

H60-A

Laboratory Testing for the Lupus Anticoagulant; Approved Guideline

This document provides guidance and recommendations regarding the proper collection and handling of the specimen; descriptions and limitations of screening and confirmatory assays, and mixing tests used to identify lupus anticoagulant (LA); determination of cutoff values and calculations associated with the various assays; and interpretation of test results in an LA panel.

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

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Laboratory Testing for the Lupus Anticoagulant; Approved Guideline

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Abstract

Identification of the lupus anticoagulant (LA) by laboratory testing is critical for diagnosing the antiphospholipid syndrome and investigating unexpectedly prolonged activated partial thromboplastin time values. The “anticoagulant” effect of LA is restricted to the prolongation of clotting times when using *in vitro*, clot-based coagulation assays that are used as surrogates for identifying LA. Clinical and Laboratory Standards Institute document H60—*Laboratory Testing for the Lupus Anticoagulant; Approved Guideline* provides guidance and recommendations regarding the proper collection and handling of the specimen; descriptions and limitations of screening and confirmatory assays, and mixing tests used to identify LA; determination of cutoff values and calculations associated with the various assays; and interpretation of test results in an LA panel. The guideline is provided for use by laboratorians, physician stakeholders, manufacturers of LA assays, researchers, external quality assessment programs, and accrediting and regulatory agencies. The intent of this guideline is to present information in a practical and easily understandable format; thereby facilitating a standardized approach to LA testing, gaining acceptance in practice, and improving testing quality.

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SAMPLE

Foreword

Synopsis of Diagnostic Criteria and Testing Recommendations

Criteria for the Laboratory Diagnosis of the Lupus Anticoagulant

In order to make a laboratory diagnosis of the lupus anticoagulant, a sample should identify with the following:

- A. **Procurement:** adherence to standardized protocols for collection and processing of blood to be used for testing
- B. **Screening:** prolongation of at least one of two different phospholipid-dependent clotting assays based on different principles and coagulation pathways
- C. **Confirmation:** evidence that prolongation of the screening test(s) demonstrates phospholipid dependence by using a similar second test(s) using altered concentrations and/or composition of phospholipids
- D. **Mixing:** if mixing assays are performed, evidence of inhibitory activity shown by the effect of patient plasma on an equal volume of normal pooled plasma
- E. **Exclusion:** distinguishing the lupus anticoagulant from other causes of prolonged clotting times that may mask, mimic, or coexist with the lupus anticoagulant, such as anticoagulant therapies or other coagulopathies
- F. **Interpretation and Reporting:** numerical results of all testing should be reported, and interpretive comments that address and integrate these results should be provided

Recommendations Specific to Each Criterion for the Laboratory Diagnosis of the Lupus Anticoagulant

A. Procurement

1. Testing should preferably be performed in the absence of anticoagulant therapy (except for antiplatelet therapy).
2. Ideally, samples should not be obtained from vascular access devices.
3. Platelet count of patient-citrated platelet-poor plasma should be $<10 \times 10^9/L$.
4. Testing may be performed on fresh or properly frozen/thawed samples.

B. Screening Assays

1. Two tests, representing different principles and coagulation pathways, that are known to be responsive to the lupus anticoagulant (eg, low phospholipid concentrations) should be used to screen for the lupus anticoagulant.
2. Lupus anticoagulant-responsive activated partial thromboplastin time and dilute Russell's viper venom time tests are recommended as the preferred minimal screening assays.

3. Other tests for the lupus anticoagulant referenced in this document may supplement the preferred minimal screening tests.
4. Where test design permits, results should be calculated using the mean of the reference interval and reported as a normalized ratio.
5. Routine coagulation tests, prothrombin time-international normalized ratio, activated partial thromboplastin time, and thrombin time, as indicated, may help to characterize anticoagulant effects (eg, heparin, vitamin K antagonists, direct thrombin inhibitors, factor Xa inhibitors) or sample suitability (eg, serum sample, improper anticoagulant tube) for lupus anticoagulant testing and interpretation.

