



# Newborn Screening in Pediatric Endocrine Disorders

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**Abstract:** Two endocrine disorders, congenital hypothyroidism (CH) and congenital adrenal hyperplasia (CAH), when untreated, can have devastating, irreversible and fatal outcomes. Permanent cognitive impairment, growth failure and dysmorphic appearance are seen in congenital hypothyroidism (CH) and early infant death in males with salt wasting CAH (as most females are discovered by presence of atypical genital appearance, while males appeared normal). Newborn screening (NBS) for CH was developed with broader engagement of centers, and was more rapidly adopted throughout the US and other large or developed countries, while NBS for CAH was pioneered by relatively few and was not fully adopted in the US until the initiation of Universal Expanded Newborn Screening Panel in 2005. Advances in genetic understanding of CH and CAH continue with NBS. Cost-benefit analysis, showing CH NBS as more successful than CAH NBS, may not fully recognize the cost of a life saved with CAH NBS. Early treatment of CH is much simpler with taking a pill a day unlike CAH requiring multiple medication doses, and possibly surgery apart from enteral and parenteral stress doses during adrenal crisis. CAH management outcomes with gender identity matters in persons with atypical genital appearance and androgen effects are still being studied.

**Keywords:** newborn screening (NBS); congenital hypothyroidism (CH); congenital adrenal hyperplasia (CAH)



**Citation:** Draznin, M.; Borgohain, P.; Kanungo, S. Newborn Screening in Pediatric Endocrine Disorders.

*Endocrines* **2022**, *3*, 107–114.

<https://doi.org/10.3390/endocrines3010010>

Academic Editor: Yukihiro Hasegawa

Received: 25 January 2022

Accepted: 11 March 2022

Published: 15 March 2022

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## 1. Introduction

Newborn screening (NBS) is considered one of the most successful public health programs in the United States and worldwide. NBS helps identify conditions in asymptomatic newborns at birth, which are known to cause severe morbidity and mortality, with timely treatment prior to disease presentation, thus preventing poor long-term outcomes [1]. Since the first screening in the 1960s for a single disorder as phenylketonuria (PKU), now, nearly 4 million newborns in the United States are screened for 60+ disorders/conditions each year, 24 h or more after birth. Most of these disorders are screened on dried blood spot (DBS) testing. Moreover, advances in testing methodology have helped ensure high sensitivity and specificity in detection and confirmation of a positive screen. In the 1960s, WHO's Wilson and Junger's "Principles and Practices of Screening for Disease" provided the initial framework for the first newborn PKU screening as a public health program. Technological advances such as tandem mass spectrometry (TMS) helped the American College of Medical Genetics, in 2005, update criteria for inclusiveness of more disorders as part of universal expanded screening panel. The Newborn Screening Saves Lives Act of 2014 helped establish a 15-member expert federal panel, the Advisory Committee on Heritable Disorders in Newborn and Children (ACHDNC), to provide guidance to the DHHS Secretary on the addition of new conditions, development of NBS policies and practice standards and advise on all issues concerning NBS [2]. Currently, each condition included in the Recommended Universal Screening Panel (RUSP)

has undergone ACHDNC's robust review of existing scientific evidence and a decision matrix weighing in on the net benefit of the screening, readiness of state public health department and feasibility of implementing the population screening for that condition. (<https://www.hrsa.gov/advisory-committees/heritable-disorders/rusp/index.html> last accessed on 10 March 2022).

In general, screening a population for a disease should satisfy Frankenburg's three criteria: the disease should be important, prevalent and amenable to prompt treatment [3]. For an effective screening program, employing a reliable test with rapid turnaround time coupled with a reporting system that will allow timely treatment to be instituted is critical. Maintenance of a data registry, analysis of outcomes, oversight by the authorizing agency such as a State Department of Health and consultation with expert advisors to facilitate continuous quality improvement are also core functions. As working with providers of all the necessary activities from sample collection and transport to notification of the medical provider of record is necessary, facilitating consultation with subspecialty providers who assist with or provide the necessary care, the programs have a sizable job. Additionally, educational outreach to providers to keep them up to date with needed information and to families to explain the program, the nature of the conditions for which it tests and the rationale for treatment require significant application of resources. Multilingual information for families is needed in states with large immigrant populations.

