Risk Management in POCT: Eliminating Errors Before They Bite You!

James H. Nichols, PhD, DABCC, FACB

Professor of Pathology, Microbiology and Immunology

Medical Director of Clinical Chemistry and Point-of-Care Testing

Vanderbilt University School of Medicine

Medical Director, Clinical Chemistry

Nashville, Tennessee, USA

james.h.nichols@vumc.org

VANDERBILT UNIVERSITY MEDICAL CENTER

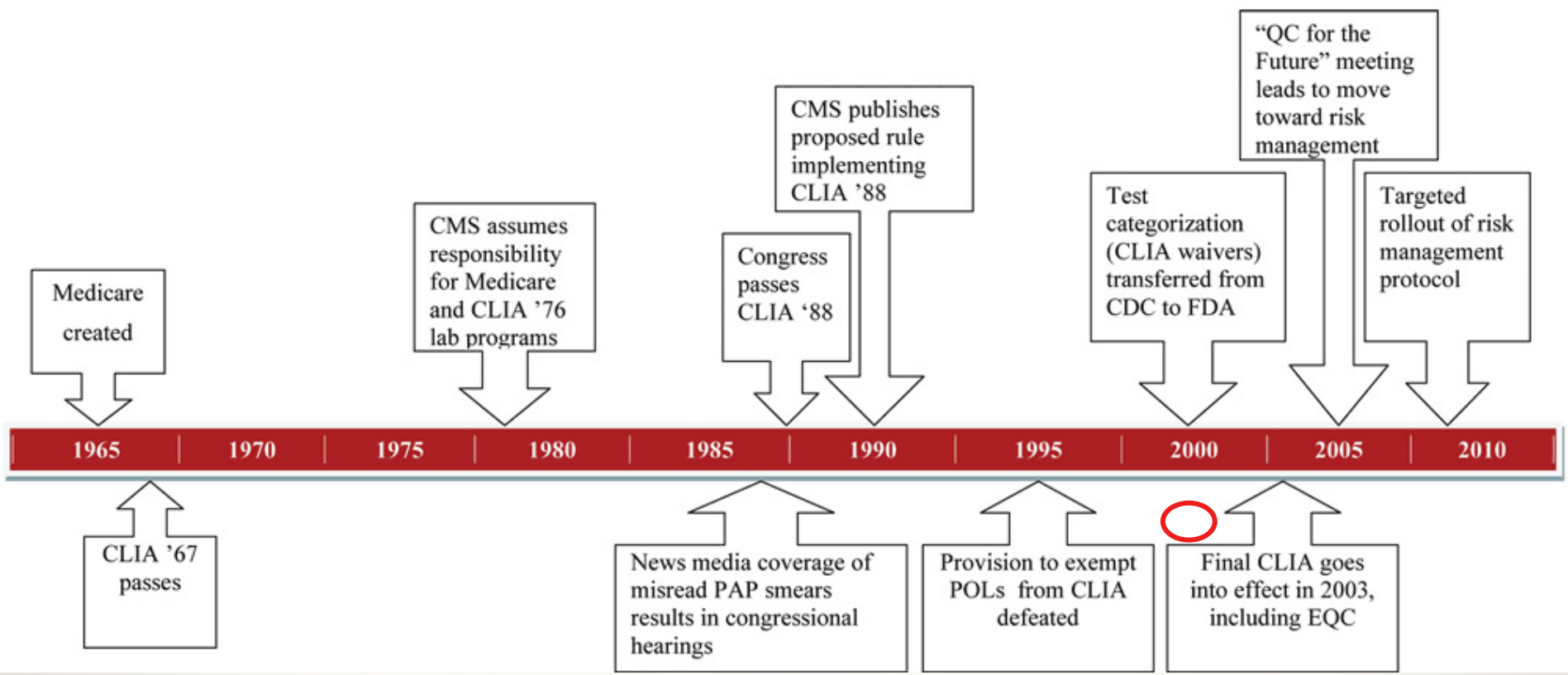
Objectives

1. Recognize common sources of laboratory error
2. Identify CLSI EP23 guideline as a resource for risk management and building an IQCP
3. Recognize the variety of engineered control processes manufacturers have built into POCT devices

History of Clinical Lab Risk Management

- CLIA 88 requires 2 levels of QC each day of testing!
- Newer lab devices offer internal and engineered control processes that make daily liquid QC duplicative and redundant.
- CMS implemented EQC in 2003 – equivalent QC
- CLSI EP23 introduces industrial and ISO risk management principles to the clinical laboratory
- CMS adopted key risk management concepts to develop the IQCP option for quality control
- IQCP replaces 2003 EQC options currently in place.

CLIA & QC


Medicare created
CMS assumes responsibility for Medicare and CLIA '76 lab programs
Congress passes CLIA '88
CMS publishes proposed rule implementing CLIA '88
Test categorization (CLIA waivers) transferred from CDC to FDA
"QC for the Future" meeting leads to move toward risk management
Targeted rollout of risk management protocol
1965
1970
1975
1980
1985
1990
1995
2000
2005
2010
CLIA '67 passes
News media coverage of misread PAP smears results in congressional hearings
Provision to exempt POLs from CLIA defeated
Final CLIA goes into effect in 2003, including EQC

IQCP 2016

- Two levels of liquid QC required each day of testing

OR

- Laboratory develops an IQCP:
  - Balance internal control processes with external controls
  - Reduce frequency of liquid QC to minimum recommended by manufacturer
  - Maximize clinical outcome, available staff resources and cost effectiveness in the lab

Individualized Quality Control Plan

Risk in the Laboratory

- There is no “perfect” laboratory device, otherwise we would all be using it!
- Any device can and will fail under the right conditions
- A discussion of risk must start with what can go wrong with a test (errors or nonconformities)
- Lab tests are not fool-proof!

What Could Go Wrong?

Risk Mitigation

- Liquid quality control is historic means of detecting and preventing errors (nonconformities or incidents)!
  - Liquid controls detect systematic errors that affect every sample the same way (calibration errors, pipette errors, reagent degradation)
  - Liquid controls do a poor job at detecting random errors that affect a single sample uniquely (hemolysis, lipemia, clots, drug interferences)
  - For unit-use tests, liquid controls consume entire test and do not ensure performance of next test
- Newer devices have built-in electronic controls, and “on-board” chemical and biological controls.


IST-502T
Strep A Twist
Test Device
Strep A
LIFESCAN
BiliChek
RAPID FFN

Types of Quality Control

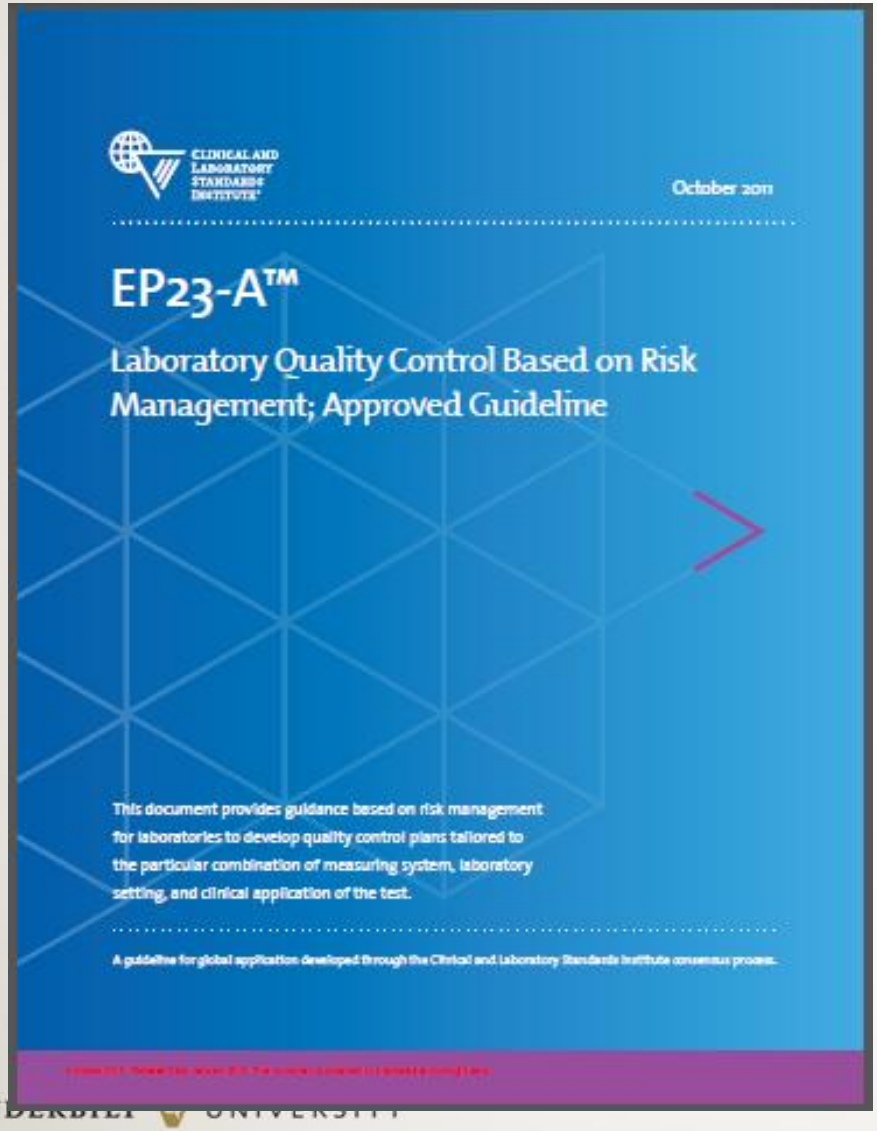
- "On-Board" or Analyzer QC – built-in device controls or system checks
- Internal QC – laboratory-analyzed surrogate sample controls
- External QC – blind proficiency survey
- Other types of QC – control processes either engineered by a manufacturer or enacted by a laboratory to ensure result reliability

