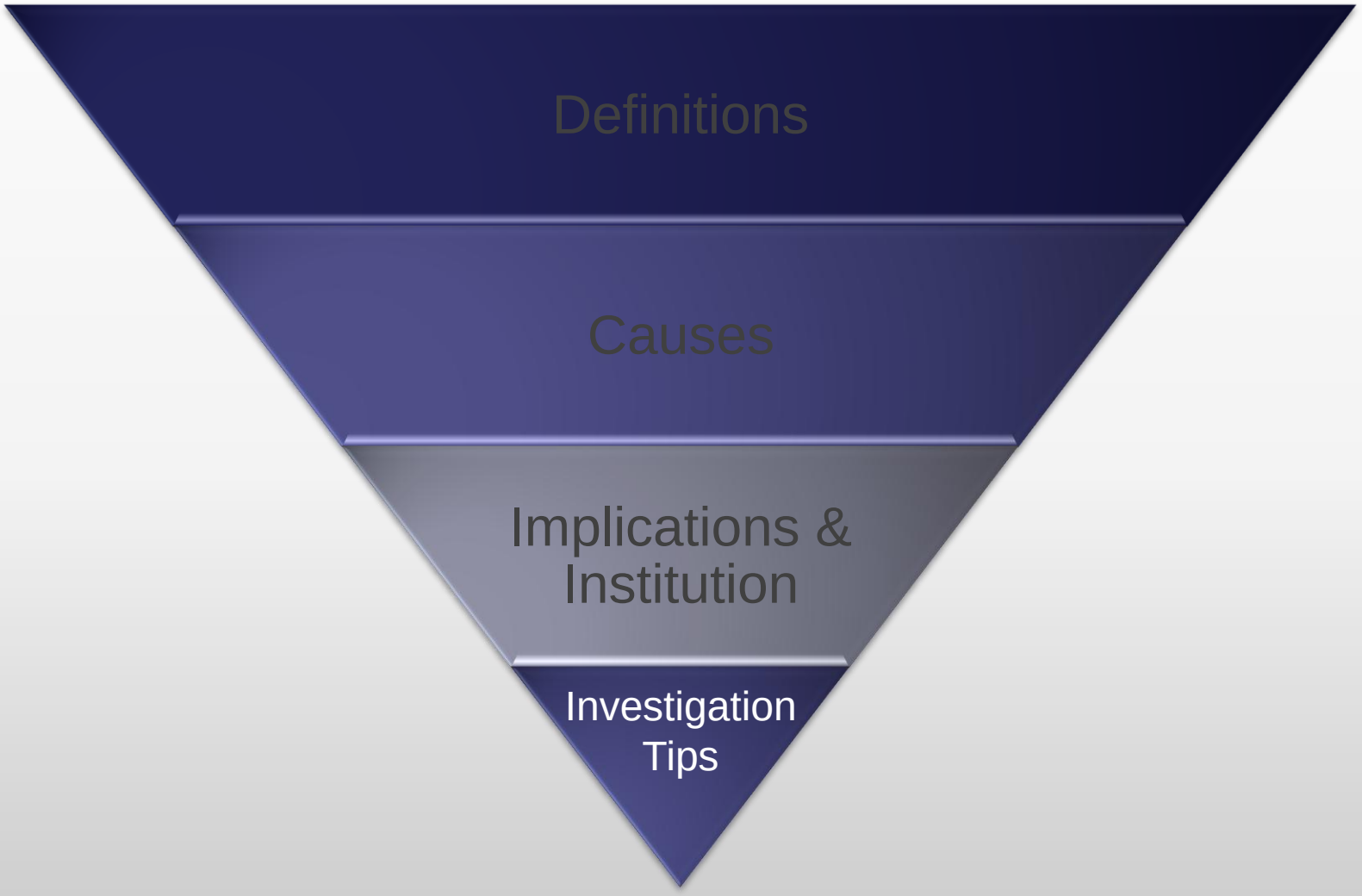
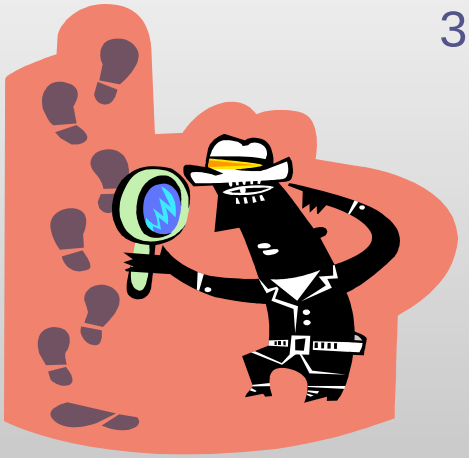


General checklist: Starting the investigation

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:

