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Vol. 22 No. 12

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Immunoglobulin and T-Cell Receptor Gene Rearrangement Assays; Approved Guideline—Second Edition

This document provides guidance on the performance of gene rearrangement assays, including indications; specimen collection, transport, and processing; assessment of specimen adequacy; and quality control.

A guideline for global application developed through the NCCLS consensus process.

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Serving the World's Medical Science Community Through Voluntary Consensus

NCCLS is an international, interdisciplinary, nonprofit, standards-developing, and educational organization that promotes the development and use of voluntary consensus standards and guidelines within the healthcare community. It is recognized worldwide for the application of its unique consensus process in the development of standards and guidelines for patient testing and related healthcare issues. NCCLS is based on the principle that consensus is an effective and cost-effective way to improve patient testing and healthcare services.

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Immunoglobulin and T-Cell Receptor Gene Rearrangement Assays; Approved Guideline—Second Edition

Abstract

Assays that detect monoclonal rearrangement of immunoglobulin or T-cell receptor genes are useful adjunct methods in the diagnosis of leukemia or lymphoma. Prudent clinical use requires a thorough understanding of the sensitivity and technical artifacts associated with these methods, together with the ability to prudently weigh the results. NCCLS document MM2—*Immunoglobulin and T-Cell Receptor Gene Rearrangement Assays* helps laboratorians perform and interpret gene rearrangement assays. It includes indications for gene rearrangement analysis and acceptable methods for specimen collection, transport, and processing. Also included are recommendations for assessing specimen adequacy, as well as technical methods for conducting gene rearrangement assays, including information on sensitivity, specificity, controls, and test interpretation. Quality assurance procedures are included throughout the document.

NCCLS. *Immunoglobulin and T-Cell Receptor Gene Rearrangement Assays; Approved Guideline—Second Edition.* NCCLS document MM2-A2 (ISBN 1-56238-466-X). NCCLS, 940 West Valley Road, Suite 1400, Wayne, Pennsylvania 19087-1898 USA, 2002.

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In addition, the area committee would also like to recognize the valuable contributions of the members the Subcommittee on Molecular Hematology that developed the first approved edition of this guideline.

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Contents

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Foreword

NCCLS document MM2-A2—*Immunoglobulin and T-Cell Receptor Gene Rearrangement Assays; Approved Guideline—Second Edition* is one in a series that address molecular methods technology. This guideline provides recommendations for performance and interpretation of molecular biologic assays in diagnostic hematopathology, specifically immunoglobulin and T-cell receptor gene rearrangement. This guideline addresses both technical methods and quality control for the performance of these two types of assays using nonamplification-based southern blot methods.

The methods and quality control approaches described herein are intended for use by both manufacturers and pathology laboratories. Such use is intended to facilitate both interlaboratory comparison of results and diagnostic interpretations, as well as to ensure accuracy in diagnosis.

This guideline is written for laboratory directors, surgical pathologists, hematopathologists, medical technologists, and manufacturers of instruments and reagents used in these assays.

Key Words

Gene rearrangement, hematopathology, leukemia, lymphoma, southern blot

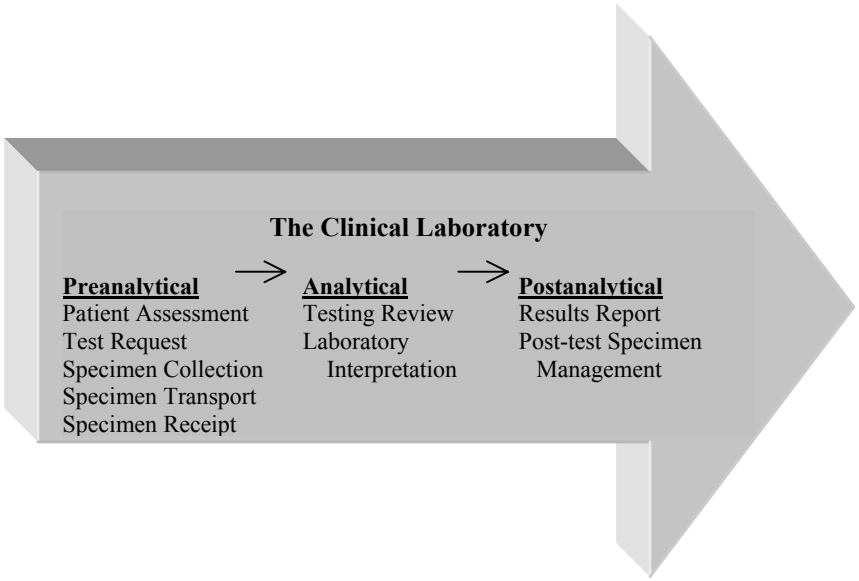
The Quality System Approach

NCCLS subscribes to a quality system approach in the development of standards and guidelines, which facilitates project management; defines a document structure via a template; and provides a process to identify needed documents through a gap analysis. The approach is based on the model presented in the most current edition of NCCLS HS1- *A Quality System Model for Health Care.* The quality system approach applies a core set of "quality system essentials (QSEs)," basic to any organization, to all operations in any healthcare service's path of workflow. The QSEs provide the framework for delivery of any type of product or service, serving as a manager's guide. The quality system essentials (QSEs) are:

