

NBS06-A

Newborn Blood Spot Screening for Severe Combined Immunodeficiency by Measurement of T-cell Receptor Excision Circles; Approved Guideline

This document addresses the detection of severe combined immunodeficiency (SCID) by population-based newborn screening using dried blood spot specimens to measure T-cell receptor excision circles. SCID is a lethal disorder of infancy that is not evident at birth, and effective treatment requires presymptomatic detection.

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

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Abstract

Severe combined immunodeficiency (SCID) is a congenital clinical disorder that is not evident at birth. Without treatment, most babies with SCID will die in infancy from virulent infection. This guideline addresses the detection of SCID by population-based newborn screening (NBS) using dried blood spot (DBS) specimens to measure T-cell receptor excision circles (TREC). Responding to recent US recommendations, the document is intended to facilitate the incorporation of SCID NBS into the routine operation of NBS programs worldwide. Based on extensive input from NBS laboratories, it describes the laboratory tests currently used to measure TREC in DBS by real-time quantitative PCR. The document also describes biological and clinical features of SCID and of other conditions potentially identified by SCID NBS. It provides an overview of laboratory operations including physical layout, instrumentation, TREC assay protocols, automated methodologies, and alternative platforms. The document includes a summary of diagnostic tests used for follow-up of abnormal TREC results as well as other short-term and long-term follow-up activities, including case tracking. It describes variants of SCID that may not be detected by TREC assays in newborn DBS. The guideline delineates the steps for implementing SCID NBS: validating the laboratory test, conducting pilot studies, and transitioning to routine screening. It is directed toward NBS laboratory personnel, public health program personnel, producers of laboratory products related to NBS, and those involved with oversight of NBS testing.

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SAMPLE

Foreword

The use of newborn screening (NBS) to detect severe combined immunodeficiency (SCID) and other T-cell defects represents a new frontier in public health and epidemiological endeavors. From its inception almost 50 years ago as a public health program to detect phenylketonuria,¹⁻³ NBS has grown into a global pursuit capable of detecting a wide spectrum of congenital metabolic and other disorders using a variety of laboratory analyses and dried blood spots (DBS) as the primary NBS specimen. The first NBS test, the bacterial inhibition assay, led to the creation of a new public health practice. The use of radioimmunoassay to detect congenital hypothyroidism⁴ coalesced public health laboratories into an international consortium and fueled the continuing expansion of NBS into new populations with more disease conditions studied. By the late 1990s, the process for selecting diseases to be included in population-based NBS had grown much more intricate⁵ due to technical advances in laboratory science and to greater public awareness, legislative action, and parental education. During this time, SCID became widely recognized as a promising candidate for NBS, provided that a suitable screening test could be developed.

The general public awareness of SCID arose largely from the life of David Vetter, often referred to as the “boy in the bubble.”⁶ His case served as the forerunner for the medical interventions used today to treat children with SCID, most notably temporary protective isolation and restoration of immune function by hematopoietic cell transplantation (HCT). Although David died from complications related to his transplant, his case prompted the refinement of HCT into a highly effective treatment for SCID when it is performed in early infancy. The first few weeks of life, before the loss of maternal antibodies leads to severe infections, provide a critical window of opportunity. Thereafter, morbidity from infections makes HCT much less effective.⁷ Early identification in the asymptomatic infant is therefore essential to successful treatment.

As the benefit of HCT in early infancy became increasingly apparent, some pediatric immunologists began to call for neonatal testing for SCID. However, a reliable high-throughput assay that uses newborn DBS was required to exploit the existing infrastructure for population-based NBS. The importance of a SCID NBS test was highlighted as a top priority at a 2001 conference at the US Centers for Disease Control and Prevention (CDC).⁸ These discussions helped to bring attention to the development and validation of a SCID NBS test at the US National Institutes of Health (NIH).⁹ This test used absolute quantitative real-time PCR to measure T-cell receptor excision circles (TREC), extra-chromosomal DNA fragments uniquely created during T-cell formation.¹⁰⁻¹³ The initial results from 23 infants newly diagnosed with SCID and 239 residual newborn DBS suggested that the TREC assay could be a sensitive and specific method for SCID NBS.⁹ NBS programs would have to develop a high-throughput capacity and demonstrate the feasibility of implementing a sufficiently controlled DNA-based technology in their population-based services.

