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Newborn screening for congenital hypothyroidism and congenital adrenal hyperplasia: the balance of benefits and costs of a public health success

Guy Van Vliet[1], **Scott D. Grosse**[2]

[1]Endocrinology Service and Research Center, Centre Hospitalier Universitaire Sainte-Justine and Department of Pediatrics, University of Montreal, 3175 Côte Sainte-Catherine, Montreal (Qc) H3T 1C5, Canada

[2]National Center on Birth Defects and Developmental Disabilities, Centers for Disease Control and Prevention, 4770 Buford Highway, Atlanta, GA, 30341, USA

Summary

Newborn screening is an important public health program and a triumph of preventive medicine. Economic analyses show that the benefits of newborn screening clearly outweigh the costs for certain diseases but not necessarily for all. This is due to the great diversity of the natural history of the diseases detected, to the fact that each of these diseases considered individually is rare, and to differences in the effectiveness of interventions. In addition, the benefit-cost ratio of screening for a particular disorder may differ between countries, specifically between high-income and low- and middle-income countries. The burden of a disorder may also be alleviated by increased clinical awareness and effective clinical services, even in the absence of newborn screening. In this article, the authors focus on economic analyses of newborn screening for primary congenital hypothyroidism, which has been in place in high-income countries for roughly 40 years, and for classic congenital adrenal hyperplasia due to 21-hydroxylase deficiency. Screening for the latter is not yet universal, even in high-income countries, although the lack of universal implementation may reflect factors other than economic considerations.

Introduction

Laboratory-based newborn screening (NBS) on dried blood spots collected on filter paper, which began with the method developed by Guthrie and Susi [1] for phenylketonuria (PKU) in 1963, is considered as one of the major advances in preventive medicine over the past half-century [2, 3]. NBS was originally justified as a publicly funded program by its ability to avoid the cost of institutional care for severely disabled individuals with untreated PKU. However, it is unclear what role has been played by the economic benefits of early detection in the establishment and maintenance of NBS for all the other diseases that can now be

guy.van.vliet@umontreal.ca, + 1-514-345-4735.

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screened for. Ever since the time of Dr Guthrie, advocacy by parents and/or professionals has certainly played a major role in the adoption and expansion of NBS.

Economic evaluations of health interventions can be either partial, looking just at costs, or full, reporting calculations of both costs and health consequences. For example, a partial economic evaluation of NBS might report the cost of screening and diagnostic testing per case detected but not the health impacts or downstream costs of screening. There are two main types of full economic evaluations, cost-effectiveness analysis (CEA) and cost-benefit analysis (CBA). CEAs calculate the sum of intervention and treatment costs with and without the intervention and compare the difference in total costs with the difference in health outcomes. A CBA converts all outcomes to monetary values. That includes health outcomes—by assigning monetary values to years of life gained and years of avoided illness. It can also include economic outcomes, such as increased economic productivity.

Both CEAs and CBAs calculate “incremental” cost relative to the costs associated with a comparison strategy. For example, the cost of adding a disorder to a newborn screening panel does not include the fixed cost of the existing newborn screening infrastructure, but only those costs that change when a new disorder is added. In a CEA, analysts are expected to calculate the sums of costs and outcomes for the strategies that are being compared. If one strategy has better outcomes and lower costs than all other strategies (i.e., negative incremental costs), it is said to be the “dominant” strategy and is “cost-saving” [4].

If net costs for a strategy with better outcomes are positive relative to the comparison, CEA analysts calculate the ratio of the incremental cost per unit of health outcome and report it as the incremental cost-effectiveness ratio or ICER. The denominator of the ICER can be life-years saved or quality-adjusted life-years (QALYs), a preference-based measure that combines improvements in both functioning and survival in terms of health utilities. A CEA that calculates outcomes in terms of QALYs can also be said to be a cost-utility analysis (CUA). If the ICER for a proposed strategy is favorable relative to that of accepted healthcare interventions, it is widely considered to be “cost-effective.”

Full economic evaluations may differ in which types of costs are assessed. Economic evaluations conducted from the societal perspective typically include “indirect” or “productivity” costs. These include the lost economic output from affected individuals due to premature death and disability. In addition to complete disability, individuals may be limited in the type or amount of work they are able to perform. Productivity costs can also include the loss of earned income resulting from providing informal care to a disabled family member. Many CEAs and CBAs include estimates of productivity costs, but differences in methods can make it difficult to compare estimates [5, 6].

Congenital disorders such as congenital hypothyroidism (CH) and PKU can result in cognitive deficits, which range in severity from overt intellectual disability to milder deficits within the usual range of cognitive ability in the population. CEAs and CBAs often include the medical, educational, and residential costs of care associated with overt intellectual disability. Some also calculate the loss in lifetime economic output among persons with

intellectual disability. Published CEAs or CBAs of NBS to date have not quantified the economic impact of milder cognitive deficits, unlike in environmental health [7].

