CLINICAL AND LABORATORY STANDARDS INSTITUTE®

1st Edition

CLSI NBS12™

Newborn Screening for Galactosemias

CLSI NBS12 describes a newborn screening (NBS) system for identifying presymptomatic newborns at increased risk for 1 or more of the galactosemias, enabling early detection, diagnosis, and the rapid treatment needed to prevent acute morbidity and mortality. CLSI NBS12 discusses biological and clinical features of classic galactosemia, which is a primary target of most NBS programs, and explains the assays used for screening tests performed on newborn dried blood spot specimens, screening strategies, and short-term and long-term follow-up. Different forms of galactosemia that can also be identified by some NBS program approaches are briefly described.

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

NBS12-Ed1
May 2026

Newborn Screening for Galactosemias

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Abstract

CLSI NBS12—*Newborn Screening for Galactosemias* describes newborn screening (NBS) strategies and methods used worldwide to identify newborns at increased risk for classic galactosemia (CG) and in some cases variant forms of galactosemia. CG is a potentially lethal autosomal recessive disease that results from profound deficiency of galactose-1-phosphate uridylyltransferase (GALT), the middle enzyme of the Leloir pathway of galactose metabolism. Variant forms of galactosemia result either from partial deficiency of GALT (eg, Duarte galactosemia) or from deficiency of other enzymes important for the efficient metabolism of galactose (eg, galactokinase, UDP-galactose 4'-epimerase, or galactose mutarotase). The birth prevalence of CG varies broadly by ancestral group; in diverse populations, such as in the United States, CG affects approximately 1 in 50 000 newborns screened at birth. Most newborns with CG are born appearing apparently healthy but present with rapidly escalating and potentially lethal acute symptoms following exposure to milk, which contains abundant galactose. Early, often presymptomatic identification of CG by NBS can be lifesaving as it enables immediate dietary restriction of galactose, preventing or resolving the acute symptoms of disease. CLSI NBS12 describes the laboratory screening tests used to detect CG, as well as the various screening algorithms in use, explaining the benefits and limitations of each. CLSI NBS12 also explains which tests and algorithms enable or exclude detection of the different variant forms of galactosemia that might or might not be targets of NBS. CLSI NBS12 is intended for use by health care providers; birthing facilities; follow-up and program personnel; public health program administrators; medical laboratories; pediatric endocrinologists; neonatologists; geneticists; NBS laboratories; regulatory agencies; public health policymakers; and manufacturers of instruments, reagents, and related NBS products.

CLSI. *Newborn Screening for Galactosemias*. 1st ed. CLSI guideline NBS12 (ISBN 978-1-68440-319-6 [Print]; ISBN 978-1-68440-320-2 [Electronic]). Clinical and Laboratory Standards Institute, USA, 2026.

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Suggested Citation

CLSI. *Newborn Screening for Galactosemias*. 1st ed. CLSI guideline NBS12. Clinical and Laboratory Standards Institute; 2026.

CLSI NBS12-Ed1

ISBN 978-1-68440-319-6 (Print)

ISBN 978-1-68440-320-2 (Electronic)

ISSN 1558-6502 (Print)

ISSN 2162-2914 (Electronic)

Volume 46, Number 9

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Foreword

The goal of newborn screening (NBS) is presymptomatic detection of at-risk newborns affected by a target disease, so that appropriate intervention(s) can be implemented for the benefit of the child. The organization of NBS programs features a comprehensive system of care that includes preanalytical, analytical, and postanalytical activities. Specifically, these activities include education, collection and transport of dried blood spot (DBS) specimens for analysis in specialized NBS laboratories, results reporting, linkage to clinical care (ie, short-term follow-up), confirmatory diagnosis, management, programmatic evaluation including clinical outcomes, QA, and quality improvement.