Laboratory-Manufacturer Partnership

- No single QC procedure can cover all devices, because the devices may differ.
- Newer devices have built-in electronic controls, and “on-board” chemical and biological controls.
- Developing a quality plan surrounding a laboratory device requires a partnership between the manufacturer and the laboratory.
- Some sources of error may be detected automatically by the device and prevented, while others may require the laboratory to take action, such as analyzing surrogate sample QC on receipt of new lots of reagents.
- Clear communication of potential sources of error and delineation of laboratory and manufacturer roles for how to detect and prevent those risks is necessary.

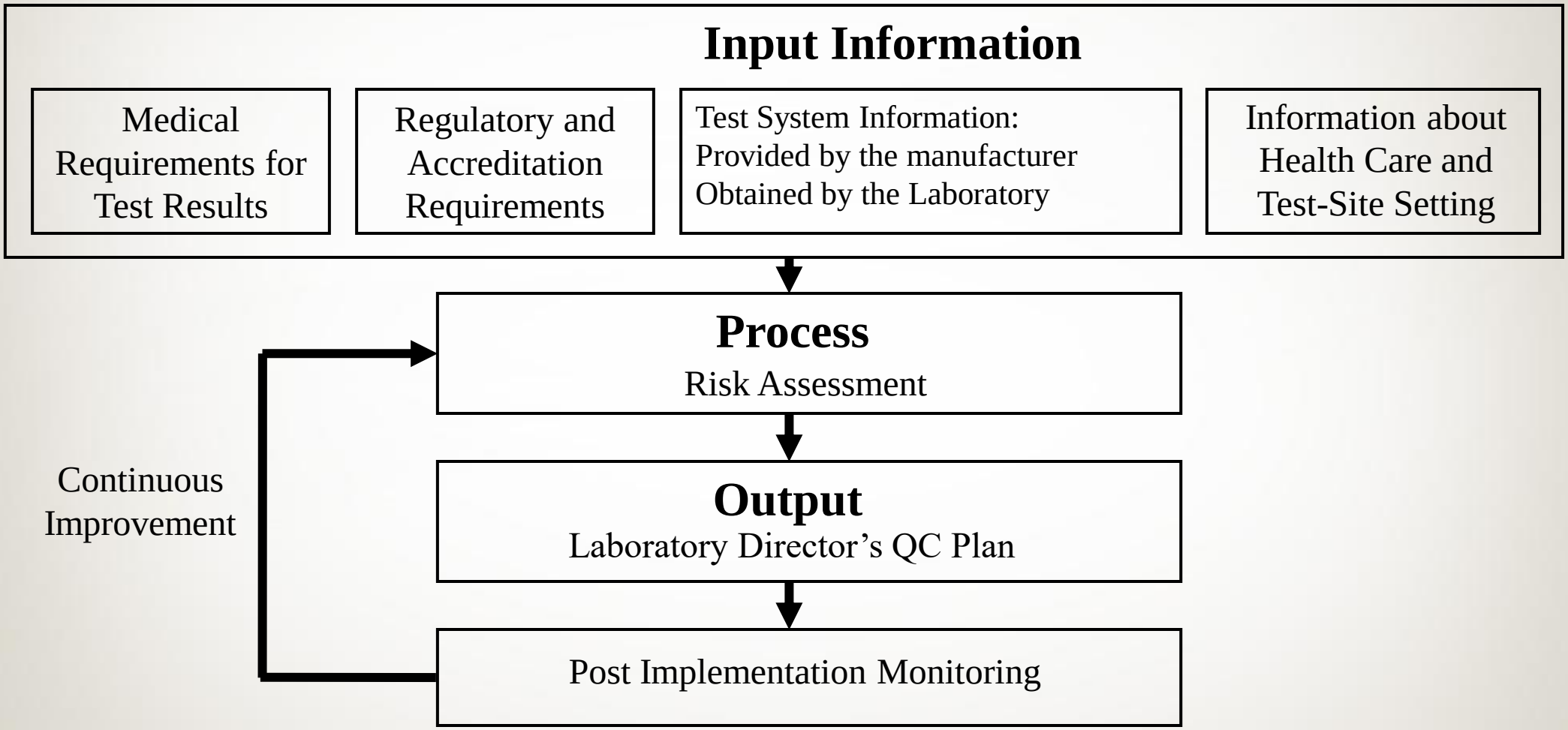
ISO. *Clinical laboratory medicine – In vitro diagnostic medical devices – Validation of user quality control procedures by the manufacturer*. ISO 15198. Geneva, Switzerland: International Organization for Standardization; 2004.

