CLINICAL AND LABORATORY STANDARDS INSTITUTE®

1st Edition

CLSI NBS11™

Newborn Screening for Congenital Adrenal Hyperplasia

CLSI NBS11 provides recommendations for using dried blood spot specimens to perform newborn screening for congenital adrenal hyperplasia.

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

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Newborn Screening for Congenital Adrenal Hyperplasia

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Abstract

CLSI NBS11—*Newborn Screening for Congenital Adrenal Hyperplasia* provides recommendations for using dried blood spot specimens to perform newborn screening (NBS) for congenital adrenal hyperplasia (CAH). CLSI NBS11 also discusses the preanalytical, analytical, and postanalytical aspects of CAH NBS, including short-term and long-term follow-up considerations.

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Foreword

The goal of newborn screening (NBS) is presymptomatic detection of at-risk newborns, generally through use of dried blood spot (DBS) specimens that are analyzed in specialized NBS laboratories. Ideally, NBS systems provide well-organized, highly effective, population-based services that apply preventive medicine principles to reduce death and disability from many congenital diseases. NBS systems should be comprehensive. They can include health care providers (HCPs), birthing facilities, public health programs, policy makers, insurers, and families, among others. NBS programs should be linked to follow-up HCPs for rapid diagnosis and initiation of treatment. NBS systems encompass preanalytical, analytical, and postanalytical activities, which include education; collection and laboratory analysis of DBS specimens; results reporting; referral to clinical care (short-term follow-up); diagnosis, intervention, programmatic evaluations, and evaluation of health outcomes (long-term follow-up); quality assurance; and quality improvement.

Congenital adrenal hyperplasia (CAH) can be caused by several different enzyme deficiencies that lead to problems with adrenal steroidogenesis. These issues ultimately result in suboptimal cortisol secretion. For the purposes of CLSI NBS11, unless otherwise specified, "CAH" refers to congenital adrenal hyperplasia due to 21-hydroxylase deficiency. NBS reports from diverse populations give a birth prevalence of classic 21-hydroxylase deficiency, the most prevalent type of CAH, to be approximately 1 in 14 000 to 1 in 18 000 births. However, the disease is more prevalent in select locations and/or ethnicities within which consanguinity is prevalent, eg, the Alaskan Yupik population[1] (see Subchapter 3.2.1). Approximately 75% of affected babies have the severe, salt-wasting form of the disease and are at risk of life-threatening, salt-wasting adrenal crises in the first few weeks of life.

Presymptomatic detection is important to prevent the morbidity and mortality that occurred before the era of screening. Early detection and treatment can prevent the more severe, salt-wasting form of adrenal crises. Timeliness is essential in achieving this goal. Thus, screen-positive screening results should be reported to clinicians as soon as possible and ideally by day 5 of life.[2] Challenges to efficient and accurate screening include a relatively low positive predictive value when the laboratory relies only on a 17-hydroxyprogesterone (17-OHP) immunoassay and a lack of consensus among laboratories for determining 17-OHP concentration cutoff values. The purpose of CLSI NBS11 is to support all elements of the screening program to achieve best outcomes for babies screened for CAH by providing an expert, unbiased assessment of the various screening strategies available.

NOTE: The content of CLSI NBS11 is supported by the CLSI consensus process and does not necessarily reflect the views of any single individual or organization.

KEY WORDS

17-hydroxyprogesterone
congenital adrenal hyperplasia
CYP21A2
fluoroimmunoassay
genetic testing
immunoassay
newborn screening
tandem mass spectrometry

Chapter 1

Introduction

Newborn Screening for Congenital Adrenal Hyperplasia

1 Introduction

1.1 Scope

CLSI NBS11 provides recommendations for using dried blood spot (DBS) specimens to perform newborn screening (NBS) for congenital adrenal hyperplasia (CAH) and discusses the preanalytical, analytical, and postanalytical aspects of CAH NBS, including short-term follow-up (STFU) and long-term follow-up (LTFU) considerations. CLSI NBS11 describes:

- Etiology and clinical manifestations of CAH associated with elevated 17-hydroxyprogesterone (17-OHP), with a focus on classic CAH due to 21-hydroxylase deficiency as the primary focus of NBS
- Nonclassic congenital adrenal hyperplasia (NCCAH) as a secondary target of CAH NBS
- Analytical methodologies for 17-OHP measurement, steroid profiling, and genetic testing in DBS
- Screening strategies and laboratory screening algorithms currently used and variations in approaches, along with the advantages and disadvantages of each strategy
- Limitations of screening for CAH using analysis of 17-OHP as the first-tier test
- Successful laboratory practices, including method validation and/or verification of analytical methods, QA, and results interpretation
- Recommendations on implementing CAH NBS for emerging programs

The intended users of CLSI NBS11 are NBS laboratories; follow-up and program personnel; birthing facilities; public health program administrators; medical laboratories; pediatric endocrinologists; neonatologists; other health care providers (HCPs); regulatory agencies; public health policy makers; and manufacturers of instruments, reagents, and related NBS products.

CLSI NBS11 does not cover:

- Screening aspects for types of CAH other than 21-hydroxylase deficiency
- Details of confirmatory diagnostic testing or treatment of CAH
- Details of CAH carrier screening
- Prenatal screening
- Comparative cost information

1.2 Background

CAH screening of newborns was developed in the late 1970s using a radioimmunoassay for 17-OHP in DBS specimens.[3] An Alaskan pilot study confirmed both the feasibility of adding CAH screening to an existing NBS system and that doing so was likely to decrease mortality and morbidity through early detection of disease.[4] NBS for CAH is now universal in the United States and in many other developed countries.[1]

The rationale for CAH NBS is that it is a relatively common inborn error of steroid metabolism in which early diagnosis and treatment confer a substantial benefit in terms of reduced morbidity and mortality. In the absence of NBS, CAH mortality is estimated to be ≤ 4% in populations with high standards of clinical awareness and care of CAH,[5] but it can be substantially higher in low-resource settings. Short-term benefits of NBS include reduced

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