NBS is conducted in numerous countries for two endocrine disorders, CH and classic congenital adrenal hyperplasia due to 21-hydroxylase deficiency (CAH). The latter is a single, lifelong, monogenic disorder with a clear pattern of autosomal recessive transmission and NBS has therefore not resulted in an increase in prevalence [8] (Table). By contrast, CH is heterogeneous, encompassing a group of disorders, some of which are monogenic and others are multifactorial in etiology [9]. Primary (or thyroidal) CH is the primary target of NBS because of clear evidence that early detection prevents intellectual disability. Depending on the screening protocol used, NBS programs may also detect cases of central CH, but because of lack of conclusive evidence of improved outcomes from early diagnosis, central CH is not a screening target in most NBS programs [10, 11].

CH may be either permanent or transient, and prevalence of permanent CH at age 3 years or later is substantially lower than CH prevalence during early infancy [12, 13]. Incomplete phenotyping through thyroid imaging and documentation of permanence of hypothyroidism hampers the assessment of causes and implications of primary CH [14] and overreliance on biochemical measures may lead to overdiagnosis at present [15].

Congenital hypothyroidism (CH)

Quebec was the first place in the world where population screening for CH was established on April 1, 1974 [16]. For technical reasons, the biomarker often used initially as the primary test was thyroxine (T_4), but this was replaced by thyroid stimulating hormone (TSH) in Quebec in 1987 and subsequently in most other NBS programs [17]. It has been reported in a partial CEA from the Netherlands that a primary T_4 testing strategy followed by TSH measurement in specimens with low T_4 values, which can detect cases of both central and primary CH, is considerably less expensive than primary TSH testing [18]. However, the remainder of this article focuses on primary CH, the main target of most NBS programs.

The positive predictive value (PPV) of a TSH concentration greater than 30 mU/L of whole blood on a sample obtained after 24 hours of life for a confirmed diagnosis of CH is 95% [19]. Since the implementation of NBS, about two thirds of newborns with confirmed overt CH have thyroid dysgenesis (either sublingual thyroid ectopy or athyreosis) [20, 21]. Prior to NBS, about 30% of children with clinically diagnosed CH received special education due to intellectual disability [22, 23]. Since the implementation of NBS, this proportion has gradually decreased and is now no higher than that of the general population [24].

Given the prevalence of CH, which is 4 to 8 times that of PKU, and the impact of NBS on the prevention of intellectual disability [23, 25], CH quickly became a model disease that illustrates the benefits of NBS. After about a decade of adding NBS for CH on the filter paper cards collected for PKU screening, it was estimated by several groups that the economic benefits of NBS for CH greatly exceeded its costs, with a ratio of 2.5-7.8 dollars in savings for every dollar spent on screening [26]. However, some estimates may have

reflected unrealistic projections of the prevalence and cost of intellectual disability among children with CH [27]. Another economic analysis projected at least 2 dollars in averted education and productivity costs per dollar spent on screening [28].

The majority of CBAs of NBS for CH assumed that most children with CH experience intellectual disability if treated late or not at all. In contrast, a meta-analysis found that 28% of children with clinically diagnosed CH in unscreened cohorts had IQ <70 (the definition of intellectual disability used by the World Health Organization) [23]. In addition, as often happens with screening, implementation of NBS quickly led to an increase in the number of children being diagnosed with CH, from one in 6,500-7,000 to one in 3,100 [12, 23]. A retrospective study in Sweden combined with systematic follow-up was able to assess cognitive and neurological development in 26 of 32 children who had a TSH on the stored NBS specimen > 40 mU/L. Of the 26, 20 (one in 4,500) had permanent hypothyroidism diagnosed at age 5 y, 14 who had been clinically diagnosed and treated at a median age of 5 months (six after 12 months) and six who had not been diagnosed or treated prior to the study. The average cognitive ability among the 20 children with permanent CH was 16 points lower relative to the six children who screened positive but were euthyroid at age 5 [12]. By subgroup, the average loss was 55 points for two children with intellectual disability, 14 points for 12 other children with clinical CH, and 7 points for six children with subclinical CH (Table).

Among children with permanent CH diagnosed by NBS, delayed initiation of treatment beyond 21 days after birth was reported in one study to be associated with an average loss of 8 IQ points [29]. However, other studies did not find a significant association between age at initiation of treatment and cognitive test scores [30]. Because early initiation of high-dose levothyroxine treatment has been shown to normalize cognitive scores in most children with permanent CH diagnosed after NBS, it would be reasonable to include the economic gain in productivity associated with higher IQ scores within the usual range in future societal perspective economic evaluations of CH NBS.

