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CLINICAL AND LABORATORY STANDARDS INSTITUTE®

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MM19-A

Establishing Molecular Testing in Clinical Laboratory Environments; Approved Guideline

This guideline provides comprehensive guidance for planning and implementation of molecular diagnostic testing, including strategic planning, regulatory requirements, implementation, quality management, and special considerations for the subspecialties of molecular genetics, infectious diseases, oncology, and pharmacogenetics.

A guideline for global application developed through the Clinical and Laboratory Standards Institute consensus process.

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For additional information on committee participation or to submit comments, contact CLSI.

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Abstract

Clinical and Laboratory Standards Institute document MM19-A—*Establishing Molecular Testing in Clinical Laboratory Environments; Approved Guideline* provides a framework for decision making and implementation of clinical molecular diagnostics, and is intended for those in established clinical laboratories that are implementing a molecular program for the first time. When implementing any diagnostic test for patient care, many elements should be addressed before the test is brought "online." This document focuses on the path of workflow, including laboratory safety and the quality management system, with emphasis on considerations for molecular diagnostics. An organized approach to strategic planning with SWOT (strengths, weaknesses, opportunities, and threats) is presented. Relevant regulatory requirements and the implementation plan are discussed in detail.

Importantly, separate sections are devoted to each of the following subspecialty areas: heritable diseases, oncology and malignant hematology, pharmacogenomics, and infectious diseases. Each of these sections addresses special considerations for molecular testing for each subspecialty.

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Foreword

This guideline was written in response to the growing migration of common molecular diagnostic tests from solely esoteric laboratories to the more routine clinical environment. Molecular assays are becoming more attractive to routine clinical laboratories based on the availability of *in vitro* diagnostic devices and the relative ease of their implementation. Incorporating molecular testing into the routine menu decreases the need for sendouts, thus improving turnaround time and the financial health of the laboratory.

Key Words

Molecular diagnostics, molecular genetics, molecular hematopathology, molecular infectious disease, molecular regulatory requirements, strategic planning, unidirectional workflow

Establishing Molecular Testing in Clinical Laboratory Environments; Approved Guideline

1 Scope

This document was written by experienced molecular laboratory professionals to provide an introduction to molecular diagnostics for nonmolecular, routine clinical laboratories, as well as a framework for decision making and implementation of molecular testing. The target audience of this guideline is the stakeholders who play a role in the strategic decision to implement a molecular diagnostic program, including the:

- Medical and technical directors who may not have previous experience with molecular testing
- Supervisory technical staff who implement molecular assays for the first time
- Quality management systems (QMS) group who will adapt the quality plan to incorporate the unique aspects of the new program
- Production staff that will perform and maintain all aspects of the assays

Because molecular diagnostics encompasses a very broad area, this document focuses on clinical applications and technologies most likely to be used in a laboratory that is venturing into molecular testing for the first time. The laboratory may have a concentration in a specific subspecialty (eg, microbiology) or not. However, given that this document is written for nonmolecular experts, several more complex areas of molecular testing were excluded from the scope, including:

- Complex technologies, including, but not limited to, laboratory-developed tests (LDTs) that require primer and/or probe design, proteomics, pulsed-field gel electrophoresis, multiple locus sequence testing, and repetitive extragenic palindromic sequence-based polymerase chain reaction (PCR)
- Complex reflex testing algorithms
- Laboratory tests that require a high degree of clinical expertise to interpret, such as donor-recipient compatibility typing, and molecular typing of strains possibly related in an outbreak
- Tests for sexual abuse and forensics
- Tests of the blood and tissue supply (eg, blood banks)

It is also out of the scope of this guideline to consider assays that should remain in specialized or esoteric testing facilities, such as:

- Methods for detecting pathogens such as bioterrorism agents that require biosafety levels (BSL) 3 or greater, which are otherwise handled in specialized facilities
- Prenatal diagnosis and preimplantation genetic diagnosis (PGD) of heritable disease

2 Introduction

Nucleic acid testing for infectious diseases, human genetics, hematology, and molecular oncology is the fastest growing field in laboratory medicine. In the past few years, the complete sequencing of the human genome and ever-increasing numbers of viral and bacterial genomes have been reported, leading to a rapid expansion of assays available to clinical laboratories. The ability to detect small deoxyribonucleic acid (DNA) and ribonucleic acid (RNA) sequence variations has provided tools that improve the ability not only to diagnose, but also identify those at risk for disease and those infected with an identifiable pathogen.

