CLINICAL AND LABORATORY STANDARDS INSTITUTE®

1st Edition

# CLSI MM26™

## Cancer Molecular Testing: Principles of Oncology Test Interpretation, Laboratory and Assay Design, and Clinical Consultation

CLSI MM26 focuses on strategies for use of effective communication and consultation channels with clinicians in addition to test utilization management to support improved diagnosis, treatment selection, and risk assessment to guide care for patients with cancer.

A CLSI report for global application.

# Clinical and Laboratory Standards Institute

*Setting the standard for quality in medical laboratory testing around the world.*

The Clinical and Laboratory Standards Institute (CLSI) is a not-for-profit membership organization that brings together the varied perspectives and expertise of the worldwide laboratory community for the advancement of a common cause: to foster excellence in laboratory medicine by developing and implementing medical laboratory standards and guidelines that help laboratories fulfill their responsibilities with efficiency, effectiveness, and global applicability.

**Consensus Process**

Consensus—the substantial agreement by materially affected, competent, and interested parties—is core to the development of all CLSI documents. It does not always connote unanimous agreement but does mean that the participants in the development of a consensus document have considered and resolved all relevant objections and accept the resulting agreement.

**Commenting on Documents**

CLSI documents undergo periodic evaluation and modification to keep pace with advances in technologies, procedures, methods, and protocols affecting the laboratory or health care.

CLSI's consensus process depends on experts who volunteer to serve as contributing authors and/or as participants in the reviewing and commenting process. At the end of each comment period, the committee that developed the document is obligated to review all comments, respond in writing to all substantive comments, and revise the draft document as appropriate.

Comments on published CLSI documents are equally essential and may be submitted by anyone, at any time, on any document. All comments are managed according to the consensus process by a committee of experts.

**Appeal Process**

When it is believed that an objection has not been adequately considered and responded to, the process for appeal, documented in the CLSI *Standards Development Policies and Processes,* is followed.

All comments and responses submitted on draft and published documents are retained on file at CLSI and are available upon request.

**Get Involved—Volunteer!**

Do you use CLSI documents in your workplace? Do you see room for improvement? Would you like to get involved in the revision process? Or maybe you see a need to develop a new document for an emerging technology? CLSI wants to hear from you. We are always looking for volunteers. By donating your time and talents to improve the standards that affect your own work, you will play an active role in improving public health across the globe.

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

Clinical and Laboratory Standards Institute
P: +1.610.688.0100
F: +1.610.688.0700
www.clsi.org
standard@clsi.org

CLSI MM26-Ed1
July 2024

# Cancer Molecular Testing: Principles of Oncology Test Interpretation, Laboratory and Assay Design, and Clinical Consultation

Daniel Jones, MD, PhD
Honey V. Reddi, PhD, FACMG
Jonathan Earle, MD
Rong He, MD
Sertac Kip, MD, PhD
Robert F. Klees, PhD
Cates Mallaney, PhD
Sara Brown, MS, CGC
Vivekananda Datta, MD, PhD
Prashant Deshpande, MBBS, MD
Elizabeth Ostrander

## Abstract

Building, growing, and maintaining a molecular oncology testing laboratory involves extensive basic and applied knowledge in oncology, anatomic pathology, and laboratory medicine, and a diverse skill set in technical operations, test interpretation, and financial and regulatory topics. Clinical and Laboratory Standards Institute MM26—*Cancer Molecular Testing: Principles of Oncology Test Interpretation, Laboratory and Assay Design, and Clinical Consultation* reviews the current key concepts in molecular oncology, indications for testing, and laboratory and test design. It is intended to provide management personnel, particularly the laboratory director as well as technical and medical directors and pathologists, with practical and actionable information for strategic planning and daily laboratory operations. CLSI MM26 includes guidance focused on providing molecular oncology laboratory consultations to clinical providers and other stakeholders, including through molecular tumor boards. Emerging areas of testing such as liquid biopsy and identifying germline variants in cancer panels are also included. The infrastructure and best practices for data sharing of cancer genomic results and keeping the laboratory up-to-date with technologies and test development in the rapidly evolving areas of cancer genomics, such as single-cell sequencing and digital spatial profiling, are also discussed.

Clinical and Laboratory Standards Institute (CLSI). *Cancer Molecular Testing: Principles of Oncology Test Interpretation, Laboratory and Assay Design, and Clinical Consultation.* 1st ed. CLSI report MM26 (ISBN 978-1-68440-236-6 [Print]; ISBN 978-1-68440-237-3 [Electronic]). Clinical and Laboratory Standards Institute, USA, 2024.

## Suggested Citation

CLSI. *Cancer Molecular Testing: Principles of Oncology Test Interpretation, Laboratory and Assay Design, and Clinical Consultation*. 1st ed. CLSI report MM26. Clinical and Laboratory Standards Institute; 2024.