In 2008, a partnership among the Children’s Hospital of Wisconsin (CHW), the Wisconsin State Laboratory of Hygiene (WSLH), and the Jeffrey Modell Foundation for primary immunodeficiency led to the first population-based application of the TREC assay in an NBS public health program.^{14,15} The TREC assay used in the program was established at WSLH and CHW and was shown to be suitable for high-throughput routine NBS. By 2009, Massachusetts had developed an internally controlled multiplex TREC assay and initiated a second population-based SCID NBS program,^{16,17} while the University of California, San Francisco began SCID NBS in certain high-risk Native American populations. During this initial phase, the CDC developed and worked with the laboratories in Wisconsin and Massachusetts to validate the DBS reference materials needed to support the expanding number of public health laboratories preparing for SCID NBS. The Wisconsin and Massachusetts experiences documented the feasibility of including SCID in routine NBS and, together with the CDC, paved the way for wider implementation. In 2010, an advisory committee to the US Department of Health and Human Services recommended the addition of SCID as a core condition in its Recommended Uniform Screening Panel, as well as the addition of related T-cell lymphocyte deficiencies to the list of secondary targets.¹⁸ The US National

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1 Scope

This guideline addresses the detection of severe combined immunodeficiency (SCID) by population-based newborn screening (NBS) using dried blood spot (DBS) specimens. The guideline is intended to facilitate the incorporation of SCID NBS into the routine operation of existing NBS programs. Methodologically, it focuses on measuring T-cell receptor excision circles (TREC) in DBS by real-time quantitative PCR^a (qPCR), the method in use by all NBS laboratories at the time of guideline publication. It also describes other qPCR methods for measuring TREC in DBS that may come into future use.

This guideline includes detailed information for laboratory practice including calibration, QC, and proficiency testing (PT). It also addresses program issues such as short-term follow-up (notification and tracking to establish or rule out a diagnosis). The guideline includes clinical and immunological background on SCID and other immunodeficiency disorders that may present with low or no TREC content in newborns. It draws heavily on the experience of the NBS programs that have already operationalized the TREC assay for population-based NBS. The document includes several appendixes that provide additional information important to the guideline. In particular, Appendix C includes the operational algorithms in use by four of the NBS programs conducting SCID NBS at the time this document development committee was convened. The guideline is primarily intended for use by NBS laboratory personnel, producers of laboratory products related to NBS, and those involved with oversight of NBS programs.

The guideline is limited to NBS applications. It discusses, but does not detail, the methods used in diagnostic laboratory tests for immune deficiencies on whole blood, including immunophenotyping by flow cytometry (addressed in CLSI document H42)²⁰ and lymphocyte function assays (some of which are addressed in CLSI document I/LA26).²¹ It does not discuss blood spot collection for NBS, which is the subject of a separate guideline (see CLSI document LA04).²² While the document includes general guidelines for short- and long-term follow-up, the knowledge base for assessing sensitivity, specificity, and predictive value is not yet sufficient to express accurate quantitative values for these parameters. These parameters will be revisited in future editions of this guideline.

2 Introduction

SCID is a lethal disorder of infancy that is often not clinically apparent until several weeks after birth. SCID can be effectively treated by hematopoietic cell transplantation (HCT), and there is strong evidence that early intervention during the asymptomatic period results in better outcomes and increased survival.⁷ Historically, the only babies 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 to 58% for newborns not tested at birth.²³ In 2001, the cumulative evidence from clinical experience led to SCID being identified as a target for public health NBS.⁸ In 2005, Chan and Puck published a method to detect SCID from newborn blood spot specimens by measuring the content of TREC using real-time qPCR.⁹ In 2008, Wisconsin began the first prospective population-based pilot study of SCID NBS using a laboratory-developed real-time qPCR assay to measure TREC.^{15,24} In 2009, Massachusetts initiated its SCID NBS pilot program using an internally controlled multiplex real-time qPCR TREC assay.^{17,25} Since then, several additional US states and other global NBS programs have incorporated SCID into their

^a *Absolute quantitative PCR* refers to qPCR assays that incorporate calibrator reference materials having values assigned in absolute copy numbers, as contrasted to calibration in relative (proportionate) values. Because the term *absolute* may be misinterpreted to mean independent of any calibrator reference material, it will not be used in the remaining sections of this guideline.

routine screening, and many more NBS programs are working toward implementation.²⁶ At the time of publication, SCID has been detected by NBS using TREC assays in more than two dozen infants who have successfully undergone HCT.