Until recently, the vast majority of molecular testing has been offered by esoteric laboratories that have great depth of resources in both the technical and clinical aspects of molecular biology. However, concomitant with new discoveries, the examination phase of testing, from extraction of clinical specimens to quantitative and qualitative detection of sequence alterations, has allowed clinical laboratories to offer molecular testing without large investments in research and development. This technology will only improve, and, over time, become increasingly technically simple and more applicable to the routine clinical laboratory environment. Ultimately, local incorporation of molecular diagnostics brings the testing closer to the patient.

Thus, the use of molecular tests is expected to increase in medical settings in which technical knowledge may be limited. This document is written for clinical laboratories that may need guidance when incorporating molecular assays into their testing menus. It begins with basic elements that factor into the decision to implement a molecular assay by describing a strategic planning approach, as well as an overview of implementation activities.

Molecular assays comprise a category of testing in which the clinical relevance of the result cannot always be derived from the analytical result alone and requires correlation between the genotype and phenotype, limitations of the method, and in the case of genetic testing, patient/family information. This guidance also presents many of the special considerations that are unique to each area of molecular testing (eg, infectious diseases, genetics, and molecular oncology), with an emphasis on descriptions of assays that clinical laboratories are most likely to implement.

Most importantly, routine clinical laboratories should implement molecular assays with personnel who not only can properly perform, but also oversee all phases of molecular testing. They should be able to advise clinicians to select the appropriate clinical specimen, order the appropriate test, maintain robust assays, and generate clinically useful, patient-specific reports. They should also be prepared to provide supplemental consultation or refer the user to available consultants who can best assist them. These activities often require appropriately trained individuals who are capable of understanding both the technical aspects and issues associated with the assay, as well as the medical rationale behind the testing and its clinical implications.

Medical directors should ensure that the clinical validity of the molecular tests they intend to provide has been adequately demonstrated and should seek evidence of clinical utility. A number of groups publish evidence-based reviews of molecular genetic and genomic tests, such as the Agency for Health Quality Research (www.ahrq.gov) and the Centers for Disease Control and Prevention (CDC)–sponsored Evaluation of Genomic Applications in Practice and Prevention Working Group (www.egappreviews.org). Other sources of information include the Blue Cross and Blue Shield Technology Evaluation Center (www.ahrq.gov/clinic/epc/bcbsatec.htm) and The Cochrane Collaboration, which provides evidence-based practice reviews through its website (www.cochrane.org/reviews).

3 Standard Precautions

Because it is often impossible to know what isolates or specimens might be infectious, all patient and laboratory specimens are treated as infectious and handled according to "standard precautions." Standard precautions are guidelines that combine the major features of "universal precautions and body substance isolation" practices. Standard precautions cover the transmission of all known infectious agents and thus are more comprehensive than universal precautions, which are intended to apply only to transmission of blood-borne pathogens. Standard and universal precaution guidelines are available from the CDC.[1] For specific precautions for preventing the laboratory transmission of all known infectious agents from laboratory instruments and materials and for recommendations for the management of exposure to all known infectious diseases, refer to CLSI document M29.[2]

4 Terminology

4.1 A Note on Terminology

CLSI, as a global leader in standardization, is firmly committed to achieving global harmonization wherever possible. Harmonization is a process of recognizing, understanding, and explaining differences while taking steps to achieve worldwide uniformity. CLSI recognizes that medical conventions in the global metrological community have evolved differently in the United States, Europe, and elsewhere; that these differences are reflected in CLSI, International Organization for Standardization (ISO), and European Committee for Standardization (CEN) documents; and that legally required use of terms, regional usage, and different consensus timelines are all important considerations in the harmonization process. In light of this, CLSI's consensus process for development and revision of standards and guidelines focuses on harmonization of terms to facilitate the global application of standards and guidelines.

In order to align the usage of terminology in this document with that of ISO, the term *accuracy*, in its metrological sense, refers to the closeness of the agreement between the result of a (single) measurement and a true value of a measurand, and comprises both random and systematic effects. *Precision* is defined as the "closeness of agreement between independent test/measurement results obtained under stipulated conditions." As such, it cannot have a numerical value, but may be determined qualitatively as high, medium, or low. For its numerical expression, the term *imprecision* is used, which is the "dispersion of results of measurements obtained under specified conditions." In addition, different components of precision are defined in MM19, primarily *reproducibility*, which describes the closeness of agreement of results of measurements under changed conditions.