CLSI EP23



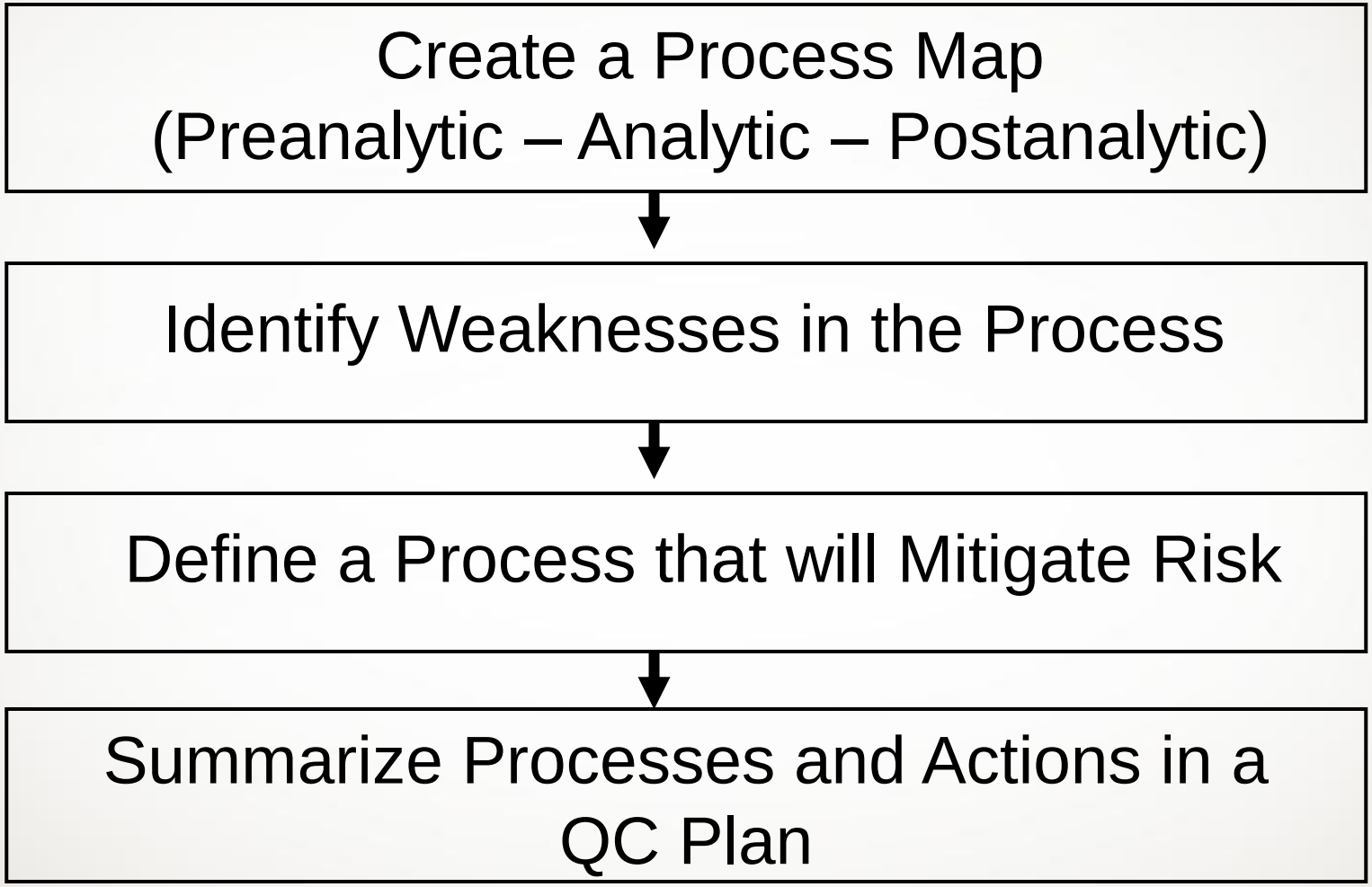
- Laboratory Quality Control Based on Risk Management.
- James H. Nichols, Ph.D., Chairholder
- EP23 describes good laboratory practice for developing a quality control plan based on manufacturer's information, applicable regulatory and accreditation requirements, and the individual healthcare and laboratory setting

EP23 Laboratory QC Based on Risk Management



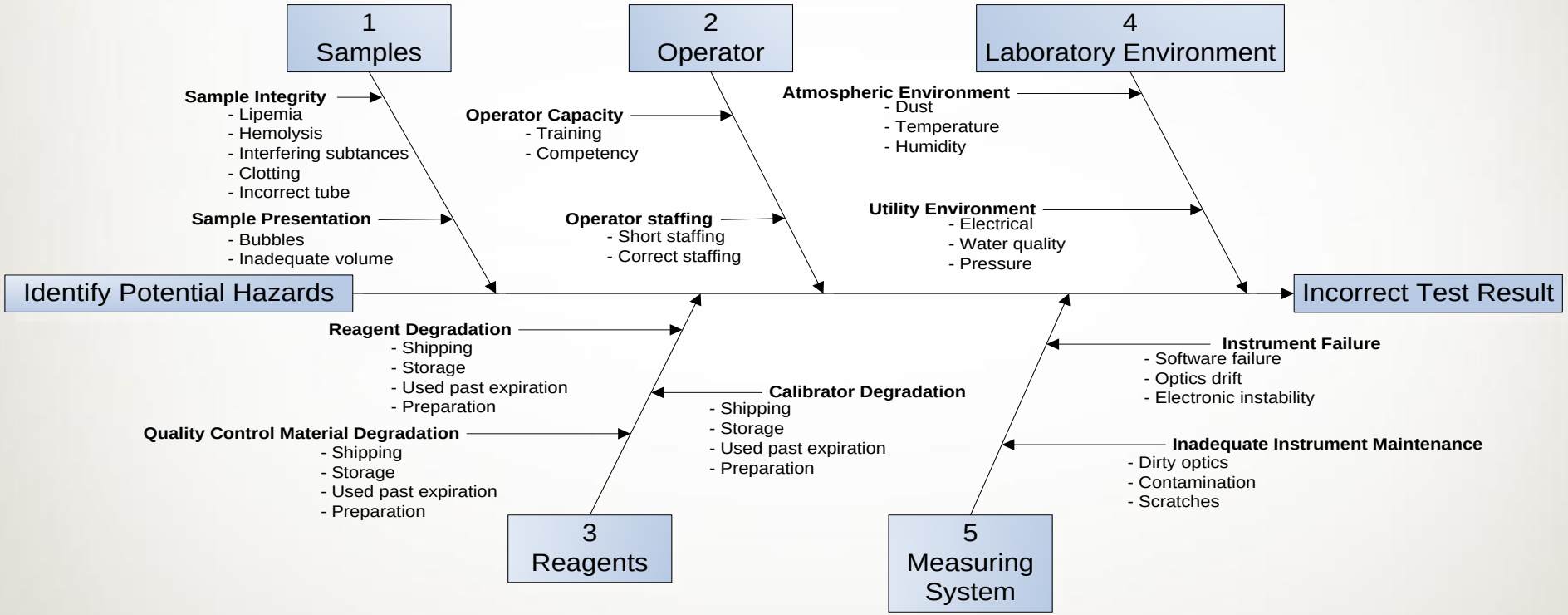
CLSI EP23 Table

EP23 Laboratory QC Based on Risk Management



Developing a Process Map

- Compile information.
- Look for weaknesses in each step of process



POCT

- Dozens of sites
- Hundreds of devices
- Thousands of operators!
- Too many cooks…

  spoil the broth!
- The number of sites, devices and operators plus the volume of testing creates a situation where rare events can become probable in every-day operations

Nothing is foolproof…

for a sufficiently talented fool!

(attributed to a distinguished colleague)

Risk Management

- Manufacturers consider potential for errors and address how these hazards are mitigated or reduced in FDA submissions based on “use-case scenarios”
- Use-case scenarios describe real-world examples of how one or more people interact with a device
- For example:
  - A POCT device may be taken to the patient’s bedside, or
  - A sample may be collected and transported to a device
- These two scenarios have different workflows and present different opportunities for error or risks!

Where is the Risk in Our Process?

Falsely Decreased Glucose Results

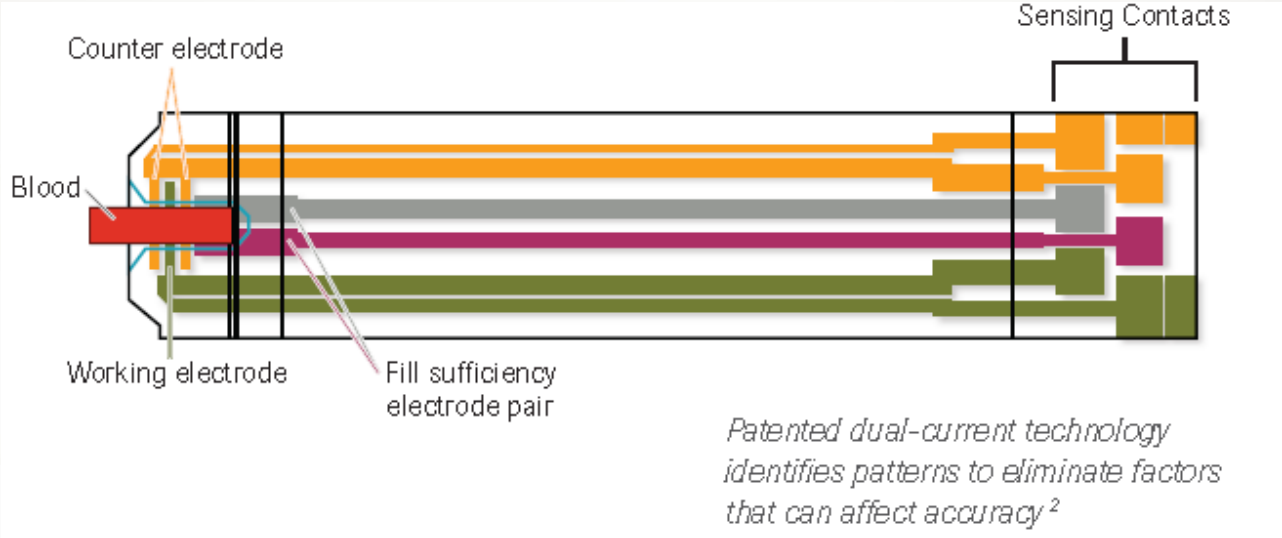
- Complaint from an ICU of sporadic falsely decreased glucose results
- Immediate repeat test on same meter, gave significantly higher “clinically sensible” values
- Inspection of unit found nurses taking procedural shortcuts to save time
- Bottles of test strips dumped on counter in spare utility room
- Some strips not making it into trash, falling back on counter and being “REUSED”

Risk of Error from Open Reagents

- Glucose test strips exposed to air for as little as 2 hours have been shown to cause -26% bias.[1]
- Strips left on counters pose risk of reuse, leading to falsely low results.
- Some meters catch reuse and "error" preventing a result. Other meters do not![2]

1. Keffer P, Kampa IS. *Diabetes* 1998; 47; abs 0170.
2. Silverman BC, Humbertson SK, Stem JE, Nichols JH. Operational errors cause inaccurate glucose results. *Diabetes Care* 2000;23:429-30.