C. Confirmatory Assays

1. Confirmatory assays should use the same assay principle as the screening test that was initially found to be abnormal (eg, if the dilute Russell's viper venom time test is abnormal, then a dilute Russell's viper venom time test–based confirmatory assay should be used).
2. For paired tests, results should be calculated using the mean of the reference interval for each screening and confirmatory test and reported as a normalized screen to confirm ratio or indication of percentage correction of screen ratio by confirm ratio.
3. Solid-phase immunoassays for antibodies against phospholipid (eg, anti-cardiolipin or anti- β 2 glycoprotein I) should not be considered as lupus anticoagulant confirmatory procedures.

D. Mixing Test (if performed)

1. The platelet count of the normal pooled plasma should be $< 10 \times 10^9/L$.
2. A mix ratio of one part plasma sample to one part normal pooled plasma is recommended as the preferred ratio for a mixing test.
3. The dilution effect of a 1:1 mixing test may mask lupus anticoagulant inhibitory activity. Other mix ratios (eg, four parts plasma sample to one part normal pooled plasma) can be used, if validated by the laboratory.
4. Mixing test inhibition is assessed by either comparison of normalized ratios to cutoff values specific for each lupus anticoagulant screening or confirmatory mixing test or by calculating an index of circulating anticoagulant.
5. Incubated mixing tests are not recommended for routine lupus anticoagulant testing, but should be performed when indicated (eg, when a specific factor inhibitor is suspected).

E. Exclusion

1. The lupus anticoagulant should be distinguished from anticoagulant therapies and/or other coagulation disorders that may interfere with lupus anticoagulant testing and interpretation.
2. If possible, perform factor assays whenever there is suspicion of a specific factor deficiency or inhibitor, using three or more dilutions of patient plasma and an activated partial thromboplastin time reagent that is unresponsive to the lupus anticoagulant.

F. Interpretation and Reporting

1. Numerical results of all testing should be reported with the reference interval or cutoff value.
2. Interpretive comments that address and integrate all test results (the lupus anticoagulant panel) should be provided.
3. The interpretive report should indicate whether the lupus anticoagulant is present, not detected, or indeterminate.
4. Solid-phase assays for antibodies against cardiolipin and/or anti- β 2 glycoprotein I are recommended as part of an evaluation for antiphospholipid syndrome.
5. If the lupus anticoagulant is present, the test panel should be repeated at or beyond 12 weeks to determine persistence of the lupus anticoagulant as part of the evaluation for antiphospholipid syndrome.

Key Words

Antiphospholipid syndrome, lupus anticoagulant, lupus anticoagulant confirmatory assays, lupus anticoagulant screening assays, mixing test

SAMPLE

Laboratory Testing for the Lupus Anticoagulant; Approved Guideline

1 Scope

This document provides guidance for the performance and interpretation of screening assays, confirmatory assays, and mixing tests used to identify the lupus anticoagulant (LA). It is intended to assist in standardization of LA testing and it addresses preexamination issues, examination concerns, and postexamination matters that pertain to interpretation of individual tests or combinations of assays. Recommendations from this guideline, when feasible, harmonize with other national and international guidelines currently in existence. Taken together, standardization and harmonization will permit laboratories to improve the quality and interpretation of their LA testing.

The intended users of this guideline are laboratory personnel responsible for performing LA testing, physicians (eg, hematologists, pathologists, rheumatologists), external quality assessment (EQA) programs, researchers, and manufacturers of reagents used in LA testing.

Two types of methodologies are used for the diagnosis of the antiphospholipid syndrome (APS). This guideline is limited to clot-based coagulation assays used as surrogates for identifying LA—a strong risk factor for thrombosis. The guideline will not address solid-phase testing for anti-phospholipid (aPL) (eg, anti-cardiolipin [aCL] or anti- β 2 glycoprotein I [β 2GPI]), because detection of these specific antibodies may or may not relate to the laboratory anomaly of a prolonged activated partial thromboplastin time (APTT).