3 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. The Centers for Disease Control and Prevention (CDC) address this topic in published guidelines that focus on the daily operations of diagnostic medicine in human and animal medicine while encouraging a culture of safety in the laboratory.²⁷ 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 M29.²⁸

4 Terminology

4.1 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 and guidelines focuses on harmonization of terms to facilitate the global application of standards and guidelines.

CLSI uses the globally applicable terms “preexamination,” “examination,” and “postexamination” in its documents. However, in the NBS laboratory, blood spot specimens are “examined” to ensure that they are satisfactory before they are “analyzed.” Hence, for the purposes of CLSI NBS documents, the terms “preanalytical,” “analytical,” and “postanalytical” are used in place of “preexamination,” “examination,” and “postexamination.” Additionally, the word “analysis” is used in place of “examination.” Though contradictions among these terms may exist between new CLSI NBS documents and already published NBS documents, these contradictions will be reconciled as documents go through the revision process.

In CLSI NBS documents, the terms *newborn* and *infant* have distinct meanings. *Newborn* indicates a person from birth to 30 days old, and *infant* indicates a person from 1 month to 1 year old. In situations that could apply to both (or either) age groups, the term *baby* is used.

4.2 Definitions

22q11.2 deletion syndrome – a highly variable clinical syndrome caused by a contiguous deletion of 1.5 to 3 Mb in the long arm of one copy of chromosome 22; **NOTE 1:** The clinical manifestations of 22q11.2 deletion syndrome can include, but are not limited to, congenital abnormalities of the heart, thymus (leading to T-cell immunodeficiencies), palate, parathyroid and thyroid glands, learning disabilities, speech and developmental delay, and psychiatric problems; **NOTE 2:** The phenotype is variable and does

The Quality Management System Approach

Clinical and Laboratory Standards Institute (CLSI) subscribes to a quality management system approach in the development of standards and guidelines, which facilitates project management; defines a document structure via a template; and provides a process to identify needed documents. The quality management system approach applies a core set of “quality system essentials” (QSEs), basic to any organization, to all operations in any health care service’s path of workflow (ie, operational aspects that define how a particular product or service is provided). The QSEs provide the framework for delivery of any type of product or service, serving as a manager’s guide. The QSEs are as follows:

- Organization
- Customer Focus
- Facilities and Safety
- Personnel
- Purchasing and Inventory
- Equipment
- Process Management
- Documents and Records
- Information Management
- Nonconforming Event Management
- Assessments
- Continual Improvement

NBS06-A addresses the QSE indicated by an “X.” For a description of the other documents listed in the grid, please refer to the Related CLSI Reference Materials section, beginning on page 74.

Organization	Customer Focus	Facilities and Safety	Personnel	Purchasing and Inventory	Equipment	Process Management	Documents and Records	Information Management	Nonconforming Event Management	Assessments	Continual Improvement
POCT04		M29 POCT04	POCT04	POCT04	POCT04	X EP12 EP17 GP29 H26 H42 H42 I/LA26 I/LA27 I/LA31 LA04 MM01 POCT04 POCT08	QMS02			GP29	H26

Path of Workflow

A path of workflow is the description of the necessary processes to deliver the particular product or service that the organization or entity provides. A laboratory path of workflow consists of the sequential processes: preexamination, examination, and postexamination and their respective sequential subprocesses. All laboratories follow these processes to deliver the laboratory's services, namely quality laboratory information.

NBS06-A addresses the clinical laboratory path of workflow steps indicated by an "X." For a description of the other documents listed in the grid, please refer to the Related CLSI Reference Materials section on the following page.

Examination ordering	Preexamination			Examination			Postexamination	
	Sample collection	Sample transport	Sample receipt/processing	Examination	Results review and follow-up	Interpretation	Results reporting and archiving	Sample management
H42 LA04 MM01	H26 H42 I/LA26 LA04 MM01	H42 I/LA26 LA04 MM01	H42 I/LA26 LA04 MM01	X H26 H42 I/LA26 MM01	X H42 I/LA26 MM01	H42 I/LA26 MM01	H42 I/LA26 MM01	H26 LA04 MM01

