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1st Edition

MM21

Genomic Copy Number Microarrays for Constitutional Genetic and Oncology Applications

This guideline provides recommendations for validation, verification, performance, and interpretation of nucleic acid microarrays used for cytogenetic applications to measure copy number imbalances and loss of heterozygosity. Both constitutional and oncology applications are addressed.

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

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Clinical and Laboratory Standards Institute
940 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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Hutton M. Kearney, PhD, FACMG
Shashikant Kulkarni, MS, PhD, FACMG
Karen E. Bijwaard, MS, RAC, MB(ASCP)
Madhuri R. Hegde, PhD
Lisa Kalman, PhD
Leming Shi, PhD
Richard Shippy, MS
Sarah T. South, PhD, FACMG
Erik C. Thorland, PhD
Patrik Vitazka, MD, PhD, FACMG
Emily S. Winn-Deen, PhD
Joanne M. Yeakley, PhD

Abstract

Clinical and Laboratory Standards Institute document MM21—*Genomic Copy Number Microarrays for Constitutional Genetic and Oncology Applications* discusses nucleic acid microarray technologies for diagnostic testing that a growing number of medical laboratories have adopted. The different types of microarrays and their uses in various types of laboratories have grown tremendously. MM21 specifically addresses validation, verification, performance, and interpretation of nucleic acid microarrays used for cytogenetic applications to measure copy number imbalances and loss of heterozygosity. Both constitutional and oncology applications are discussed.

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Committee Membership

Consensus Committee on Molecular Methods

Frederick S. Nolte, PhD, D(ABMM), F(AAM)
Chairholder
Medical University Hospital Authority
USA

Barbara Zehnbauer, PhD, FACMG, FACB
Vice-Chairholder
Centers for Disease Control and Prevention
USA

Sherry A. Dunbar, PhD
Luminex Corporation
USA

Helen Fernandes, PhD
New York Presbyterian Hospital
USA

Charles E. Hill, MD, PhD
Emory University Hospital
USA

Thomas J. Lenk, PhD
Celera Diagnostics
USA

Ronald M. Przygodzki, MD
Department of Veterans Affairs
USA

Yi-Wei Tang, MD, PhD, D(ABMM)
Memorial Sloan Kettering Cancer Center
USA

Zivana Tezak-Fragale, PhD
FDA Center for Devices and Radiological Health
USA

Document Development Committee on Microarrays for Cytogenetics and Oncology

Hutton M. Kearney, PhD, FACMG
Co-Chairholder
Mayo Clinic
USA

Shashikant Kulkarni, MS, PhD, FACMG
Co-Chairholder
Washington University School of Medicine
USA

Karen E. Bijwaard, MS, RAC, MB(ASCP)
FDA Center for Devices and Radiological Health
USA

Madhuri R. Hegde, PhD
Emory University School of Medicine
USA

Lisa Kalman, PhD
Centers for Disease Control and Prevention
USA

Leming Shi, PhD
Fudan University
China

Richard Shippy, MS
Illumina, Inc.
USA

Sara J. South, PhD, FACMG
University of Utah and ARUP Laboratories
USA

Patrik Vitazka, MD, PhD, FACMG
GeneDx
USA

Joanne M. Yeakley, PhD
BioSpyder Technologies
USA

Staff

Clinical and Laboratory Standards Institute
USA

Luann Ochs, MS
Senior Vice President – Operations

Marcy Hackenbrack, MCM, M(ASCP)
Project Manager

Megan L. Tertel, MA, ELS
Editorial Manager

Joanne P. Christopher, MA
Editor

Alexander B. Phucas
Editor

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Erik C. Thorland, PhD
Mayo Clinic
USA

Emily S. Winn-Deen, PhD
Rx Dx Advisors, Inc.
USA

Contents

Foreword

MM21 was developed to provide more targeted guidance on molecular microarrays. It focuses on the appropriate performance, validation, verification, and interpretation of nucleic acid microarrays primarily used for cytogenetic applications to measure copy number (CN) imbalances.

When the first guideline on molecular microarrays was published (see CLSI document MM12[1]) nucleic acid microarrays were not a major part of medical laboratory test options. Today, many medical laboratories have adopted a variety of testing platforms and, as a result, the types of arrays and laboratories using arrays have increased tremendously. After reviewing CLSI document MM12,[1] the subject matter experts determined that the document, in its current form, is quite broad in scope. To allow for the most clinically relevant applications to be addressed in greater depth, CLSI document MM12 was split into three documents, with each document focusing on a particular field of clinical genetics.

- CN and absence of heterozygosity detection arrays (MM21)
- Expression arrays and methylation profiling (see CLSI document MM12[1])
- Nucleic acid microarrays for use in microbiology/immunology laboratories (eg, pathogen profiling) (see CLSI document MM22[2])

NOTE: Mandates are occasionally allowed in CLSI guidelines in cases in which the document development committee feels strongly that a particular action is either required or prohibited, or when a guideline addresses provisions based on regulations. Throughout MM21, the use of the term "must" was evaluated by the document development committee and deemed appropriate because the uses are either 1) based on a requirement or 2) indicative of a necessary step to ensure patient safety or proper fulfillment of a procedure.

Key Words

Array-based comparative genomic hybridization, chromosomal microarrays, genomic copy number microarrays, whole genome testing

Genomic Copy Number Microarrays for Constitutional Genetic and Oncology Applications

Chapter 1: Introduction

This chapter includes:

- Document scope and applicable exclusions
- Background information pertinent to the document content
- Standard Precautions information
- Terms and definitions used in the document
- "Note on Terminology" that highlights particular use and/or variation in use of terms and/or definitions
- Abbreviations and acronyms used in the document

1.1 Scope

This guideline provides recommendations for the appropriate performance, validation or verification, and interpretation of nucleic acid microarrays used primarily for cytogenetic applications to measure copy number (CN) imbalances, traditional array-based comparative genomic hybridization (aCGH), and single nucleotide polymorphism (SNP) arrays for CN imbalances and absence of heterozygosity (AOH). Both constitutional (prenatal/postnatal) and oncology applications are addressed.

The intended users of this guideline are clinical genetics laboratorians who perform cytogenetics and molecular genetics testing.

This guideline:

- Is not intended for research laboratorians
- Is not intended to provide guidance to manufacturers
- Does not address methylation arrays, RNA expression microarrays, resequencing and genotyping arrays not intended for CN detection, microarrays for the diagnosis and monitoring of infectious diseases, or non-nucleic acid microarrays (eg, protein arrays)

1.2 Background

Chromosome abnormalities play a significant role in human genetic diseases. Abnormalities may involve chromosome number (eg, aneuploidy characterized by extra or missing chromosomes) and/or chromosome structure (eg, structural aberrations such as deletion, duplication, inversion, translocation, ring chromosome, isochromosome, and marker chromosome). Chromosomal structural defects are balanced (eg, reciprocal translocations, Robertsonian translocation) or, more often, they are unbalanced, associated with CN gains or losses in the DNA. Historically, conventional cytogenetic techniques (eg, G-