Best Practices in Implementing a Structured Quality Assured COVID-19 Testing Program

ASLM Special COVID-19 ECHO Session #10

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Presentation Overview

- Introduction - CLSI's Support Role with COVID-19 Testing
- Planning and Preparation for COVID-19 Testing
- Selection and Verification/Validation Process for New Testing Methods
- Current Commercial Testing Technologies
- Operator Training & Competence
- Safety Practices to Protect Laboratory Staff
- CLSI Reference Documents

CLSI's Role in COVID-19 Testing Support

- CLSI's mission: "Develop clinical and laboratory practices and promote their use worldwide"

- Recognizes important contributions of laboratory professionals & the health care community and applauds efforts in global fight against COVID-19

- Helpful documents list available for laboratory community's use during the current pandemic: https://clsi.org/standards-development/helpful-documents-for-covid-19-testing/

- *Presentation to highlight best practices in implementing a structured, quality assured COVID-19 testing program across all phases of testing*
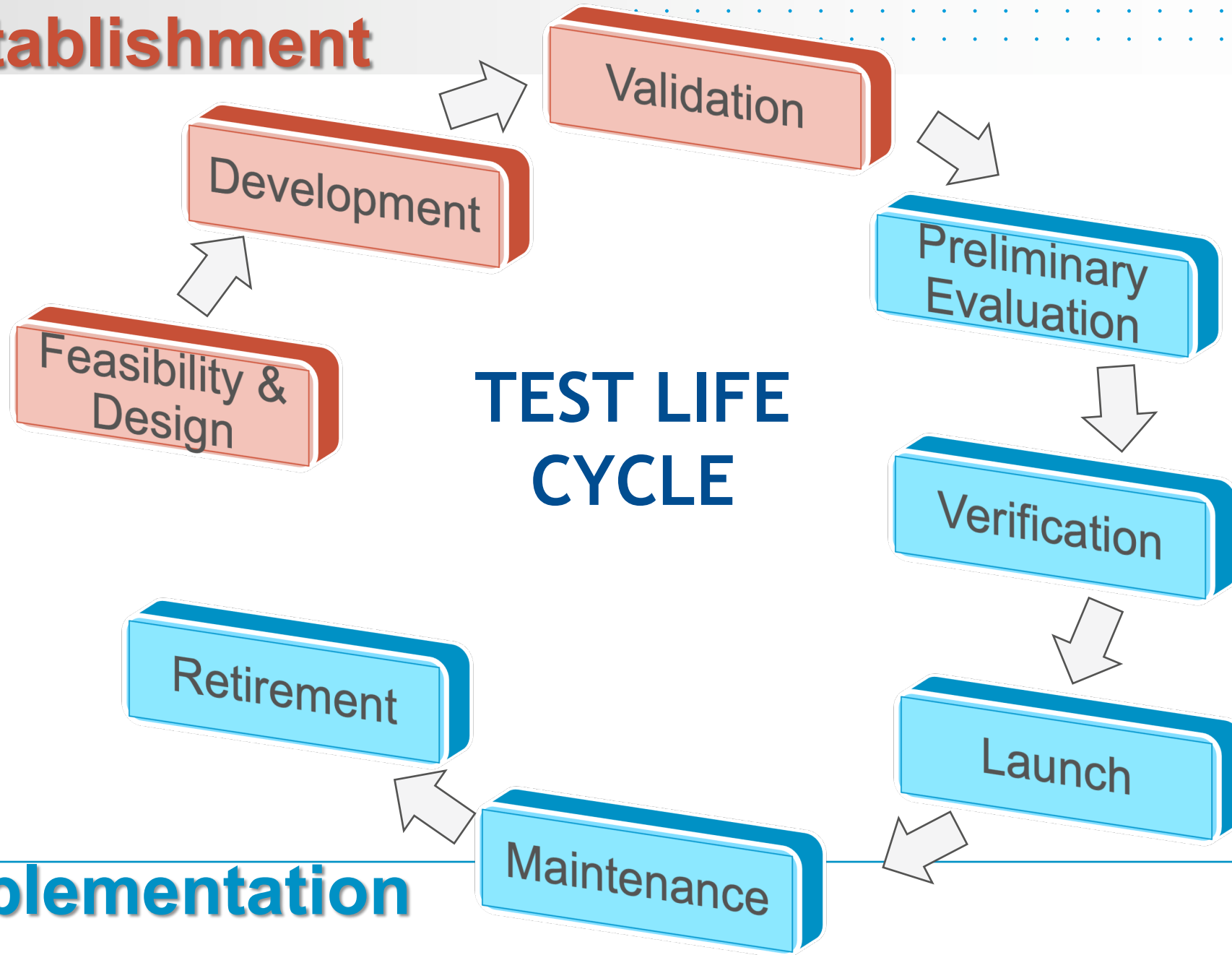
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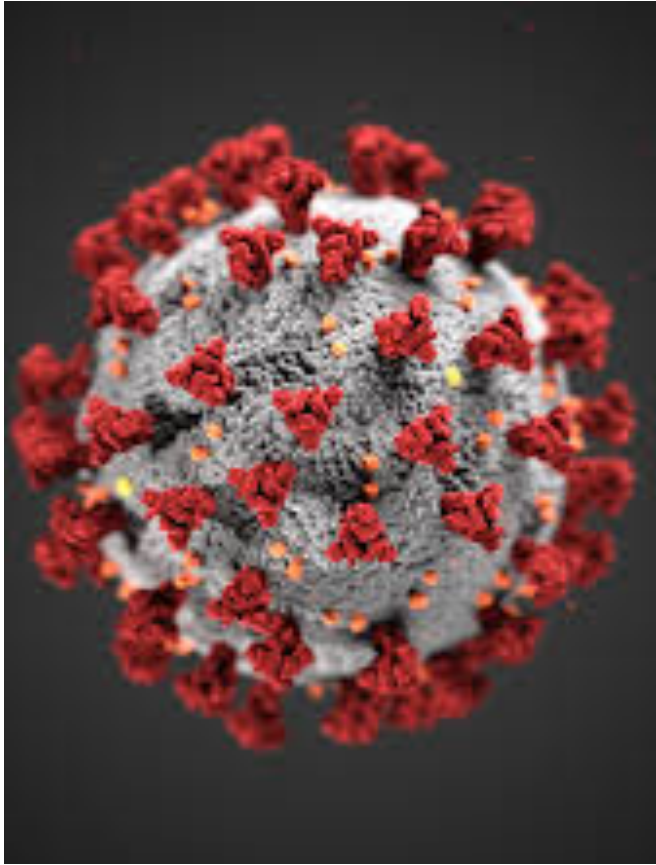# COVID-19 Testing – Planning & Preparation
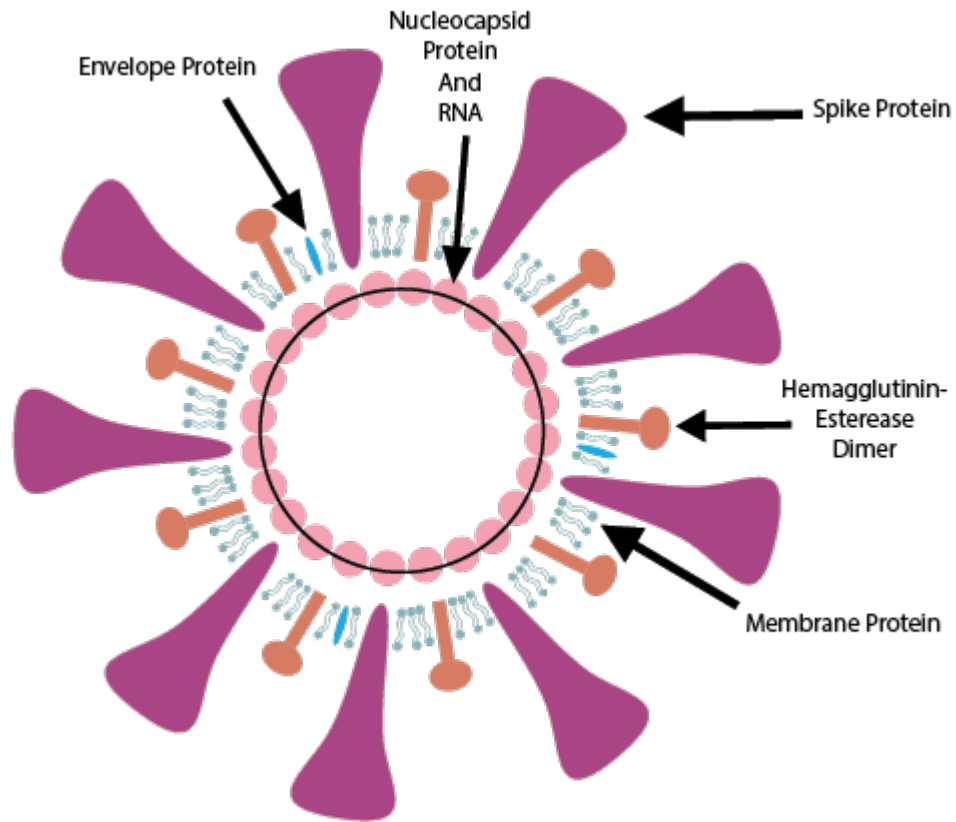
COVID-19 Test Technology