Over time, lowering TSH cut-offs and adding screening samples has predictably led to a further progressive increase in estimated prevalence of CH, typically more than one in 2,000 [14, 19]. Very recently, a program even reported a prevalence of one in 911 births [15] - seven-fold higher than pre-NBS. Many of these children may have isolated hyperthyrotropinemia (transient or permanent) and not CH [31, 32]. Most additional infants diagnosed with permanent CH through lower screening cutoffs or repeat specimens have a normal thyroid anatomy [13, 21, 33, 34], and the benefit of early treatment for such children has not been demonstrated. Accurately projecting the economic benefits of NBS for CH to include all newborns diagnosed with CH is not currently feasible given the controversy about cognitive and educational outcomes for the complete spectrum of children diagnosed with CH through various NBS programs [35].

Children with CH or mild hyperthyrotropinemia at NBS may have behavioral or learning difficulties even if IQ is in the normal range [36, 37]. It appears that abnormal thyroid hormone status in a child is associated with a range of behavioral and developmental

challenges, such as attention problems [38]. However, it is not established whether NBS and early diagnosis avoids those issues.

Lastly, it is sobering to realize that 70% of the world's newborns do not benefit from any NBS at all [17, 39]. In some low- and middle-income countries (LMICs), sending filter papers to a central laboratory may not be feasible because of a high proportion of home deliveries and transportation hurdles hampering same-day sample transfer to the laboratory. A bedside TSH measurement (*point-of-care test or POCT*) by a health worker attending the birth or visiting the mother and newborn soon after could potentially overcome the lack of NBS infrastructure. Although POCT technology for TSH measurement suitable for NBS is not currently available, it has already been developed and tested for sickle cell anemia [40], another major public health problem in many LMICs for which NBS appears cost-effective in pilot studies [41]. It is not yet clear how the POCT approach to NBS might be implemented on a population basis. As with centralized laboratory testing, POCT screening, if implemented as a public health program, would require quality assurance. Quality assurance could be facilitated through prompt transmittal of screen-positive results by cell phone to the relevant professionals and use of information technologies by public health authorities for regular audits of program performance. Importantly, NBS is just the beginning of a process that leads to confirmation of the diagnosis of CH and ideally of its etiology, adequate continuous treatment and documentation of outcomes [42]. All of these downstream aspects of NBS are particularly a challenge in LMICs.

In conclusion, the costs of NBS for overt CH are clearly justified by the ensuing benefits. However, the full achievement of the benefits of NBS requires prompt follow-up and initiation of treatment along with continued monitoring and lifelong treatment for individuals with permanent CH.

Congenital Adrenal Hyperplasia (CAH)

NBS for classic CAH due to 21-hydroxylase deficiency, a condition with a prevalence in high-income countries of about one in 18,000, both before and after NBS [8], was first proposed in 1977 with the primary objective of preventing the death of affected boys [43]. Many historical case series had shown a marked female predominance [44]. Because the mode of inheritance of CAH is autosomal recessive, this imbalance likely reflected underdiagnosis of affected boys, since in contrast to genetic females, their external genitalia are unambiguous and there is no clinical clue to the diagnosis at birth. Increased clinical recognition has led to the expected Mendelian ratio of males and females, even in the absence of NBS [45], including in middle-income countries, such as Brazil [46]. Losing a newborn because the diagnosis of an eminently treatable disease has not been made is a tragedy for parents, which cannot be expressed in monetary terms [47]. Fortunately, this tragedy has become exceptional in high income countries [8], although it still occurs in a few cases, even where NBS has been implemented [48]. Regardless of NBS, healthcare professionals caring for newborns should think of this diagnosis in cases of dehydration or insufficient weight gain, a very sensitive indicator of the severe, potentially fatal salt-wasting form of CAH [49].

Another often quoted argument in favor of NBS for CAH is to “avoid misassignment” of a fully virilized genetic female newborn to a male sex, which can also lead to genital surgical reconstruction. However, this major and contentious challenge for parents is not “avoided” by NBS. Rather, in the majority of these cases, genetic sex is established a few days earlier than it would be when a salt-wasting crisis leads to the diagnosis.

Screening for CAH using 17-hydroxyprogesterone (17OHP) as the biomarker was implemented in New Zealand and some US states and Canadian provinces in the early 1980s but was not universally recommended in France until 1995 and in the USA until 2005. Over time, NBS for CAH has been gradually implemented in most high-income countries, with holdouts including the United Kingdom [50] and some Australian states and Canadian provinces [45].

