CLINICAL AND LABORATORY STANDARDS INSTITUTE®

2nd Edition

CLSI NBS06™

Newborn Screening for Severe Combined Immunodeficiency and Other Related Severe T-cell and B-cell Immunodeficiencies

CLSI NBS06 discusses the detection of severe combined immunodeficiency by population-based newborn screening using dried blood spot specimens to measure T-cell receptor excision circles. The relevance, clinical utility, and feasibility of using κ-deleting recombination excision circles are also discussed.

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

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Newborn Screening for Severe Combined Immunodeficiency and Other Related Severe T-cell and B-cell Immunodeficiencies

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Abstract

CLSI NBS06—*Newborn Screening for Severe Combined Immunodeficiency and Other Related Severe T-cell and B-cell Immunodeficiencies* provides an update on newborn screening (NBS) for severe combined immunodeficiencies (SCID). It discusses the importance of harmonizing T-cell receptor excision circle cutoffs and reporting in NBS of infants with SCID and non-SCID severe T-cell lymphopenia. CLSI NBS06 also discusses the relevance of NBS for severe B-cell deficiencies using κ-deleting recombination excision circles as a biomarker in dried blood spots. CLSI NBS06 is written in the context of a decade of SCID NBS testing in the United States and global implementation in several regions and countries.

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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. NBS programs are organized, population-based, public health services that apply preventive medicine principles in defined regions to reduce morbidity and mortality from certain congenital diseases. Severe combined immunodeficiency (SCID) is a disease that, without early diagnosis, is uniformly lethal. The use of a public health tool, such as NBS, has significantly affected the lives of newborns with SCID globally.[1] Most babies with SCID are asymptomatic at birth and, without SCID NBS, are usually diagnosed with opportunistic or other fulminant infections and failure to thrive between 4 and 6 months of age.

SCID includes numerous genetic defects characterized by severe T-cell lymphopenia, along with quantitative and functional deficits in 1 or more of the other lymphocyte subsets (ie, B cells and natural killer cells) and meets the criteria to be added to the NBS program. These criteria include a lag phase in diagnosis (asymptomatic in the newborn), availability of sensitive biomarkers (eg, T-cell receptor excision circles [TREC] and κ-deleting recombination excision circles [KREC], the latter being a marker for severe B-cell immunodeficiency), and definitive treatment in the form of hematopoietic cell transplantation (HCT) and gene therapy. The use of NBS to detect SCID and other T-cell defects caused by athymia began in 2008 with the first population-based application of the TREC assay in an NBS public-health program.[2,3] In 2010, SCID NBS was added to the US Recommended Uniform Screening Panel (RUSP),[4] and related T-cell lymphocyte deficiencies were added to the list of secondary targets.[5] TREC-based NBS for SCID has revolutionized the diagnosis, management, and early intervention in babies with SCID. The early diagnosis of SCID through NBS enables identification of affected babies before they develop life-threatening infections and allows rapid institution of prophylactic therapies (eg, replacement immunoglobulin, antibiotics, enzyme replacement), avoidance of live vaccines, and definitive treatment with either HCT, thymus implantation, or gene therapy.

Since 2013, several advances have been made in the field of NBS for SCID, including implementation by all 50 US states, as well as adoption in several other countries and regions. Although the widespread acceptance and implementation of TREC-based NBS for SCID represents a significant public health success, considerable heterogeneity still exists in the reporting, interpretation, and application of TREC results and subsequent follow-up. This heterogeneity has been raised as a concern by clinicians caring for babies with SCID around the world, and is an area where future advocacy efforts can be directed to improve the outcomes of babies diagnosed with SCID through TREC-based NBS. Recently, there have been efforts to improve the nomenclature associated with NBS for SCID, and this represents the first step of using a consensus approach to resolve the above-mentioned variability.[6,7] In addition, although certain countries and regions have incorporated screening for severe B-cell immunodeficiencies into their NBS protocols, this has not gained universal acceptance yet. Therefore, this revised guideline provides recommendations on the reporting and interpretation of TREC-based NBS for SCID to facilitate development of consensus-based harmonization of procedures. CLSI NBS06 also seeks to provide guidance on the follow-up and confirmatory testing of screen-positive SCID results. Because some global programs have instituted NBS for severe B-cell deficiencies, the utility of universal KREC-based screening is discussed. This second edition of CLSI NBS06 is the first time the topic of NBS programs incorporating KREC-based screening is introduced in CLSI NBS06.