The term *measurand* (a particular quantity subject to measurement) is used in combination with the term *analyte* (component represented in the name of a measurable quantity) when its use relates to a biological fluid/matrix.

The term *diagnostic sensitivity* is combined with the term *clinical sensitivity*, and correspondingly the term *diagnostic specificity* is combined with the term *clinical specificity*, because in Europe, the term "clinical" often refers to clinical studies of drugs under stringent conditions.

In order to align the usage of terminology in this document with that of ISO and CLSI document GP02,[3] the term *standard operating procedure (SOP)* has been replaced with the term *procedures/instructions.* For the sake of introduction and to avoid confusion, the subcommittee has chosen to include the acronym for *standard operating procedure (SOP)* parenthetically where the term *procedures/instructions* appears in the text.

The Quality Management System Approach

Clinical and Laboratory Standards Institute (CLSI) subscribes to a quality management system approach in the development of standards and guidelines, which facilitates project management; defines a document structure via a template; and provides a process to identify needed documents. The quality management system approach applies a core set of "quality system essentials" (QSEs), basic to any organization, to all operations in any health care service's path of workflow (ie, operational aspects that define how a particular product or service is provided). The QSEs provide the framework for delivery of any type of product or service, serving as a manager's guide. The QSEs are as follows:

Organization	Personnel	Process Management	Nonconforming Event Management
Customer Focus	Purchasing and Inventory	Documents and Records	Assessments
Facilities and Safety	Equipment	Information Management	Continual Improvement

MM19-A addresses the QSEs indicated by an "X." For a description of the other documents listed in the grid, refer to the Related CLSI Reference Materials section, beginning on page 236.

Organization	Customer Focus	Facilities and Safety	Personnel	Purchasing and Inventory	Equipment	Process Management	Documents and Records	Information Management	Nonconforming Event Management	Assessments	Continual Improvement
X	X	X	X	X	X	X C03 C24 C28 EP05 EP06 EP09 EP10 EP12 EP15 EP17	X	X	X	X EP10	X
GP26	GP26	GP26 M29	GP26	GP26	GP26	GP26 GP29 MM01 MM03 MM05 MM06 MM09 MM10 MM12 MM13 MM14 MM16 MM17 MM18	GP02 GP26	GP02 GP26	GP26	GP26 GP29 MM03 MM05 MM06 MM14	GP26
POCT04		POCT04	POCT04	POCT04	POCT04	POCT04 X07					

Path of Workflow

A path of workflow is the description of the necessary processes to deliver the particular product or service that the organization or entity provides. A laboratory path of workflow consists of the sequential processes: preexamination, examination, and postexamination and their respective sequential subprocesses. All laboratories follow these processes to deliver the laboratory's services, namely quality laboratory information.

MM19-A addresses the clinical laboratory path of workflow steps indicated by an "X." For a description of the other documents listed in the grid, please refer to the Related CLSI Reference Materials section on the following page.

Preexamination				**Examination**			**Postexamination**	
Examination ordering	Sample collection	Sample transport	Sample receipt/processing	Examination	Results review and follow-up	Interpretation	Results reporting and archiving	Sample management
X	X	X	X	X	X	X		
GP26	GP26	GP26	GP26	GP26	GP26	GP26	GP26	GP26
MM01	MM01	MM01	MM01	MM01	MM01	MM01	MM01	MM01
	MM03	MM03	MM03	MM03	MM03		MM03	
MM05	MM05		MM05	MM05	MM05	MM05	MM05	MM05
MM06	MM06	MM06	MM06	MM06	MM06	MM06	MM06	
	MM09	MM09	MM09	MM09	MM09	MM09	MM09	MM09
				MM10	MM10	MM10	MM10	
		MM12	MM12	MM12	MM12	MM12	MM12	MM12
	MM13	MM13	MM13					MM13

Related CLSI Reference Materials*

C03-A4 **Preparation and Testing of Reagent Water in the Clinical Laboratory; Approved Guideline—Fourth Edition (2006).** This document provides guidelines on water purified for clinical laboratory use; methods for monitoring water quality and testing for specific contaminants; and water system design considerations.

