CLINICAL AND LABORATORY STANDARDS INSTITUTE®

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H59-A

Quantitative D-dimer for the Exclusion of Venous Thromboembolic Disease; Approved Guideline

This document provides guidelines regarding the use of D-dimer in exclusion of venous thromboembolism (VTE) including a description of the value of clinical determination of the pretest probability of VTE; the proper collection and handling of the specimen; assays used for D-dimer analysis; determination of the threshold for exclusion of VTE; interpretation of test results; and aspects of regulatory and accreditation requirements.

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

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Quantitative D-dimer for the Exclusion of Venous Thromboembolic Disease; Approved Guideline

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Abstract

D-dimer is a product of fibrinolysis that is assayed in the blood. It is elevated following intravascular thrombosis, disseminated intravascular coagulation, and other conditions that can cause fibrin generation. Assay of D-dimer is a useful tool when evaluating patients with possible venous thromboembolism (VTE), as the absence of D-dimer is helpful in excluding VTE. Clinical and Laboratory Standards Institute document H59-A—*Quantitative D-dimer for the Exclusion of Venous Thromboembolic Disease; Approved Guideline* provides guidance regarding the use of D-dimer in exclusion of VTE including a description of the value of clinical determination of the pretest probability of VTE; the proper collection and handling of the specimen; assays used for D-dimer analysis; determination of the threshold for exclusion of VTE; interpretation of test results; and aspects of regulatory and accreditation requirements. The guideline is provided for use by laboratorians, manufacturers of D-dimer assays, clinicians who use the D-dimer for VTE exclusion, and accrediting and regulatory agencies.

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Foreword

Since the 1960s, clinicians have measured the products of plasmin action on fibrin, in the form of fibrin(ogen) degradation products (FDPs), as an indicator of intravascular fibrinolysis. Initial use of the FDP assay was to assist in the evaluation and monitoring of patients with disseminated intravascular coagulation (DIC). In the mid-1980s, the first monoclonal antibody-based assays for D-dimer, a specific FDP, were described, providing an assay with greater specificity for fibrin.[1] Fibrin is the basic structural molecule constituting the thrombus, and D-dimer is the smallest crosslinked degradation product of crosslinked fibrin. Because the D-dimer test is very sensitive, with the concentration being elevated whenever fibrin, formed in the vasculature, is being degraded, the test has generally replaced the assay for FDP in the clinical setting.

Many clinical conditions are associated with increased blood concentrations of D-dimer. Some of these include venous thromboembolism (VTE), arterial thrombosis (including myocardial infarction and stroke), DIC, association with recurrent thrombotic risk following anticoagulation, the postoperative state, significant liver disease, malignancy, and normal pregnancy.[2] However, the current clinical use of the D-dimer assay is primarily for the diagnosis and monitoring of DIC and for the exclusion of VTE, in particular, deep vein/venous thrombosis, and pulmonary embolism/embolus, which are the focuses of this document.

Patients who present with signs and symptoms that may be caused by VTE require evaluation to exclude or confirm the diagnosis of a thrombus. Objective confirmation is needed because venous thrombosis is not reliably diagnosed on clinical grounds alone; omission of therapy if a thrombus is missed could be life-threatening, and the administration of anticoagulant therapy also carries risk. The most reliable of such tests are imaging studies that are time-consuming and expensive to perform. Knowing that the presence of an acute intravascular thrombus is associated with fibrinolysis and elevation of D-dimer in the blood has led to the concept that below a certain threshold D-dimer may be an effective way to exclude VTE and proceed without performing the imaging studies. If effective, such an approach may, of course, provide savings in time and resources. However, there are many possible causes of elevations of the D-dimer and using the test for VTE exclusion in these settings may actually lead to imaging studies of limited value. The approach also carries the inherent risk of incorrectly excluding VTE, placing the patient at risk of thrombus growth or embolus without appropriate anticoagulation, which is a potentially life-threatening situation. Thus, the power of the D-dimer test for exclusion of VTE must be very high to provide the best protection for the patient and it is best applied only in settings where known alternative causes of elevations are not present.[3]

The development of commercial assays for D-dimer has grown rapidly, approaching 24 at the time of this writing. Considerable variability has been reported among these commercial offerings. One major source of variability is in the units reported. Quantitative D-dimer results are provided in mass units. As these assays have evolved, two different types of units of significantly different molecular weight have been used to represent D-dimer, the fibrinogen equivalent unit at 340 kDa and the D-dimer unit at 195 kDa. Adding to the complexity of reporting these values is variability in the magnitude of the units reported, eg, nanograms per milliliter, micrograms per milliliter, and micrograms per liter. This variability in both the type and magnitude of units contributes to the general inconsistency among assays performed with different methods in different laboratories, as do the differences in the specificities of the antibodies used. This inconsistency has led to confusion in some laboratories, especially when the threshold for the exclusion of VTE must be set. This issue of the type of units is not well recognized by laboratorians or clinicians and is often ignored in some publications by recognized experts in the field.

