CLINICAL AND LABORATORY STANDARDS INSTITUTE®

November 2011

EP24-A2

Assessment of the Diagnostic Accuracy of Laboratory Tests Using Receiver Operating Characteristic Curves; Approved Guideline—Second Edition

This document provides a protocol for evaluating the accuracy of a test to discriminate between two subclasses of subjects when there is some clinically relevant reason to separate them. In addition to the use of receiver operating characteristic curves and the comparison of two curves, the document emphasizes the importance of defining the question, selecting the sample group, and determining the "true" clinical state.

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

Clinical and Laboratory Standards Institute

Setting the standard for quality in medical laboratory testing around the world.

The Clinical and Laboratory Standards Institute (CLSI) is a not-for-profit membership organization that brings together the varied perspectives and expertise of the worldwide laboratory community for the advancement of a common cause: to foster excellence in laboratory medicine by developing and implementing medical laboratory standards and guidelines that help laboratories fulfill their responsibilities with efficiency, effectiveness, and global applicability.

Consensus Process

Consensus—the substantial agreement by materially affected, competent, and interested parties—is core to the development of all CLSI documents. It does not always connote unanimous agreement, but does mean that the participants in the development of a consensus document have considered and resolved all relevant objections and accept the resulting agreement.

Commenting on Documents

CLSI documents undergo periodic evaluation and modification to keep pace with advancements in technologies, procedures, methods, and protocols affecting the laboratory or health care.

CLSI's consensus process depends on experts who volunteer to serve as contributing authors and/or as participants in the reviewing and commenting process. At the end of each comment period, the committee that developed the document is obligated to review all comments, respond in writing to all substantive comments, and revise the draft document as appropriate.

Comments on published CLSI documents are equally essential, and may be submitted by anyone, at any time, on any document. All comments are managed according to the consensus process by a committee of experts.

Appeals Process

When it is believed that an objection has not been adequately considered and responded to, the process for appeals, documented in the CLSI Standards Development Policies and Processes, is followed.

All comments and responses submitted on draft and published documents are retained on file at CLSI and are available upon request.

Get Involved—Volunteer!

Do you use CLSI documents in your workplace? Do you see room for improvement? Would you like to get involved in the revision process? Or maybe you see a need to develop a new document for an emerging technology? CLSI wants to hear from you. We are always looking for volunteers. By donating your time and talents to improve the standards that affect your own work, you will play an active role in improving public health across the globe.

For additional information on committee participation or to submit comments, contact CLSI.

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

ISBN 1-56238-777-4 (Print)
ISBN 1-56238-778-2 (Electronic)
ISSN 1558-6502 (Print)
ISSN 2162-2914 (Electronic)

EP24-A2
Vol. 31 No. 23
Replaces GP10-A
Vol. 15 No. 19

Assessment of the Diagnostic Accuracy of Laboratory Tests Using Receiver Operating Characteristic Curves; Approved Guideline—Second Edition

Volume 31 Number 23

Martin H. Kroll, MD
Bipasa Biswas
Jeffrey R. Budd, PhD
Paul Durham, MA
Robert T. Gorman, PhD
Thomas E. Gwise, PhD
Abdel-Baset Halim, PharmD, PhD, DABCC
Aristides T. Hatjimihail, MD, PhD
Jørgen Hilden, MD
Kyunghee Song, PhD

Abstract

Clinical and Laboratory Standards Institute document EP24-A2—*Assessment of the Diagnostic Accuracy of Laboratory Tests Using Receiver Operating Characteristic Curves; Approved Guideline—Second Edition* provides guidance for laboratorians and manufacturers who assess clinical test accuracy. It is not a recipe; rather, it is a set of concepts to be used to design an assessment of test performance or to interpret data generated by others. In addition to the use of ROC curves and comparison of two curves, the document emphasizes the importance of defining the question, selecting a sample group, and determining the "true" clinical state. The statistical data generated can be useful whether one is considering replacing an existing test, creating or adding a new test, or eliminating a current test.

Clinical and Laboratory Standards Institute (CLSI). *Assessment of the Diagnostic Accuracy of Laboratory Tests Using Receiver Operating Characteristic Curves; Approved Guideline—Second Edition.* CLSI document EP24-A2 (ISBN 1-56238-777-4 [Print]; ISBN 1-56238-778-2 [Electronic]). Clinical and Laboratory Standards Institute, 950 West Valley Road, Suite 2500, Wayne, Pennsylvania 19087 USA, 2011.

Suggested Citation

CLSI. *Assessment of the Diagnostic Accuracy of Laboratory Tests Using Receiver Operating Characteristic Curves; Approved Guideline—Second Edition.* CLSI document EP24-A2. Wayne, PA: Clinical and Laboratory Standards Institute; 2011.

