

# Archived Document

This archived document is no longer being reviewed through the CLSI Consensus Document Development Process. However, this document is technically valid as of September 2023. Because of its value to the laboratory community, it is being retained in CLSI's library.



April 2011

---

## CLSI I/LA25

### Maternal Serum Screening

This document addresses the steps required to provide reliable screening and reporting using examples of serum markers currently in common use (AFP, hCG, uE3, inhibin A, PAPP-A). Emphasized is first-trimester screening, in which serum markers used are PAPP-A and hCG $\beta$ , and the main ultrasound marker is nuchal translucency. Outcome evaluation, information management, and calculation of risk are also emphasized.

---

A standard 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

500 West Valley Road, Suite 2500

Wayne, PA 19087 USA

T: +1.610.688.0100

F: +1.610.688.0700

[www.clsi.org](http://www.clsi.org)

[standard@clsi.org](mailto:standard@clsi.org)

ISBN 1-56238-749-9  
ISSN 0273-3099

I/LA25-A2  
Vol. 31 No. 8  
Replaces I/LA25-A  
Vol. 24 No. 39

---

## Maternal Serum Screening; Approved Standard—Second Edition

Volume 31 Number 8

Sanda Clejan, PhD  
Edward R. Ashwood, MD  
George Bashirians, PhD  
Sonja A. Rasmussen, MD, MS  
Jennifer A. Snyder, PhD  
Kevin Spencer, DSc, FRSC, FRCPath  
Nicholas Wald, FRS, DSc(Med), FRCP

### Abstract

Clinical and Laboratory Standards Institute document I/LA25-A2—*Maternal Serum Screening; Approved Standard—Second Edition* is written for clinical laboratorians who participate in prenatal screening for open neural tube defects and trisomy 21 (Down syndrome) involving alpha-fetoprotein (AFP), human chorionic gonadotropin (hCG), unconjugated estriol (uE3), inhibin A, and/or pregnancy-associated plasma protein-A (PAPP-A) measurements, as well as for clinicians and manufacturers who have a direct interest in the tests. First-trimester screening (including nuchal and ultrasound measurements) and integrated first- and second-trimester screening are emphasized. The standard is intended to present necessary considerations: preanalytical, analytical, and postanalytical (preexamination, examination, and postexamination); and to ensure the reliability of the tests, including the risk calculation, the outcome evaluation, and the accuracy of the information management. If properly applied, the five biochemical determinations and the risk calculations can contribute constructively to the field of prenatal screening and to the welfare of pregnant women and the fetus.

Clinical and Laboratory Standards Institute (CLSI). *Maternal Serum Screening; Approved Standard—Second Edition*. CLSI document I/LA25-A2 (ISBN 1-56238-749-9). Clinical and Laboratory Standards Institute, 950 West Valley Road, Suite 2500, Wayne, Pennsylvania 19087 USA ©2011.

The Clinical and Laboratory Standards Institute consensus process, which is the mechanism for moving a document through two or more levels of review in the health care community, is an ongoing process. Users should expect revised editions of any given document. Because rapid changes in technology may affect the procedures, methods, and protocols in a standard or guideline, users should replace outdated editions with the current editions of CLSI documents. Current editions are listed in the CLSI catalog and posted on our website at [www.clsi.org](http://www.clsi.org). If your organization is not a member and would like to become one, and to request a copy of the catalog, contact us at: Telephone: 610.688.0100; Fax: 610.688.0700; E-Mail: [customerservice@clsi.org](mailto:customerservice@clsi.org); Website: [www.clsi.org](http://www.clsi.org).



CLINICAL AND  
LABORATORY  
STANDARDS  
INSTITUTE®

Copyright ©2011 Clinical and Laboratory Standards Institute. Except as stated below, any reproduction of content from a CLSI copyrighted standard, guideline, companion product, or other material requires express written consent from CLSI. All rights reserved. Interested parties may send permission requests to [permissions@clsi.org](mailto:permissions@clsi.org).

CLSI hereby grants permission to each individual member or purchaser to make a single reproduction of this publication for use in its laboratory procedure manual at a single site. To request permission to use this publication in any other manner, e-mail [permissions@clsi.org](mailto:permissions@clsi.org).