2 Introduction

Identification of LA by laboratory testing is critical for investigating unexpectedly prolonged APTT values and diagnosing APS. According to recent consensus classification criteria, two conditions must be met for defining APS: 1) the **persistent** presence of circulating aPL in plasma and/or serum, and 2) a history of thrombosis and/or pregnancy morbidity including fetal loss.^{1,2} APS is an autoimmune disorder that occurs in patients who, in general, also show laboratory evidence of antibodies directed against plasma proteins that have an affinity for anionic phospholipids (PL). The dominant antigenic targets recognized by aPL in patients with APS are β 2GPI or prothrombin.³⁻⁵

The terms APS and LA are both misnomers and LA itself is a double misnomer.^{6,7} The autoantibodies associated with APS are not directed against PL in general but specifically against proteins that bind to anionic PL. LA comprises a heterogeneous group of autoantibodies that can develop in individuals with autoimmune conditions (systemic lupus erythematosus [SLE], APS, or other autoimmune disorders) or can arise spontaneously.⁸⁻¹⁰ LA can also be found transiently in plasma from patients with infections or malignancies, or from patients using certain drugs. The “anticoagulant” effect of LA is restricted to the prolongation of clotting times (competition between these antibodies and coagulation proteins for PL surfaces) in clot-based assays (ie, *in vitro*), whereas *in vivo*, these antibodies are variably associated with thrombosis.^{11,12} Persistent LA is the most important acquired risk factor for thrombosis (or its recurrence) in APS.^{8,13} LA may also cause bleeding due to immune-mediated deficiencies of coagulation factors II (FII) or X (FX) (see Section 7.1.1). Infection- or drug-induced LA tend to be transient, disappearing after the infection resolves or when the medication is discontinued. Transient LA due to infections have rarely been reported to increase thrombotic risk in association with immune-mediated protein S deficiency (see Section 7.1.1). LA due to certain medications may not be transient and can increase thrombotic risk.¹⁴ LA associated with malignancy might also resolve after the malignancy is treated.^{15,16}

Two types of laboratory testing are used in making a diagnosis of APS:

- Solid-phase assays for aCL and a β 2GPI
- Liquid-phase (plasma-based) assays for LA

Solid-phase (commonly ELISA) methods are used to identify and quantify the antibody isotypes (immunoglobulin G [IgG], immunoglobulin M [IgM], immunoglobulin A [IgA]) to β 2GPI, cardiolipin (either dependent or independent of β 2GPI), and prothrombin. These assays will not be discussed in this document.

This guideline will focus on the detection of LA activity (antibodies against β 2GPI/PL and/or antibodies against prothrombin/PL) by surrogate, functional, liquid-phase, clot-based assays. These tests are associated with all three laboratory pathways of coagulation: intrinsic, common, and extrinsic. Numerous assays have been designed through the years, as shown in Table 1. Though potentially promising, many have not been widely used or commercialized.¹⁷⁻²⁰ Commercially available assays, in general, manipulate PL concentration (or type) that permits LA to either showcase inhibitory action or to have this activity neutralized. Hence, test systems have been segregated into those having “low” levels of PL to screen or “tease out” the inhibitory action of LA vs those assays in which high concentrations of PL neutralize the inhibitory effect. Due to antibody heterogeneity, different clot-based assays can detect different antibody populations in the same patient.^{21,22} LA is considered to be more strongly associated with thrombotic risk than ELISA assays for aCL and a β 2GPI.^{8,23} A provocative concept is that this stronger association may be related to antibody titers, ie, a relatively high concentration of antibodies is required to prolong the clotting time of LA assays, which are analytically relatively insensitive.²⁴

Consensus criteria for the classification (not diagnosis) of APS were initially outlined in 1999¹ and updated in 2006.² Both documents include laboratory criteria for LA as set forth by the Scientific and Standardization Committee (SSC) on Lupus Anticoagulant/Phospholipid-Dependent Antibodies of the International Society on Thrombosis and Haemostasis (ISTH). Guidelines for LA testing from the ISTH were first published in 1983,²⁵ updated in 1991²⁶ and 1995,²⁷ and revised in 2009.²⁸ Guidelines are also available globally from various national and international organizations.^{9,29,30} Many guidelines have built upon recommendations and criteria from preceding works. This guideline seeks to continue this building process while harmonizing with, and adding clarity to, the current guidelines. This will aid laboratories in the laboratory diagnosis of LA and to assist clinicians in determining the presence of APS.

