

# I/LA25-A2

## Maternal Serum Screening; Approved Standard—Second Edition

This document addresses the steps required to provide reliable screening and reporting using examples of serum markers currently in common use (AFP, hCG, uE<sub>3</sub>, 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.

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## Maternal Serum Screening; Approved Standard—Second Edition

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### 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.

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## 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 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

# 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

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 focuses on harmonization of terms to facilitate the global application of standards and guidelines.

## 4.2 Definitions

**analyte** – component represented in the name of a measurable quantity (ISO 17511).<sup>3</sup>

**detection rate (DR)** – proportion of affected individuals with positive test results.

**false-positive rate (FPR)** – proportion of unaffected individuals with positive test results.

**gestational age** – time from the first day of the last menstrual period (LMP); **NOTE:** This can be determined directly by asking a woman the date of her LMP (ie, using her “dates”) or indirectly by using an ultrasound scan measurement (usually the crown-rump length [CRL] or a biparietal diameter [BPD]). Ultrasound measures that confirm the LMP provide the most accurate assessment of gestational age. Gestational age can be calculated to the day. When tabulated gestational age is grouped into “completed” weeks; so for example, 16 weeks 0 days to 16 weeks 6 days are all classified as 16 completed weeks.

**likelihood ratio (LR)** – for a population of screened individuals, this is the detection rate divided by the false-positive rate (DR/FPR). It is the number of times individuals with positive results are more likely to have the disorder for which they are being tested than individuals who have not been tested; **NOTE:** This should not be confused with the LR applicable to individuals, which is the ratio of the heights of the relative frequency distributions in affected and unaffected individuals at the value of the test result. It is the number of times an individual with that value is more likely to have the disorder for which he or she is being tested than individuals who have not been tested.

**multiple of the median (MoM)** – the value of a screening marker in unaffected pregnancies of the same gestational age measured in the same laboratory (or in the case of ultrasound measurements at the same center or by the same sonographer); **NOTE:** It is the observed marker concentration divided by the expected concentration where the expected is the median. The median is often calculated using measurements from all pregnancies (not just unaffected pregnancies); this makes little or no difference to estimating the MoM value because affected pregnancies are rare and, therefore, have little or no influence on the median. The MoM allows for the change in concentrations of the serum markers with gestation and from center to center.

**odds of being affected given a positive result (OAPR)** – ratio of the number of affected to unaffected individuals among those with positive test results, ie, ratio of true-positives to false-positives.

**positive predictive value** – probability of being affected given a positive result expressed as a proportion or percentage, ie, the number of true-positives divided by the total number of positives (true and false).

**sensitivity** – synonym of detection rate; **NOTE:** An advantage of the term detection rate over sensitivity is that it avoids confusion because sensitivity has a different meaning in analytical biochemistry. In cancer screening, the cancer “detection rate” can have a different meaning, namely the prevalence of detected cancers at a screening examination, perhaps better described as the screen-positive cancer prevalence instead of the proportion of all individuals with cancer who have positive results.

**specificity** – proportion of unaffected individuals with a negative test result; **NOTE:** It is the complement of the false-positive rate, ie, the false-positive rate, expressed as a percentage subtracted from 100%.

## 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 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 Organization Personnel	Equipment Purchasing and Inventory Process Control	Information Management Occurrence Management Assessments—External and Internal	Process Improvement Customer Service Facilities and Safety
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I/LA25-A2 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 C24 EP09			X	X		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.

I/LA25-A2 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	X	X	X	X		

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

## Related CLSI Reference Materials\*

- C24-A3**      **Statistical Quality Control for Quantitative Measurement Procedures: Principles and Definitions; Approved Guideline—Third Edition (2006).** This guideline provides definitions of analytical intervals, planning of quality control procedures, and guidance for quality control applications.
- EP09-A2-IR**      **Method Comparison and Bias Estimation Using Patient Samples; Approved Guideline—Second Edition (Interim Revision) (2010).** This document addresses procedures for determining the bias between two clinical methods, and for the design of a method comparison experiment using split patient samples and data analysis.
- 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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