### *The Need for Newborn Endocrine Screening*

Two endocrine disorders, congenital hypothyroidism (CH) and congenital adrenal hyperplasia (CAH) satisfied all three Frankenburg criteria and met Wilson Jungers' framework. Untreated, each of these disorders has potentially devastating and irreversible effects, e.g., permanent cognitive impairment, growth failure and dysmorphic appearance in congenital hypothyroidism (CH), when treatment was too late, as well as early infant death in males with salt wasting CAH. Even though most females were thought to be discovered by the presence of what is now called atypical genital appearance, NBS has identified cases in females, when clinically not suspected.

## **2. Congenital Hypothyroidism**

### *2.1. History*

Congenital hypothyroidism had been recognized for many decades, existing in endemic and sporadic forms. Endemic hypothyroidism was associated with population-wide iodine deficiency and was eliminated in the US by the addition of iodide to salt, while the sporadic form could be treated initially with extract of desiccated thyroid, and later with synthetic thyroxine. The problem with clinical diagnosis was that the signs of hypothyroidism in the newborn are often subtle, delaying treatment for several months or more.

The outcomes varied; early replacement therapy spared IQ with scores ranging 64–107 when treated before 3 months, 35–96 when treated between 3 and 6 months and 25–80 when treated after 6 months [4], with similar early detection results and supporting the need for worldwide CH screening [5].

### *2.2. CH NBS Developments*

Screening for congenital hypothyroidism was initiated in the Province of Quebec in 1974, assaying T4 from the dried blood spots on filter paper already in use for screening for PKU [6]. Moreover, the pediatric endocrine group in Pittsburgh demonstrated assaying TSH (Thyroid-Stimulating Hormone) using cord blood [7]. Subsequently TSH was assayed from dried blood spots as well [8–11]. Japan was the first country to implement national CH screening using TSH value on dried blood spots in 1979 [12].

Earlier estimates of the frequency from case-based studies were in the range of 1:8000. In a report from the screening programs in Quebec, New England, Pittsburgh, Oregon and Toronto, the incidence was 1:3684 including primary and secondary-tertiary forms [13]. Of these one million screened, only seven infants were not identified, demonstrating the high sensitivity,

while only 8 of the nearly 300 affected were suspected based on clinical signs and symptoms. The average time to treatment in the five programs ranged from 18 to 38 days. Newborn screening for congenital hypothyroidism was widely adopted in the US. Newborn Screening for Congenital Hypothyroidism: Recommended Guidelines, by the American Academy of Pediatrics Section on Endocrinology and Committee on Genetics, and the American Thyroid Association Committee on Public Health Pediatrics summarized the progress of screening programs, estimating that more than five million infants were screened annually in the developed world, with 1400 affected infants detected each year [14]. A subsequent review compared the findings of screening T4 initially with reflex testing of TSH for the lowest T4 decile, which identified primary as well as secondary-tertiary hypothyroidism and flagged TBG (Thyroxine-Binding Globulin) deficiency for further evaluation to initial screening for TSH, which also had a lower recall rate than programs recalling all the lowest T4 [15]. This review also referred to a summary of the IQ outcomes of infants identified and treated in 10 screening programs, where 6 reports showed no significant difference in overall IQ, and the 4 with statistically significant differences were still an improvement over the prescreen era. Over the decades, some programs continued the T4 with reflex TSH system, while others moved to screening TSH alone.

The uniform employment of standardized commercial assays and automated assay platforms replaced systems employing radioimmunoassays (RIAs) developed by individual university research laboratories.

By the definition of screening, false positive tests must be expected and effectively addressed in order to minimize false negatives, and to avoid unnecessary negative psychological effects on parents. While initial assay for T4 with reflex to TSH has low recall for false positives, initial T4 alone is no longer employed. Initial screening with TSH will not identify central CH due to TRH (Thyrotropin-Releasing Hormone) or TSH deficiency. Among advances in identifying and treating CH are more rapid normalization of thyroid status with an increase in initial thyroxine dose from 8–10 mcg/kg to 10–15 mcg/kg [16,17] and the ability to identify infants with the rare genetically inherited forms earlier. False-negative results may be due to prematurity or twin-to-twin transfusion with the CH in the recipient twin obscured by the T4 of the donor twin [18,19].

