



MM20-A

Quality Management for Molecular Genetic Testing; Approved Guideline

SAMPLE

This document provides guidance for implementing international quality management system standards in laboratories that perform human molecular genetic testing for inherited or acquired conditions.

Clinical and Laboratory Standards Institute

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Abstract

Clinical and Laboratory Standards Institute document MM20-A—*Quality Management for Molecular Genetic Testing; Approved Guideline* provides guidance for implementing international QMS standards in laboratories that perform human molecular genetic testing for inherited or acquired conditions. The QMS approach is increasingly used globally to assure quality of laboratory services with a focus on user needs and requirements. This guideline stresses quality management activities in all facets of a molecular genetic laboratory's path of workflow, including assuring the quality of the laboratory's interactions with users and enhancing laboratory/user communication.

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Foreword

QMS practices have been increasingly implemented worldwide in medical laboratories to help improve the quality of laboratory services and the effectiveness of laboratory operations. The rapid growth of molecular genetic testing is accompanied by the continuing challenges of ensuring the quality of performance and delivery of testing services. This document provides guidance for implementing and maintaining a QMS in molecular genetic laboratories by streamlining laboratory activities and services into an extended QMS path of workflow, discussing the use of quality system essentials to address specific quality management challenges in molecular genetic testing, and applying QMS policies, processes, and procedures to the technical processes of molecular genetic laboratory services. This guideline also acts as a resource that facilitates harmonized approaches to accreditation to international laboratory standards.

Key Words

Molecular genetic testing, path of workflow, quality, quality assurance, quality laboratory service, quality management system, quality system essentials

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Quality Management for Molecular Genetic Testing; Approved Guideline

1 Scope

This guideline addresses quality management activities for nucleic acid–based human molecular genetic testing, including the development and maintenance of a QMS for improving the quality of molecular genetic laboratory services. MM20 provides guidance for implementing the quality system framework and applying the policies, processes, and procedures for quality system essentials (QSEs) to all aspects of molecular genetic laboratory services. The general principles and essentials of a QMS, as described in international standards and guidelines such as the International Organization for Standardization (ISO) medical laboratory standard ISO 15189¹ and CLSI document GP26,² are referenced and discussed in the context of molecular genetic testing. This guideline also stresses quality management activities in all facets of a molecular genetic laboratory’s path of workflow, including assuring the quality of the laboratory’s interactions with users and enhancing laboratory/user communications. These activities should improve the utilization of genetic laboratory services and achieve optimal patient outcomes. CLSI guidelines that provide specific details on the use of particular molecular methods for genetic diseases, such as CLSI documents MM01,³ MM12,⁴ MM17,⁵ and MM19,⁶ and other guidelines addressing molecular methods are referenced and their use in combination with this document is discussed.

This guideline is intended for use by medical laboratories that perform molecular genetic testing for inherited or acquired conditions, including pharmacogenetic testing and molecular oncology testing for medical purposes. It also provides a useful reference to individuals or organizations that assess laboratory quality and competence in the area of molecular genetic testing.

Though many quality system principles described in this document are applicable to most medical laboratories, this guideline does not intend to address, in depth, molecular infectious disease testing, biochemical genetic testing, cytogenetic testing, the specific technical processes of molecular cytogenetic testing (eg, array comparative genome hybridization), massively parallel sequencing (eg, whole exome or whole genome sequencing), molecular testing not for clinical purposes, or direct-to-consumer laboratory services. However, the overall quality system framework and path of workflow should be appropriate for quality management and quality improvement of most laboratory examinations involving nucleic acid–based testing.

2 Introduction

2.1 Overview of Types and Applications of Molecular Genetic Tests

Molecular genetic testing examines constitutional or somatic changes of nucleic acids using both DNA-based and RNA-based methods. Molecular genetic testing can detect alterations that underlie heritable diseases and conditions (genetics and pharmacogenetics), in addition to somatic changes that occur in cancer and other conditions. Such tests can be requested for disease diagnosis, carrier screening, and presymptomatic/predisposition testing, as well as for directing therapeutic intervention (pharmacogenetics). Table 1 lists major types of genetic tests that, when performed using molecular or nucleic acid–based methods, would be included in the scope of this document. (**NOTE:** Wide variations exist worldwide in definitions of genetic testing and genetic test categories.⁷ Each category listed in Table 1 may only reflect certain aspects of a genetic test and a particular test may fit more than one category.) Genetic test results can have ramifications not only for the person being tested, but also for his/her family members. In addition, genetic testing, especially prenatal or fetal diagnosis and presymptomatic/predisposition testing, often requires special informed consent and test requisitions.

