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Expert Opinion on Orphan Drugs

ISSN: (Print) 2167-8707 (Online) Journal homepage: informahealthcare.com/journals/ieod20

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To cite this article: Andrea E DeBarber (Research Assistant Professor) & Robert D Steiner (Executive Director-Marshfield Clinic Research Foundation and Visiting Professor) (2014) A US perspective on newborn screening: a powerful tool for prevention, Expert Opinion on Orphan Drugs, 2:11, 1151-1157, DOI: 10.1517/21678707.2014.978857

To link to this article: https://doi.org/10.1517/21678707.2014.978857

EXPERT OPINION

A US perspective on newborn screening: a powerful tool for prevention

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This article describes the rise of newborn screening in the USA, where it has become a powerful tool to prevent the mortality, morbidity and disability otherwise associated with many undetected rare conditions. In an effort to improve harmonization of newborn screening across the USA, a Recommended Uniform Screening Panel (RUSP) of core conditions was proposed in 2005 that is now near universally screened for. An evidence-based procedure has been developed to assess candidate conditions nominated for addition to the RUSP. Multiple stakeholders must play a role to generate the high-quality evidence required to support successful nomination of a condition for addition to the RUSP. The nomination, and potential addition, of conditions to the RUSP, can be a difficult and lengthy process. Screening newborns for new conditions requires significant effort not only on the part of researchers to develop screening tests and treatments but also on the part of newborn screening programs to implement new testing methodologies, in quality management, follow up, diagnosis and education. Continued advances in newborn screening methodologies and development of new treatments for rare conditions not currently screened for in newborns offer exciting new avenues to prevent mortality, morbidity and disability in newborns affected with rare conditions.

Keywords: addition of new conditions to the RUSP, newborn screening, rare conditions, Recommended Uniform Screening Pane

Expert Opinion on Orphan Drugs (2014) 2(11):1151-1157

1. History of newborn screening in the USA

The birth of modern newborn screening as a powerful tool to detect rare diseases and prevent morbidity and mortality took place with the introduction of newborn screening for phenylketonuria (PKU) in the 1960s. PKU is an autosomal recessive genetic metabolic disorder associated with an inability to process phenylalanine. If it is detected early enough, treatment with a phenylalanine-restricted diet can prevent severe morbidity. Late treatment generally leads to intellectual disability, though the disability can be mild or profound depending on age at initiation. Prior to the introduction of newborn screening for this disorder, new cases of untreated or late-treated PKU numbered in the hundreds each year [1]. In a 1961 study to validate the bacterial inhibition assay and filter-paper disc for blood collection he developed to screen for PKU (Guthrie card), Robert Guthrie reported that almost 1 in every 142 cases of intellectual disability at the Newark state School were caused by PKU [2]. Guthrie went on to show that the bacterial inhibition assay and filter-paper disc specimen collection could successfully detect elevated phenylalanine in blood to enable screening for the disorder in large populations of newborn infants [3]. At the same time, advocacy to begin screening newborns for PKU from Guthrie and groups such as the National Association of Retarded Citizens

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(this term reflects the language of the time and no endorsement through its use is intended) and the March of Dimes in the USA led to the legislation requiring newborn screening for PKU in Massachusetts, Oregon, Delaware and Vermont by 1963 [4] (implementation of newborn screening for PKU may have occurred sooner in some of these states) [5]. Over the next decades, development of new tests using dried blood spots from the Guthrie card allowed for a number of additional conditions to be screened for in newborns, notably congenital hypothyroidism, sickle-cell disease, congenital adrenal hyperplasia and galactosemia. Screening for sickle-cell disease and other hemoglobin disorders [6] was the first use of a single procedure to detect a number of significant disorders.

From these beginnings, newborn screening recently celebrated its 50th birthday in the USA, where newborn screening has grown to become the largest coordinated population-based screening public health endeavor ever undertaken with > 4 million newborns tested annually for a wide range of conditions. Although the estimated 12,000 affected newborns identified each year by US Newborn Screening Programs [7] includes infants that may remain asymptomatic or who are affected with mild conditions, the mortality, morbidity and disability prevented in a large number of children justifies newborn screening as one of the most successful public health programs ever implemented. Although some of the conditions screened for may be quite rare individually, collectively > 1:300 newborns have a condition detectable by newborn screening.