### 2.3. Present Day Status of CH screening

Worldwide screening for CH has been expanded to about 29% of the newborns in the world; the estimate is that 30,000 infants are missed each year [20].

With application of lower TSH cutoff levels, more infants are identified who may have less severe forms of CH; as many as 50% of these infants may not need permanent treatment [21].

Whether or not to screen with lab testing during pregnancy to minimize the risk of profoundly hypothyroid babies born with CH without mitigating maternal thyroid hormone transmission during gestation has been of interest. The evidence was not strongly in favor of universal screening, but appropriate treatment of known maternal thyroid disease and communication with the care team of the infant was a firm recommendation by the American Thyroid Association (ATA). Screening all gravidas for thyroid dysfunction before or during pregnancy did not have sufficient evidence to be recommended [22]. Likewise, the American College of Obstetrics and Gynecology (ACOG Update: Thyroid Disease in Pregnancy—The ObG Project <https://www.obproject.com>, last accessed on 10 March 2022) suggested detailed history and physical assessment to identify at-risk pregnancies rather than routine laboratory screenings.

Applying cost-benefit analysis to newborn CH screening, it was concluded that “individual and societal-level health and economic benefits of NBS for permanent CH have been clearly demonstrated” [23], with a positive cost to benefit ratio (10:1) and impact on public health [24,25].

#### 2.4. Etiology

Most cases of congenital hypothyroidism are due to defects of thyroid gland development (dysgenesis) during embryogenesis (sporadic primary hypothyroidism). Dysgenesis, which includes agenesis, hypoplasia and ectopy, is the most common cause of congenital hypothyroidism. Dysgenesis usually occurs sporadically, with 2–5% of cases being attributable to identifiable genetic mutations.

The thyroid hormone stimulating receptor (THSR) and the transcription factors PAX8, NKX2-1 and FOXE1 are expressed in the developing thyroid [26]. Normal thyroid gland formation can be disrupted by defect in expression of any of these genes. Other developing tissues are also affected, as these transcription factors are expressed in other tissues as well. Therefore, there can be associated additional syndromic features, such as interstitial lung disease, chorea (NKX2-1), renal abnormalities (PAX8), cleft palate, bifid epiglottis, choanal atresia and spiky hair (FOXE1). There are several other genes implicated as well. Aplasia and ectopic thyroid are less likely to be genetic, unless they have other associated anomalies, such as renal and cardiac.

Although dysgenesis is the most important cause, the incidence of dysmorphogenesis is increasing. Dysmorphogenesis is due to autosomal recessive genetic defects in thyroid hormone synthesis [27–29], and is further detailed in the Thyroid Disorder article of this issue. Congenital hypothyroidism of central origin caused by dysfunction of hypothalamic or pituitary control of thyroid axis leading to inadequate production of TSH is rare [13,30,31]. Males carrying inactivating mutations in the immunoglobulin superfamily, member 1 (*IGSF1*) causing X-linked *IGSF1* deficiency, manifest a clinical syndrome of central hypothyroidism, macro-orchidism (88% of patients) and prolactin deficiency (60% of patients) [32].

#### 2.5. Management

The key management of CH positive screen includes:

- Confirming diagnosis with serum TSH and free T4 levels;
- Prompt treatment initiation with thyroxine 10–15 mcg/kg;
- Post treatment repeat serum free T4 and TSH at follow-up in two weeks.

Imaging should be done to differentiate the type of dysgenesis using either technetium 99 or iodine 123 scans or ultrasound. There has been no difference in efficacy in using generic LT4 vs. Synthroid [33]. Thyroxine tablets can be crushed between two spoons in a small amount of water/formula/breast milk, but is not advisable to mix in a feeding bottle or give with multivitamin as absorption is altered with iron and Vitamin C.

Monthly follow-up with TSH and T4 levels as and when indicated can help. The sex, birth weight, age, age of treatment, initial L-thyroxine dose or L-thyroxine dose at one year of age were not predictive factors for more frequent monitoring [34].