Manufacturer Engineered Checks

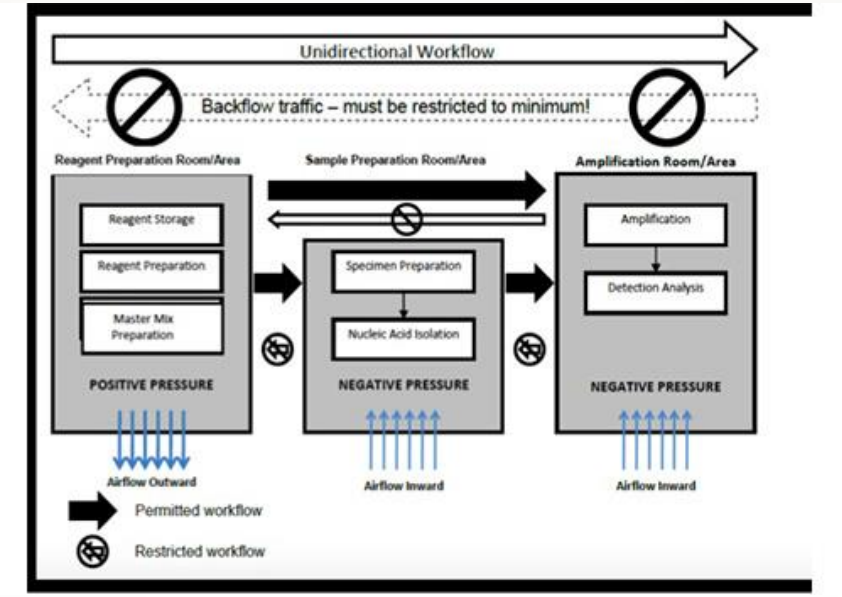


- Internal test strip checks can detect damage or abuse to strip (scratches, humidity, temperature)
- Used or wetted test strips
- Strip and code key match
- Compensate for hematocrit and temperature

POCT Molecular Infectious Disease

- Single-use cartridges – no carry-over
- Connectivity – cell or wired/wireless
- STDs, respiratory viruses, MRSA, C. difficile, next?
- Portable
- Minimal education for operation
- CLIA waived in US
- Clinic and other healthcare settings
- Developing countries/emerging markets
- Military deployment
- Disaster relief

Typical Molecular Lab Workflow



- Separation of reagent preparation, sample preparation and amplification to prevent cross-contamination
- With POCT sample prep and amplification is contained in same cartridge

Donato L. et al., Assessment of Test Performance and Potential for Environmental Contamination Associated with a Point-of-Care Molecular Assay for Group A Streptococcus in an End User Setting JCM 2019 http://doi.org/10.1128/JCM.01629-18

Sample Errors: Contamination

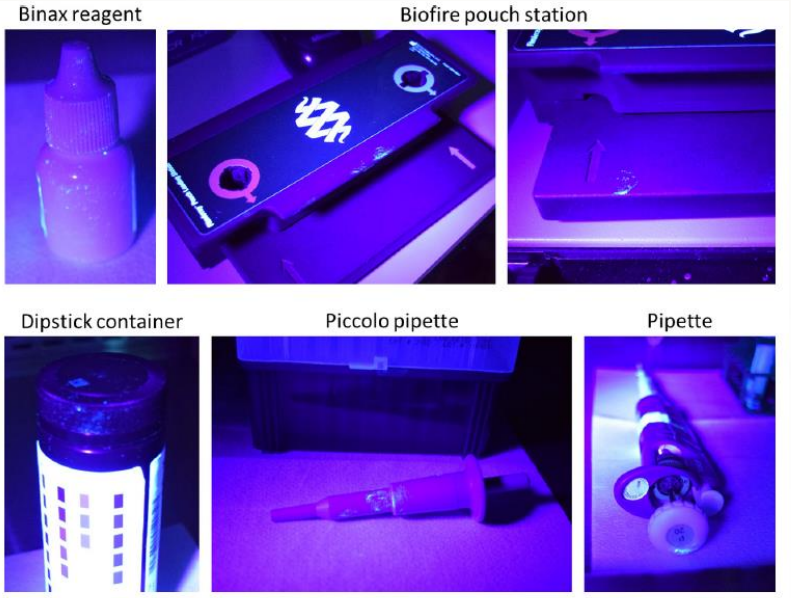


FIG 2 Examples of reagent bottles and accessory equipment contaminated during test setup.

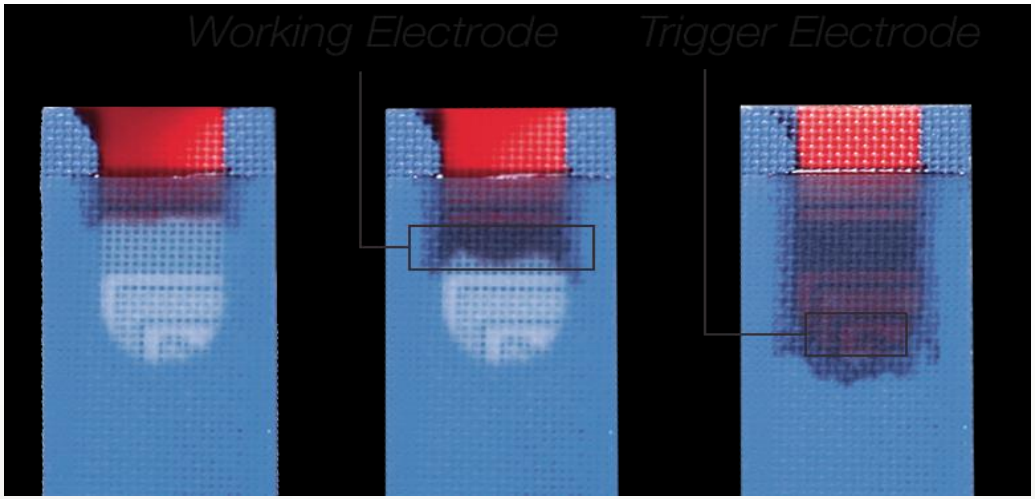
- Highly sensitive – small amounts nucleic acid amplified many fold!
- Yarbrough ML, et al. Frequency of Instrument, Environment, and Laboratory Technologist Contamination during Routine Diagnostic Testing of Infectious Specimens. J Clin Microbio 2018; Vol 56; e00225-18.
- Despite common spread of fluorescent powder, few amplifications of harmless bacteriophage noted during routine testing (3/268 = 1%)

Sample Errors: Contamination

- Environmental - virus and fomites can persist on surfaces –
  - We teach staff common sources of contamination. Handle one sample at a time, routinely clean counter and instrument. Change gloves between samples, use integrated disposable pipette to transfer, do not allow swabs to drip on counters.
- Carry-over – single tube sampling, reaction contained in cartridge – train operators to not touch positive control swabs and then handle samples
- Waste contained - Dispose of cartridge/amplicons after reaction – do not crush cartridges (trash compactor)
- Color coded - sample device snaps to reaction cartridge – protects amplicon tubes
- Some literature noting false-positives from vaccines – physically separate testing and vaccination sites and do not store molecular reagents/controls in vaccine refrigerators

Sample Errors: Specimen Volume

- Some glucose meters recommend that operators visually inspect strips for uniform color development after each test (detects underfilling and bubbles)
- Other meters have automate sample detection. (Fill-trigger is designed to prevent short-sampling.)
- Test starts only when enough blood has been applied.