- Molecular - *Qualitative* tests measure the viral RNA component:
  - Real Time PCR
  - Fluorescent PCR

- Serology - *Qualitative* Immunoassays:
  - ELISA IgG Antibodies
  - IgM/IgG

Establishment

TEST LIFE CYCLE

Validation

Development

Feasibility & Design

Preliminary Evaluation

Verification

Launch

Retirement

Maintenance

Implementation

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Implementing COVID-19 Tests

Follow a structured process:

- o Plan
- o Prepare
- o Select and verify the test
- o Train the test operators
- o Collect and transport the sample
- o Perform the testing
  - POCT specific considerations
  - Quality control
  - Proficiency testing

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Implementation Considerations - Emergency Use

Leverage helpful guidance of CLSI documents with recommendations & guidelines from your regulatory body:

- *FDA's Coronavirus Disease 2019 (COVID-19) EUA Information*
  - https://www.fda.gov/medical-devices/emergency-situations-medical-devices/emergency-use-authorizations

- *WHO's Coronavirus disease (COVID-19) Pandemic – Emergency Use Listing Procedure (EUL) open for in vitro diagnostics*
  - https://www.who.int/diagnostics_laboratory/EUL/en/

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Before Beginning Testing

- GP36, Planning for Laboratory Operations During a Disaster
  - Available free at clsi.org
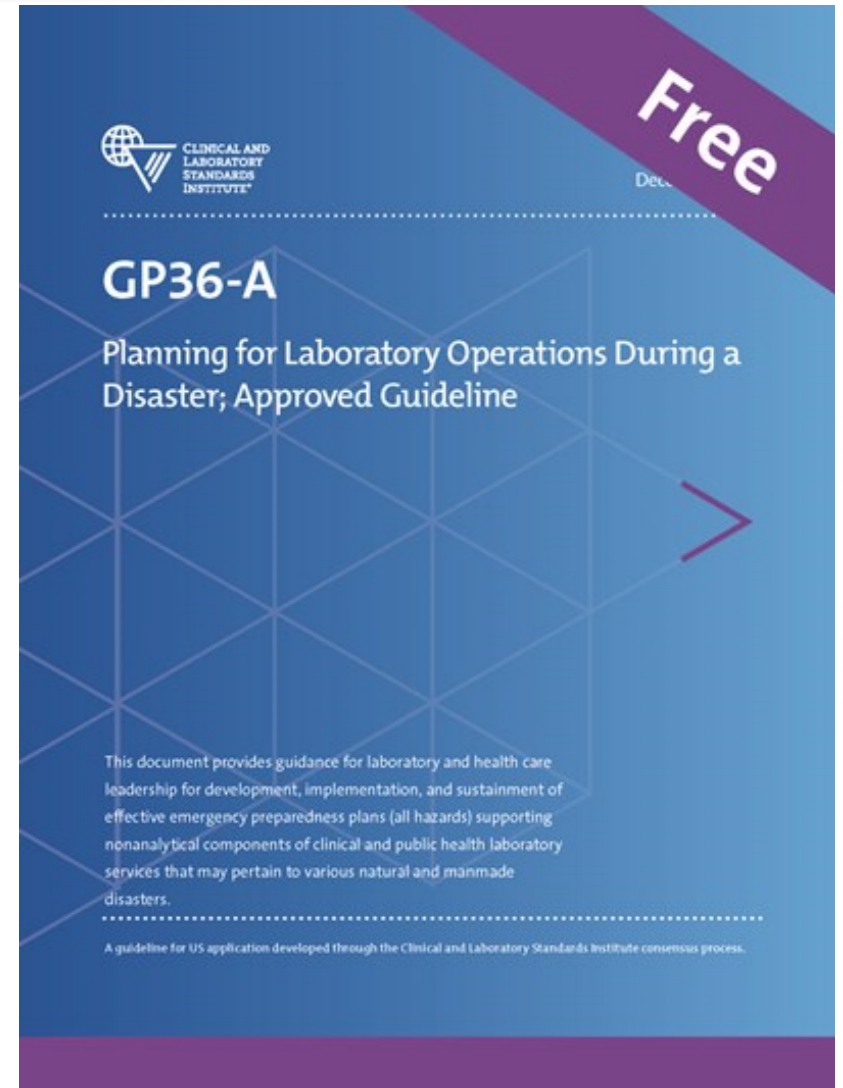
COVID-19 Testing – Selection & Validation/Verification