### 3. Congenital Adrenal Hyperplasia

#### 3.1. History

In 1865, Luigi De Crecchio, an Italian pathologist, described the case of a person who had lived as a man but at autopsy was found to have female internal anatomy and large adrenal glands. This was the first presumed case of congenital adrenal hyperplasia reported in Western medical literature. In 1930, chemical structures of adrenal hormones were identified. In 1940, the Hypothalamic Pituitary Adrenal Axis (HPA) was conceptualized. Cortisone had been synthesized and was used for treatment for rheumatoid arthritis. In 1950 cortisone was used for treatment for CAH for the first time [35,36]. The biochemical era elucidated enzyme-mediated pathways between cholesterol and steroid hormones. There are multiple causes of CAH including defects in: 21-steroid hydroxylation, 11 steroid-hydroxylation, 17 alpha hydroxylation-20–22 lyase action and 3 beta hydroxy steroid dehydrogenase. Defective side chain cleavage enzyme was suggested to be a major cause of lipoid adrenal hyperplasia until the Steroidogenic acute regulatory protein was shown to be the major actor in that rare form. In the next decades, multiple gene mutations and multiple abnormalities of microsomal mixed function oxidase (later known as POR deficiency) were

described. As CAH from 21-hydroxylase deficiency comprises 90–95% of all cases, causes early fatality, can be easily detected and is treatable, it met the screening criteria to include it in NBS. A recent review focused mostly on CAH due to 21-hydroxylase deficiency details the mechanisms of mutations, including deletion as well as gene conversion due to high rate of unequal crossover in meiosis [37].

### 3.2. CAH NBS Development

A screening test for CAH using the 17-hydroxyprogesterone level on DBS first became available in 1977 with the objective to prevent death of affected males by preventing salt wasting crisis [38]. Results of a pilot NBS program for 21-hydroxylase deficiency CAH conducted in Alaska were promising [39]. In this pilot program, sixteen newborns had 17-OHP values greater than 57 pg/disc, of which 4 (3 Yupik and 1 Caucasian) were proven to have the salt-losing form of CAH. In addition, these data suggested an increased prevalence of this disorder of 1 in 282 Yupik Alaskans compared to case survey results previously reported in this population. This pilot program demonstrated not only the feasibility of a newborn screening program for CAH but also indicated that the frequency of the salt-losing form of CAH may be greater than previously reported.

With the availability of a reliable screening test for classical CAH, a 1987 report of worldwide incidence, from newborn screening programs in France, Italy, Japan, New Zealand, Scotland, and the United States, found 1 in 18,921 live births of the salt wasting form and 1 in 63,068 live births of the simple virilizing forms, with a female-to-male sex ratio of approximately 1:1 [40]. This collaborative report showed that newborn screening improved overall case detection of congenital adrenal hyperplasia worldwide. The screening also improved detection of the salt wasting form, which had previously been missed in some male infants, resulting in deaths.

CAH newborn screening that started from Alaska in 1977 was widely implemented across the United States, when it was added to the Expanded Newborn Screening Panel in 2005. An Endocrine Society Clinical Practice Guideline for CAH, published in 2010, recommended initial screening immunoassay to be followed by liquid chromatography/mass spectrometry, to increase the positive predictive value and reduce morbidity and mortality from salt wasting crises [41]. The guidelines also updated the understanding of genetics and biochemistry as well as aspects of medical, surgical and psychological treatments of CAH. The subsequent 2018 guidelines emphasized employment of standardized common technology for first-tier screening and LC/MS-MS for second-tier screening. It added recommendations and cautions about prenatal diagnosis and steroid treatment. It further updated information about the pathways of steroidogenesis [42].

For 21-hydroxylase deficiency screening, the assayed analyte cutoff levels used for first tier screening may vary from state to state and the second-tier LC/MS-MS cut-offs whether done in-state or out-of-state may also vary. This creates a paucity of uniform parameters and the varying landscape of CAH NBS systems is being addressed by NewSTEPS [43]. The Newborn Screening Technical assistance and Evaluation Program (NewSTEPS) data repository can analyze timeliness of testing, reporting and intervention, and thus, helping with the continuous quality improvement processes in CAH screening programs (<https://www.newsteps.org/> last accessed on 10 March 2022).