Molecular Sample Errors: Specimen Volume

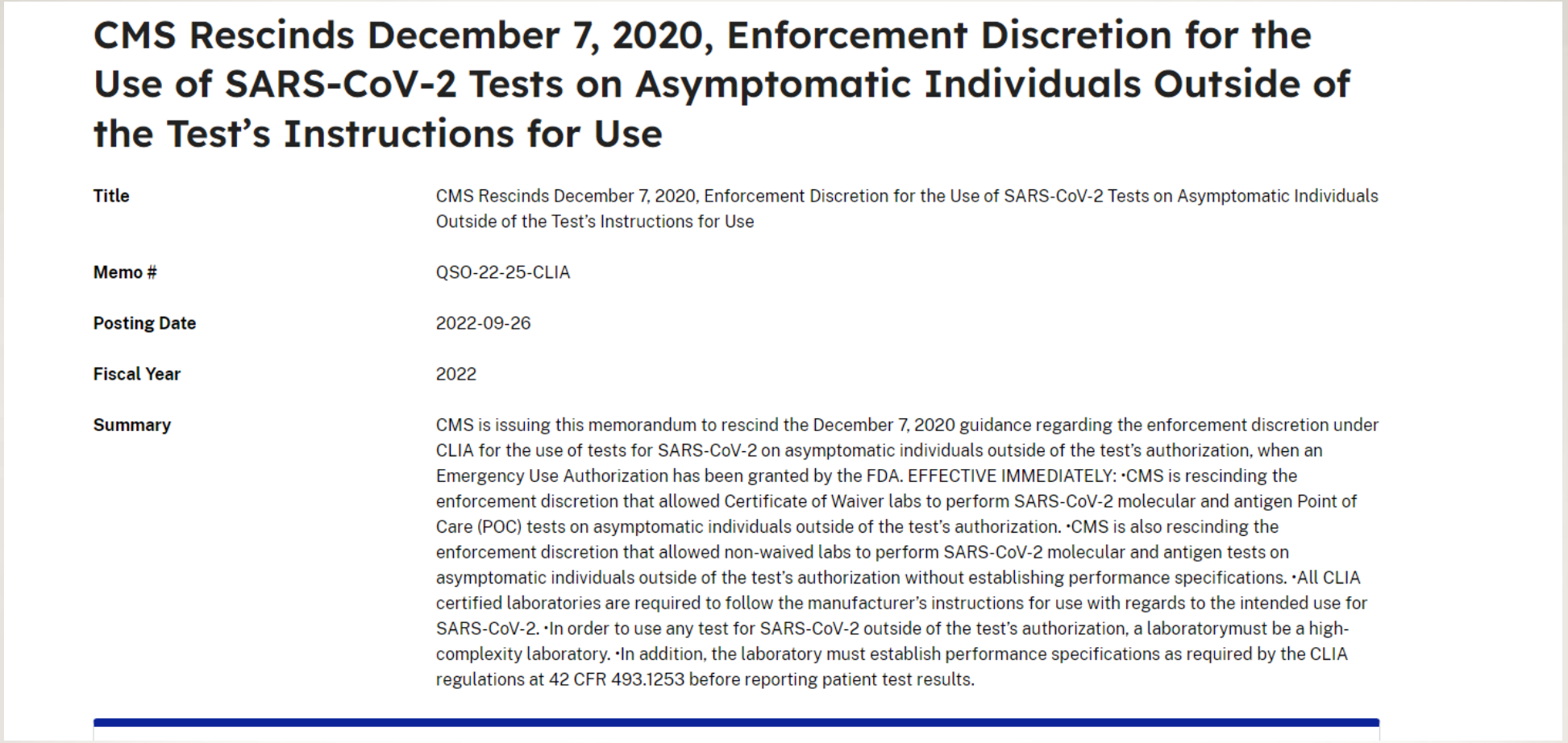
- Internal/procedural control with each assay – flags invalid if doesn't react appropriately - adequate sample, no interference with molecular amplification reaction
- Nasopharyngeal swab – included with test kit to ensure collects sufficient sample or included with transport media to ensure appropriate swab placed in appropriate media.
- Swab placed in transfer media/collection buffer, snap off top of swab.– alternatively some devices test the swab directly – no media.
- In tube sampling, or transfer via integrated pipette

Sample Errors: Specimen Volume

- Reagent controls – performed on every cartridge after sample preparation, but before amplification – checks probe fluorescence readings
- Sample processing and sample adequacy controls – one is exogenous nuclei acid added to cartridge and other is endogenous single-copy human gene from patient sample – both coextract and co-amplify with other nucleic acids in sample
  - Sufficiency of sample collection
  - Effectiveness of on-board sample processing
  - Integrity of extracted nucleic acid
  - Favorable amplification reaction conditions
  - Absence of amplification reaction inhibitors
- Software controls – relational algorithms to verify baseline correction, amplification cutoffs, and reduce effects of unusual amplification curves

Molecular Sample Errors: Patient Considerations

- Molecular diagnostics should be an aid in care of patient – test is only as good as the clinician using the test
- Strep A/MRSA – may detect carriers without active infection
- Should assess clinical symptoms in conjunction with positive test result
- Part of antibiotic stewardship is also being a good steward of the test!



CMS Rescinds December 7, 2020, Enforcement Discretion for the Use of SARS-CoV-2 Tests on Asymptomatic Individuals Outside of the Test's Instructions for Use

Title	CMS Rescinds December 7, 2020, Enforcement Discretion for the Use of SARS-CoV-2 Tests on Asymptomatic Individuals Outside of the Test's Instructions for Use
Memo #	QSO-22-25-CLIA
Posting Date	2022-09-26
Fiscal Year	2022
Summary	CMS is issuing this memorandum to rescind the December 7, 2020 guidance regarding the enforcement discretion under CLIA for the use of tests for SARS-CoV-2 on asymptomatic individuals outside of the test's authorization, when an Emergency Use Authorization has been granted by the FDA. EFFECTIVE IMMEDIATELY: •CMS is rescinding the enforcement discretion that allowed Certificate of Waiver labs to perform SARS-CoV-2 molecular and antigen Point of Care (POC) tests on asymptomatic individuals outside of the test's authorization. •CMS is also rescinding the enforcement discretion that allowed non-waived labs to perform SARS-CoV-2 molecular and antigen tests on asymptomatic individuals outside of the test's authorization without establishing performance specifications. •All CLIA certified laboratories are required to follow the manufacturer's instructions for use with regards to the intended use for SARS-CoV-2. •In order to use any test for SARS-CoV-2 outside of the test's authorization, a laboratorymust be a high-complexity laboratory. •In addition, the laboratory must establish performance specifications as required by the CLIA regulations at 42 CFR 493.1253 before reporting patient test results.

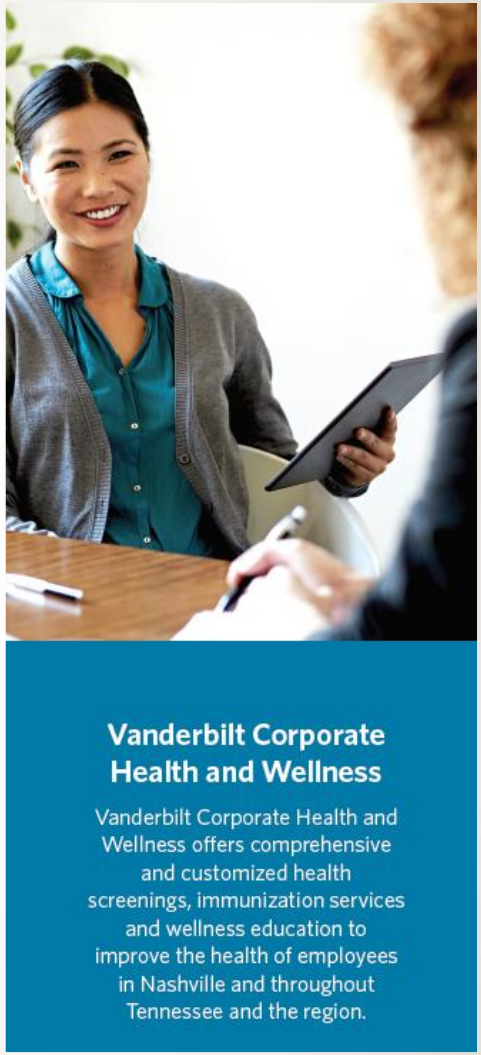
- For Liat, for instance, COVID only molecular cartridge is approved for symptomatic and asymptomatic patients, while respiratory panel COVID/Flu A/B only approved for symptomatic patients.
- Makes difference for testing for travel testing, exposure, testing for resuming work.