Table 1. Types of Genetic Tests Performed for Clinical and Health Assessment Purposes⁸⁻¹⁰

| Intent of Test | Description |
|---|--|
| Preimplantation testing | <ul style="list-style-type: none"> Performed on early embryos resulting from <i>in vitro</i> fertilization in order to decrease the probability of implanting an embryo with a specific genetic condition producing an affected fetus Generally offered to couples with a high probability of having a child with a serious disorder Provides an option to increase the likelihood of having healthy fetuses in assisted pregnancies |
| Fetal/prenatal testing | <ul style="list-style-type: none"> Performed during a pregnancy to assess the health status of a fetus Performed when there is an increased risk of having a child with a genetic condition as indicated by maternal age, family history, ethnicity, and other factors May be performed as a stand-alone test or in conjunction with a multiple marker screen or fetal ultrasound examination |
| Newborn/neonatal screening | <ul style="list-style-type: none"> Performed for infants shortly after birth to identify genetic disorders and other conditions that can be treated early in life |
| Diagnostic testing | <ul style="list-style-type: none"> Used to identify, confirm, or exclude a known or suspected genetic disorder in a symptomatic individual Can be performed before birth or at any time during a person's life |
| Carrier testing | <ul style="list-style-type: none"> Performed to identify individuals who have a gene mutation for a disorder inherited in an autosomal recessive or X-linked recessive manner Offered to individuals who have family members with genetic conditions or who are identified carriers, and individuals in ethnic or racial groups known to have higher carrier rates for particular conditions |
| Predisposition or susceptibility testing | <ul style="list-style-type: none"> Identifies genetic risk factor(s) that predispose an individual to a hereditary disorder (eg, <i>BRCA1/BRCA2</i> testing for increased, heritable risk for breast, ovarian, and other cancers) or a common disease (eg, diabetes) |
| Presymptomatic testing | <ul style="list-style-type: none"> Used to detect mutations associated with disorders that appear after birth, often later in life Can be helpful to asymptomatic individuals with a family history of a genetic disorder Can include presymptomatic testing (eventual development of symptoms is certain when the gene mutation is present, eg, testing of trinucleotide repeats in the <i>HD</i> gene for Huntington disease) and predictive testing (eventual development of symptoms is likely, eg, testing of germline <i>RET</i> mutations for multiple endocrine neoplasia type 2) |
| Prognostic testing | <ul style="list-style-type: none"> Evaluates the likely outcome or course of disease (eg, disease progression, risk for metastatic malignancy, cancer recurrence or relapse) |
| Pharmacogenetic and pharmacogenomic testing | <ul style="list-style-type: none"> Pharmacogenetic testing may examine individual variations in single-nucleotide polymorphisms and haplotype markers to help personalize medical care and treatments based on genetic information Pharmacogenomic testing examines the impact of many pharmacogenetic polymorphisms or multiple genes involved in drug metabolism pathways |
| Cancer diagnosis and treatment monitoring | <ul style="list-style-type: none"> Uses genetic markers to determine stratification to effective treatment regimens (eg, <i>BRAF</i>, <i>EGFR</i>, and <i>KRAS</i>) Monitors treatment efficacy such as minimal residual disease (eg, <i>BCR-ABL1</i>) and targeted therapeutics (eg, imatinib) |

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

MM20-A addresses the QSEs indicated by an “X.” For a description of the other documents listed in the grid, please refer to the Related CLSI Reference Materials section, beginning on page 126.

| 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 EP05 EP12 EP23 | X | X | X | X | X |
| | | | | GP09 | | | GP02 | GP02 | | | |
| GP19 | GP19 | GP17 GP19 | GP19 GP21 | GP19 | GP19 | GP19 | GP19 | GP19 | GP19 | | GP19 |
| GP26 | GP26 | GP26 | GP26 | GP26 | GP26 | GP26 GP27 GP29 GP32 | GP26 | GP26 | GP26 | GP26 GP27 GP29 | GP22 GP26 GP27 |
| | | | | | GP37 | | | | GP32 | | GP35 |
| | | M29 | | | | | | | | | |
| | | MM07 | MM07 | | MM07 | MM01 MM05 MM07 MM09 MM12 MM13 MM14 MM16 MM17 MM19 | MM07 | | | MM05 MM07 | |
| MM19 | MM19 | MM19 | MM19 | MM19 | MM19 | MM19 | MM19 | MM19 | MM19 | MM19 | MM19 |

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.