Two published CEAs of NBS for CAH in the USA yielded conflicting results as to whether NBS would be considered cost-effective relative to other preventive strategies [51, 52]. The two studies assumed different probabilities of death in the absence of NBS [8, 53], with the less favorable cost-effectiveness results reflecting an evidence-based assessment of mortality data suggesting that no more than 3% of infants with CAH in high-income countries die in the absence of NBS versus an infant mortality rate of 10% assumed in the other CEA. An erratum to the second CEA concluded that, even correcting for calculation problems, NBS for CAH would not meet conventional cost-effectiveness criteria [54]. The less favorable cost-effectiveness findings on NBS for CAH relative to CH reflect the very small number of potentially preventable deaths from this rare disorder in high-income countries, even taking into account the preventable costs of hospitalizations due to salt-wasting crises [53]. Nonetheless, decisions on screening for particular disorders are primarily determined on the basis of better outcomes for affected children, not considerations of economic benefits [27].

Newer economic evaluations of NBS for CAH have explored two additional avenues for showing economic value. First, a Canadian study reported greater preventable hospitalization costs than previously reported but assumed no reduction in mortality with NBS [55]. Second, even though relatively few children with clinically diagnosed CAH experience neurocognitive effects similar to those that were observed in CH before NBS [45, 56], two economic evaluations of NBS for CAH, an unpublished study from Australia and a recently published study from Brazil, have modeled reductions in neurocognitive impairment as an expected benefit [53]. The Brazilian study provided supporting evidence of an excess rate of neurological impairment in children with CAH in that country [46]. The magnitude of benefit of NBS may be more evident in LMICs because of limited access to qualified professionals, a higher neonatal mortality or more severe neonatal morbidity from CAH [46]. An interesting question is whether more thorough education of professionals might achieve the primary objective of screening, to prevent the death of affected boys, possibly at a lower cost than with NBS [44].

Although NBS for CAH is recommended by expert opinion [57], the lack of its universal implementation may result from questions about its rationale, different priorities in expanding NBS and the rarity of severe outcomes. One challenge is the short turnaround time required for reporting results, especially if the blood spots are collected late in the first

week of life (as is the case in the UK), since death from a salt-wasting crisis can occur as early as day 8 [47]. Another challenge is the very low (<10%) PPV of 17OHP [58, 59], the biomarker used as first-tier screening for CAH. Elevated 17OHP is frequent in children born prematurely, but since CAH is not frequently observed in premature infants [45], a different strategy in this subgroup may be warranted [48]. The PPV of screening for CAH can be improved by adding other biomarkers or repeat specimens. Although second-tier screening increases costs, the reduction in false-positive screening results may justify the added expenditure. For example, the New South Wales screening program in Australia recently reported a PPV of 71% for 17OHP immunoassay screening of specimens collected at 48-72 hours followed by steroid profiling using liquid chromatography tandem mass spectrometry of specimens in the top 2% of 17OHP values by birthweight as well as repeat specimens for first-tier positive screens [60]. The program notified providers of presumptive results in all cases by day 9, prior to the occurrence of any adrenal crisis among the 10 infants identified with CAH. These recent developments may lead to the universal adoption of NBS for CAH.

Conclusion

The individual and societal-level health and economic benefits of NBS for permanent CH have been clearly demonstrated, which is why CH is typically among the first disorders for which newborn screening is established. The economic benefits of NBS for CH may have been incompletely calculated, i.e., understated, by not taking into account changes in the overall distribution of cognitive and behavioral endpoints. On the other hand, some newborns, especially those born preterm, have transient hyperthyrotropinemia and are currently identified with CH and treated with levothyroxine, the benefits of which are unclear. It has been argued that this can result in overdiagnosis of CH and the undue medicalization of a large number of premature infants [61], which future economic analyses of NBS might consider [62]. The economic benefits of NBS for CAH are ambiguous, as mortality has become very rare in high income countries and a causal relationship between the initial dehydration episode and neurocognitive sequelae has not been established [53].

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Table.

Comparison of economic analyses of NBS for primary CH and classic CAH

Disease	**CH**	**CAH**
Prevalence before NBS	1/6,500	1/18,000
Prevalence after NBS	1/2,000 or more	1/18,000
Benefits of NBS	Normalizes IQ in all	-Prevents neonatal deaths -Shortens initial hospital stay -Shortens duration of sex misassignment
PPV of biomarker	95% for TSH > 30 mU/L	1-10% for 17OHP > 50 nmol/L
Savings (per US $ spent on NBS)	2 $ or more (negative net cost)	<1 $ (positive net cost)
Gain of IQ among children with permanent CH (prevalence of 1 in 4,500 in Swedish study by Alm et al. 1984) [12]	Variable impact of timely treatment – mean increase of 16 IQ points (range 7-55)	NA
ICER (if positive net cost)	NA	Less than USD 150,000 per life-year saved

CAH – congenital adrenal hyperplasia

CH – congenital hypothyroidism

ICER – incremental cost-effectiveness ratio

IQ – intelligence quotient

NA – not applicable

NBS – newborn screening

PPV – positive predictive value

TSH – thyroid stimulating hormone