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2nd Edition

CLSI MM23™

Molecular Diagnostic Methods for Solid Tumors (Nonhematologic Neoplasms)

CLSI MM23 covers the current state of molecular diagnostic methods intended for characterization of solid tumors and covers a range of clinical applications, including diagnosis, prognosis, therapeutic response prediction for available drugs and drugs still in clinical trials, monitoring, and presymptomatic and predisposition testing.

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

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Abstract

Clinical and Laboratory Standards Institute MM23—*Molecular Diagnostic Methods for Solid Tumors (Nonhematologic Neoplasms)* describes development and implementation of nucleic acid biomarker assays for accurate detection of somatic alterations, with applications to clinical decision-making for cancer patients with solid tumors. CLSI MM23 is intended for molecular diagnostic laboratory directors, industry laboratory professionals, health care professionals (including anatomic and clinical pathologists), manufacturers and developers, and regulatory and accreditation organizations. The methods and recommendations discussed in CLSI MM23 focus primarily on detection of tumor-specific (ie, somatic) genetic abnormalities that are acquired during tumorigenesis and that are distinct from normal variations in nonmalignant cells of the same tissue.

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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/>

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Contents

Abstract	i
Committee Membership	iii
Foreword	vii
Chapter 1: Introduction	1
1.1 Scope	1
1.2 Background	2
1.3 Standard Precautions	5
1.4 Standard Precautions	5
Chapter 2: Path of Workflow	13
Chapter 3: Clinical Use of Molecular Assays in Solid Tumor Testing	15
3.1 Diagnosis and Classification	16
3.2 Prognosis	16
3.3 Prediction of Therapeutic Response	17
3.4 Screening	20
3.5 Germline Testing in Patients With Cancer	21
Chapter 4: Assay Development and Validation	23
4.1 Molecular Oncology Assay Development	24
4.2 Measurement Validation	28
4.3 Clinical Validity and Utility	32
Chapter 5: Preexamination	35
5.1 Precollection Patient Assessment and Preparation	36
5.2 Specimen Types and Collection	37
5.3 Specimen Transport, Receipt, and Storage	42
5.4 Specimen Processing	43
5.5 Nucleic Acid Isolation	46
5.6 Strategies for Specimen Referral for Outside Testing	51
Chapter 6: Examination	53
6.1 Next-Generation Sequencing	54
6.2 Non-Next-Generation Sequencing Methods	57

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Contents (Continued)

Chapter 7: Data Analysis and Postexamination	65
7.1 Clinical Bioinformatics	66
7.2 Laboratory Results Interpretation	73
7.3 Reporting of Results	76
7.4 Consultation Services	80
7.5 Data Sharing and Cancer Genetics Databases	81
7.6 Postexamination Specimen Storage	84
Chapter 8: Quality System Essentials for Molecular Diagnostic Methods for Solid Tumors	85
8.1 Overview of Quality System Essentials	86
8.2 Policies and Processes for Solid Tumor Testing	87
8.3 Risk-Based Quality Control Plan	88
8.4 Revisions of Quality System Essentials to Support Solid Tumor Molecular Testing	91
8.5 Summary	94
Chapter 9: Conclusion	95
Chapter 10: Supplemental Information	97
References	98
Appendix . Example of a Specimen Requisition Form	112
The Quality Management System Approach	114

Foreword

With the completion of the Human Genome Project and subsequent large-scale international cancer genomics projects, researchers have identified germline and somatic changes involved in many diverse aspects of tumor biology. Identification of genetic changes that drive neoplastic transformation of normal tissue, as well as progression to more advanced disease states, provides insight into tumor biology and associated therapies. Massively parallel sequencing technologies, also referred to as “next-generation sequencing” (NGS), have been rapidly adopted for detection of somatic variants in the medical laboratory to guide therapy selection, as well as to assist with prognostication, cancer diagnosis, and classification. The field has witnessed the development of validated predictive cancer biomarkers that are independent of the tumor of origin. Additionally, identification of somatic variants in molecular oncology is increasingly used as an inclusion or stratifying criteria in cancer clinical trials. It is essential that these new tests be useful for medical decision-making purposes and that their clinical validity and utility be evaluated as quickly and efficiently as possible.