MM20-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.

| Examination ordering | Preexamination | | | Examination | | | Postexamination | |
|----------------------|-------------------|------------------|---------------------------|-------------|------------------------------|----------------|---------------------------------|-------------------|
| | 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 | X | X |
| GP26 | GP26 | GP26 | GP26 | EP23 | EP23 | EP23 | GP26 | GP26 |
| MM01 | MM01 | MM01 | MM01 | GP26 | GP26 | GP26 | MM01 | MM01 |
| MM05 | | | MM05 | MM01 | MM01 | MM01 | MM05 | MM05 |
| MM06 | MM06 | MM06 | MM06 | MM05 | MM05 | MM05 | MM06 | MM06 |
| MM07 | MM07 | MM07 | MM07 | MM06 | MM06 | MM06 | MM07 | MM07 |
| | MM09 | MM09 | MM09 | MM07 | MM07 | MM07 | MM09 | MM09 |
| | | MM12 | MM12 | MM09 | MM09 | MM09 | MM12 | MM12 |
| | MM13 | MM13 | MM13 | MM12 | MM12 | MM12 | | MM13 |
| | MM19 | MM19 | MM19 | MM19 | MM19 | MM19 | | |

Related CLSI Reference Materials*

- 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.
- 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.
- EP23-A™** **Laboratory Quality Control Based on Risk Management; Approved Guideline (2011).** This document provides guidance based on risk management for laboratories to develop quality control plans tailored to the particular combination of measuring system, laboratory setting, and clinical application of the test.
- 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.
- GP09-A2** **Quality Management System: Qualifying, Selecting, and Evaluating a Referral Laboratory; Approved Guideline—Second Edition (2012).** This guideline provides recommended criteria and easily implemented processes for qualifying, selecting, and evaluating a referral laboratory.
- GP17-A3** **Clinical Laboratory Safety; Approved Guideline—Third Edition (2012).** This document contains general recommendations for implementing a high-quality laboratory safety program, which are provided in a framework that is adaptable within any laboratory.
- GP19-A2** **Laboratory Instruments and Data Management Systems: Design of Software User Interfaces and End-User Software Systems Validation, Operation, and Monitoring; Approved Guideline—Second Edition (2003).** This document identifies important factors that designers and laboratory managers should consider when developing new software-driven systems and selecting software user interfaces. Also included are simple rules to help prepare validation protocols for assessing the functionality and dependability of software.
- GP21-A3** **Training and Competence Assessment; Approved Guideline—Third Edition (2009).** This document provides background information and recommended processes for the development of training and competence assessment programs that meet quality and regulatory objectives.
- GP22-A3** **Quality Management System: Continual Improvement; Approved Guideline—Third Edition (2011).** This guideline considers continual improvement as an ongoing, systematic effort that is an essential component of a quality management system. A continual improvement program may consist of fundamental processes and common supporting elements described in this guideline.
- 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.
- GP27-A2** **Using Proficiency Testing to Improve the Clinical Laboratory; Approved Guideline—Second Edition (2007).** This guideline provides assistance to laboratories in using proficiency testing as a quality improvement tool.
- 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 Materials (Continued)

- GP32-A** **Management of Nonconforming Laboratory Events; Approved Guideline (2007).** This guideline provides an outline and the content for developing a program to manage a health care service's nonconforming events that is based on the principles of quality management and patient safety.
- GP35-A** **Development and Use of Quality Indicators for Process Improvement and Monitoring of Laboratory Quality; Approved Guideline (2010).** This document provides guidance on development of quality indicators and their use in the medical laboratory.
- GP37-A** **Quality Management System: Equipment; Approved Guideline (2011).** This guideline provides recommendations for establishing equipment management processes from selection through decommissioning of equipment used in the provision of laboratory services.
- 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-A3** **Molecular Methods for Clinical Genetics and Oncology Testing; Approved Guideline—Third Edition (2012).** This document provides guidance for the use of molecular biological techniques for detection of mutations associated with inherited medical disorders, somatic or acquired diseases with genetic associations, and pharmacogenetic response.
- MM05-A2** **Nucleic Acid Amplification Assays for Molecular Hematopathology; Approved Guideline—Second Edition (2012).** This guideline addresses the performance and application of assays for gene rearrangement and translocations by both polymerase chain reaction (PCR) and reverse-transcriptase PCR techniques, and includes information on specimen collection, sample preparation, test reporting, test validation, and quality assurance.
- MM07-A** **Fluorescence *In Situ* Hybridization (FISH) Methods for Medical Genetics; Approved Guideline (2004).** This document addresses FISH methods for medical genetic determinations, identification of chromosomal abnormalities, and gene amplification. Recommendations for probe and assay development, manufacture, qualification, verification, and validation; instrument requirements; quality assurance; and evaluation of results are also included.
- 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.
- 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; analytic 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 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 analytic verification and validation of multiplex assays, as well as a review of different types of biologic and synthetic reference materials.
- MM19-A** **Establishing Molecular Testing in Clinical Laboratory Environments; Approved Guideline (2011).** 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.

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