2. Recommendations at the national level for newborn screening in the USA

In the 1990s development of tandem mass spectrometry (MS/MS) methodology for newborn screening was a transformative event in the field of newborn screening that enabled expanded screening for amino acid and fatty acid oxidation disorders, as well as organic acid conditions, using a single dried blood spot specimen [8-10]. By the late 1990s, significant differences existed between the states in the number of conditions that were screened for in newborns [11]. In which state babies affected with certain conditions were born could determine whether their condition was detected or not. In an effort to improve harmonization of newborn screening across the USA, an expert panel was convened in 2004 by the American College of Medical Genetics (ACMG) who proposed a Recommended Uniform Screening Panel (RUSP) of 29 core conditions that all states should screen for [12]. The expert panel convened by the ACMG developed a set of guiding principles followed by the development of criteria with which conditions were to be evaluated for inclusion in the RUSP and the identification of conditions to be evaluated, based in part on Wilson–Jungner criteria established by the World Health organization in 1968 [13], for example, that the clinical implications of the condition are significant and well characterized, that there is readily available effective treatment and that there is a diagnostic test for the condition, as well as a suitable screening test. Proposed conditions included amino acid and fatty acid oxidation disorders, organic acid conditions, endocrine disorders (primary congenital hypothyroidism and congenital adrenal hyperplasia), hemoglobin disorders and other disorders including biotinidase deficiency, cystic fibrosis, classical galactosemia and hearing impairment. Hearing impairment is the only condition of the 29 original core conditions to be screened for using point-of-care testing; for all other conditions, screening is performed using a filter-paper dried blood spot routinely collected by pricking a newborn's heel 24 – 48 h after birth.

The proposed RUSP [12] was endorsed by the responsible body for newborn screening recommendations at the national level in the USA: the Discretionary Advisory Committee on Heritable Disorders in Newborns and Children (DACHDNC) (formerly Secretary's Advisory Committee on Heritable Disorders in Newborns and Children). The DACHDNC provides evidence-based recommendations to the US Secretary of Health and Human Services (HHS) who in turn provides guidance to state newborn screening programs about which conditions should be screened for in newborns. The Secretary endorsed the proposed RUSP in 2010 [14]. The core RUSP conditions are now near universally screened for across the USA, with many states also identifying secondary conditions detected in the process of screening for core conditions [12]. For secondary conditions that are extremely rare and/or for which the clinical implications are unknown, the benefits of screening are questionable. For core conditions, the benefits of newborn screening to those affected, their families and society are fairly clear. An example of a condition for which there is particularly strong evidence of benefit is medium-chain acyl-coenzyme A dehydrogenase deficiency (MCADD). A study in the Netherlands demonstrated this disorder is fatal in approximately 25% of children at the time of their first febrile illness [15]. In another study, it was noted that 19% of children with MCADD died before a diagnosis was made [16]. For MCADD-affected infants identified through newborn screening, an excellent outcome can be expected with simple treatment. Newborn screening also identifies mildly affected MCADD children, who would not undergo metabolic crisis and be diagnosed in the absence of screening. Studies have confirmed that presymptomatic detection of MCADD through newborn screening is healthcare cost-effective compared to no screening [17,18].

3. Addition of new conditions to state newborn screening panels in the USA

Addition of conditions to newborn screening panels is driven in the USA either by individual state mandates that require screening for conditions currently outside of the RUSP or nationally by addition of new conditions to the RUSP. To add a new condition to the RUSP the DACHDNC has

Table 1. Outcome for conditions nominated for addition to the RUSP [47].