Related CLSI Reference Materials*

- EP12-A2** **User Protocol for Evaluation of Qualitative Test Performance; Approved Guideline—Second Edition (2008).** This document provides a consistent approach for protocol design and data analysis when evaluating qualitative diagnostic tests. Guidance is provided for both precision and method-comparison studies.
- EP17-A2** **Evaluation of Detection Capability for Clinical Laboratory Measurement Procedures; Approved Guideline—Second Edition (2012).** This document provides guidance for evaluation and documentation of the detection capability of clinical laboratory measurement procedures (ie, limits of blank, detection, and quantitation), for verification of manufacturers' detection capability claims, and for the proper use and interpretation of different detection capability estimates.
- GP29-A2** **Assessment of Laboratory Tests When Proficiency Testing Is Not Available; Approved Guideline—Second Edition (2008).** This document offers methods to assess test performance when proficiency testing (PT) is not available; these methods include examples with statistical analyses. This document is intended for use by laboratory managers and testing personnel in traditional clinical laboratories as well as in point-of-care and bedside testing environments.
- H26-A2** **Validation, Verification, and Quality Assurance of Automated Hematology Analyzers; Approved Standard—Second Edition (2010).** This document provides guidance for the validation, verification, calibration, quality assurance (QA), and quality control (QC) of automated multichannel hematology analyzers for manufacturers, end-user clinical laboratories, accrediting organizations, and regulatory bodies. In addition, end-user clinical laboratories will find guidance for establishment of clinically reportable intervals and for QA for preexamination and examination aspects of their systems.
- H42-A2** **Enumeration of Immunologically Defined Cell Populations by Flow Cytometry; Approved Guideline—Second Edition (2007).** This document provides guidance for the immunophenotypic analysis of non-neoplastic lymphocytes by immunofluorescence-based flow cytometry; sample and instrument quality control; and precautions for acquisition of data from lymphocytes.
- I/LA26-A** **Performance of Single Cell Immune Response Assays; Approved Guideline (2004).** This document contains methods of intracellular cytokine evaluation, major histo-compatibility complex (MHC) tetramer quantitation, and enzyme-linked immunospot (ELISPOT) technology. This document provides basic aspects of specimen collection, transport, and preparation, in addition to quality assurance and test validation approaches. An NCCLS-IFCC joint project.
- I/LA27-A** **Newborn Screening Follow-up; Approved Guideline (2006).** This guideline describes the basic principles, scope, and range of follow-up activities within the newborn screening system.
- I/LA31-A** **Newborn Screening for Preterm, Low Birth Weight, and Sick Newborns; Approved Guideline (2009).** This guideline outlines the recommended protocols for screening preterm, sick, or low birth weight infants for hearing loss and disorders detectable through dried blood spot testing.
- LA04-A5** **Blood Collection on Filter Paper for Newborn Screening Programs; Approved Standard—Fifth Edition (2007).** This document addresses the issues associated with specimen collection, the filter paper collection device, and the application of blood to filter paper, and provides uniform techniques for collecting the best possible specimen for use in newborn screening programs.
- M29-A3** **Protection of Laboratory Workers From Occupationally Acquired Infections; Approved Guideline—Third Edition (2005).** Based on US regulations, this document provides guidance on the risk of transmission of infectious agents by aerosols, droplets, blood, and body substances in a laboratory setting; specific precautions for preventing the laboratory transmission of microbial infection from laboratory instruments and materials; and recommendations for the management of exposure to infectious agents.

* CLSI documents are continually reviewed and revised through the CLSI consensus process; therefore, readers should refer to the most current editions.

Related CLSI Reference Materials (Continued)

- MM01-A3** **Molecular Methods for Clinical Genetics and Oncology Testing; Approved Guideline—Third Edition (2012).** This document provides guidance for the use of molecular biological techniques for detection of mutations associated with inherited medical disorders, somatic or acquired diseases with genetic associations, and pharmacogenetic response.
- POCT04-A2** **Point-of-Care *In Vitro* Diagnostic (IVD) Testing; Approved Guideline—Second Edition (2006).** This document provides guidance to users of *in vitro* diagnostic (IVD) devices outside the clinical laboratory, to ensure reliable results comparable to those obtained within the clinical laboratory.
- POCT08-A** **Quality Practices in Noninstrumented Point-of-Care Testing: An Instructional Manual and Resources for Health Care Workers; Approved Guideline (2010).** This instructional guideline delivers laboratory science concepts and activities with the goal of increasing knowledge and quality of laboratory testing for testing personnel with no laboratory background.
- QMS02-A6** **Quality Management System: Development and Management of Laboratory Documents; Approved Guideline—Sixth Edition (2013).** This document provides guidance on the processes needed for document management, including creating, controlling, changing, and retiring a laboratory's policy, process, procedure, and form documents in both paper and electronic environments.



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