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MM20-A

Quality Management for Molecular Genetic Testing; Approved Guideline

NOTE: CLSI document MM20-A provides guidance for implementing the quality system framework and applying the policies, processes, and procedures for quality system essentials to all aspects of molecular genetic laboratory services. Molecular genetic human leukocyte antigen testing and identity testing for human stem cell transplantation (bone marrow engraftment) are not included, nor is precision medicine testing for targeted gene therapies. CLSI document MM20-A does not cover, in depth, molecular infectious diseases testing, biochemical genetic testing, cytogenetic testing, the specific technical processes of molecular cytogenetic testing (eg, array comparative genomic hybridization), or massively parallel sequencing (eg, whole-exome or whole-genome sequencing).

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

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

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Quality Management for Molecular Genetic Testing; Approved Guideline

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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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Contents

Contents (Continued)

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

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 15189[1] 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 Purposes[8-10]

Intent of Test	Description
Preimplantation testing	• Performed on early embryos resulting from *in vitro* 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	• 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	• Performed for infants shortly after birth to identify genetic disorders and other conditions that can be treated early in life
Diagnostic testing	• 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	• 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	• Identifies genetic risk factor(s) that predispose an individual to a hereditary disorder (eg, *BRCA1/BRCA2* testing for increased, heritable risk for breast, ovarian, and other cancers) or a common disease (eg, diabetes)
Presymptomatic testing	• 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 *HD* gene for Huntington disease) and predictive testing (eventual development of symptoms is likely, eg, testing of germline *RET* mutations for multiple endocrine neoplasia type 2)
Prognostic testing	• Evaluates the likely outcome or course of disease (eg, disease progression, risk for metastatic malignancy, cancer recurrence or relapse)
Pharmacogenetic and pharmacogenomic testing	• 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	• Uses genetic markers to determine stratification to effective treatment regimens (eg, *BRAF*, *EGFR*, and *KRAS*) • Monitors treatment efficacy such as minimal residual disease (eg, *BCR-ABL1*) 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	Personnel	Process Management	Nonconforming Event Management
Customer Focus	Purchasing and Inventory	Documents and Records	Assessments
Facilities and Safety	Equipment	Information Management	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
							GP02	GP02			
				GP09							
		GP17									
GP19	GP19	GP19	GP19 GP21	GP19	GP19	GP19	GP19	GP19	GP19		GP19
											GP22
GP26	GP26	GP26	GP26	GP26	GP26	GP26 GP27 GP29 GP32	GP26	GP26	GP26 GP32	GP26 GP27 GP29	GP26 GP27 GP35
					GP37						
		M29									
		MM07	MM07		MM07	MM01 MM05 MM07 MM09 MM12 MM13 MM14 MM16 MM17	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.

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	X	X
				EP23	EP23	EP23		
GP26	GP26	GP26	GP26	GP26	GP26	GP26	GP26	GP26
MM01	MM01	MM01	MM01	MM01	MM01	MM01	MM01	MM01
MM05			MM05	MM05	MM05	MM05	MM05	MM05
MM06	MM06	MM06	MM06	MM06	MM06	MM06	MM06	
MM07	MM07	MM07	MM07	MM07	MM07	MM07	MM07	MM07
	MM09	MM09	MM09	MM09	MM09	MM09	MM09	MM09
		MM12	MM12	MM12	MM12	MM12	MM12	MM12
	MM13	MM13	MM13					MM13
	MM19	MM19	MM19	MM19	MM19	MM19		

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