Condition	Date of nomination	Underwent external evidence review	Recommended for addition to the RUSP	Date of addition to the RUSP
Severe combined immunodeficiency	2007	Yes	Yes	2010
Pompe disease	2007	Yes	No	
Niemann-Pick disease	2007	No		
Fabry disease	2007	No		
Krabbe disease	2008	Yes	No	
Spinal muscular atrophy	2008	No		
Hemoglobin H disease	2009	Yes	No	
Neonatal hyperbilirubinemia	2009	Yes	No	
Critical congenital heart disease	2009	Yes	Yes	2011
22q11.2 deletion syndrome	2011	No		
MPS 1 (α-L-iduronidase deficiency)	2012	Yes		
Pompe disease	2012	Yes	Yes*	
X-linked adrenoleukodystrophy	2012	No		
X-linked adrenoleukodystrophy	2013	Yes‡		

*To be determined by Health and Human Services Secretary.

‡Under external review.

RUSP: Recommended Uniform Screening Panel.

developed a transparent, evidence-based procedure to assess conditions nominated for addition [19]. This was recently revised to allow formal evaluation of the challenges that state newborn screening programs face in adopting screening for new conditions [14]. The procedure consists of nomination of a condition with supporting evidence available demonstrating that the condition fulfills Wilson–Jungner criteria for screening (wisdom that has guided newborn screening efforts over many decades). The DACHDNC makes a determination regarding addition of the condition to the RUSP on the basis of net benefit to the population of screened newborns that could result from screening [14]. A systematic evidence review performed by an external review workgroup may take place and based on the results of the evidence review the DACHDNC will recommend to the Secretary of HHS whether the condition should be added to the RUSP. Conditions that have been nominated since 2006 include severe combined immunodeficiency (SCID), a number of the lysosomal storage disorders (LSDs), including Pompe disease, Niemann-Pick disease, Fabry disease Krabbe disease and mucopolysaccharidoses (MPS 1), as well as spinal muscular atrophy, hemoglobin H, critical congenital heart disease, neonatal hyperbilirubinemia, X-linked adrenoleukodystrophy and 22q11.2 deletion syndrome (for each nomination outcome see **Table 1**). Of the conditions evaluated to date, the DACHDNC has recommended to the Secretary of HHS the addition of SCID, critical congenital heart disease and, most recently, Pompe disease to the RUSP. Approval by the Secretary in 2010 to add SCID and in 2011 to add critical congenital heart disease to the RUSP (the addition of Pompe disease is still under review), brought the recommended number of core conditions to be screened for in newborns in the USA to 31. Universal pulse oximetry testing with clinical examination was proposed to screen newborns for critical congenital heart disease; point-of-care testing similar to was performed to screen for hearing impairment. Most states require hospitals to perform point-of-care testing for critical congenital heart disease, with no oversight required by newborn screening programs. state newborn screening programs are working toward implementing screening for SCID, despite barriers including significant resource constraints. Although the development of new quantitative polymerase chain reaction-based methodology to screen for severe T-cell lymphopenias, including SCID, played an important role in successful nomination of this condition for addition to the RUSP [20-23], it has been a challenge for many newborn screening laboratories to adopt this testing methodology, and implementation of screening for SCID has been slower than hoped for. Kwan *et al.* recently reported that newborn screening for SCID in 11 US newborn screening programs (out of 23 performing screening for SCID, along with the District of Columbia and the Navaho Nation) identified SCID in one in 58,000 infants, with high survival through diagnosis and treatment [24]

4. Expert opinion

The nomination and potential addition of new rare conditions to the RUSP can be a difficult and lengthy process. Nomination of a candidate condition for addition to the RUSP requires supporting evidence regarding the clinical characteristics and natural history of the condition, available treatment, available diagnostic confirmation and a suitable high-throughput test to screen newborns for the condition. The DACHDNC assesses net benefit by considering health benefits that could result from screening, the harms associated with screening, the efficacy and effectiveness of testing and follow up compared with usual clinical practice. Multiple