C24-A3 **Statistical Quality Control for Quantitative Measurement Procedures: Principles and Definitions; Approved Guideline—Third Edition (2006).** This guideline provides definitions of analytical intervals, planning of quality control procedures, and guidance for quality control applications.

C28-A3c **Defining, Establishing, and Verifying Reference Intervals in the Clinical Laboratory; Approved Guideline—Third Edition (2008).** This document contains guidelines for determining reference values and reference intervals for quantitative clinical laboratory tests. A CLSI-IFCC joint project.

EP05-A2 **Evaluation of Precision Performance of Quantitative Measurement Methods; Approved Guideline—Second Edition (2004).** This document provides guidance for designing an experiment to evaluate the precision performance of quantitative measurement methods; recommendations on comparing the resulting precision estimates with manufacturers' precision performance claims and determining when such comparisons are valid; as well as manufacturers' guidelines for establishing claims.

EP06-A **Evaluation of the Linearity of Quantitative Measurement Procedures: A Statistical Approach; Approved Guideline (2003).** This document provides guidance for characterizing the linearity of a method during a method evaluation; for checking linearity as part of routine quality assurance; and for determining and stating a manufacturer's claim for linear range.

EP09-A2-IR **Method Comparison and Bias Estimation Using Patient Samples; Approved Guideline—Second Edition (Interim Revision) (2010).** This document addresses procedures for determining the bias between two clinical methods, and the design of a method comparison experiment using split patient samples and data analysis.

EP10-A3 **Preliminary Evaluation of Quantitative Clinical Laboratory Measurement Procedures; Approved Guideline—Third Edition (2006).** This guideline provides experimental design and data analysis for preliminary evaluation of the performance of a measurement procedure or device.

EP12-A2 **User Protocol for Evaluation of Qualitative Test Performance; Approved Guideline—Second Edition (2008).** This document provides a consistent approach for protocol design and data analysis when evaluating qualitative diagnostic tests. Guidance is provided for both precision and method-comparison studies.

EP15-A2 **User Verification of Performance for Precision and Trueness; Approved Guideline—Second Edition (2006).** This document describes the demonstration of method precision and trueness for clinical laboratory quantitative methods utilizing a protocol designed to be completed within five working days or less.

EP17-A **Protocols for Determination of Limits of Detection and Limits of Quantitation; Approved Guideline (2004).** This document provides guidance for determining the lower limit of detection of clinical laboratory methods, for verifying claimed limits, and for the proper use and interpretation of the limits. An NCCLS-IFCC joint project.

GP02-A5 **Laboratory Documents: Development and Control; Approved Guideline—Fifth Edition (2006).** This document provides guidance on development, review, approval, management, and use of policy, process, and procedure documents in the medical laboratory community.

GP26-A4 **Quality Management System: A Model for Laboratory Services; Approved Guideline—Fourth Edition (2011).** This document provides a model for medical laboratories that will assist with implementation and maintenance of an effective quality management system.

GP29-A2 **Assessment of Laboratory Tests When Proficiency Testing Is Not Available; Approved Guideline—Second Edition (2008).** This document offers methods to assess test performance when proficiency testing (PT) is not available; these methods include examples with statistical analyses. This document is intended for use by laboratory managers and testing personnel in traditional clinical laboratories as well as in point-of-care and bedside testing environments.

* CLSI documents are continually reviewed and revised through the CLSI consensus process; therefore, readers should refer to the most current editions.

Related CLSI Reference Materials (Continued)

M29-A3 **Protection of Laboratory Workers From Occupationally Acquired Infections; Approved Guideline—Third Edition (2005).** Based on US regulations, this document provides guidance on the risk of transmission of infectious agents by aerosols, droplets, blood, and body substances in a laboratory setting; specific precautions for preventing the laboratory transmission of microbial infection from laboratory instruments and materials; and recommendations for the management of exposure to infectious agents.

MM01-A2 **Molecular Diagnostic Methods for Genetic Diseases; Approved Guideline—Second Edition (2006).** This document provides guidance for the use of molecular biological techniques for clinical detection of heritable mutations associated with genetic disease.

MM03-A2 **Molecular Diagnostic Methods for Infectious Diseases; Approved Guideline—Second Edition (2006).** This guideline addresses topics relating to clinical applications, amplified and nonamplified nucleic acid methods, selection and qualification of nucleic acid sequences, establishment and evaluation of test performance characteristics, inhibitors, and interfering substances, controlling false-positive reactions, reporting and interpretation of results, quality assurance, regulatory issues, and recommendations for manufacturers and clinical laboratories.