CLSI MM26-Ed1

ISBN 978-1-68440-236-6 (Print)

ISBN 978-1-68440-237-3 (Electronic)

ISSN 1558-6502 (Print)

ISSN 2162-2914 (Electronic)

Volume 44, Number 20

# 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/

## Document Development Committee on Laboratory Consult for Cancer Genetics Testing

**Daniel Jones, MD, PhD**
**Chairholder**
**The Ohio State University**
**USA**

**Honey V. Reddi, PhD, FACMG**
**Vice-Chairholder**
**Belay Diagnostics**
**USA**

Jonathan Earle, MD
Hartford Pathology Associates, PC
USA

Rong He, MD
Mayo Clinic
USA

Sertac Kip, MD, PhD
PathGroup
USA

Robert F. Klees, PhD
New York State Department of Health
USA

Cates Mallaney, PhD
PierianDx
USA

## 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/

## Staff

Clinical and Laboratory Standards Institute
USA

Katharine I. Castagna, MS, MLS(ASCP) CT, MB
*Program Manager*

Catherine E.M. Jenkins, ELS
*Editor*

Kristy L. Leirer, MS
*Editor*

Lisa M.W. Walker, MS, ELS
*Editor*

# Acknowledgment

CLSI, the Consensus Council, and the Document Development Committee on Laboratory Consult for Cancer Genetics Testing gratefully acknowledge the following volunteers for their important contributions to the development of CLSI MM26.

Sara Brown, MS, CGC
ARUP Laboratories
USA

Vivekananda Datta, MD, PhD
Quest Diagnostics Major Laboratory Facilities – Marlborough
USA

Prashant Deshpande, MBBS, MD
Sultan Qaboos Comprehensive Cancer Care & Research Centre
India

Birgit Funke, PhD, FACMG
Icahn School of Medicine at Mount Sinai
USA

Elizabeth Ostrander
Pfizer Inc.
USA

Barbara Zehnbauer, PhD
Emory University Hospital
USA

# Contents

# Contents (Continued)

# Foreword

The translation of the human genome sequencing project and basic science advances in cancer biology into oncology diagnosis and treatment over the last two decades have dramatically increased the breadth and complexity of clinical molecular diagnostics of cancer. These advances have been linked with rapid advances in sequencing technologies and the development and maturation of a range of other testing methods. Because of the varying throughput, sensitivity, and performance characteristics of these platforms, extensive knowledge is needed to select the best platform and gene content for each new oncology test. The fundamental role of bioinformatics and complex software for performance of next-generation sequencing has introduced new skill sets and validation paradigms into the clinical oncology laboratory.

In parallel with these advances, there has been increasingly stringent regulatory requirements requiring rigorous planning and documentation of molecular oncology assay validations with training and ongoing proficiency of laboratorians, bioinformatics personnel, and laboratory directors (LDs). The costs of molecular reagents and the complex multistep testing protocols warrant careful financial projections to ensure sustainable laboratory operations. This planning informs decisions on obtaining reference laboratory services and contracting services for some aspects of oncology testing.

Communicating molecular oncology results has also become more complex because germline and somatic cancer testing has expanded to include stakeholders such as genetic counselors and other medical specialists. As oncologic protocols have incorporated more molecular biomarkers into diagnostic, therapeutic, and monitoring algorithms, the need for laboratory involvement in interdisciplinary planning conferences has increased. Finally, interlaboratory data exchanges and use of public and commercial databases have become integral to somatic variant interpretation. Therefore, a holistic approach to managing the initial setup, expansion, assay selection, reporting protocols, and quality processes of the molecular oncology laboratory has become critical. CLSI MM26 provides the LD and other stakeholders with an overview of the testing and result communication processes, which are imperative to successful oncology testing.

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


## KEY WORDS

**cancer biology**

**comprehensive reporting**

**laboratory design**

**laboratory director responsibilities**

**laboratory management**

**laboratory personnel management**

**quality management**

**sequencing technology**

**tumor biomarkers**

**variant annotation**

# Chapter 1

# Introduction

# Cancer Molecular Testing: Principles of Oncology Test Interpretation, Laboratory and Assay Design, and Clinical Consultation

## 1 Introduction

### 1.1 Scope

CLSI MM26 emphasizes the essential role of the laboratory director (LD) and/or other applicable personnel in the molecular oncology laboratory in:

- Launching well-designed and well-validated genomic assays and/or monitoring external providers for seamless delivery of testing services
- Engaging effectively with medical care personnel to accurately describe and convey the appropriate clinical indications for requesting genetic analysis for malignancies
- Ensuring accurate interpretation(s) of genetic test findings and the implications of the test results for establishing the patient's diagnosis, prognosis, and treatment selection; monitoring patient's response to therapy; and detecting cancer progression
- Ensuring awareness of the limitations of test findings, such as additional genes or variants that might not have been included in the analyses but can also contribute to the patient's condition
- Sustaining laboratory quality, innovative testing, and laboratory programs that keep pace with technologic developments and the clinical needs of the laboratory's stakeholders

CLSI MM26 does not include detailed descriptions of molecular testing methods or analytical techniques that are covered in CLSI MM01,[1] MM07,[2] MM09,[3] MM17,[4] and MM21.[5] Other CLSI documents provide comprehensive overviews of hematopathology (CLSI MM06[6]), solid tumor diagnostics (CLSI MM23[7]), and new molecular laboratory start-up (CLSI MM19[8]).

The target audience includes:

- Directors and supervisors employed by laboratories that perform cancer molecular testing
- Pathologists, scientists, and genetic counselors who are involved in selecting cancer tests and interpreting results
- LDs who are involved in developing curriculum for training purposes
- Personnel who are involved in developing cancer research protocols
- Field application specialists who work in the cancer diagnostics industry

### 1.2 Background

In the more than 50 years that genetic and genomic techniques have been applied to cancer testing, great progress has been made in understanding the molecular events underlying the initiation and progression of cancer as well as the selection of appropriate therapeutic modalities. Features that are common and different between cancers arising at different locations and with different histopathologic features have been clarified. Detection of the wide variety of molecular events now described has been facilitated by the emergence of suitable methods for detection, principally next-generation sequencing (NGS). Given the complexity of NGS