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NBS04-A

Newborn Screening by Tandem Mass Spectrometry; Approved Guideline

This guideline serves as a reference source for the numerous activities related to operating a tandem mass spectrometry laboratory as part of public and private newborn screening programs with the goal of creating greater test accuracy, performance, and consistency among laboratories, thereby ensuring data quality that will ultimately benefit all newborns worldwide.

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

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

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Newborn Screening by Tandem Mass Spectrometry; Approved Guideline

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Abstract

Clinical and Laboratory Standards Institute document NBS04-A—*Newborn Screening by Tandem Mass Spectrometry; Approved Guideline* provides guidance on specimen and reagent preparation, instrument and analyte calibration, method validation, quality assurance and control, run acceptance criteria with multianalyte platforms, external treatment effects on test results (eg, transfusions and total parenteral nutrition [TPN]), result interpretation and reporting, follow-up recommendations, and the use of tandem mass spectrometry (MS/MS) for second-tier testing. This document describes the best practice procedures.

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Foreword

Nearly 10 million newborns worldwide are screened annually for metabolic and genetic disorders. The goal of these tests is that they will lead to an early diagnosis and treatment that will likely prevent or reduce the severe medical outcomes that occur in untreated infants. The number of disorders screened from a newborn's dried blood spot (DBS) specimen has increased significantly in the last two decades. The essential methods for detection of fatty acylcarnitines and amino acids from DBSs using tandem mass spectrometry (MS/MS) were developed in the early 1990s and put into clinical practice by private and academic laboratories in the mid-1990s. By the year 2000, MS/MS analysis of these metabolites was adopted for use in three public health laboratories in the United States. It has now expanded to almost all screening programs worldwide. The number of disorders detectable by MS/MS depends on how the analysis is performed. In its original configuration, the method could detect more than 60 biomarkers. Each biomarker could indicate one or more disorders. The exact number of disorders that are reported is often debated because it relies on the number of metabolites measured, interpretation of data, and public policy. In 2004, the American College of Medical Genetics (ACMG) made an official statement that suggested that of the 54 disorders currently available for screening, 35 are detected through the use of MS/MS.

MS/MS is a fundamentally different technology than systems previously used by most newborn screening laboratories. It is a versatile and somewhat complex system that can be easily adapted to the users' preferred testing approach. This has led to numerous variations of newborn screening by MS/MS, and it became a challenge to compare results between laboratories. There is a recognized need to develop consensus solutions to provide more consistency between MS/MS screening programs. There have been numerous workshops, training courses, and publications over the last few years,[1] with many methodological issues remaining unresolved. Variations to the original method include specimen and reagent preparation, instrument and analyte calibration, method validation, quality assurance and control, run acceptance criteria with multianalyte platforms, external treatment effects on test results (eg, transfusions and total parenteral nutrition [TPN]), result interpretation and reporting, and follow-up recommendations. In addition to MS/MS being used as the primary screening method, the use of this technology as a second-tier test has been introduced to improve the sensitivity and specificity of other newborn screening tests. A consensus document developed by experts in the use of MS/MS in newborn screening will ensure that babies tested using MS/MS have the opportunity to get equivalent screening services throughout the world.

Efforts have been made to reach consensus among a representative group of stakeholders, as they seek to describe practices for the use of MS/MS for newborn screening purposes. It is anticipated that these guidelines will require periodic review and update as advances in methodologies and instrumentation occur. Public comment to review and update these guidelines is invited.

Key Words

Acylcarnitines, amino acids, cutoffs, dried blood spot, method validation, multiplex assay, newborn screening, quality assurance, quality control, result interpretation and reporting, tandem mass spectrometry

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1 Scope

This document is designed to assist newborn screening laboratory personnel in the routine use of tandem mass spectrometry (MS/MS) for the detection of metabolites that may indicate certain metabolic disorders using dried blood spot (DBS) specimens. The document describes the preparation procedures for reagents, specimens, standards, and controls; calibration (both instrument and analyte); standardization; control acceptance criteria; disorder profiles (interpretation of MS/MS spectra); external effects on results (eg, transfusion and total parenteral nutrition [TPN]); result reporting; and follow-up recommendations.

2 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 (CDC).[2] 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.[3]

3 Terminology

3.1 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.

All terms and definitions will be reviewed again for consistency with international use, and revised appropriately during the next scheduled revision of this document.