Corporate Health Services

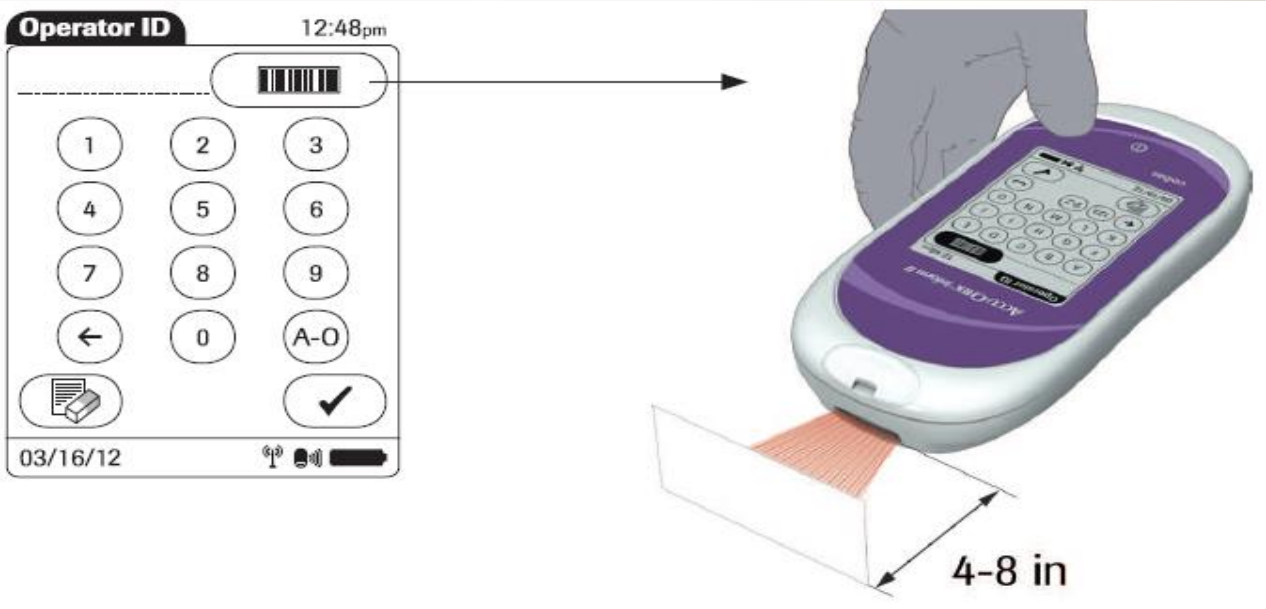
- Corporate Health Services encompasses Executive Health, Corporate Health and Wellness and Workman's Compensation to corporate clients and their employees
- COVID pandemic led to new opportunities for testing
- Concierge medicine
  - Football, Hockey, Soccer and other sports team player testing
  - Attendees to events who have not been vaccinated or require COVID testing for entry to show, event, or concert

- Challenges
  - The only COVID "antigen" test offered in health enterprise
  - Concern over using a COVID or Flu antigen reader that is intended to remain plugged in, on a lab counter, not portable.
  - Wants to offer COVID molecular using a device on same asymptomatic population (ie screening), but package insert states:

    is a molecular in vitro diagnostic test utilizing polymerase chain reaction (PCR) and lateral flow technologies for the qualitative, visual detection of nucleic acid from SARS-CoV-2 in clinician-collected nasal or nasal mid-turbinate swab specimens or clinician-instructed self-collected (collected on site) nasal swab specimens, collected from individuals suspected of COVID-19 by their healthcare provider.



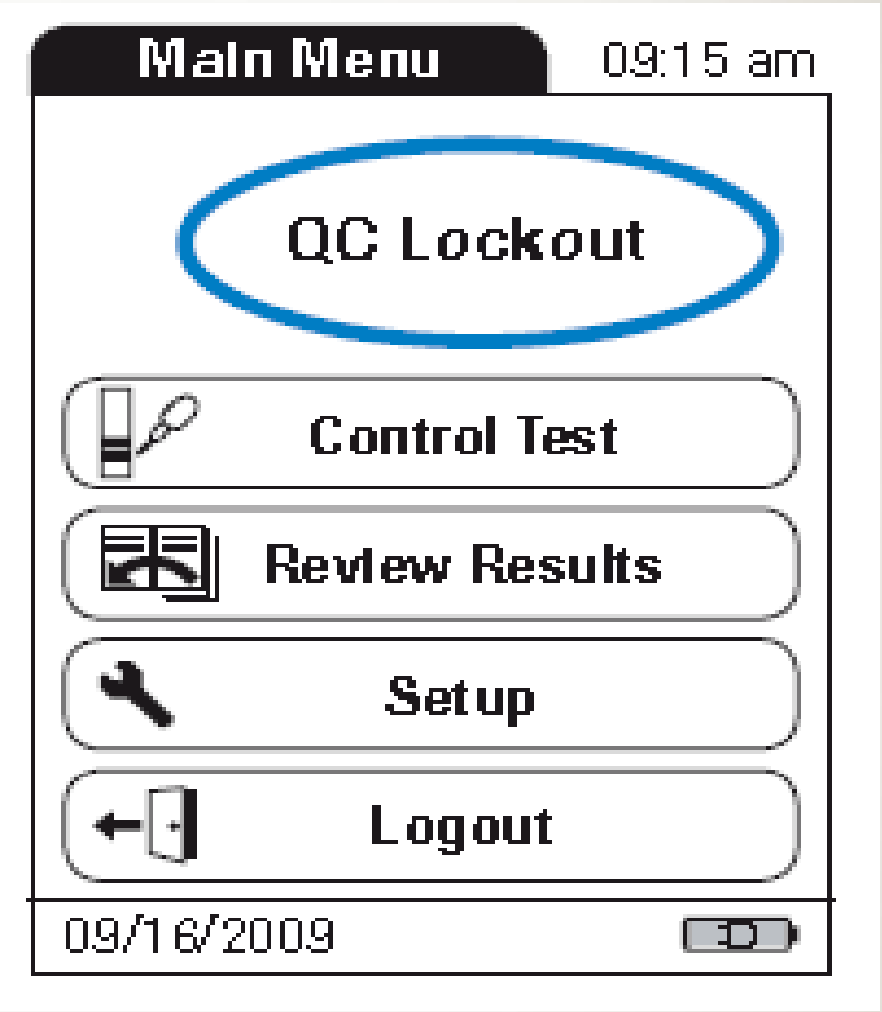
Operator Errors: Training/Competency



- Operator lockout
- Functions through number code, name or barcoded ID
- List of operators and training/competency dates maintained in data manager system–
- Devices can warn operators of impending certification due dates (in advance of lockout)

Operator Errors: Performing QC

- Devices require periodic QC
- QC lockout shuts off patient testing if QC not performed or fails target ranges.
- Prevents patient testing unless QC documented
- Operators workaround QC lockout by performing patient testing in QC mode!
- Newer devices distinguish QC samples, prevent patient testing in QC

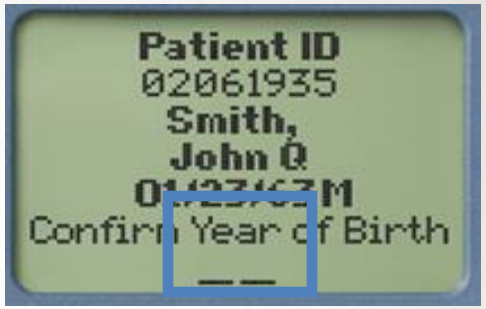


Operator Errors: Patient Identification

- Incorrect entry of patient identification can
  - Chart results to the wrong patient's medical record
  - Lead to inappropriate medical decisions and treatment
  - Improper billing and compliance
- Barcoded patient wristbands reduce the chance of misidentification, but patients can be banded with:
  - Another institution's identification
  - Outdated account numbers
  - A wrong patient's wristband
- Residual risk of error even with barcoded ID bands
- Barcoded ID entry alone doesn't satisfy requirement for patient safety - 2 unique identifiers

Operator Errors: Patient Identification

- Some devices have positive patient ID – ADT feed to device
- Two identifiers plus active confirmation (also satisfies Joint Commission time out)
- Positive patient ID reduced errors from 61.5 errors/month to 3 errors/month.[1] (unregistered patients; 2 ED and 1 non-ED) conducted over 2 months—38,127 bedside glucose tests.



