



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.

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.

The Clinical and Laboratory Standards Institute consensus process, which is the mechanism for moving a document through two or more levels of review by the health care community, is an ongoing process. Users should expect revised editions of any given document. Because rapid changes in technology may affect the procedures, methods, and protocols in a standard or guideline, users should replace outdated editions with the current editions of CLSI documents. Current editions are listed in the CLSI catalog and posted on our website at www.clsi.org.

If you or your organization is not a member and would like to become one, or to request a copy of the catalog, contact us at:

P: +1.610.688.0100 **F:** +1.610.688.0700 **E:** customerservice@clsi.org **W:** www.clsi.org



Copyright ©2024 Clinical and Laboratory Standards Institute. Except as stated below, any reproduction of content from a CLSI copyrighted standard, guideline, or other product or material requires express written consent from CLSI. All rights reserved. Interested parties may send permission requests to permissions@clsi.org.

CLSI hereby grants permission to each individual member or purchaser to make a single reproduction of this publication for use in its laboratory procedures manual at a single site. To request permission to use this publication in any other manner, e-mail permissions@clsi.org.

To read CLSI's full Copyright Policy, please visit our website at <https://clsi.org/terms-of-use/>.

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.

Sample

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

Contents

Abstract	i
Committee Membership	iii
Foreword	vii
Chapter 1: Introduction	1
1.1 Scope	2
1.2 Background	2
1.3 Terminology	3
Chapter 2: Principles of Tumor Classification and Types of Genomic Testing	9
2.1 Classifications and Therapy Selection in Cancer	10
2.2 Organization of the Genome and Types of Alterations	16
2.3 Genetic and Epigenetic Changes in the Cancer Genome	19
2.4 The Molecular Diagnostic Toolkit: Assay Types and Analysis Methods	21
2.5 Analytics for Next-Generation Sequencing Studies: Classifying, Categorizing, and Scoring Cancer-Associated Changes	28
2.6 Effects of Precision Medicine on Cancer Therapy	31
2.7 Summary: The Integrated Cancer Diagnosis	32
Chapter 3: Building and Growing a Cancer Testing Program	33
3.1 Business Strategy	34
3.2 Laboratory Operations	38
3.3 Building a New Assay: Method Selection, Design, and Specifications	43
3.4 Test Launch	47
3.5 Example Test Process for a Comprehensive Genomic NGS Assay	48
Chapter 4: Interpretation	49
4.1 General Considerations	50
4.2 General Principles for Reporting Laboratory Results	50
4.3 Interpretative Framework for a Positive Test Result	57
4.4 Interpretative Framework for a Negative Test Result	66
4.5 Reinterpretation: Periodic Assessment of Variants of Uncertain Significance	68
4.6 Integration of Genetic Data into the Electronic Health Record	69

Contents (Continued)

Chapter 5: Maintaining and Improving a Cancer Genomics Laboratory and New Frontiers in Testing	71
5.1 The Role of the Laboratory Director and Other Supervisory Personnel in the Laboratory	72
5.2 Maintaining and Driving Excellence in the Laboratory	76
5.3 Developing a Customer Satisfaction Program.	85
5.4 Positioning the Laboratory: Institutional Effect, Collaboration, and Clinical Research	85
5.5 Integration of Laboratory Data Into Clinical Records	88
5.6 Future of Cancer Testing: Evolving Technologies and Assay Indications.	89
Chapter 6: Conclusion	91
6.1 Effect of Advancement in Cancer Genetics on Therapies and Assay Design	92
6.2 Laboratory Design, Personnel, and Bioinformatic Requirements for Genomics	92
6.3 Lifecycle and Best Practices for Development and New Test Sustainability.	93
6.4 Communicating Complex Genomics Results.	93
Chapter 7: Supplemental Information	95
References	96
Appendix A. Sequence Quality Metrics	105
Appendix B. Databases for Evaluation and Interpretation of Germline and Somatic Variants	108
Appendix C. Correlation of Functional Alterations, Biomarkers, Detection Methods, and Treatments.	110
Appendix D1. Laboratory-Developed Test Validation.	113
Appendix D2. Clinical Validation Metrics	116
Appendix D3. Validation Study Considerations	117
Appendix E. Laboratory Director Responsibilities: Strategies for Ongoing Management	120
The Quality Management System Approach	126

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

Sample

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 MM06⁶), solid tumor diagnostics (CLSI MM23⁷), and new molecular laboratory start-up (CLSI MM19⁸).

