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Molecular Methods for Clinical Genetics and Oncology Testing; Approved Guideline—Third Edition

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.

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

Clinical and Laboratory Standards Institute

Advancing Quality in Health Care Testing

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

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Abstract

Clinical and Laboratory Standards Institute document MM01-A3—*Molecular Methods for Clinical Genetics and Oncology Testing; Approved Guideline—Third Edition* provides general recommendations for all phases of the operation of a molecular genetics diagnostic laboratory. Clinical molecular testing has application to inherited and acquired medical conditions with genetic etiologies as well as variations associated with drug metabolism. In a clinical molecular laboratory, techniques and practices require strict adherence to quality performance measures. This revised guideline will address the total testing process.

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Contents

Foreword

This document replaces the second edition of the approved guideline, MM01-A2, *Molecular Diagnostic Methods for Genetic Diseases; Approved Guideline—Second Edition*, which was published in June 2006. Several changes were made in this edition; chief among them is the revision of the title and the inclusion of somatic or acquired genetic changes associated with nonhematological cancers, which have not been addressed in other molecular guidelines. The rapid development of new molecular genetic testing methods has prompted the third edition of this guideline to include more current technologies and applications. In addition, this version has been expanded to include topics such as epigenetic testing, mitochondrial disorders, chimerism, and pharmacogenetics. In a rapidly evolving technological area, this document also presents newer molecular methods that are starting to appear in clinical laboratories, such as next-generation DNA sequencing.

Key Words

Amplification, arrays, gene, genetic disease, genotyping, molecular diagnostic test, mutation detection, nucleic acid, polymerase chain reaction, sequencing, Southern blot

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1 Scope

This revision of MM01 provides guidelines for laboratory testing practices, methods, and technologies for detection of inherited and somatic genetic variation. Because not all genetic testing is done for the purpose of diagnosing disease, the title of this document has been revised to reflect the wide range of indications for molecular genetic testing. This document is intended as a source of reference material for medical genetic testing laboratories performing nucleic acid–based testing. This information includes performance characteristics of the total molecular genetics laboratory testing process, ie, preexamination, examination, and postexamination. This document is intended to provide guidance to experienced laboratory directors, supervisors, and manufacturers involved in assay development, verification, validation, and interpretation of molecular genetic testing.

This document is not intended to serve as an introductory manual for laboratories without experience in molecular genetics. Conversely, the performance characteristics of complex, multivariate diagnostic assays that employ nontransparent, mathematical algorithms to interpret genetic risk or likelihood of drug response are beyond the scope and consideration of this guideline but are addressed in CLSI document MM17.[1] Although some description of pharmacogenetic traits has been included, a full consideration of both targeted therapeutics and inherited variation in drug metabolism and response is beyond the scope of this guideline. This document also does not include molecular virology or molecular microbiology. These topics are addressed in CLSI documents MM03,[2] MM06, [3] MM10,[4] MM11,[5] and MM18.[6]

2 Introduction

Molecular genetic testing has become a staple method for the assessment of a growing number of inherited disorders, somatic or acquired diseases with genetic associations, and pharmacogenetic responses. Genotyping can provide useful indicators of disease diagnosis, prognosis, and progression; can be used to guide treatment selection and response; and can interrogate targets for gene-specific therapies. Genetic variations can be used for carrier screening, presymptomatic testing, and predisposition testing, in addition to diagnostic testing, newborn screening, and prenatal testing for heritable disorders.

The purpose of this guidance is to inform laboratories performing nucleic acid–based molecular genetic testing of the appropriate and effective qualities of genetics laboratory operations, assay design and performance characteristics, frequent clinical contexts and applications of these strategies, and the most common molecular methods included in clinical genetic testing practice.

Mutations associated with heritable disorders are detectable in all nucleated cells and thus are considered to be germline or constitutional genetic changes. Somatic genetic changes are characteristic of acquired or sporadic diseases, such as cancer. The molecular biology methods applied to investigate these two scenarios are very similar and focus on detection of DNA and RNA variations. However, the interpretation and utility of the laboratory results may be quite distinct. For example, the impact for screening at-risk family members and predictive risk assessment are important considerations for heritable disease genetic testing, while sensitivity threshold of detection is a defining feature of quantitative testing for the genetic signatures of acquired disease conditions such as cancer.

Although CLSI document MM05[7] addresses molecular methods for select hematopathology oncology applications (which will not be duplicated in this document), there currently is no guidance document to encompass assays to detect acquired genetic changes for many other tumor types. With increasing use of

