CLINICAL AND LABORATORY STANDARDS INSTITUTE®

3rd Edition

CLSI MM14™

Design of Molecular Proficiency Testing/ External Quality Assessment

CLSI MM14 provides guidelines for a quality proficiency testing/external quality assessment program, including reliable databases; design control in the choice of materials and measurands; good manufacturing processes; documentation procedures; complaint handling; corrective and preventive action plans; and responsive timing of reports.

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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Design of Molecular Proficiency Testing/External Quality Assessment

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Abstract

As medical laboratory tests involving detection of nucleic acids become more common, well-designed and implemented proficiency schemes are needed to assure quality and to further the development of this complex and rapidly growing area of laboratory medicine. CLSI MM14—*Design of Molecular Proficiency Testing/External Quality Assessment* has been developed to guide the individuals and organizations responsible for providing proficiency testing (PT)/external quality assessment (EQA). It will also serve medical laboratories with a benchmark for evaluation of new programs or to facilitate development of laboratory-based PT/EQA or alternative assessment schemes when appropriate schemes are not available from formal programs. Specific subchapters discuss the design of PT/EQA programs; sources of materials; production, manufacture, and QA of samples; sample distribution; receipt and evaluation of data; and reporting responsibilities. Also discussed are examples of method-based PT/EQA programs and alternative assessment strategies and how they can be used to evaluate laboratory test performance. CLSI MM14 also lists and describes relevant regulatory and guidance documents related to PT/EQA.

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Committee Membership

Consensus Council

The Consensus Council sets priorities for CLSI standards development and votes on Final Draft documents to confirm that process requirements have been met. Consensus Council members are listed on the CLSI website: https://clsi.org/standards-development/consensus-council/

Expert Panel on Molecular Diagnostics

Expert panel volunteers support the development of CLSI documents by providing technical expertise in specialty areas. Expert panel members are listed by area of expertise on the CLSI website: https://clsi.org/standards-development/expert-panels/

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Content (Continued)

Foreword

Medicine is science, experience, and art. While physicians, nurses, and other practitioners provide diagnosis, treatment, counseling, and patient management, their decisions and actions are based on scientific data, as well as their knowledge, experience, and approach. Medical (clinical) laboratories provide a major source of information about the patient to the practitioners; therefore, the accuracy of the data and their interpretation is critical. This fact is intuitive among laboratory professionals. Medical laboratory directors organized blinded-sample testing and sample exchange studies long before the establishment of formal programs or laws and standards prescribing participation. Today, PT/EQA is an integral part of laboratory QA and, as such, the organizations that administer these programs carry a great responsibility. Programs should be designed to identify laboratory errors and recognize tests offered by medical laboratories that are not performing as expected. They also have an important role in educating laboratories about how their testing practices compare to those of other laboratories and ways in which they can improve the quality of their tests.

In CLSI MM14, the basic principles and practices for PT/EQA organizations, as well as laboratories that provide PT/EQA through informal sample exchange programs, for molecular tests in the areas of human genetics, infectious diseases, molecular oncology, and pharmacogenetics are outlined. In addition, practices such as method-based PT/EQA programs that can increase the scope of laboratory PT/EQA and provide valuable educational experiences are described. A subchapter specifically addressing the medical laboratory as a provider of PT/EQA and PT/EQA materials for internal or external use is also included.

Overview of Changes

CLSI MM14-Ed3 was revised in 2025 under the Limited Revision Process and replaces CLSI MM14-A2, which was published in 2013. Several changes were made in this edition, including:

- Improving the terminology to also accommodate CLSI's recommendation for harmonization of terms
- Including additional types of reference samples, such as *in silico* modified nucleic acid sequence data files, clustered regularly interspaced short palindromic repeat–engineered cell lines, cell-free tumor DNA, and formalin-fixed, paraffin-embedded tissue sections or cores
- Including additional sources of reference samples from commercial and other sources
- Discussing different formats for PT and EQA

NOTE: The content of CLSI MM14 is supported by the CLSI consensus process and does not necessarily reflect the views of any single individual or organization.

KEY WORDS

alternative assessment
external quality assessment
laboratory testing
manufacturers
molecular testing
proficiency testing
proficiency testing material
sample exchange

Chapter 1

Introduction

Design of Molecular Proficiency Testing/External Quality Assessment

1 Introduction

1.1 Scope

The purpose of CLSI MM14 is to complement currently available regulatory and guidance documents regarding the management and operations of proficiency testing (PT)/external quality assessment (EQA) programs. Presently, these documents guide the administration of such programs, but consideration of panel selection, analysis of data for evolving technologies and tests with many possible measurands, method-based PT/EQA, and reporting to participants are not addressed. For molecular methods, these issues are important for all stakeholders, including regulatory agencies, accrediting agencies, PT/EQA providers/organizations, PT/EQA materials manufacturers, medical (clinical) laboratories, and test/reagent manufacturers. CLSI MM14 addresses both large formal PT/EQA programs as well as medical laboratorians who produce, distribute, and administer PT/EQA schemes, and should provide guidance for the development and implementation of new PT/EQA programs for nucleic acid testing or modifying existing schemes.

CLSI MM14 does not address the process of testing and reporting PT/EQA in the medical laboratory, medical laboratory inspection, accreditation, or other regulatory processes.

CLSI MM14 focuses on nucleic acid (DNA and RNA) PT/EQA in the areas of human genetics, infectious diseases, molecular oncology, and pharmacogenetics. Although written specifically to address needs in this area, the principles stated may be applicable to programs outside of nucleic acid testing.

Organizations and programs that send blinded samples to laboratories and analyze the submitted results carry several different names. These challenge programs may be called PT/EQA, quality assessment or assurance programs, QC programs, ring trials, sample exchange, and EQA/assurance. Countries or regions may place regulatory distinctions on these names. To facilitate the readability of CLSI MM14, the terms PT/EQA, PT/EQA provider/organization, and PT/EQA program have been chosen to describe such activities, and regulatory categorization is not implied unless specifically noted.

1.2 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. Published guidelines are available that discuss the daily operations of diagnostic medicine in humans and animals while encouraging a culture of safety in the laboratory.[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 M29.[2]