### **Suggested Citation**

CLSI. *Maternal Serum Screening; Approved Standard—Second Edition*. CLSI document I/LA25-A2. Wayne, PA: Clinical and Laboratory Standards Institute; 2011.

### **Previous Editions:**

March 2004, December 2004

### **Reaffirmed:**

March 2013

September 2018

### **Archived:**

September 2023

ISBN 1-56238-749-9

ISSN 0273-3099

## Committee Membership

### Consensus Committee on Immunology and Ligand Assay

**Ronald J. Whitley, PhD**  
**Chairholder**

University of Kentucky Medical  
Center  
Lexington, Kentucky, USA

**Robert F. Vogt, Jr., PhD**  
**Vice-Chairholder**

Centers for Disease Control and  
Prevention  
Atlanta, Georgia, USA

Bernard C. Cook, PhD, DABCC,  
FACB  
Beckman Coulter, Inc.  
Chaska, Minnesota, USA

W. Harry Hannon, PhD  
Consultant  
Buford, Georgia, USA

Stephen M. Hewitt, MD, PhD  
National Institutes of Health, Clinical  
Center  
Bethesda, Maryland, USA

Elizabeth Sheppard, MBA,  
HT(ASCP)  
Ventana Medical Systems Inc.  
Tucson, Arizona, USA

Tom H. Stahlberg  
PerkinElmer Finland Oy  
Turku, Finland

Robert W. Veltri, PhD  
Johns Hopkins Hospital  
Baltimore, Maryland, USA

### Document Development Committee on Maternal Serum Screening

**Sanda Clejan, PhD**  
**Chairholder**

Tulane University Medical School  
New Orleans, Louisiana, USA

Edward R. Ashwood, MD  
University of Utah Medical Center/  
ARUP Laboratories  
Salt Lake City, Utah, USA

George Bashirians, PhD  
Ortho-Clinical Diagnostics, Inc.  
Rochester, New York, USA

Sonja A. Rasmussen, MD, MS  
Centers for Disease Control and  
Prevention  
Atlanta, Georgia, USA

Jennifer A. Snyder, PhD  
Siemens Healthcare Diagnostics Inc.  
Newark, Delaware, USA

Kevin Spencer, DSc, FRSC,  
FRCPath  
Barking, Havering and Redbridge  
Hospital NHS Trust  
Essex, United Kingdom

Nicholas Wald, FRS, DSc (Med)  
FRCP  
Wolfson Institute of Preventive  
Medicine  
London, England, United Kingdom

#### Staff

Control and Laboratory Standards  
Institute  
Wayne, Pennsylvania, USA

Lois M. Schmidt, DA  
*Vice President, Standards  
Development*

Ron Quicho, BS  
*Staff Liaison*

Melissa A. Lewis, ELS  
*Editorial Manager*

Megan P. Larrisey, MA  
*Assistant Editor*

Currently in preview, click buy full version

**Contents**

Abstract.....	i
Committee Membership.....	iii
Foreword.....	vii
1 Scope.....	1
2 Introduction.....	1
3 Standard Precautions.....	1
4 Terminology.....	1
4.1 A Note on Terminology.....	1
4.2 Definitions.....	2
4.3 Abbreviations and Acronyms.....	3
5 Specimen Collection.....	3
5.1 Specimen Handling and Preparation.....	4
5.2 Sample Storage and Transportation.....	4
6 Screening Markers.....	4
6.1 Human Chorionic Gonadotropin.....	5
6.2 Alpha-fetoprotein.....	8
6.3 Unconjugated Estriol.....	9
6.4 Inhibin A.....	10
6.5 Pregnancy-Associated Plasma Protein A.....	10
6.6 Nuchal Translucency.....	11
7 Maternal Serum Screening for Open Neural Tube Defects.....	13
8 Screening for Trisomy 21.....	14
8.1 Maternal Age.....	15
8.2 Previous Pregnancy Affected by Trisomy 21.....	16
8.3 <i>In Vitro</i> Fertilization.....	16
8.4 Screening Principles and Statistical Methodology.....	16
8.5 Maternal Screening Tests.....	21
8.6 Comparative Screening Performance.....	26
8.7 Refinements to Screening.....	29
9 Relationship of False-Positive Screen Test to Adverse Outcome.....	35
10 Quality Control.....	35
10.1 External Quality Control.....	36
10.2 Internal Quality Control.....	36
10.3 Screening Workload.....	38
11 Management of Women With Screen-Positive Results.....	38
11.1 Women Who Are Screen-Positive for Neural Tube Defect.....	38
11.2 Women Who Are Screen-Positive for Trisomy 21.....	38