Previous Editions:
March 1987, December 1993, December 1995

Reaffirmed:
April 2016

ISBN 1-56238-777-4 (Print)
ISBN 1-56238-778-2 (Electronic)
ISSN 1558-6502 (Print)
ISSN 2162-2914 (Electronic)

Contents

Assessment of the Diagnostic Accuracy of Laboratory Tests Using Receiver Operating Characteristic Curves; Approved Guideline—Second Edition

1 Scope

This guideline outlines the steps and principles of prospectively planned and retrospective studies to evaluate the intrinsic diagnostic accuracy of a clinical laboratory test, defined as its fundamental ability to discriminate correctly among alternative states of health. It is not intended to help determine how best to use a diagnostic test in clinical practice, but instead to determine how accurate a laboratory test is in terms of diagnostic sensitivity and specificity.

Receiver operating characteristic (ROC) curve methodology arose in response to needs in electronic signal detection and problems with radar in the early 1950s.[2] It is derived from conditional probabilities, as originally formulated by Bayes.[3] This guideline aims to define ROC curves and to explain how to design, construct, interpret, and apply the information from ROC studies to evaluate diagnostic tests. For simplicity, only continuous scales, such as those typical for *in vitro* diagnostic tests, are discussed. The clinical condition that the test is intended to detect must be verifiable through some means other than the test under investigation. In other words, there must be an independent clinical reference standard against which one can compare the test. By selecting cutoffs between positive and negative diagnoses along the continuous scale of the test, the diagnostic outcomes for these decision levels are compared to the true clinical condition, which, in turn, generates the ROC curve.

This guideline will be of value to a wide variety of possible users, including:

- Investigators who are developing new tests for specific applications
- Manufacturers of reagents and devices for performing tests who are interested in assessing or validating test performance in terms of diagnostic accuracy
- Regulatory agencies interested in establishing requirements for claims related to diagnostic accuracy
- Clinical laboratorians who are reviewing data or the literature, and/or generating their own data, to make decisions about which tests to employ in their laboratories
- Health care or scientific workers interested in critical evaluation of data being presented on clinical test performance

2 Introduction

An ROC curve provides the following advantageous properties:

- It visually displays the performance of one or more diagnostic markers or tests across the entire measuring interval.
- By plotting unitless values (sensitivity vs specificity or sensitivity vs 1 − specificity), one can compare the diagnostic performance of two or more diagnostic markers or tests regardless of:
  – Units of expression of different markers or tools (eg, mg/dL, mmol/L, U/L)
  – Type of diagnostic test (eg, a clinical laboratory test, pulmonary function test, radiography)
  – Type of biological sample analyzed (eg, serum vs urine, saliva vs blood)

- It gives a clinician flexibility to select the appropriate medical decision level depending upon the medical situation and the clinical setting. (**NOTE:** In a pivotal study, selecting the optimal cutoff and evaluating the diagnostic accuracy in the same study leads to the biased estimation [overestimation] of the diagnostic accuracy. These issues are discussed in detail in the literature.[4-6])

By evaluating (or examining) ROC based on a marker, the clinician could choose a decision level offering high sensitivity but lower specificity. In another situation using this marker, the clinician could choose a different decision level offering high specificity but lower sensitivity to reduce false positives (FPs).

3 Standard Precautions

Because it is often impossible to know what isolates or specimens might be infectious, all patient and laboratory specimens are treated as infectious and handled according to "standard precautions." Standard precautions are guidelines that combine the major features of "universal precautions and body substance isolation" practices. Standard precautions cover the transmission of all known infectious agents and thus are more comprehensive than universal precautions, which are intended to apply only to transmission of blood-borne pathogens. Standard and universal precaution guidelines are available from the Centers for Disease Control and Prevention.[7] For specific precautions for preventing the laboratory transmission of all known infectious agents from laboratory instruments and materials and for recommendations for the management of exposure to all known infectious diseases, refer to CLSI document M29.[8]

4 Terminology

4.1 A Note on Terminology

CLSI, as a global leader in standardization, is firmly committed to achieving global harmonization wherever possible. Harmonization is a process of recognizing, understanding, and explaining differences while taking steps to achieve worldwide uniformity. CLSI recognizes that medical conventions in the global metrological community have evolved differently in the United States, Europe, and elsewhere; that these differences are reflected in CLSI, International Organization for Standardization (ISO), and European Committee for Standardization (CEN) documents; and that legally required use of terms, regional usage, and different consensus timelines are all important considerations in the harmonization process. In light of this, CLSI's consensus process for development and revision of standards and guidelines focuses on harmonization of terms to facilitate the global application of standards and guidelines.