J Pathol Inform

Technical Note

Reducing patient identification errors related to glucose point-of-care testing

Gaurav Alreja[1], Namrata Setia[2], James Nichols[2], Liron Pantanowitz[3]

[1]Department of Internal Medicine and [2]Pathology, Baystate Medical Center, Tufts University School of Medicine, Springfield, MA, [3]Department of Pathology, University of Pittsburgh Medical Center, Pittsburgh, PA, USA

E-mail: *Liron Pantanowitz – pantanowitzl@upmc.edu
*Corresponding author

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Alreja G, Setia N, Nichols J, Pantanowitz L. Reducing patient identification errors related to glucose point-of-care testing. J Pathol Inform 2011;2:22.

Abstract

Background: Patient identification (ID) errors in point-of-care testing (POCT) can cause test results to be transferred to the wrong patient's chart or prevent results from being transmitted and reported. Despite the implementation of patient barcoding and ongoing operator training at our institution, patient ID errors still occur with glucose POCT. The aim of this study was to develop a solution to reduce identification errors with POCT.
Materials and Methods: Glucose POCT was performed by approximately 2,400 clinical operators throughout our health system. Patients are identified by scanning in wristband barcodes or by manual data entry using portable glucose meters. Meters are docked to upload data to a database server which then transmits data to any medical record matching the financial number of the test result. With a new model, meters connect to an interface manager where the patient ID (a nine-digit account number) is checked against patient registration data from admission, discharge, and transfer (ADT) feeds and only matched results are transferred to the patient's electronic medical record. With the new process, the patient ID is checked prior to testing, and testing is prevented until ID errors are resolved.
Results: When averaged over a period of a month, ID errors were reduced to 3 errors/

1. Alreja G, Setia N, Nichols J, Pantanowitz L. Reducing patient identification errors related to glucose point- of-care testing. J Pathol Inform 2011; 2: 22 [http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3097526/]

Reagent Errors: Expired Reagents

- **Centers for Disease Control**
- "Check and record expiration dates of reagents/kits, and discard any reagents or tests that have expired."[1]

- **U.S. Food and Drug Administration**
- "Check the expiration date on the test strips. As a test strip ages, its chemical coating breaks down. If the strip is used after this time, it may give inaccurate results."[2]

1. Ready? Set? Test! Centers for Disease Control booklet http://wwwn.cdc.gov/dls/waivedtests/ReadySetTestBooklet.pdf
2. Useful Tips to Increase Accuracy and Reduce Errors in Test Results from Glucose Meters, U.S. Food and Drug Administration http://www.fda.gov/MedicalDevices/Safety/AlertsandNotices/TipsandArticlesonDeviceSafety/ucm109519.htm

Strip Wastage When Outdated

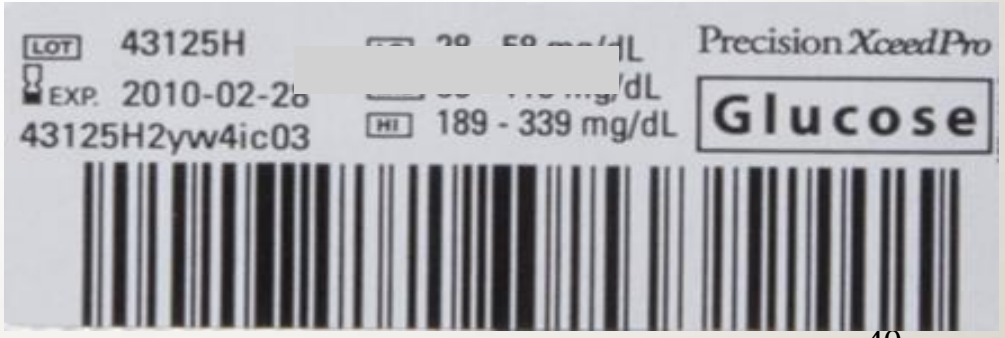
- Operator must check manufacturer's expiration date prior to testing.
- Vials/strips and controls must be manually dated when opened by operator (prematurely expires once opened)
- Undated, opened vials must be discarded. (? expiration)

Discarded strips due to no date[1]

1. Undated vials between September, 2010 and May, 2011, Willis-Knighton Medical Center, Shreveport, Louisiana

Reagent Errors: Expired Reagents

- Serialized vials/strips and controls barcoded for lot number and expiration date (good to stamped expiration date) can recognize individual vials on opening (30, 60 or 90 day open expiration)
- Automatic lockout for expired test strips and controls
- Some devices can also recognize exposure to humidity (few hours), wet or reused strips as additional control measure



Operator Errors: Data Transfer

- POCT results may not get recorded in patient's medical record, particular problem for manual tests
- POCT data management ensures capture of data in device (QC and Patient results), but doesn't guarantee transfer until operators dock device
- Wireless ensures data transmitted to patient record. (Need continuous wireless or operators may forget to push send button)

Molecular vs Antigen Testing

- Antigen based influenza tests require an annual update to report reactivity of test to CDC challenge strains
- The flu reclassification highlighted antigen test limitations particularly to physician office labs (Merckx J et al., Diagnostic Accuracy of Novel and Traditional Rapid Tests for Influenza Infections Compared with Reverse Transcriptase Polymerase Chain Reaction: Systematic Review and Meta-analysis. Ann Intern Med 2017. doi:10.7326/M17-0848)
  - Not a requirement for molecular testing
  - NAAT is the optimal diagnostic modality for flu (Uyeki TM, et al., Clinical Practice Guidelines of the Infectious Diseases Society of America: 2018 Update on Diagnosis, Treatment, Chemoprophylaxis, and Institutional Outbreak Management of Seasonal Influenza. DOI: 10.1093/cid/ciy866)
- No need to confirm Strep A testing! – If test achieves 98% sensitivity, no need to confirm - Can treat definitively on first test result – streamlines patient workflow (Rao A et al., Diagnosis and Antibiotic Treatment of Group A Streptococcal Pharyngitis in Children in a Primary Care Setting: Impact of Point-of-Care Polymerase Chain Reaction. BMC Peds, 2019 http://www.ncbi.nlm.nih.gov/pubmed/30651115)

New CAP Molecular POCT Checklist Questions

***NEW** 09/17/2019*

POC.08675 Quality Monitoring Statistics **Phase I**

There are written procedures to monitor for the presence of false positive results (eg, due to nucleic acid contamination) for all molecular microbiology tests.

NOTE: Examples of this may include review of summary statistics (eg, monitoring percentage of positive results relative to current local and regional rates and increased positive Strep results above historical rate within a run or over multiple runs), performance of wipe (environmental) testing, review and investigation of physician inquiries, and use of process controls to minimize risk of contamination.

***NEW** 09/17/2019*

POC.08690 Specimen Handling Procedures **Phase II**

There are written procedures to prevent specimen loss, alteration, or contamination during collection, transport, processing and storage.

NOTE: Specimen collection, processing and storage must follow manufacturer's instruction and limit the risk of preanalytical error. For example, there must be a procedure to ensure absence of cross-contamination of samples during processing/testing for respiratory specimens tested at the point-of-care that may be sent to the laboratory for further testing.