In addition to the technical issues in the analytical (examination) aspects of the test, when applied to the exclusion of VTE, the clinical evaluation of the pretest probability of VTE, specimen collection and handling, and the reporting and interpretation of results are also critical elements of the use of the test in this clinical setting.

CLSI document H59-A reviews the clinical application of the D-dimer assay for the exclusion of VTE for nonhospitalized, ambulatory patients. Use of D-dimer for the exclusion of VTE on hospitalized patients is less effective, as most of these patients have an elevated D-dimer concentration because of immobilization, surgery, or other conditions. The purpose of this document is to focus on the preanalytical, analytical, and postanalytical (preexamination, examination, and postexamination) elements of the use of the D-dimer test as it is applied to the exclusion of VTE. It addresses the evaluation of the patient in the determination of the probability of VTE; specimen collection, transport, and processing; analytical (examination) methods (measurement procedures/analytical method); reference intervals; establishment and reporting of the threshold for exclusion of VTE; and interpretation of results. It is intended to provide valuable guidance to laboratorians, clinicians, manufacturers, and regulators as the use of the D-dimer assay for the exclusion of VTE continues to evolve.

Key Words

D-dimer, deep vein/venous thrombosis (DVT), negative predictive value (NPV), pretest probability (PTP), pulmonary embolism/embolus (PE), quantitative D-dimer, threshold, thrombosis, venous thromboembolism (VTE)

Quantitative D-dimer for the Exclusion of Venous Thromboembolic Disease; Approved Guideline

1 Scope

This document provides guidelines regarding preanalytical, analytical, and postanalytical (preexamination, examination, and postexamination) elements of testing including, but not limited to:

- A description of the value of clinical determination of the pretest probability (PTP) of venous thromboembolism (VTE)
- The proper collection and handling of the specimen
- Assays used for D-dimer analysis
- Establishment of the threshold for exclusion of VTE and its interpretation related to the reference interval (RI)
- Interpretation of test results
- Aspects of regulatory and accreditation requirements

The guideline is intended for clinical laboratorians and laboratory directors, for manufacturers of the methods used to perform the test, for clinicians with an interest in the laboratory elements of the tests, and for regulatory and accrediting agencies overseeing the use of D-dimer for this purpose.

This guideline is not intended for use by patients with clinical conditions that require D-dimer evaluation. Patients reading this document are encouraged to discuss its content with their health care providers. Issues of intermethod standardization or the development of calibrators for standardization are discussed; however, guidelines regarding standardization and calibration are beyond the scope of this document. The document does not address other clinical settings in which the measurement of D-dimer may be clinically useful, including diagnosis and monitoring of overt and nonovert disseminated intravascular coagulation (DIC); risk of recurrence of VTE following the completion of anticoagulant therapy; detection of occult malignancy; staging or risk stratification of diagnosed malignancy; risk of future myocardial infarction in patients presenting with chest pain; and evaluation for subarachnoid hemorrhage.[2] Studies have demonstrated some value in the combined use of the D-dimer and ultrasonography in the exclusion of VTE. However, the focus of this document is the value of D-dimer to potentially avoid the need for imaging studies. The combined use of D-dimer with imaging studies in the evaluation of VTE is not addressed.

2 Introduction

Because of the potential to efficiently evaluate patients with VTE, many assays have been developed to measure D-dimer in the blood. The assays vary in their sensitivity to D-dimer, the type and magnitude of units used to report results, the type of specimen used, and other characteristics. Experience has uncovered a number of limitations of the test as it applies to the exclusion of VTE.