QSEs	
Documents & Records	Information Management
Organization	Occurrence Management
Personnel	Assessment
Equipment	Process Improvement
Purchasing & Inventory	Service & Satisfaction
Process Control	Facilities & Safety

Path of Workflow

A path of workflow is the description of the necessary steps to deliver the particular product or service that the organization or entity provides. For example, NCCLS document GP26-A2 defines a clinical laboratory path of workflow that consists of three sequential processes: preanalytical, analytical, and postanalytical. All clinical laboratories follow these processes to deliver the laboratory's services, namely quality laboratory information. The arrow depicts the sequence, from left to right, that any clinical laboratory follows. In addition, the necessary steps or subprocesses are listed below them.



Adapted from NCCLS document HS1—*A Quality System Model for Health Care*

Most of NCCLS's documents relate to the clinical laboratory, so the most common path of workflow will be that depicted above. The path of workflow for other healthcare activities, e.g., respiratory services, imaging services, etc., or for other types of organizations, e.g., medical device manufacturers, will differ from that of the clinical laboratory. All such paths of workflow describe the sequence of activities necessary to produce the organization's or an entity's specific product or services. For those documents that relate to other paths of workflow, the icon will reflect different process steps.

MM2-A2 Addresses the Following Steps Within the Clinical Laboratory Path of Workflow

Preanalytical					**Analytical**		**Postanalytical**	
Patient Assessment	Test Request	Specimen Collection	Specimen Transport	Specimen Receipt	Testing Review	Laboratory Interpre-tation	Results Report	Post-test Specimen Management
X	X	X	X	X	X	X	X	X

Adapted from NCCLS document HS1—*A Quality System Model for Health Care*

Immunoglobulin and T-Cell Receptor Gene Rearrangement Assays; Approved Guideline—Second Edition

1 Introduction

The interpretation of biopsy and aspirate results, through which atypical lymphoid cells are identified, is often difficult. Malignant diseases can occasionally masquerade as benign processes, while reactive processes may simulate malignancies. The emergence of an understanding of normal and abnormal development of the lymphoid system has enabled development of immunological and molecular markers for the identification of monoclonal populations of lymphocytes; identification of such a monoclonal population can significantly assist the diagnostician in arriving at the diagnosis of leukemia or lymphoma.[1-7]

Prudent clinical use of the ability to identify monoclonal proliferations of lymphoid cells using molecular methods requires a thorough understanding of the sensitivity and technical artifacts associated with these methods. Avoiding erroneous interpretation of B- and T-cell gene rearrangement assays requires careful attention to technical detail and the use of rigorous quality assurance measures.[8,9] This guideline helps laboratorians that rely on gene rearrangement assays to perform these techniques using the appropriate controls. The guideline also helps laboratorians decide what types of materials and records are to be kept following the laboratory procedure, as well as the length of time each is to be kept. Finally, the guideline helps both manufacturers of diagnostic kits and reagents, and those responsible for monitoring compliance with quality assurance programs.

2 Scope

The use of molecular methods that use deoxyribonucleic acid (DNA) probes in clinical diagnosis presents new challenges to the pathologist. Despite the clear benefits of having another method by which to identify proliferation of monoclonal cell populations, issues of sensitivity and false-positive results mandate the application of stringent laboratory practice. To ensure the success of nucleic acid diagnostics, several key areas warrant attention. This document addresses the following topics as they relate to the direct detection of T- and B-cell gene rearrangements:

- indications for gene rearrangement analysis;
- specimen collection, transport, and processing;
- assessment of specimen adequacy;
- conduct of the gene rearrangement assay;
- sensitivity, specificity, controls, and artifacts;
- quality assurance; and
- interpretation of results.

3 Standard Precautions

Because it is often impossible to know what might be infectious, all human blood specimens are to be treated as infectious and handled according to "standard precautions." Standard precautions are new guidelines that combine the major features of "universal precautions and body substance isolation"