Method Evaluation – Validation versus Verification

- **Method Evaluation**:
  - Validation
  - Verification
- **Validation**:
  - Confirmation through the provision of objective evidence that the requirements for a specific intended use or application have been fulfilled.
- **Verification**:
  - Confirmation that the assay performance characteristics as stated by manufacturer are the same when the testing is performed in your laboratory settings.
    - For validated methods used without modification (e.g. commercial kit used as directed → "intended use")

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When to Validate or Verify?

Information	Action
Fully validated standard methods – have been validated before and data available	Verification
Standard Methods – but being used with some modifications e.g. on new instrument other than where they were validated	Validation
Standard Methods – being used outside of their intended scope	Validation
Laboratory developed test methods	Validation

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Method Verification – Key Performance Characteristics

- For current *qualitative* COVID-19 testing, range of performance characteristics to assess depending upon test method:

Test Method	Key Performance Characteristics
Molecular Testing	Limit of Detection (LoD) *(Analytical Sensitivity)*
	Inclusivity *(Analytical Sensitivity)*
	Cross-Reactivity *(Analytical Specificity)*
Serology Testing	Inclusivity *(Analytical Sensitivity)*
	Cross-Reactivity *(Analytical Specificity)*
	Class Specificity, *if applicable*

IMPORTANT: Utilize available Emergency Use guidance (i.e., EUL from WHO and EUA from FDA)

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Method Evaluation – Concept Review: Sensitivity & Specificity

- **Analytic Sensitivity:** smallest quantity of an analyte that can be reproducibly distinguished from background levels in a given assay system
  - Usually defined at the 0.95 confidence level (2 standard deviations)
  - Limit of detection
  - Inclusivity considerations
- **Analytic Specificity:** ability of an analytical method to detect only the analyte that it was designed to measure
  - Cross-reactivity considerations

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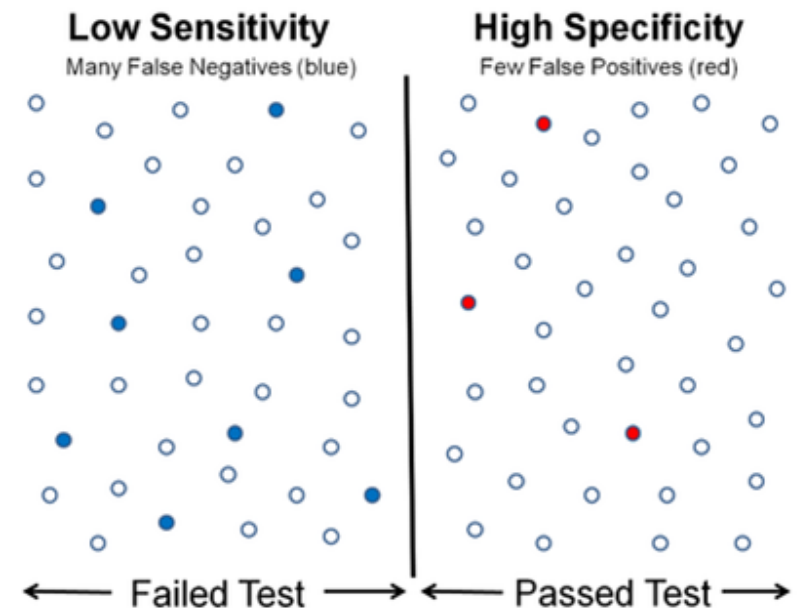
# Suggested Protocol for Qualitative Method Verification

- Run at 10 known positive and 10 known negative samples for a condition.

- Calculate specificity and sensitivity

- Apply the acceptance criteria

- Review results and make a decision to accept/reject the method.

