CLINICAL AND LABORATORY STANDARDS INSTITUTE®

2nd Edition

NBS05

Newborn Screening for Cystic Fibrosis

This guideline describes newborn screening laboratory tests for detecting analytes and genetic markers associated with cystic fibrosis (CF). It includes both the first-tier and second-tier screening tests performed on newborn dried blood spot specimens, as well as the screening strategies for identifying newborns at increased risk for developing CF.

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

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NBS05, 2nd ed.
December 2019
Replaces NBS05-A

Newborn Screening for Cystic Fibrosis

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Abstract

Clinical and Laboratory Standards Institute guideline NBS05—*Newborn Screening for Cystic Fibrosis* describes newborn screening (NBS) laboratory tests and screening strategies used worldwide to identify newborns at increased risk of developing cystic fibrosis (CF). CF is a common genetic disorder caused by variants in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene. Presymptomatic detection through NBS leads to early diagnosis and improves the outcomes of babies with CF. This guideline describes comprehensively the laboratory tests for detecting CF risk among newborns as well as recommendations for follow-up evaluation. It describes the use of immunoreactive trypsinogen assays and second-tier NBS testing, including DNA analysis for detecting specific *CFTR* variants and pancreatitis-associated protein assays. A core panel of *CFTR* variants for routine testing is discussed with guidance included on NBS program considerations for core panel expansion. This guideline is intended for use by NBS laboratory, follow-up, and program personnel; public health program administrators; medical laboratories; CF center personnel and organizations responsible for CF center networks; health care providers (eg, primary care providers, neonatologists, pediatricians, disease specialists); regulatory agencies; public health policy makers; and manufacturers of instruments, reagents, and related products for NBS testing.

Clinical and Laboratory Standards Institute (CLSI). *Newborn Screening for Cystic Fibrosis.* 2nd ed. CLSI guideline NBS05 (ISBN 978-1-68440-064-5 [Print]; ISBN 978-1-68440-065-2 [Electronic]). Clinical and Laboratory Standards Institute, 950 West Valley Road, Suite 2500, Wayne, Pennsylvania 19087 USA, 2019.

CLINICAL AND LABORATORY STANDARDS INSTITUTE®

Suggested Citation

CLSI. *Newborn Screening for Cystic Fibrosis.* 2nd ed. CLSI guideline NBS05. Wayne, PA: Clinical and Laboratory Standards Institute; 2019.

Previous Edition:
November 2011

ISBN 978-1-68440-064-5 (Print)
ISBN 978-1-68440-065-2 (Electronic)
ISSN 1558-6502 (Print)
ISSN 2162-2914 (Electronic) Volume 39, Number 14

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Acknowledgment for the Expert Panel on Newborn Screening

CLSI, the Consensus Council, and the Document Development Committee on Newborn Screening for Cystic Fibrosis gratefully acknowledge the Expert Panel on Newborn Screening for serving as technical advisors and subject matter experts during the revision of this guideline.

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Foreword

Newborn screening (NBS) is a highly effective public health program that saves or improves the lives of thousands of babies every year.[1] NBS programs are organized, population-based public health services applying preventive medicine principles in defined regions to reduce morbidity and mortality from certain congenital disorders. NBS programs are part of NBS systems that include birthing facilities, public health programs, health care providers, and families. NBS's goal is presymptomatic detection of at-risk newborns through screening platforms for newborn dried blood spot (DBS) specimens that are analyzed in specialized NBS laboratories, newborn hearing screening, and cyanotic congenital heart disease screening. NBS programs are linked to medical follow-up programs for diagnosis and rapid initiation of specialized therapies. The organization of NBS programs features a system of care that includes preanalytical, analytical, and postanalytical activities. They include education, collection of DBS specimens, laboratory analysis, result reporting, linkage to clinical care (short-term follow-up), diagnosis, management, programmatic evaluation, evaluation of clinical outcomes (including long-term follow-up), QA, and quality improvement.