stakeholders must play a role to generate the high-quality evidence required to support successful nomination of a condition for addition to the RUSP including researchers, healthcare professionals and organizations, newborn screening programs, advocacy groups (specialized rare condition and general groups such as the National Organization for Rare Disorders), as well as affected individuals and their families. Collaboration between these stakeholders is critical as, for many rare conditions, the high-quality supporting evidence required for successful nomination, including test and clinical benefit data for affected individuals, is often not available and can be difficult to generate. Reasons for this include lack of funding for rare disease research and difficulty obtaining an adequate sample size for experimental treatment trials or for natural history studies. Frequently, clinical presentation and outcome data, as well as incidence data, for rare conditions are not well characterized (paradoxically, performing newborn screening may be the only way to generate data for certain conditions). For conditions with treatments available, it can be challenging to develop and validate new screening technologies that require the use of residual dried blood spots left over after newborn screening has been completed, in particular specimens from affected infants. There have recently been a number of lawsuits pertaining to the storage and use of residual dried blood spots by newborn screening laboratories [25]. Although residual dried blood spots are primarily used for newborn screening laboratory quality control and quality assurance purposes, they are an essential for development and validation of new newborn screening tests. Pilot screening studies to evaluate newly developed screening methodologies on a population level are also essential for nomination. These can be difficult to perform as state newborn screening programs are health department-based with generally no research mission or budget. Pilot screening studies are, therefore, usually research investigator-initiated and dependent on collaborative state newborn screening programs. To support this type of newborn screening research, the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development at the US National Institutes of Health (NIH) has provided funding to the ACMG to develop and maintain the Newborn Screening Translational Research Network and its Coordinating Center – a resource to facilitate research through an infrastructure that provides the research community access to newborn screening resources (e.g., a virtual repository of dried blood spots and ethical and regulatory guidance).

Although it can be challenging to generate the supporting evidence required to successfully nominate a candidate condition for addition to the RUSP, evidence-based review through the DACHDNC ensures that screening for new conditions is feasible and will provide clinical benefit for affected children. Limited public health resources mean that newborn screening programs must proceed judiciously, employing a strategic process of adding new conditions to their newborn screening panels [25]. Newborn screening is a multi-part system comprising sample collection, laboratory testing, follow up, diagnosis, timely treatment, following outcomes [11], with education of healthcare professionals and parents also a priority (educational information for healthcare professionals and families can be found at the National Newborn Screening and Global Resource Center website http://genes-r-us.uthscsa.edu/, also the Genetic Alliance website http://www.babysfirsttest.org and Save Babies Through Screening Foundation's website http://www.savebabies.org). Screening for new conditions in newborns requires significant effort not only on the part of researchers to develop new screening tests and treatments but also on the part of newborn screening programs to implement new testing methodologies, in quality management, follow up, diagnosis and education.

Lobbying from affected families and advocacy groups has played a role in driving the legislation in some states across the USA that mandates screening of newborns for additional conditions outside of the RUSP. These include conditions that may not previously have been considered as good candidates for newborn screening according to classical Wilson–Jungner criteria. One such example is the recent implementation of newborn screening for Krabbe disease in New York state. Addition of Krabbe disease to the New York state Screening Program has been controversial [26]. Krabbe disease is a member of the LSD family; a large group of almost 50 disorders bound by the accumulation of disorder-specific substrates in the lysosome. The accumulation is progressive, leading to cellular and ultimately tissue and organ dysfunction. Symptoms differ by disorder but can be severe, often with CNS involvement. Individual LSD may be rare, but collectively the LSDs are thought to be relatively common (1 in ~ 7 – 8000 individuals). Treatments are available for some LSDs including hematopoietic stem cell transplant which has been variably successful for MPS I (Hurler), MPS VI (Maroteaux-Lamy), Gaucher disease, metachromatic leukodystrophy and Krabbe disease [27,28], though this would generally no longer be offered for non-neuronopathic MPS 1, MPS VI or Gaucher disease. The US FDA has approved intravenous recombinant enzyme replacement therapy for Gaucher disease, Fabry disease, MPS I/II/VI and Pompe disease [29]. Therapy with small-molecule 'chaperones' (molecules that restore some enzyme functionality by stabilizing misfolded proteins) has been being explored for Fabry disease, Gaucher disease and Pompe disease. As with SCID, screening newborns for LSD was made possible by development of new methodologies to screen dried blood spots for LSD, including MS/MS methodology for concurrent detection of multiple LSDs using a single dried blood spot and digital microfluidics, a cost-effective lab-on-a-chip platform enabling enzyme assays or immunoassays and molecular testing [30]. The MS/MS methodology to screen for LSD is based on reconstituting the deficient enzyme and measuring enzyme activity by incubation with (non-naturally occurring or stable-isotope labeled) enzyme-substrate, with little or no enzyme product formed for dried blood spots from affected newborns [31-36].