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Method Evaluation – Contingency Tables

Method	Known Results		Total
	Positive	Negative	
Positive	TP (10)	FN (0)	TP + FN = 10
Negative	FN (0)	TN (10)	FN + TN = 10
Total	TP + FN = 10	FP + TN = 10	

Sensitivity = 100 x [TP/(TP+FN)]
Specificity = 100 x [TN/(FP+TN)]
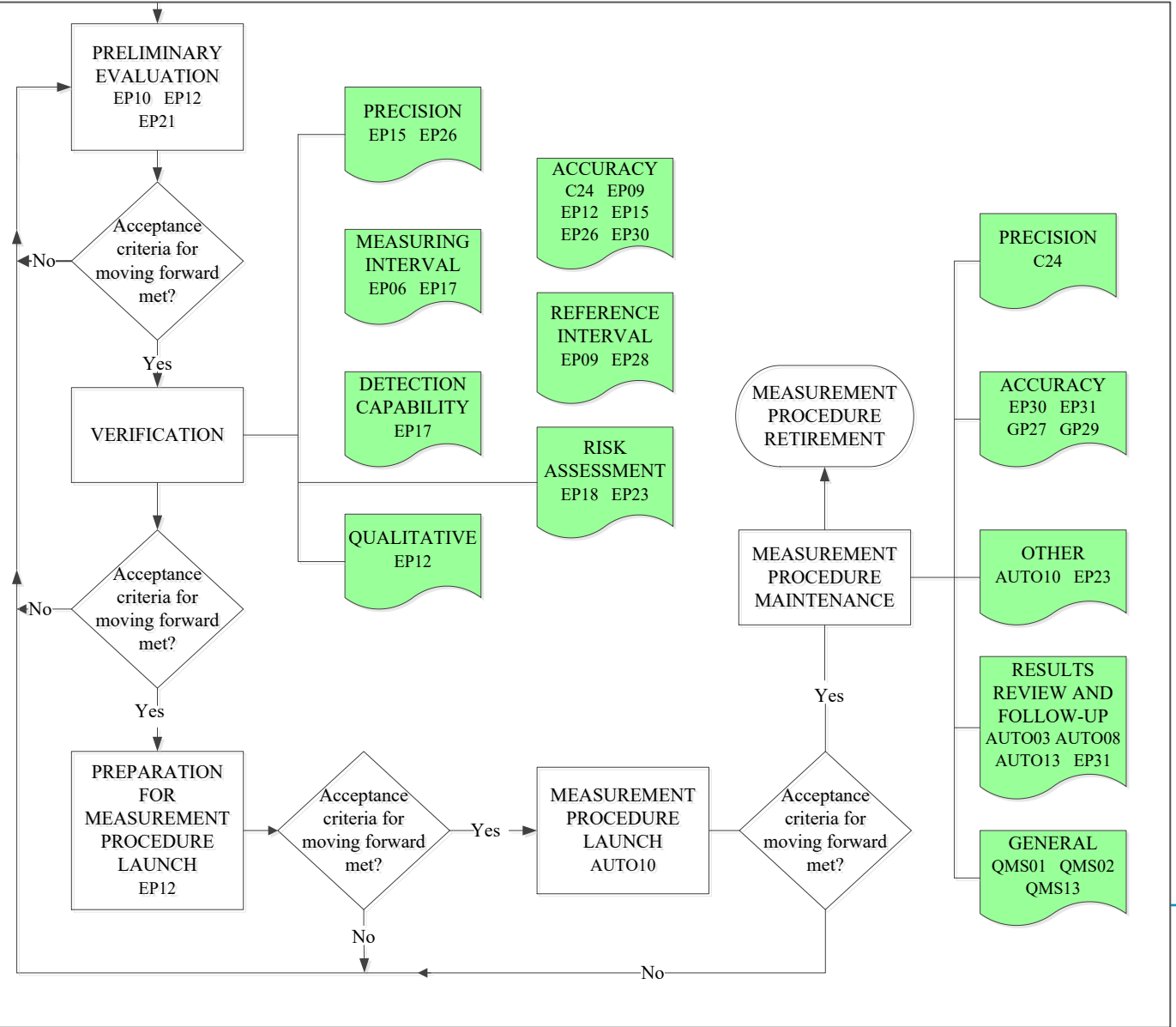
Method Verification: Start with CLSI EP19