It is also essential to follow the manufacturer's instructions for the handling of wastes (eg, used test cartridges) to prevent contamination.

***NEW** 09/17/2019*

POC.08715 Safe Specimen Handling/Processing **Phase II**

There are written policies for the safe handling and processing of samples from patients with suspected infections due to avian influenza, SARS, Ebola, or similar emerging pathogens.

NOTE: These policies may be part of an institution's plan, but the plan must specifically address point-of-care.

***NEW** 09/17/2019*

POC.08730 Final Report **Phase I**

The final report includes a summary of the test method and information regarding clinical interpretation if appropriate.

NOTE: For tests that may be performed by either direct antigen or molecular-based methods (PCR), including the test method in the report is important for interpretation of the results. The report must include a brief description of the method if the methodology is not explicit in the test name.

Where is the Risk in the Process?

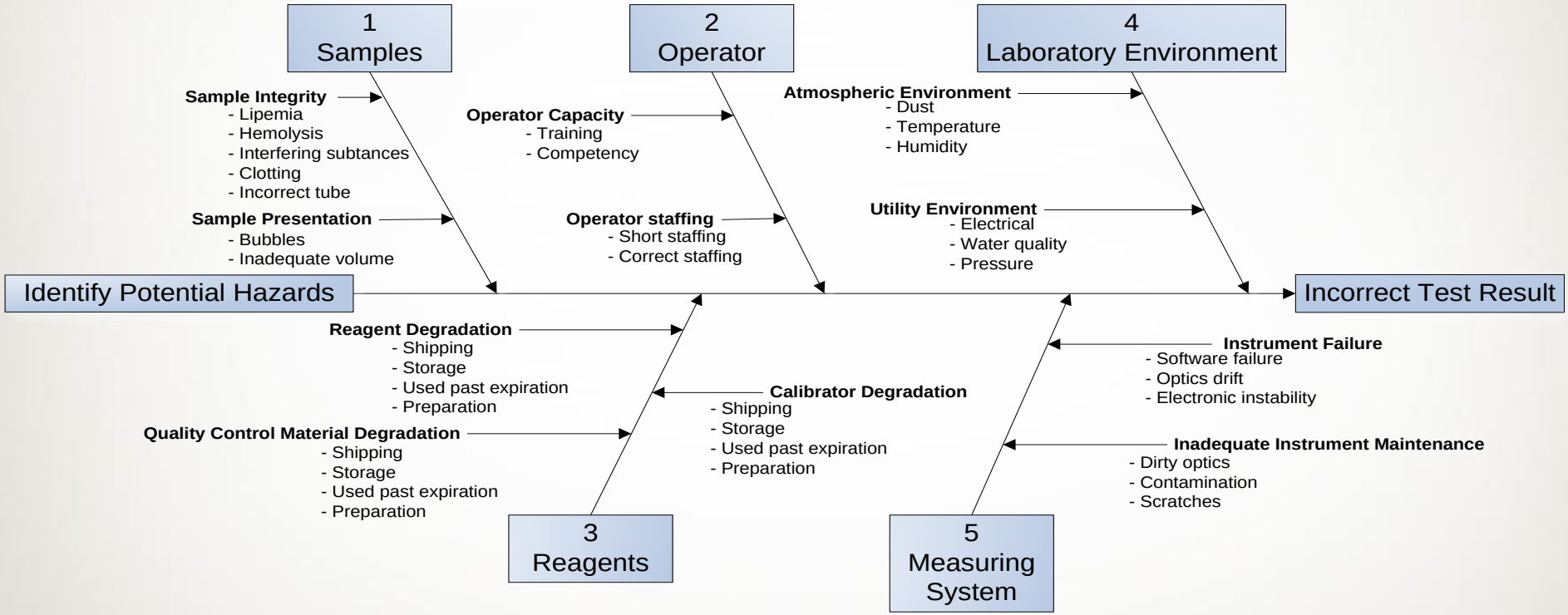
What Could Possibly Go Wrong?

Falsely Increased Hgb Results

- Spurious increased Hgb results 18 – 23 g/dL (55 – 70% Hct) on ICU patients
- Meter, QC and reagents examined and fine, no single operator tied to trend
- Continue to experience spuriously high results, trend went on for several weeks
- One day, POC coordinator watching operator perform Hgb test in spare utility room. Operator took shortcut (procedure is to load cuvette from fresh drop of well mixed sample)
- Instead, operator was filling cuvette from drop of blood remaining from glucose test. Test strip was absorbing plasma portion of sample and artificially increasing Hgb/Hct in remaining drop!
- Remedial action to retrain entire unit staff!

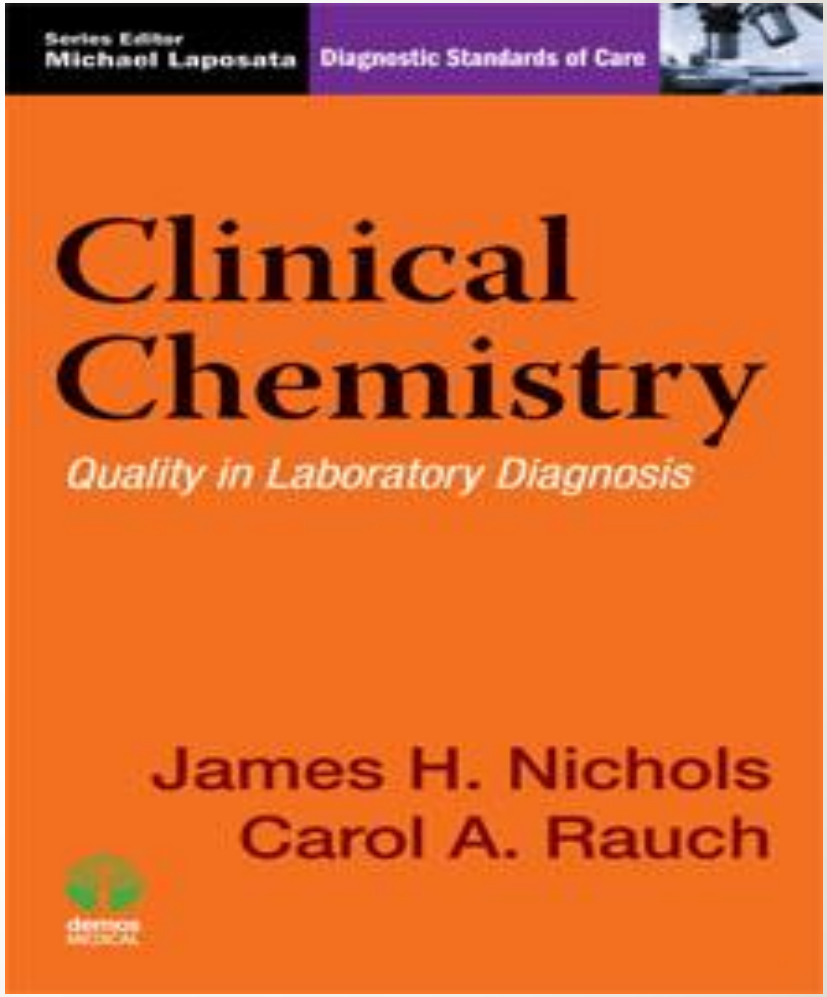
Developing a Process Map

- Look for weaknesses in each step of process



Resource for Reducing Errors

- Clinical Chemistry book recently released!
- Focus on errors in the Chemistry Laboratory including POCT
- Discussion of real-world errors and what can be done to detect and prevent errors.



CLSI EP23 Revision Changes to Expect

- Align CLSI EP23 with ISO 22367 and ISO 14971
- Incorporate detectability in the risk assessment
- Replace “Glucose Concentration Measurement on an Automated Measuring System” example with real-world examples of quality control plans for non-instrumented, single-use device;instrumented, single-use device; and exempt microbiological media.
- Update references

Summary

- Many sources of laboratory error!
- Risk management assesses workflow for weaknesses and allows labs to take action before errors occur
- IQCPs are more than reducing the frequency of QC
- IQCPs provide opportunity for laboratories to interact with clinical departments on a shared QI project
- Improve workflow and operational efficiency
- IQCPs justify our actions, giving meaning to why we need to perform certain activities – beyond meeting regulations