Given ongoing advancements in molecular testing of tumor specimens, guidelines are needed to address the performance and reporting practices of such tests. CLSI MM23 covers the current state of molecular diagnostic techniques intended for characterization of solid tumors, as well as a range of clinical applications, including diagnosis, prognosis, monitoring of tumor burden, presymptomatic and predisposition testing, and therapeutic response prediction for both available drugs and drugs still in clinical trials. CLSI MM23 includes a brief discussion of heritable cancer syndromes and pharmacogenetics, which are covered in more depth in CLSI MM01¹ and CLSI MM19.² The rapid development of new molecular diagnostic techniques might render CLSI MM23 incomplete after its publication.

The methods and QC approaches described in CLSI MM23 are not absolute or immutable. They represent expert consensus recommendations presented by the document development committee and are intended for use by diagnostic laboratories. Such use is intended to facilitate interlaboratory comparisons of results and diagnostic interpretations and to ensure accuracy in diagnosis and tumor characterization.

Overview of Changes

CLSI MM23-Ed2 replaces CLSI MM23-Ed1, published in 2015. Several changes were made in this edition, including:

- Removing most of the discussion on heritable disease testing, except for a brief discussion of heritable cancer syndromes and pharmacogenetics for anticancer therapies
- Adding cancer biomarkers and updating nomenclature introduced into clinical practice or late phase clinical trials since the previous edition was published
- Expanding the discussion of test development, with a focus on somatic, solid tumor testing
- Updating methods and technologies commonly used in the molecular pathology and genetics laboratory for solid tumor testing, with an emphasis on NGS methods
- Adding discussion of bioinformatics pipelines, computer and storage infrastructure, and related topics, with a focus on tumor NGS
- Revising considerations for preexamination, examination, and postexamination phases of testing, with an emphasis on molecular oncology testing

Incorporating discussion of cell-free circulating tumor DNA assays and other liquid biopsy assays throughout the relevant subchapters

- Expanding discussion of quality systems, with a focus on molecular oncology testing

NOTE: The content of CLSI MM23 is supported by the CLSI consensus process and does not necessarily reflect the views of any single individual or organization.

KEY WORDS

biomarkers

cancer

cell-free DNA (cfDNA)

circulating tumor DNA (ctDNA)

companion diagnostic devices

genetics

genomics

laboratory-developed test (LDT)

liquid biopsy

methylation

next-generation sequencing (NGS)

oncology

solid tumor

somatic variants

test development

Chapter ①

Introduction

Molecular Diagnostic Methods for Solid Tumors (Nonhematologic Neoplasms)

1 Introduction

1.1 Scope

CLSI MM23 focuses on descriptions of various technologies and method selection for specific oncology applications. It describes the development and implementation of nucleic acid biomarker assays for accurate detection of somatic alterations, with applications for clinical decision-making in oncology. The methods and recommendations discussed focus primarily on detection of tumor-specific genetic abnormalities that are acquired during tumorigenesis and that are distinct from normal variations in nonmalignant cells of the same tissue. CLSI MM23 also includes new biomarkers described for a wide variety of tumors and newer approaches with multigene panels and complex data interpretations developed since the previous edition was published.

CLSI MM23 focuses on the underlying nucleic acid tumor markers and variants but does not examine cell-surface antigens, immunohistochemistry (IHC), or protein markers. CLSI MM23 focuses on neoplasms that are not hematopoietic or lymphoid. Other CLSI documents provide more detailed guidance on molecular testing for heritable genetics and specimen identification (CLSI MM01¹), molecular hematopathology (CLSI MM05³), FISH (CLSI MM07⁴), microarrays (CLSI MM12⁵), and multiplex nucleic acid assays (CLSI MM17⁶). Although also covered in CLSI MM23, additional details on next-generation sequencing (NGS), including multigene DNA panels, RNA sequencing, and liquid biopsy, are covered in CLSI MM09.⁷

CLSI MM23 is intended for molecular diagnostic laboratory directors, industry laboratory professionals, health care professionals (including anatomic and clinical pathologists), manufacturers and developers, and regulatory and accreditation organizations.

1.2 Background

1.2.1 Tumorigenesis

Tumorigenesis is a multistep process involving multiple factors. The hallmarks of cancer, first proposed in 2000,⁸ was expanded in 2011 to include eight hallmark capabilities and two enabling characteristics (see Figure 1).⁹ Recently, additional emerging hallmarks and enabling characteristics have been proposed, including unlocking phenotypic plasticity, nonmutational epigenetic reprogramming, polymorphic microbiomes, and senescent cells.¹⁰ It is anticipated that the understanding of tumorigenesis will continue to evolve with increasingly sophisticated experimental investigations.