- Free resource

- Describes method verification activities

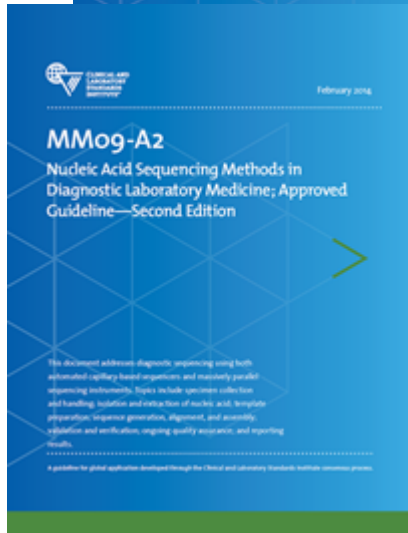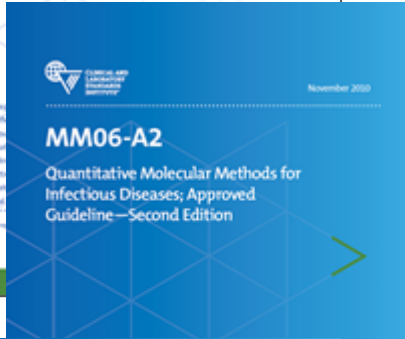- Lists CLSI documents for method verification

General Method Verification Standards

EP05, Precision Testing
EP06, Linearity Testing
EP07 & EP37, Interference Testing
EP12, Qualitative Test Evaluation
EP17, Limits of Detection

EP18, Risk Management
EP23, QC Based on Risk Management
EP35, Equivalence of Specimen Types

Method-Specific Standards

MM03, Molecular Diagnostic Methods for Infectious Diseases

MM06, Quantitative Molecular Methods for Infectious Diseases

MM09, Nucleic Acid Sequencing Methods in Diagnostic Laboratory Medicine

MM17, Validation and Verification of Multiplex Nucleic Acid Assays

MM19, Establishing Molecular Testing in Clinical Laboratory Environments

MM22, Microarrays for Diagnosis and Monitoring of Infectious Diseases
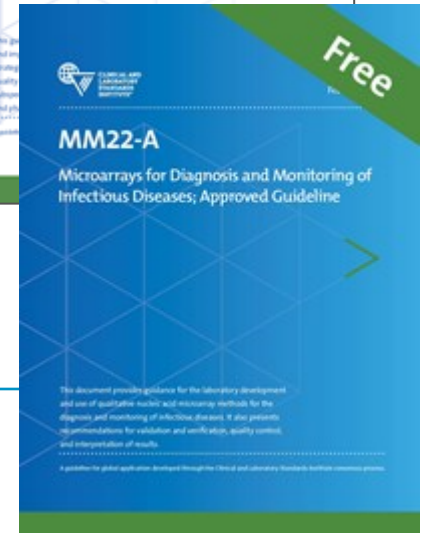
Quality Control Testing Events – COVID-19 Testing

- During method evaluation
- Checking instrument integrity
- Before patient testing
- Receiving new test shipment
- Training new test operators

Quality Control Samples – COVID-19 Testing

- For current *qualitative* COVID-19 testing, following assay quality controls are recommended :

Test Method	Key Performance Characteristics
Molecular Testing	Positive* and Negative Control *Preferably, positive control used to confirm performance near the test LoD*
	Extraction Control
	Internal Control, if present/provided
Serology Testing	Positive Control (for each antibody class, test is intended to detect)
	Negative Control
	Any other controls recommended by manufacturer

IMPORTANT: Utilize available Emergency Use guidance (i.e., EUL from WHO and EUA from FDA)

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Quality Assurance – COVID-19 Current Challenges

- Early phase of COVID-19 testing = challenges expected
- Little performance data available for COVID-19 test kits
- Lack of positive control material for COVID-19 method evaluation studies
- Lack of confidence in ensuring true positives and true negatives samples (i.e., what is really a true positive and true negative?)
  - How to overcome challenge? Use contrived samples and utilize negative samples collected before outbreak; try to obtain positive samples from reference lab
- COVID-19 serology currently has no reference test

- IMPORTANT: *Our understanding of COVID-19 test kits is currently limited; Different quality paradigm currently exists*
  - *Understand impact of governments waiving regulatory requirements to allow use of kits without complete manufacturer evidence normally required*

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COVID-19 Testing – Operator Training & Competence

Operator Training and Competence

Prove that your workers are properly trained by assessing their competence to perform the testing.