The purpose of this document, based on currently available evidence, is to provide guidelines regarding the use of the D-dimer assay for the exclusion of VTE. Elements of the clinical evaluation of the patient, specimen collection and processing, analytical (examination) methods, developments of thresholds for the exclusion of VTE, and the interpretation of results are addressed. It is important to remember that the data regarding the use of clinical PTP and the D-dimer test for exclusion were developed in the clinical setting of deep vein/venous thrombosis (DVT) and pulmonary embolism/embolus (PE). Application of these guidelines in evaluation of other thrombotic events is not recommended and may be misleading. Patients with distal DVT will have a normal D-dimer 35% of the time and the test cannot be used to avoid

ultrasound evaluation.[4] All patients with suspected distal DVT require ultrasound evaluation. D-dimer testing used in concert with lower extremity ultrasound evaluation may be helpful.

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 US Centers for Disease Control and Prevention.[5] 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.[6]

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.

To align the use of terminology in this document with that of ISO, the term *precision* is defined as the "closeness of agreement between indications or measured quantity values obtained by replicate measurements on the same or similar objects under specified conditions." As such, it cannot have a numerical value but may be determined qualitatively as high, medium, or low. For its numerical expression, the term *imprecision* is used, which is the "dispersion of independent results of measurements obtained under specified conditions." In addition, one other component of precision is defined in H59-A, *reproducibility,* which is "measurement precision (closeness of agreement between indications or measured quantity values obtained by replicate measurements on the same or similar objects under specified conditions) under reproducibility conditions of measurement (condition of measurement, out of a set of conditions that includes different locations, operators, measuring systems, and replicate measurements on the same or similar objects)."

The term *measurand* (quantity intended to be measured) is used in combination with the term *analyte* (component represented in the name of a measurable quantity) when its use relates to a biological fluid/matrix; and the term *measurement procedure* is combined with *analytical method* for a set of operations, used in the performance of particular measurements according to a given method.

4.2 Definitions

aid in diagnosis – as defined by the US Food and Drug Administration, an adjunct assay that is used in conjunction with clinical indications. The assay's threshold value has been validated and device

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 approach is based on the model presented in the most current edition of CLSI document HS01—*A Quality Management System Model for Health Care.* 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:

Documents and Records	Equipment	Information Management	Process Improvement
Organization	Purchasing and Inventory	Occurrence Management	Customer Service
Personnel	Process Control	Assessments—External and Internal	Facilities and Safety

H59-A addresses the QSEs 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.

Documents and Records	Organization	Personnel	Equipment	Purchasing and Inventory	Process Control	Information Management	Occurrence Management	Assessments–External and Internal	Process Improvement	Customer Service	Facilities and Safety
					X C28 EP05 EP07 EP12 EP15 H21 I/LA30				EP07		M29

Adapted from CLSI document HS01—*A Quality Management System Model for Health Care.*

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, CLSI document GP26—*Application of a Quality Management System Model for Laboratory Services* defines a clinical laboratory path of workflow, which consists of three sequential processes: preexamination, examination, and postexamination. All clinical laboratories follow these processes to deliver the laboratory's services, namely quality laboratory information.

H59-A addresses the clinical laboratory path of workflow steps 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.

Preexamination				**Examination**			**Postexamination**	
Examination ordering	Sample collection	Sample transport	Sample receipt/processing	Examination	Results review and follow-up	Interpretation	Results reporting and archiving	Sample management
X	X H21	X H21				X	X	X

Adapted from CLSI document HS01—*A Quality Management System Model for Health Care.*

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.

EP05-A2 **Evaluation of Precision Performance of Quantitative Measurement Methods; Approved Guideline—Second Edition (2004).** This document provides guidance for designing an experiment to evaluate the precision performance of quantitative measurement methods; recommendations on comparing the resulting precision estimates with manufacturers' precision performance claims and determining when such comparisons are valid; as well as manufacturers' guidelines for establishing claims.

EP07-A2 **Interference Testing in Clinical Chemistry; Approved Guideline—Second Edition (2005).** This document provides background information, guidance, and experimental procedures for investigating, identifying, and characterizing the effects of interfering substances on clinical chemistry test results.

EP12-A2 **User Protocol for Evaluation of Qualitative Test Performance; Approved Guideline—Second Edition (2008).** This document provides a consistent approach for protocol design and data analysis when evaluating qualitative diagnostic tests. Guidance is provided for both precision and method-comparison studies.