Most LSDs have not been considered good candidates for newborn screening as there is no good genotype–phenotype correlation for many LSDs, with phenotype expression often highly variable and difficult to predict [26]. For example, with Krabbe disease, clinical manifestations can range from an early infantile form to intermediate and adult forms, and additional asymptomatic forms may exist. Treatment with hematopoietic stem cell transplantation is generally more effective before the onset of irreversible pathology, but complications can be severe after transplantation that is typically performed using umbilical cord blood, a procedure with a 10% mortality and significant morbidity [27-29,37,38]. Of the ~ 550,000 newborns reported to have been screened for Krabbe in New York state between 2006 and 2008, four newborns were identified to be high risk for early onset Krabbe disease [39]. Two underwent stem cell transplantation, one of whom died from complications, whereas the other had no symptoms of early infantile Krabbe disease but was developmentally delayed. The other two remained normal (without transplant) at 8 and 16 months of age, ages at which they would be expected to have shown signs of Krabbe disease if they had the early infantile form [39]. The anxiety felt by parents of children who have serious and progressive conditions like Krabbe disease with variable phenotype expression and age of onset, and treatment that is not without risk, is often shared by healthcare professionals who must provide clinical management [26]. Screening for rare conditions with variable phenotype expression and age of onset or with no treatment yet available may provide broader benefit than to just the affected infant; for example, the 'diagnostic odyssey' described by many parents is prevented and reproductive choices are enabled for future pregnancies [40]. A number of candidate conditions that may be nominated for addition to the RUSP in the near future include Duchenne muscular dystrophy [41], Fragile X syndrome [42], Wilson disease, familial hypercholesterolemia, Friedreich's ataxia [43], cerebrotendinous xanthomatosis [44] and creatine synthesis disorders (glycine amidinotransferase and guanidinoacetate methyltransferase deficiency). In contrast to addition of discrete conditions to the RUSP, whole-genome and whole-exome sequencing newborn screening research is currently being performed [45] that has the potential to diagnose a vast array of conditions at birth but which is associated with a host of ethical, legal and social implications. Genome-scale technologies may reduce the cost and time required to sequence an entire human genome and, in the context of newborn screening, could facilitate more accurate diagnosis and allow for the detection of more conditions. Newborn screening has rapidly evolved over the past decades and will continue to evolve, with the classical wisdom guiding screening [13] challenged by a new vision for the future articulated by Duane Alexander former head of the US National Institute for Child Health and Human Development [46]. Alexander argues that newborn screening should be expanded to identify as many infants with rare conditions as possible as the classical wisdom 'dooms us to continued ignorance and unavailability of treatment because affected individuals are not identified till they exhibit symptoms too late for effective preventative interventions to be tested or applied'. The future of newborn screening is unknown but what is certain is that continued advances in newborn screening methodologies and development of new treatment and disease management strategies for rare conditions not currently screened for in newborns offer exciting new avenues to prevent mortality, morbidity and disability in newborns affected with rare conditions.

Acknowledgments

The authors gratefully acknowledge Marie Fleisner's help to edit this article.

Declaration of interest

AE DeBarber has been supported as a KL2 awardee by the Oregon Clinical and Translational Research Institute (OCTRI), grant number (KL2TR000152) from the National Center for Advancing Translational Sciences (NCATS) at the National Institutes of Health (NIH) and also as a training grant awardee by the Sterol and Isoprenoid Diseases (STAIR) consortium. STAIR is part of the NIH Rare Diseases Clinical Research Network (RDCRN). Funding and/or programmatic support for this project has been provided by a grant (1U54HD061939) from the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) and the NIH Office of Rare Diseases Research (ORDR). The authors have an awarded patent and a pending patent related to newborn screening for sterol disorders, with no enumeration received. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony or grants or patents received or pending, or royalties.

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