MM05-A **Nucleic Acid Amplification Assays for Molecular Hematopathology; Approved Guideline (2003).** This guideline addresses the performance and application of assays for gene rearrangement and translocations by both polymerase chain reaction (PCR) and reverse-transcriptase polymerase chain reaction (RT-PCR) techniques and includes information on specimen collection, sample preparation, test reporting, test validation, and quality assurance.

MM06-A2 **Quantitative Molecular Methods for Infectious Diseases; Approved Guideline—Second Edition (2010).** This document provides guidance for the development and use of quantitative molecular methods, such as nucleic acid probes and nucleic acid amplification techniques of the target sequences specific to particular microorganisms. It also presents recommendations for quality assurance, proficiency testing, and interpretation of results.

MM09-A **Nucleic Acid Sequencing Methods in Diagnostic Laboratory Medicine; Approved Guideline (2004).** This document addresses automated, PCR-based, dideoxy-terminator, and primer extension sequencing done on gel- or capillary-based sequencers. Topics covered include specimen collection and handling; isolation of nucleic acid; amplification and sequencing of nucleic acids; interpretation and reporting of results; and quality control/assessment considerations as appropriate.

MM10-A **Genotyping for Infectious Diseases: Identification and Characterization; Approved Guideline (2006).** This guideline describes currently used analytical approaches and methodologies applied to identify the clinically important genetic characteristics responsible for disease manifestation, outcome, and response to therapy in the infectious disease setting. It also provides guidance on the criteria to be considered for design, validation, and determination of clinical utility of such testing.

MM12-A **Diagnostic Nucleic Acid Microarrays; Approved Guideline (2006).** This guideline provides recommendations for many aspects of the array process including: a method overview; nucleic acid extraction; the preparation, handling, and assessment of genetic material; quality control; analytical validation; and interpretation and reporting of results. A CLSI-IFCC joint project.

MM13-A **Collection, Transport, Preparation, and Storage of Specimens for Molecular Methods; Approved Guideline (2005).** This document provides guidance related to proper and safe biological specimen collection and nucleic acid isolation and purification. These topics include methods of collection, recommended storage and transport conditions, and available nucleic acid purification technologies for each specimen/nucleic acid type. A CLSI-IFCC joint project.

MM14-A **Proficiency Testing (External Quality Assessment) for Molecular Methods; Approved Guideline (2005).** This document provides guidelines for a quality proficiency testing program, including reliable databases; design control in the choice of materials and analytes; good manufacturing processes; documentation procedures; complaint handling; corrective and preventive action plans; and responsive timing of reports. A CLSI-IFCC joint project.

Related CLSI Reference Materials (Continued)

MM16-A **Use of External RNA Controls in Gene Expression Assays; Approved Guideline (2006).** This document provides protocols supporting the use of external RNA controls in microarray and QRT-PCR-based gene expression experiments, including preparation of control transcripts, design of primers and amplicons, quality control, use in final experimental or clinical test application, and analysis and interpretation of data obtained. A CLSI-IFCC joint project.

MM17-A **Verification and Validation of Multiplex Nucleic Acid Assays; Approved Guideline (2008).** This guideline provides recommendations for analytical verification and validation of multiplex assays, as well as a review of different types of biological and synthetic reference materials.

MM18-A **Interpretive Criteria for Identification of Bacteria and Fungi by DNA Target Sequencing; Approved Guideline (2008).** Sequencing DNA targets of cultured isolates provides a quantitative metric within which to perceive microbial diversity, and can serve as the basis to identify microorganisms. This document is an effort to catalyze the entry of molecular microbiology into clinical usage by establishing interpretive criteria for microorganism identification.

POCT04-A2 **Point-of-Care *In Vitro* Diagnostic (IVD) Testing; Approved Guideline—Second Edition (2006).** This document provides guidance to users of *in vitro* diagnostic (IVD) devices outside the clinical laboratory, to ensure reliable results comparable to those obtained within the clinical laboratory.

X07-R **Surveillance for Methicillin-Resistant *Staphylococcus aureus*: Principles, Practices, and Challenges; A Report (2010).** This document was developed to provide infection preventionists (infection control practitioners), infectious disease specialists, and microbiologists with the latest information regarding the development and implementation of a successful MRSA surveillance program.

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