This guideline also introduces new paradigms for LA testing. The key shift is in the order in which tests are performed: screening, confirmation, and mixing. This guideline recognizes that many interferences affect the mixing test as shown in recent publications addressing the potential for false-negative or false-positive test results when significant reliance is placed on the mixing test. Therefore, this guideline suggests that less importance be assigned to the mixing test and places it last in the sequence of testing. Additionally, this guideline stresses the need for and understanding of test principles and their association with the three coagulation pathways. Thus, screening assays should not only be performed using two test principles, but each should represent a different coagulation pathway, as recommended by the document development committee. Finally, this guideline acknowledges the importance of not only performing an LA panel of tests, but interpreting LA tests in total rather than in isolation. The need for appropriate cutoff values that differentiate whether LA is or is not detected is inherent in the interpretation of LA tests. Numerous sections of this guideline strive to reinforce this point.

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

H60-A 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 page 94.

| Organization | Customer Focus | Facilities and Safety | Personnel | Purchasing and Inventory | Equipment | Process Management | Documents and Records | Information Management | Nonconforming Event Management | Assessments | Continual Improvement |
|--------------|----------------|-----------------------|-----------|--------------------------|-----------|--|-----------------------|------------------------|--------------------------------|-------------|-----------------------|
| | | GP41 M29 | | GP41 | H57 | X EP05 EP06 EP09 EP12 EP15 EP24 EP28 GP41 H21 H47 H57 | | | | H57 | |

Path of Workflow

A path of workflow is the description of the necessary processes to deliver the particular product or service that the organization or entity provides. A laboratory path of workflow consists of the sequential processes: preexamination, examination, and postexamination and their respective sequential subprocesses. All laboratories follow these processes to deliver the laboratory’s services, namely quality laboratory information.

H60-A addresses the clinical laboratory path of workflow processes 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 |
| GP41 | X GP41 H21 | X GP41 H21 | X GP41 H47 | X GP41 H47 | X GP41 H47 H57 | X | X | |



Related CLSI Reference Materials*

- 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.
- EP06-A** **Evaluation of the Linearity of Quantitative Measurement Procedures: A Statistical Approach; Approved Guideline (2003).** This document provides guidance for characterizing the linearity of a method during a method evaluation; for checking linearity as part of routine quality assurance; and for determining and stating a manufacturer's claim for linear range.
- EP09-A3** **Measurement Procedure Comparison and Bias Estimation Using Patient Samples; Approved Guideline—Third Edition (2013).** This document addresses the design of measurement procedure comparison experiments using patient samples and subsequent data analysis techniques used to determine the bias between two *in vitro* diagnostic measurement procedures.
- 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 (2006).** 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.
- EP24-A2** **Assessment of the Diagnostic Accuracy of Laboratory Tests Using Receiver Operating Characteristic Curves; Approved Guideline—Second Edition (2011).** 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.
- EP28-A3c** **Defining, Establishing, and Verifying Reference Intervals in the Clinical Laboratory; Approved Guideline—Third Edition (2010).** This document contains guidelines for determining reference values and reference intervals for quantitative clinical laboratory tests. A CLSI-IFCC joint project.
- GP41-A6** **Procedures for the Collection of Diagnostic Blood Specimens by Venipuncture; Approved Standard—Sixth Edition (2007).** This document provides procedures for the collection of diagnostic specimens by venipuncture, including line draws, blood culture collection, and venipuncture in children.
- 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.
- H47-A2** **One-Stage Prothrombin Time (PT) Test and Activated Partial Thromboplastin Time (APTT) Test; Approved Guideline—Second Edition (2008).** This document provides guidelines for performing the PT and APTT tests in the clinical laboratory, for reporting results, and for identifying sources of error.
- H57-A** **Protocol for the Evaluation, Validation, and Implementation of Coagulometers; Approved Guideline (2008).** This document provides guidance and procedures to the end user and manufacturer for the selection, evaluation, validation, and implementation of a laboratory coagulometer.
- 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.

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