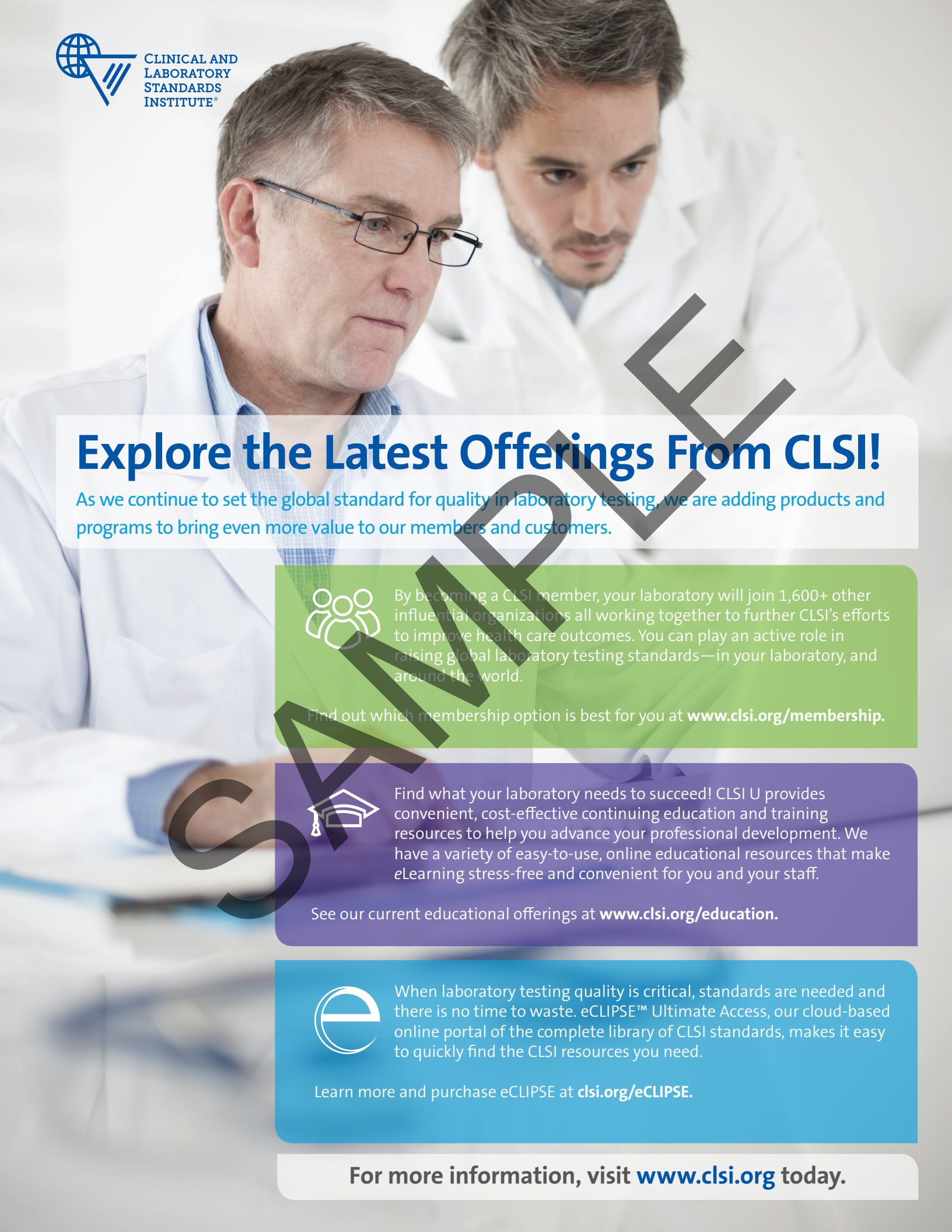
EP15-A2 **User Verification of Performance for Precision and Trueness; Approved Guideline—Second Edition (2005).** This document describes the demonstration of method precision and trueness for clinical laboratory quantitative methods utilizing a protocol designed to be completed within five working days or less.

H21-A5 **Collection, Transport, and Processing of Blood Specimens for Testing Plasma-Based Coagulation Assays and Molecular Hemostasis Assays; Approved Guideline—Fifth Edition (2008).** This document provides procedures for collecting, transporting, and storing blood; processing blood specimens; storing plasma for coagulation testing; and general recommendations for performing the tests.

I/LA30-A **Immunoassay Interference by Endogenous Antibodies; Approved Guideline (2008).** This guideline discusses the nature and causes of interfering antibodies, as well as their effects on immunoassays and mechanisms by which interference occurs. Methods to identify and characterize the interferences are addressed along with assessment of methods used to eliminate interference.

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.



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