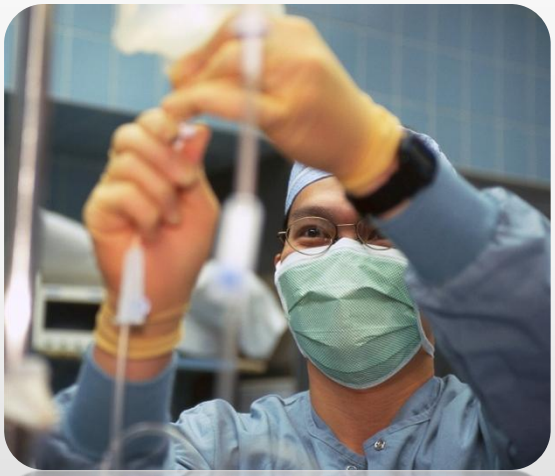
- Do lab values match previous results?
  - Look at test history and overall trends
  - Look at > 2 results to confirm trends
- Were the previous results questionable?
- Look at patient location
  - NICU, Labor & Delivery, Oncology, etc.
  - Recent surgery?
- Was a type and screen ordered?
  - Patient may have been transfused, which may cause multiple hematology discrepancies
- Were therapeutic drug monitoring tests ordered?
  - "None Detected" result for a patient maintained on therapeutic drugs suggests possible misidentification

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

Specimen quality: Important questions to ask

Suspect dilution with IV fluid, EDTA, etc.?

- What was the order of draw?
- How was specimen obtained – through a central line, PICC, etc.
- Does patient have an IV?
  - Was specimen collected from the same arm as IV?
  - Was IV paused/stopped during specimen collection?
- Was patient receiving TPN during specimen collection?



Specimen quality: Important questions to ask

Questionable glucose results suggest IV dilution?

- Review past lab values for diabetic fluctuations
- Confirm specimen collection method
- Request a stat finger stick glucose, if available
- Refer to other lab tests ordered for comparison

Specimen quality: Important questions to ask

Suspect wrong patient was drawn (misidentified specimen)?

- Consult with patient's Provider, explain change you have detected:
  - Does the Provider expect to see a change?
  - Has the patient been given blood products?
  - Discuss dialysis, chemotherapy, other invasive procedures that may cause change in lab results

MCV DELTA CHECK FAILURES: INVESTIGATION TIPS

- Investigate past lab values for low hemoglobin & hematocrit, ABO Ab Screen: patient possibly transfused
- Also review WBC, platelet count and RDW to determine if same patient or line dilution
- Investigate the patient's location (e.g., SICU, NICU, Onc): MCV decreases as gestational age increases; MCV may be elevated due to meds, lipids, etc. in oncology patients
- Compare Hematology results with patient's Chemistry results to aid in your investigation

Chemistry Deltas: Investigation Tips

- LFT's: post-surgery may rise, post-dialysis may fall, otherwise relatively stable
- Total protein/Albumin: Post-surgery and oncology patients may have shifts in TP/Alb due to nutrition status
- Multiple electrolytes (Na^+, K^+, and Cl^-): May indicate IV line dilution or possible patient misidentification
  - Example of a multiple delta check rule:
    - "≥ 3 analytes have delta failures or ≥ 1 analytes fail by ≥ 3 times delta limit."
    - This will trigger an alert to the technologist referring to possible sample misidentification, which warrants further investigation before results are released

Sentinel event: Wrap-up

The misidentified patient was immunocompromised (HIV+), thus did not experience a lethal transfusion reaction when given the wrong blood type.

It was discovered that the floor nurse receiving the MCV delta check did not understand what a "delta check" referred to, thus discounted its importance.

What do we do now? Corrective Actions:

- Sentinel events such as these cause detailed policy review. The following hospital-wide changes were instituted following these important delta check failures:
  - Staff education and in-service presentations
  - Discrepant Results Forms (filled out by technologist, reviewed by senior staff)
  - Flow charts to help direct a systematic discrepant result investigation in the laboratory
  - Adverse event reporting system
  - Bar code readers implemented for phlebotomy
  - Handheld scanners for use with barcoded wrist bands
  - Monthly phlebotomy competency reviews
- Additionally, CLSI Guidelines have been proposed to advise on proper delta check use

Items to document in a Discrepant Results Investigation Form:

- Copies of lab results in question
- Previous relevant results
- Other tests ordered at the same collection time
- Documentation that other lab areas have been notified of the discrepancy
  - Especially blood bank! Also include send out tests, molecular and genetic tests, etc.
- Documentation that lab tests have been cancelled, if warranted
- Further investigation by supervisor or lead technologist to confirm proper conclusions were drawn
  - If available, residents and fellows may be helpful for reviewing and determining biological relevance of discrepant results

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 may 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 and recommended reading:

- Fraser, CG. Biological Variation: From Principles to Practice. ASCP 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).

Thank you

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