Classic galactosemia (CG) is among the most prevalent metabolic diseases identified by NBS in some populations. Early identification of CG enables lifesaving intervention in the form of dietary restriction of galactose, generally achieved by switching the newborn from breast milk or a milk-based formula to a low-galactose formula, such as soy-based formula. In the past 50 years or more, many countries have implemented highly effective NBS for CG based on analysis of galactose-1-phosphate uridylyltransferase enzyme activity and/or galactose metabolite levels in DBS.

CLSI NBS12 provides recommendations on methodology considerations for screening. In different NBS laboratories, technology selection might be complicated by regulatory considerations, realities of the conditions of specimen collection and transport, reagent availability, and the need to include other diseases in a combined first-tier screening. On a practical level, the platform choice also depends on factors such as local funding, internal capabilities and expertise, differences in diseases included or added to NBS programs' screening panels, and current and future test methods. CLSI NBS12 suggests specifics about factors to be considered in setting up or revising a program for galactosemia NBS. Once a decision has been made, CLSI NBS12 provides the user with essential information for implementing newborn DBS screening for galactosemia.

NOTE: The content of CLSI NBS12 is supported by the CLSI consensus process and does not necessarily reflect the views of any single individual or organization.

KEY WORDS

algorithm

analytical

galactose

galactosemia

postanalytical

preanalytical

Chapter 1

Introduction

Newborn Screening for Galactosemias

1 Introduction

1.1 Scope

CLSI NBS12 specifies recommendations for newborn screening (NBS) for galactosemias and routine use of dried blood spot (DBS) specimens for identifying potentially affected newborns. CLSI NBS12 also discusses the preanalytical, analytical, and postanalytical activities of existing NBS for galactosemias, including short-term follow-up (STFU) and long-term follow-up (LTFU) considerations.

CLSI NBS12 includes background information on the biological and clinical features of classic galactosemia (CG), a disease of carbohydrate metabolism that is often a primary target of NBS, and to a lesser extent of variant forms of galactosemia, that might or might not be targets or secondary findings for different NBS programs. It provides descriptions of the different methodologies and screening algorithms and discusses preanalytical, analytical, and postanalytical issues for laboratory practices. Also, CLSI NBS12 includes a discussion of STFU and LTFU procedures, including case tracking, as well as the diagnostic tests needed to confirm a CG diagnosis.

The intended users of CLSI NBS12 are NBS laboratories; follow-up and program personnel; birthing facilities; public health program administrators; medical laboratories; pediatric endocrinologists; neonatologists; geneticists; other health care providers (HCPs); regulatory agencies; public health policymakers; and manufacturers of instruments, reagents, and related NBS products.

CLSI NBS12 does not cover:

- Laboratory testing performed to confirm or exclude a diagnosis (ie, diagnostic testing)
- Detailed recommendations for diagnosis, treatment, or LTFU care of CG
- Comparative cost information

1.2 Background

Newborns with CG can appear healthy at birth and yet can experience potentially lethal symptoms within days to weeks following exposure to breast milk or a dairy milk–based formula. As such, CG is a time-critical disease.[1] Early, often presymptomatic, detection enables rapid and continued dietary restriction of galactose, which can prevent or resolve the acute sequelae that would otherwise occur.[2] NBS is therefore essential to the survival of most newborns with CG. Many HCPs might not recognize the symptoms of CG and make the diagnosis quickly enough to save the newborn's life. NBS for galactosemia began in the mid-1960s but was not included in all US NBS programs until 2004.[3] The time frame of implementing NBS for CG in many other countries is similar, although, worldwide, as of 2015 close to two-thirds of all babies were born into communities that did not have the benefit of NBS.[4,5] One reason some regions do not yet include CG in their NBS programs is that the age at specimen collection (> 72 hours) might be too late to identify affected newborns before serious symptoms develop; however, later detection can still be beneficial because the baby might be asymptomatic or, if symptomatic, the correct diagnosis might not yet have been reached.[6]

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PRINT ISBN 978-1-68440-319-6

ELECTRONIC ISBN 978-1-68440-320-2

CLSI NBS12-Ed1