**Contents (Continued)**

12 Incidental Detection of Edwards Syndrome (Trisomy 18) .....39  
    12.1 Identification of Trisomy 18 .....39  
13 Program Evaluation .....39  
    13.1 Reporting .....40  
References .....41  
Appendix. Amniotic Fluid Alpha-fetoprotein for Detection of Open Neural Tube Defects ..... 47  
The Quality Management System Approach .....52  
Related CLSI Reference Materials .....53

Currently in preview, click buy full version

## Foreword

This document updates, extends, and replaces I/LA25-A to provide recommendations on maternal serum screening techniques. Many new options are available since publication of I/LA25-A, including testing in the first trimester, in the second trimester, and testing that combines both the first and second trimester.

At this time, the principles of serum screening remain similar regardless of which assay(s) is/are used as part of the evaluative service. The standard addresses the steps required to provide reliable screening and reporting using examples of serum markers currently in common use (alpha-fetoprotein [AFP], human chorionic gonadotropin [hCG], unconjugated estriol [uE3], inhibin A, pregnancy-associated plasma protein-A [PAPP-A]). It is recognized that the list of assays and methods of pregnancy screening will continue to change. First-trimester screening relies on, in addition to the biochemical markers hCG $\alpha$  or hCG $\beta$  and PAPP-A, a nuchal translucency (NT) measurement that requires the expertise of experienced ultrasonographers. Outcome evaluation, information management, and risk calculation are also emphasized in this standard. Screening for trisomy 21 (Down syndrome) also includes the incidental detection of trisomy 18 (Edwards syndrome) in both the first and second trimester, along with trisomy 13 (Patau syndrome) and monosomy X (Turner syndrome) in the first trimester.

## Key Words

Alpha-fetoprotein, amniotic fluid, chromosomal abnormalities, human chorionic gonadotropin, inhibin A, monosomy X (Turner Syndrome), nuchal translucency, open neural tube defects, pregnancy-associated plasma protein A, prenatal diagnosis, trisomy 13 (Patau Syndrome), trisomy 18 (Edwards Syndrome), trisomy 21 (Down syndrome), unconjugated estriol

Currently in preview, click buy full version

# Maternal Serum Screening; Approved Standard—Second Edition

## 1 Scope

This standard specifies requirements and recommendations for maternal serum aspects of prenatal screening for neural tube defects (NTDs) and trisomy 21 (T21) (Down syndrome [DS]) and incorporates ultrasound measurements to ensure that screening methods and quality control procedures are carried out to a high standard. It offers guidance that may be used by manufacturers and clinical laboratories that provide prenatal screening services. This document also addresses the standards that should be maintained by manufacturers and by laboratories and clinicians when providing screening services used to evaluate pregnancies and risks of fetal disease.

This document intends to strike a balance between being sufficiently specific to be clear but not too prescriptive, allowing laboratory directors to use their professional judgment in setting policy.

The intended users of this standard are manufacturers, diagnostic laboratories, regulatory agencies, and public health authorities involved in providing or regulating prenatal screening services used to evaluate pregnancies and risks of fetal disease.

## 2 Introduction

Prenatal screening for serious fetal abnormalities has made significant advances since the 1970s, when maternal serum alpha-fetoprotein (MSAFP) started to be used as a screening test for open NTDs. Additional maternal serum measurements have been shown to be useful, for example, in screening for T21. Laboratories have not only had to extend the number of measurands they offer but also become proficient in risk assessment calculations based on the pattern of the results. The maternal serum screening (MSS) laboratory reports must be designed so that clinicians can inform patients of the risk of having an affected fetus.

The goal of this document is to update information on MSS for NTDs and T21, and especially introduce first-trimester and integrated screening standards.

## 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.<sup>1</sup> 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.<sup>2</sup>

## 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