Cystic fibrosis (CF) is a common genetic disorder caused by genetic variants in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene. These variants result in defective chloride transport. Affected children develop a life-threatening chronic disease with digestive defects leading to severe malnutrition and respiratory tract abnormalities that are associated with recurrent bronchopulmonary infections and persistent cough. Detecting newborns at risk for CF by identifying increased immunoreactive trypsinogen (IRT) concentrations in DBS specimens (often followed by DNA analysis of variants in the CF gene) provides an opportunity for presymptomatic detection before irreversible pathology develops.

This guideline describes newborn DBS screening algorithms for CF using IRT assays alone or, most commonly, in combination with second-tier DNA testing for detecting specific *CFTR* variants. CF NBS algorithms are among the first NBS models incorporating DNA technologies. Variations in the IRT/DNA method, including the use of pancreatitis-associated protein (PAP) testing after IRT testing, are also summarized with explanations of their advantages and disadvantages.

Despite its widespread use since rapid implementation began in 2005, CF NBS is complicated by several challenges and controversies regarding laboratory science and public health applications that have resulted in NBS programs adopting diverse approaches.[2] Implementing NBS for CF provides new opportunities for enhanced care, education, and research. However, the multitude of methodologies has highlighted the need for quality improvement and QA. For example, a variety of methods are used for reaching decisions regarding IRT concentrations cutoff values for in-range results and out-of-range results. In addition, given that over 2000 *CFTR* variants have been reported, some debate exists about which *CFTR* panels should be used for IRT/DNA NBS strategies. This consensus guideline on CF NBS provides a global resource for NBS programs to evaluate and refine their current procedures and practices for all aspects of the CF NBS system, including the challenging follow-up components of sweat chloride testing and genetic counseling.

Overview of Changes

This guideline replaces the previous edition of the approved guideline, NBS05-A, published in 2011. Several changes were made in this edition, including:

- Reassessed IRT cutoff value guidelines and discussed the use of a floating rather than fixed cutoff value
- Revised recommendations regarding *CFTR* variant panels based on the most current information, including new biotechnologies such as next-generation sequencing

- Assessed using PAP for detecting newborns at risk for CF
- Discussed communication strategies related to detecting CF heterozygote newborns and providing genetic counseling
- Reviewed emerging issues related to using genetic and genomic sequencing in NBS
- Described the existing CF NBS algorithms

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

Key Words

Cystic fibrosis, cystic fibrosis transmembrane conductance regulator gene, DNA analysis, genetic counseling, immunoreactive trypsinogen, newborn dried blood spot screening, pancreatitis associated protein, quality assurance, sensitivity, variants

Newborn Screening for Cystic Fibrosis

Chapter 1: Introduction

This chapter includes:

- Guideline's scope and applicable exclusions
- Standard precautions information
- "Note on Terminology" that highlights particular use and/or variation in use of terms and/or definitions
- Terms and definitions used in the guideline
- Abbreviations and acronyms used in the guideline

1.1 Scope

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

This guideline describes:

- Screening methodologies for immunoreactive trypsinogen (IRT), pancreatitis-associated protein (PAP), and cystic fibrosis transmembrane conductance regulator (*CFTR*) gene variant analysis
- Screening algorithms currently used, including the use of IRT assays alone or in combination with DNA analysis for detecting specific *CFTR* variants through second-tier NBS with the IRT/DNA strategy
- Variations in the IRT/DNA strategy, including the use of PAP testing after IRT testing, with explanations of their advantages and disadvantages
- Selecting *CFTR* variant panels that enable equal detection of CF in all populations within the screening jurisdiction
- Reporting results
- Roles and responsibilities during STFU through diagnosis

This guideline recommends the use of *CFTR* variant panels in CF NBS algorithms when resources allow. The intended users of this guideline are NBS laboratory, follow-up, and program personnel; public health program administrators; medical laboratories; CF center personnel and organizations responsible for CF center networks; health care providers (HCPs) (eg, primary care providers, neonatologists, pediatricians); regulatory agencies; public health policy makers; and manufacturers of instruments, reagents, and related products used for NBS testing.