### 3.3. Etiology and Genetics

CAH comprises a group of autosomal recessive disorders, caused by mutations in genes encoding enzymes in pathways involved in cortisol biosynthesis: 21-hydroxylase, 11 beta-hydroxylase, 17 alpha-hydroxylase 20–22 lyase, 3 beta-hydroxy steroid dehydrogenase, steroidogenic acute regulatory protein (StAR) and cytochrome P450 oxidoreductase. CAH clinical presentation depends on which of the above is deficient, causing alterations in glucocorticoid, mineralocorticoid and sex steroid production, which lead to disordered physiology and anatomy. More than 95% cases of CAH are due to 21-OH deficiency, characterized by impaired cortisol and aldosterone production and androgen excess. There



are three phenotypes of CAH due to 21-OH deficiency: classic salt losing, classic non-salt losing and non-classic (previously termed late onset). Screening programs target 21-hydroxylase deficiency as it is the most prevalent with the salt wasting form being the most devastating form if missed [44].

### 3.4. Management

The key management of CAH positive screen includes:

- Confirming diagnosis with serum electrolytes and 17-OHP levels;
- Consultation with pediatric endocrinologist, and subsequent ACTH stimulation testing in some cases;
- Prompt treatment with cortisol (10–15 mg/m<sup>2</sup>/day divided in three doses) and mineralocorticoid (fludrocortisone 0.05–0.1 mg/day), and salt supplementation;
- Education of family on how to administer medication and adrenal crisis management with stress dose of oral steroids during stress/intercurrent illnesses or IM glucocorticoid if any oral intolerance to be followed by an emergency call to 911;
- Evaluation of internal genital anatomy by ultrasound in presumed females;
- Consultation with surgical specialists with expertise in disorders of sexual differentiation to help with family 's decision making;
- Follow-up with pediatric endocrinology in two weeks, one month, and every three months when stable.

## 4. Further Considerations with CAH

- The cost and emotional impact on families of evaluating those who have a false-positive result. Improving the positive predictive value of screening to safely lower false-positive rates without increasing false negatives. Recent summaries suggest a need for improvement [45]. Cross reacting immunoassays, apart from illness and stress in newborns and prematurity, can be confounding factors. Adjusting cut-off levels based on gestational age or birth weight in premature newborns can help, while adoption of LS/MS secondary screening assaying ratios of various steroids can also help mitigate these [46].
- The lack of screening in developing countries due to expense and need for infrastructure to support programs. As of 2020 the US, 35 other countries and only parts of 17 countries had CAH newborn screening in place [42].
- One cost-benefit analysis suggested that CAH newborn screening may be of lesser merit than screening for CH when strict cost-effectiveness or cost-benefit analysis is performed [23]. However, the demonstrated value of the screening in saving lives suggests that this cost-benefit analysis may not adequately highlight the benefit of a child's life saved for that family or the cost of a child lost to a treatable condition such as CAH.
- Use of prenatal dexamethasone therapy to mitigate or prevent virilization of external genitalia in females with CAH. While this has shown some efficacy in clinical trials, risk to unaffected fetuses continues to raise ethical concerns.

## 5. Summary

There have been significant advances in the diagnosis and treatment in patients with congenital hypothyroidism. The search for novel genetic causes that might contribute to congenital hypothyroidism continues. Management of mild congenital hypothyroidism and neurodevelopmental outcomes in all cases continue to be areas of interest. Overall, CH screening has been a successful public health program, where it has been implemented.

In the seventy years since the initial reports of successful treatment of CAH, advances in knowledge of the underlying biochemistry and genetics have allowed for substantial improvements in medical, psychological and surgical treatment. The impact of advances in genetic analysis and understanding of the pathophysiology of this disorder and the development and adoption of newborn screening have been major foundations of this progress.

**Author Contributions:** Conceptualization, S.K.; resources, S.K., M.D.; writing—original draft preparation, S.K., M.D. and P.B.; writing—review and editing, M.D. and S.K. All authors have read and agreed to the published version of the manuscript.

**Funding:** This research received no external funding.

**Institutional Review Board Statement:** Not applicable.

**Informed Consent Statement:** Not applicable.

**Data Availability Statement:** Not applicable.

**Conflicts of Interest:** The authors declare no conflict of interest.

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