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.

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

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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.

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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

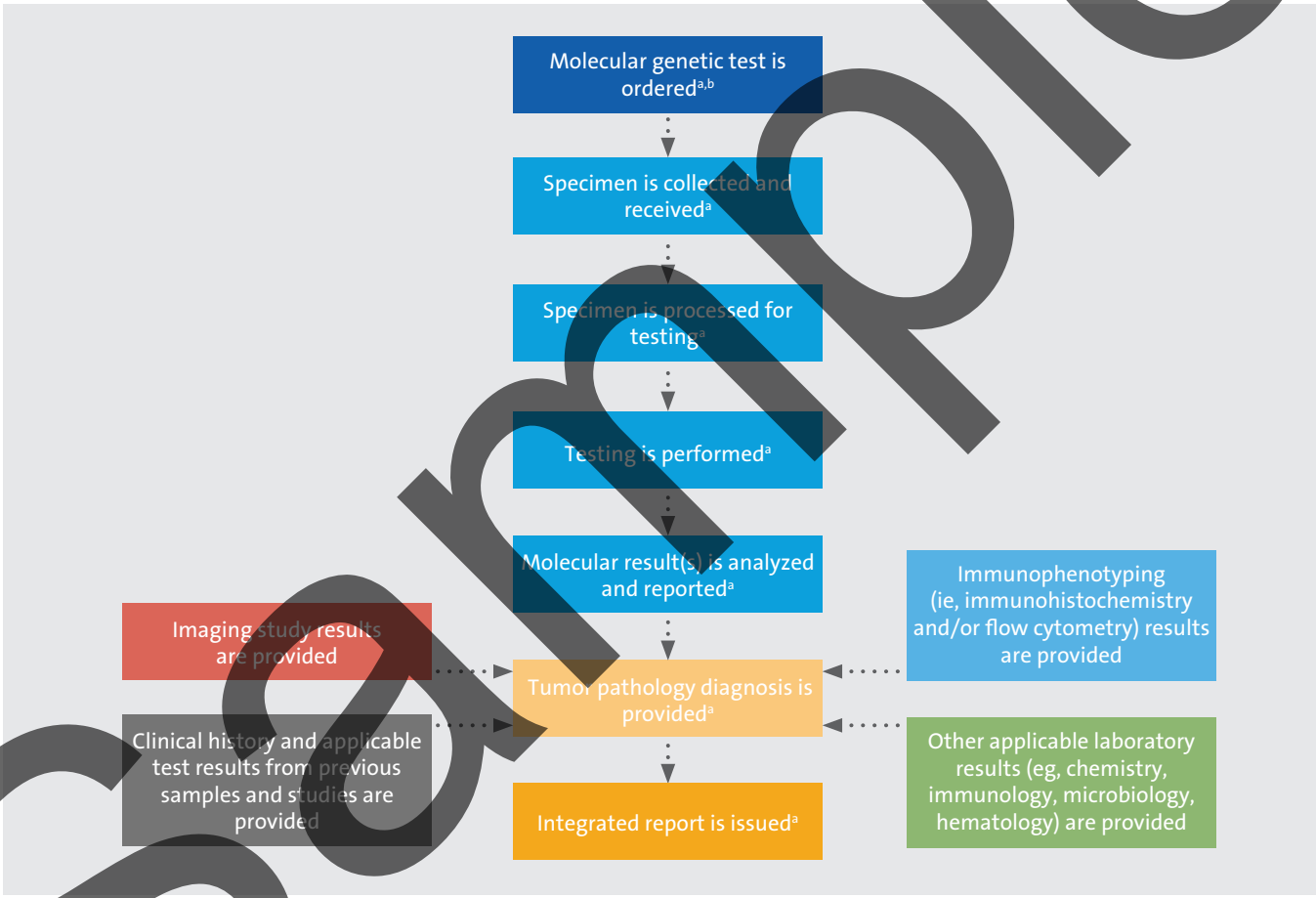
In the more than 50 years that genetic and genomic techniques have been applied to cancer testing, great progress has been made in understanding the molecular events underlying the initiation and progression of cancer as well as the selection of appropriate therapeutic modalities. Features that are common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

- 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

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