QMS03, Training and Competence Assessment

Laboratory Training Program - *Example*

Component	Contents
Quality training	Organization's/laboratory's code of ethics, quality management system, problem-solving approach, quality objectives, and quality control program
	Staff members' roles in each of the above to include: - Receiving training; maintaining competence; following procedures as written; reporting complaints & nonconformance; practicing good customer service skills; collecting data for quality indicators & monitoring; participating in quality improvement initiatives
Safety training	Laboratory's general safety, universal precautions, hazard communication, spill containment and clean-up, fire/disaster preparedness, accident reporting system, bioterrorism preparedness
	Work area-specific safety, special safety precautions, disposal of hazard waste, personal protective equipment, chemical hygiene plan
Job-related training	Work processes (i.e. workflow) and related procedures (i.e. task instructions)
	Recording of all required information

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Operator Competence Assessment Plan - *Example*

Technologist/Scientist Competence Assessment Plan
Document Number/Version:

Effective Date: mm/dd/yyyy

TECHNOLOGIST/SCIENTIST COMPETENCE ASSESSMENT PLAN – 20xx

Employee Name	Position	Date

Type of Assessment: ☐ 6-month ☐ Annual

ASSESSMENT CATEGORIES:
Direct observation
Monitoring the recording/reporting of test results
Review of intermediate test records, worksheets, QC, and PM

Direct observation of instrument maintenance/function
Blind testing/proficiency testing
Evaluation of problem-solving skills

SECTION	SKILL/TASK/KNOWLEDGE	HOW ASSESSED (see above)	DOES NOT MEET STANDARD (follow-up required)	MEETS STANDARD	EXCEEDS STANDARD (can assess/ teach)
		1			
		2			
		2			
		3			
		4			
		5			
		6 (written)			

Facility Name, Location
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COVID-19 Testing – Safety Practices
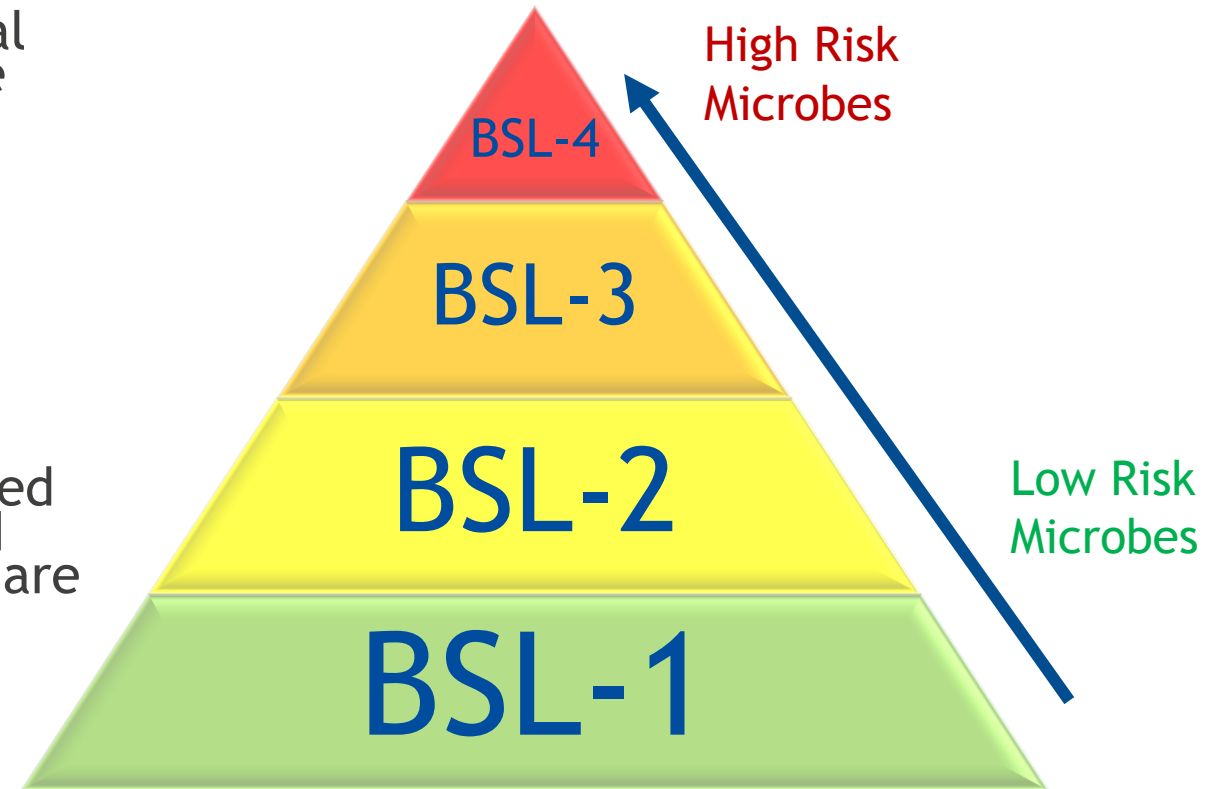
Ensure Laboratory Safety