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

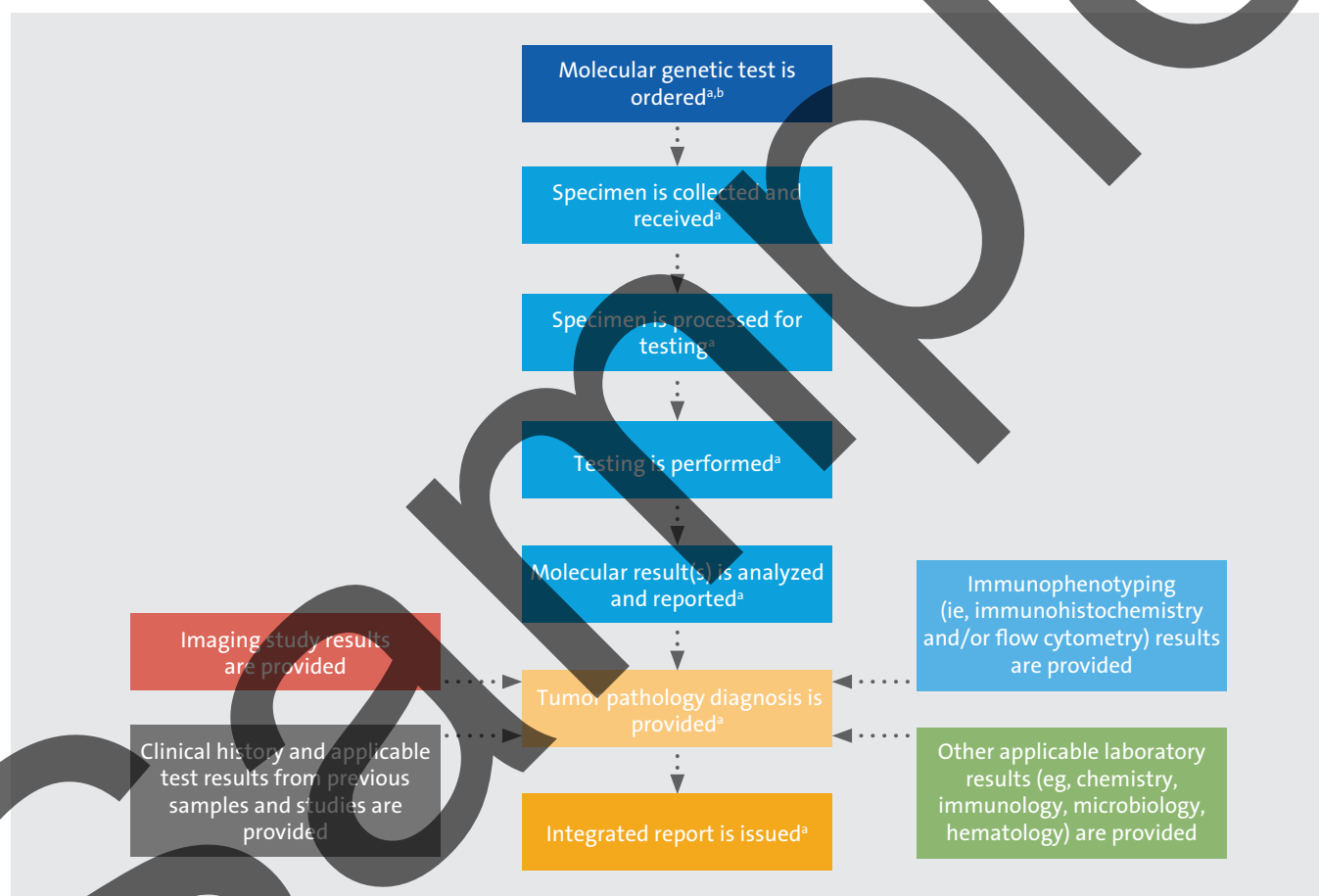
In the more than 50 years that genetic and genomic techniques have been applied to cancer testing, great progress has been made in understanding the molecular events underlying the initiation and progression of cancer as well as the selection of appropriate therapeutic modalities. Features that are common 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

- Test limitations (including but not limited to relevant regions not tested, limitations of methodology, limitations of sample type)
- Recommended follow-up, next steps, and/or reflex testing

4.2.2 Integrated Report

Principle elements to consider for an integrated report include:

- Integrated reporting provides a combination of results and interpretations of multiple related individual laboratory reports (eg, pathology, immunophenotyping, cytogenetics, molecular diagnostics). This type of report includes an interpretation summarizing all the data and implications in the context of other relevant clinical information as a concise, integral diagnostic summary. Figure 3 illustrates points of consultation and how integrated reporting is applied to the cancer molecular genetic testing and reporting workflow.



Abbreviation: FISH, fluorescence *in situ* hybridization.

^a Testing phases laboratory consultation can occur.

^b Includes cytogenetic studies of chromosome karyotyping and FISH.

Figure 3. Molecular Genetic Testing and Reporting Workflow in Cancer

Sample



CLINICAL AND
LABORATORY
STANDARDS
INSTITUTE.

PRINT ISBN 978-1-68440-236-6

ELECTRONIC ISBN 978-1-68440-237-3

CLSI MM26-Ed1