CLINICAL AND LABORATORY STANDARDS INSTITUTE®

1st Edition

CLSI NBS14™

Newborn Screening for Lysosomal Diseases

CLSI NBS14 describes a newborn screening system for identifying presymptomatic newborns that are at an increased risk for lysosomal diseases (LDs), with the goal of early diagnosis and treatment to reduce morbidity and mortality. The list of diseases includes acid sphingomyelinase deficiency, Fabry disease, Gaucher disease, Krabbe disease, metachromatic leukodystrophy, mucopolysaccharidosis type I, mucopolysaccharidosis type II, and Pompe disease. It discusses biological and clinical features of the diseases, the screening tests performed on newborn dried blood spot specimens, screening strategies, and the short-term and long-term follow-up for each of the LDs.

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

CLSI NBS14-Ed1
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Replaces CLSI NBS07-Ed1

Newborn Screening for Lysosomal Diseases

Joseph Orsini, PhD
Patricia L. Hall, PhD
Henry Akinbi, MD
Rejwi Dahal, PhD
Andy De Souza, PhD
Taraka Donti, PhD
M. Christine Dorley, PhD
Ralph Fingerhut, PhD
Maria Fuller, PhD
Jaya Ganesh, MD
Uttam Garg, PhD
Mamta Goswami, PhD
Anu Kiviniemi, PhD
Tracy Klug, BS
Gwendolyn McKee, MBA, MLS
Jamie Mills, MLS
Michelle Mills, MS
Jodi Philippon, RN, BSN
Katie Sapp, MS
Jon Washburn, MS
Tim Wood, PhD

Abstract

CLSI NBS14—*Newborn Screening for Lysosomal Diseases* describes the currently available laboratory tests used to screen for 8 lysosomal diseases (LDs), which include measuring the enzyme activity for 7 LDs (acid sphingomyelinase deficiency, Fabry disease, Gaucher disease, Krabbe disease, mucopolysaccharidosis type I, mucopolysaccharidosis type II, and Pompe disease) and the concentrations of biochemical markers used in first-tier screening for metachromatic leukodystrophy. All of these LDs are inborn errors of metabolism characterized by the accumulation of substrates in excess in various organs' cells because of the defective functioning of the lysosomes. Variants in the associated gene for each disease cause the associated enzyme deficiency. Early detection of these diseases is critical for the associated therapy to be effective. For many of these diseases, there are second-tier biochemical and genetic approaches to reducing false-positive screens; these are discussed, along with an overview of the laboratory operations that detail the instrumentation, assay protocols, automated methodologies, information on validations, and implementation of routine screening.

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Foreword

In 2001, it was demonstrated that enzyme function assays using fluorescent substrates could be applied to dried blood spot specimens to identify mucopolysaccharidosis type I (MPS I) and Fabry disease (FD). This discovery led to newborn screening (NBS) for lysosomal diseases (LDs). Since then, multiple approaches to NBS have been reported with varied LD panels and methodologies. Currently, the US Department of Health and Human Services includes 4 LDs on the Recommended Uniform Screening Panel (RUSP) core conditions. In 2015, Pompe disease (PD) was the first to be added to the RUSP, then in 2016, MPS I was added, followed by mucopolysaccharidosis type II (MPS II) in 2022. In 2024, infantile Krabbe disease (KD) was added to the RUSP.

There are many states in the United States and at least 4 other countries[1-4] performing NBS for at least 1 of 7 LDs (acid sphingomyelinase deficiency [ASMD], FD, Gaucher disease [GD], KD, MPS I, MPS II, and PD), so there is a global need for an NBS guideline for LDs. CLSI NBS07 provided information on incorporating PD into the operations of existing NBS programs. There are no published guidelines for NBS for any of the other LDs, and there are methods published to improve the selectivity of screening for LDs, which include methods to reduce false-positive results through multienzyme analytical and second-tier biochemical and genetic approaches. CLSI NBS14 includes information on these and updated approaches to screen for LDs. Additionally, disease-specific information, such as the associated gene and affected enzyme, prevalence, screening approaches, diagnosis requirements, and therapies, is included.

Overview of Changes

CLSI NBS14-Ed1 replaces CLSI NBS07-Ed1, published in 2017. Several changes were made in this edition, including:

- Adding discussions for diseases, including ASMD, FD, GD, KD, metachromatic leukodystrophy (MLD), MPS I, and MPS II
- Adding methodologies for second-tier testing and molecular analysis of targeted genes
- Adding details regarding multiplexing targeted assays
- Expanding the scope beyond first-tier enzyme testing with sulfatide analysis for MLD

NOTE: The content of CLSI NBS14 is supported by the CLSI consensus process and does not necessarily reflect the views of any single individual or organization.

KEY WORDS

dried blood spot
fluorometry
follow-up
liquid chromatography
lysosomal disease
newborn screening
tandem mass spectrometry

Chapter 1

Introduction

Newborn Screening for Lysosomal Diseases

1 Introduction

1.1 Scope

CLSI NBS14 discusses the detection of multiple lysosomal diseases (LDs) by population-based dried blood spot (DBS) newborn screening (NBS). The list of diseases included is acid sphingomyelinase deficiency (ASMD), which is historically known as Niemann-Pick disease types A, A/B, and B; Fabry disease (FD); Gaucher disease (GD); Krabbe disease (KD); metachromatic leukodystrophy (MLD); mucopolysaccharidosis type I (MPS I); mucopolysaccharidosis type II (MPS II); and Pompe disease (PD). A liquid chromatography-tandem mass spectrometry (LC-MS/MS) assay can screen for other LDs that are not included in CLSI NBS14.[5] CLSI NBS14 focuses on multitiered assays, which primarily start with a first-tier enzyme assay followed by a second-tier biochemical assay; this approach is used to detect all LDs except MLD. For MLD, an opposite approach is used that includes a first-tier biochemical assay followed by a second-tier enzyme assay. CLSI NBS14 provides information for incorporating LD DBS into the routine operations of existing NBS programs.

Also included in CLSI NBS14 is background information on the biological and clinical features of all listed LDs, detailed descriptions of the different first-tier enzyme activity assays currently in use, and the preanalytical, analytical, and the postanalytical laboratory practices used in screening for these diseases. Finally, a discussion of short- and long-term follow-up (STFU and LTFU) procedures, including case tracking, as well as the diagnostic tests needed to confirm a diagnosis for each of the diseases is included.

The intended users of CLSI NBS14 are:

- NBS laboratory personnel
- Public health program personnel
- Follow-up program personnel
- Health care providers (HCPs) and professionals, such as pediatric endocrinologists, neonatologists, hematologists, pediatric neurologists, pediatric bone marrow transplant specialists, and geneticists, who are involved with the oversight of NBS testing
- Manufacturers of NBS instruments, reagents, and related products
- Birthing facility personnel
- Medical laboratory personnel
- Regulatory agencies
- Public health policy makers

CLSI NBS14 does not cover:

- DBS specimen collection for LD DBS NBS (see CLSI NBS01[6])
- Immunoreactive assays for LD detection[7] because the reagents are not generally available
- Method performance comparisons of assays currently used for LD DBS NBS

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