- GP17, Clinical Laboratory Safety
  - Protect your lab workers by implementing a high-quality safety program

- M29, Protection of Laboratory Workers from Occupationally Acquired Infections
  - Specific precautions for preventing infection

Laboratory Biosafety – COVID-19 Testing – CDC Guidance

- Virus isolation and characterization of viral agents from SAR-CoV-2 specimens must be processed within a BSL-3 laboratory space using BSL-3 procedures

- BSL-2 laboratory may perform routine diagnostic testing (refer to CDC for list of tests) of specimens using Standard Precautions

- Procedures like virus concentration, precipitation or filtration may be performed in a unidirectional air-flow BSL-2 provided certain BSL-3 precautions and procedures are followed

https://www.cdc.gov/coronavirus/2019-nCoV/lab/lab-biosafety-guidelines.html

High Risk Microbes

BSL-4

BSL-3

BSL-2

BSL-1

Low Risk Microbes

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Laboratory Biosafety – COVID-19 Testing – WHO Guidance

- All procedures must be performed based on risk assessment and only by personnel with demonstrated capability, in strict observance of protocols

- Initial processing (before inactivation) of all specimens should take place in a validated biological safety cabinet (BSC) or primary containment device

- Non-propagative diagnostic laboratory work (for example, sequencing, nucleic acid amplification test [NAAT]) should be conducted at a facility using procedures equivalent to Biosafety Level 2 (BSL-2)

- Propagative work (for example, virus culture, isolation or neutralization assays) should be conducted at a containment laboratory with inward directional airflow (BSL-3)

- Appropriate disinfectants with proven activity against enveloped viruses should be used (for example, hypochlorite [bleach], alcohol, hydrogen peroxide, quaternary ammonium compounds, phenolic compounds)

https://www.who.int/publications-detail/laboratory-biosafety-guidance-related-to-coronavirus-disease-2019-(covid-19)

COVID-19 Testing – Additional CLSI Reference Documents & Considerations

# Sample Collection, Handling, and Transport

GP33, Accuracy in Patient and Sample Identification

MM13, Collection, Transport, Preparation, and Storage of Specimens for Molecular Methods

M40, Quality Control of Microbiological Transport Systems

GP41, Collection of Diagnostic Venous Blood Specimens

GP44, Procedures for the Handling and Processing of Blood Specimens for Common Laboratory Tests
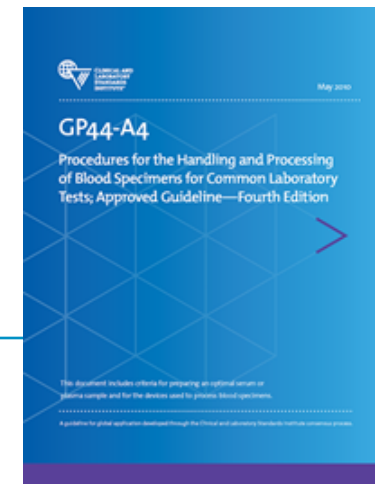
Point-of-Care Testing

POCT04, Essential Tools for Implementation and Management of a Point-of-Care Testing Program

POCT07, Quality Management: Approaches to Reducing Errors at the Point of Care

POCT15, Point-of-Care Testing for Infectious Diseases

Summary

- Develop a structured plan for emergency testing
- Ensure the safety of your personnel
- Verify your selected tests
- Implement your tests properly
- Ensure effective training
- Ensure proper sample collection, handling, and transport
- Manage point-of-care testing

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Thank you!

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