Essentially, new documents are obliged to adhere to the most current version of the *International Vocabulary of Metrology – Basic and General Concepts and Associated Terms* (VIM)[9] whenever an ambiguity occurs in the interpretation or understanding of terms. In the latest edition, many definitions have become more explicit and understandable, but the language of the VIM is difficult and compact. VIM deals with general metrology and terminology that should be useful for most disciplines that measure quantities.

The understanding of a few terms has changed during the last decade as the concepts have developed. *Precision* (measurement precision) is defined as closeness of agreement between indications or measured quantity values obtained by replicate measurements on the same or similar objects under specified conditions. The term *measurand* is used when referring to the quantity intended to be measured, instead of *analyte* (component represented in the name of a measurable quantity) when its use relates to a biological fluid/matrix. Additionally, *clinical accuracy* has been changed to *diagnostic accuracy* because the term "clinical" has a regulatory connotation in Europe and elsewhere.

The Quality Management System Approach

Clinical and Laboratory Standards Institute (CLSI) subscribes to a quality management 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. The quality management system approach applies a core set of "quality system essentials" (QSEs), basic to any organization, to all operations in any health care service's path of workflow (ie, operational aspects that define how a particular product or service is provided). The QSEs provide the framework for delivery of any type of product or service, serving as a manager's guide. The QSEs are as follows:

Organization	Personnel	Process Management	Nonconforming Event Management
Customer Focus	Purchasing and Inventory	Documents and Records	Assessments
Facilities and Safety	Equipment	Information Management	Continual Improvement

EP24-A2 addresses the QSE indicated by an "X." For a description of the other documents listed in the grid, please refer to the Related CLSI Reference Materials section on the following page.

Organization	Customer Focus	Facilities and Safety	Personnel	Purchasing and Inventory	Equipment	Process Management	Documents and Records	Information Management	Nonconforming Event Management	Assessments	Continual Improvement
		M29				X C28 EP17					

Related CLSI Reference Materials*

C28-A3c **Defining, Establishing, and Verifying Reference Intervals in the Clinical Laboratory; Approved Guideline—Third Edition (2008).** This document contains guidelines for determining reference values and reference intervals for quantitative clinical laboratory tests. A CLSI-IFCC joint project.

EP17-A **Protocols for Determination of Limits of Detection and Limits of Quantitation; Approved Guideline (2004).** This document provides guidance for determining the lower limit of detection of clinical laboratory methods, for verifying claimed limits, and for the proper use and interpretation of the limits. An NCCLS-IFCC joint project.

M29-A3 **Protection of Laboratory Workers From Occupationally Acquired Infections; Approved Guideline—Third Edition (2005).** Based on US regulations, this document provides guidance on the risk of transmission of infectious agents by aerosols, droplets, blood, and body substances in a laboratory setting; specific precautions for preventing the laboratory transmission of microbial infection from laboratory instruments and materials; and recommendations for the management of exposure to infectious agents.

* CLSI documents are continually reviewed and revised through the CLSI consensus process; therefore, readers should refer to the most current editions.

CLINICAL AND LABORATORY STANDARDS INSTITUTE®

Explore the Latest Offerings From CLSI!

As we continue to set the global standard for quality in laboratory testing, we are adding products and programs to bring even more value to our members and customers.

By becoming a CLSI member, your laboratory will join 1,600+ other influential organizations all working together to further CLSI's efforts to improve health care outcomes. You can play an active role in raising global laboratory testing standards—in your laboratory, and around the world.

Find out which membership option is best for you at **www.clsi.org/membership.**

Find what your laboratory needs to succeed! CLSI U provides convenient, cost-effective continuing education and training resources to help you advance your professional development. We have a variety of easy-to-use, online educational resources that make *e*Learning stress-free and convenient for you and your staff.

See our current educational offerings at **www.clsi.org/education.**

When laboratory testing quality is critical, standards are needed and there is no time to waste. eCLIPSE™ Ultimate Access, our cloud-based online portal of the complete library of CLSI standards, makes it easy to quickly find the CLSI resources you need.

Learn more and purchase eCLIPSE at **clsi.org/eCLIPSE.**

For more information, visit www.clsi.org today.

CLINICAL AND
LABORATORY
STANDARDS
INSTITUTE®

950 West Valley Road, Suite 2500, Wayne, PA 19087 USA

P: 610.688.0100 **Toll Free (US):** 877.447.1888 **F:** 610.688.0700

E: customerservice@clsi.org **www.clsi.org**

PRINT ISBN 1-56238-777-4
ELECTRONIC ISBN 1-56238-778-2