Overview of Changes

CLSI NBS06-Ed2 replaces CLSI NBS06-Ed1, published in 2013. Several changes were made in this edition, including:

- Summarizing advances in the field of NBS for SCID since 2013, as well as the current status of global NBS for SCID
- Updating methodology for measuring TREC
- Updating TREC screening changes for multiplexing with other molecular assays, such as assays for survival motor neuron genes when screening for spinal muscular atrophy since its addition to the RUSP in 2018
- Adding methodology for measuring KREC for detecting severe B-cell deficiencies
- Adding recommendations for harmonizing results interpretation and reporting practices for SCID NBS
- Providing a more prescriptive approach to follow-up and confirmatory testing

Compared with the previous edition of CLSI NBS06, a more in-depth review of these topics, based on nearly a decade of screening experience in certain programs, lessons learned about limitations and successes, and practical application of SCID NBS in terms of identification of secondary target diseases and their adjudication for diagnostic confirmation and management, is provided.

NOTE: The content of CLSI NBS06 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

immunological deficiency syndromes

inborn errors of immunity

κ-deleting recombination excision circles

newborn screening

polymerase chain reaction

primary immunodeficiency disease

severe combined immunodeficiency

T-cell receptor excision circles

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Chapter 1

Introduction

Newborn Screening for Severe Combined Immunodeficiency and Other Related Severe T-cell and B-cell Immunodeficiencies

1 Introduction

1.1 Scope

CLSI NBS06 discusses the current global status of newborn screening (NBS) for severe combined immunodeficiency (SCID) and describes the methodology used to measure T-cell receptor excision circles (TREC), the extrachromosomal DNA fragments uniquely created during T-cell formation in the thymus in newborns. The relevance, clinical utility, and feasibility of including another marker, κ rearrangement excision circles (KREC), in routine NBS for identification of early-onset B-cell immunodeficiencies are also discussed.

CLSI NBS06 covers key concepts in the biology of T- and B-cell development, immunologic and clinical features of SCID, and severe B-cell deficiencies, as well as the current state of SCID NBS and screening for early-onset B-cell disorders. It also includes information on diagnostic testing, treatment, and outcomes of current therapies for SCID and early B-cell defects and provides an update to the clinical and economic effects of SCID NBS. Detailed discussion of preanalytical, analytical, and postanalytical assessment of TREC-based NBS for SCID, as well as strategies and implications of potentially including a second marker for immunodeficiency, KREC, into the NBS program, are reviewed. Particular emphasis is placed on updating methodologies for TREC and KREC analysis, multiplexing of analytes in the screening laboratory, follow-up testing, and harmonization, interpretation, and reporting of SCID NBS results. Detailed discussion on clinical interpretation of SCID NBS data, short-term follow-up (STFU), long-term follow-up (LTFU), and coordination of results between the screening laboratory, clinician, and follow-up diagnostic laboratory is included.

CLSI NBS06 is intended for use by public health laboratories currently performing SCID NBS; laboratories, countries, and regions contemplating the use of NBS for SCID and/or diagnosis of inborn errors of immunity (IEI); diagnostic immunology laboratories; and health care providers (HCPs) for patients with these diseases.

CLSI NBS06 is restricted solely to NBS for SCID and the potential inclusion of severe B-cell immunodeficiencies. It does not cover basic aspects of NBS follow-up, which are covered in CLSI NBS02,[8] nor does it provide detailed information on the analytical and interpretive nuances of diagnostic testing. Details on validation of flow cytometric assays in the medical laboratory are covered in CLSI H62.[9]

1.2 Background

SCID is a lethal disorder of infancy that is often not clinically apparent until several weeks after birth. SCID can be definitively treated by hematopoietic cell transplantation (HCT) or gene therapy, and strong evidence suggests early intervention using preventive and prophylactic measures during the asymptomatic period results in better outcomes and increased survival.[10] Historically, the only newborns tested at birth were those with a family history of SCID. A family-based survey revealed that the survival rate was 85% for those newborns tested at birth compared with 58% for those not tested at birth.[1] In 2001, the cumulative evidence from clinical experience led to SCID being identified as a potential target for NBS.[11]

In 2005, a method to detect SCID from newborn dried blood spot (DBS) specimens by measuring the content of TREC using real-time quantitative polymerase chain reaction (qPCR) was published.[12] NBS for SCID uses DNA from newborn DBS specimens to measure TREC number as a marker of early thymic emigrants, thus permitting early identification of babies with severe T-cell lymphopenia (TCL) who have low or absent TREC. SCID is the primary target disease screened for by measuring low or absent TREC. The justification for adding SCID to population

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