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May 2006

MM12-A

Diagnostic Nucleic Acid Microarrays; Approved Guideline

This guideline provides recommendations for many aspects of the array process including: a method overview; nucleic acid extraction; the preparation, handling, and assessment of genetic material; quality control; analytic validation; and interpretation and reporting of results.

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

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Clinical and Laboratory Standards Institute
950 West Valley Road, Suite 2500
Wayne, PA 19087 USA
P: +1.610.688.0100
F: +1.610.688.0700
www.clsi.org
standard@clsi.org

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Joseph L. Hackett, PhD
Kellie J. Archer, PhD
Adolfas K. Gaigalas, PhD
Carleton T. Garrett, MD, PhD
Loren J. Joseph, MD
Walter H. Koch, PhD
L. J. Kricka, D Phil
Ronald C. McGlennen, MD
Vivianna Van Deerlin, MD, PhD
Gregory B. Vasquez, PhD

Abstract

Clinical and Laboratory Standards Institute document MM12-A, *Diagnostic Nucleic Acid Microarrays; Approved Guideline* provides general recommendations for the operation of diagnostic nucleic acid microarrays. The recommendations cover nucleic acid extraction; preparation, handling, and assessment of genetic material; and interpretation and reporting of results. The guideline addresses array-based detection of variations in DNA sequence and gene expression analysis as it relates to: heritable variations, somatic changes, methylation profiling, pathogen profiling including antibiotic resistance analysis, expression profiling, and gene dosage/comparative genomic hybridization.

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Foreword

Molecular genetics has now become firmly entrenched as the third major subdiscipline of clinical laboratory medical genetics, emerging more recently than the other subspecialties, biochemical genetics and cytogenetics. Just as with any diagnostic method or test, in order to fully benefit the patient, it must be developed and practiced under appropriate conditions. The purpose of this guideline is to define conditions and principles, which will optimize the provision of accurate molecular information.

In producing MM12, the intention of the CLSI Subcommittee on Molecular Methods for Microarrays was to reach a consensus so an approved guideline can be distributed to laboratories that use molecular diagnostic tests. The subcommittee also intends the document to be broad in perspective and an educational resource for molecular genetics.

Key Words

Amplification, gene, genetic disease, molecular diagnostic test, mutation detection, nucleic acid, Southern blot

SAMPLE

Diagnostic Nucleic Acid Microarrays; Approved Guideline

1 Scope

MM12—*Diagnostic Nucleic Acid Microarrays* addresses array-based detection of variations in DNA sequence and gene expression analysis as it relates to:

- heritable variations;
- somatic changes;
- methylation profiling;
- pathogen profiling including antibiotic resistance analysis;
- expression profiling; and
- gene dosage/comparative genomic hybridization (CGH).

This guideline provides recommendations for many aspects of the microarray process, including: a method overview; nucleic acid extraction; the preparation, handling, and assessment of genetic material; and interpretation and reporting of results. Quality control, as well as analytic and clinical validation, is also addressed.

This guideline is limited to clinically relevant targets and does not address tissue and protein microarrays, non-nucleic acid microarrays, or research applications of microarrays.

2 Introduction

2.1 Diagnostic Microarrays

Diagnostic nucleic acid microarrays are a relatively recent outgrowth of more traditional molecular diagnostic methods, and have the potential to allow rapid, simultaneous genetic testing of individuals for multiple traits (e.g., polymorphisms, haplotypes) or multiple different mutations in a single disease gene. Nucleic acid-based microarrays also have diagnostic potential for identification of infectious disease organisms from a variety of sample matrices. Other configurations of microarrays enable comparative surveys of gene expression in selected tissues and samples, resulting in diagnostic and response predictions. These devices represent multiplexed analysis of clinical specimens and have unique manufacturing and quality control concerns, as well as analytical and clinical validation differences and novel interpretation algorithms when compared to simple unitary tests.

2.2 Diagnostic Utility

The usefulness of microarrays for diagnostic applications can be traced to advances in the identification of disease genes for a number of genetic diseases and susceptibilities, and to the increased knowledge of transcriptional loci provided by the sequencing and analysis of the human genome, as well as development of molecular signatures for identification of disease-causing organisms. It is now possible to rapidly test for specific mutations, polymorphisms, and gene expression patterns that may direct medical management, prophylaxis, and treatment for any number of conditions. These tests may complement or supplant more traditional diagnostic methods, and in some cases, may be the only available approach for diagnosis. The utility of diagnostic microarrays encompasses predicting disease susceptibility, identifying pathological organisms, screening for carriers of recessive traits, performing prenatal diagnosis, making earlier or more reliable diagnosis of cancer, classifying tissues and tumors by molecular signature, and making treatment decisions based on polymorphic markers of response and toxicity.

Related CLSI/NCCLS Publications

- C24-A2** **Statistical Quality Control for Quantitative Measurements: Principles and Definitions; Approved Guideline—Second Edition (1999).** This guideline provides definitions of analytical intervals; plans for quality control procedures; and guidance for quality control applications.
- EP10-A2** **Preliminary Evaluation of Quantitative Clinical Laboratory Methods; Approved Guideline—Second Edition (2002).** This guideline addresses experimental design and data analysis for preliminary evaluation of the performance of an analytical method or device.
- GP29-A** **Assessment of Laboratory Tests When Proficiency Testing is Not Available; Approved Guideline (2002).** This guideline suggests workable alternatives for evaluating the accuracy of an assay when standard interlaboratory comparison programs are unavailable.
- MM1-A** **Molecular Diagnostic Methods for Genetic Diseases; Approved Guideline (2000).** This document provides guidance for the use of molecular biologic techniques for clinical detection of heritable mutations associated with genetic disease.
- MM2-A2** **Immunoglobulin and T-Cell Receptor Gene Rearrangement Assays; Approved Guideline (2002).** This document is a guideline for conducting molecular tests of immunoglobulin and T-cell receptor gene arrangements.
- MM3-A2** **Molecular Diagnostic Methods for Infectious Diseases; Approved Guideline—Second Edition (2006).** This guideline addresses topics relating to clinical applications, amplified and nonamplified nucleic acid methods, selection and qualification of nucleic acid sequences, establishment and evaluation of test performance characteristics, inhibitors, and interfering substances, controlling false-positive reactions, reporting and interpretation of results, quality assurance, regulatory issues, and recommendations for manufacturers and clinical laboratories.
- MM5-A** **Nucleic Acid Amplification Assays for Molecular Hematopathology; Approved Guideline (2003).** This guideline addresses the performance and application of assays for gene translocations by both PCR and RT-PCR techniques and includes information on specimen collection, sample preparation, test reporting, test validation, and quality assurance.
- MM6-A** **Quantitative Molecular Methods for Infectious Diseases; Approved Guideline (2003).** This document provides guidance for the development and use of quantitative molecular methods, such as nucleic acid probes and nucleic acid amplification techniques of the target sequences specific to particular microorganisms. It also presents recommendations for quality assurance, proficiency testing, and interpretation of results.
- MM14-A** **Proficiency Testing (External Quality Assessment) for Molecular Methods; Approved Guideline (2005).** This document provides guidelines for a quality proficiency testing program, including reliable databases; design control in the choice of materials and analytes; good manufacturing processes; documentation procedures; complaint handling; corrective and preventive action plans; and responsive timing of reports.