Newborn screening for neuromuscular disorders from around the world:

Lessons for the United States

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Abbreviations

ACHDNC = Advisory Committee for Heritable Disorders in Newborns and Children

CDC = Centers for Disease Control and Prevention

CK = creatinine kinase

DMD = Duchenne Muscular Dystrophy

ERT = Enzyme replacement therapy

FDA = Food and Drug Administration

GAA = acid-alpha-glucosidase

HHS = Health and Human Services

MDG = Muscular Dystrophy Group

NBS = Newborn screening

PKU = Phenylketonuria

RUSP = Recommended uniform screening panel

SMA = Spinal muscular atrophy

SMN = survival motor neuron

UK = United Kingdom

US = United States

Workgroup = Advisory Committee for Heritable Disorders in Newborns and Children Internal

Nomination and Prioritization Workgroup

ABSTRACT (248 words)

The history of newborn screening (NBS) for neuromuscular disorders began in 1975 with screening male infants for Duchenne Muscular Dystrophy (DMD) by measuring creatinine kinase on the newborn blood spots from two Midwestern hospitals in the United States (US). Over the next 40 years, 10 programs were implemented around the globe, although only one country continues to do so. The longest running program was in Wales (1990-2011) and it collected both clinical as well as psychosocial data. In the last 2 decades, two other neuromuscular disorders have been proposed for NBS: Pompe Disease and Spinal Muscular Atrophy (SMA). The first pilot program for Pompe Disease began in 2005 in Taiwan and it was adopted into their national NBS program in 2008. Missouri was the first US state to implement Pompe NBS and, with its inclusion in the Recommended Universal Screening Panel by the Advisory Committee on Heritable Disorders in Newborns and Children (US) in 2015, other states will follow quickly. The only pilot SMA NBS program to date was scheduled for Utah and Colorado, but in the end recruitment occurred only in Utah, recruitment was slow, and no data have been released to-date. In this manuscript, we argue that there are lessons to be learned from the Wales DMD program that could benefit the US public health departments as they develop screening protocols for neuromuscular disorders like DMD, Pompe and SMA. We argue that screening for all three conditions challenge traditional screening criteria and should require parental permission.

Introduction

Traditionally, the main justification for adding a condition to a state newborn screening (NBS) panel was to identify a disorder that would present in infancy for which early intervention was necessary to reduce morbidity or mortality. The criteria for such public health screening were first enumerated by Wilson and Jungner in 1968,[1] but many other advisory committees in the United States [US] [2-11] and around the world [12-19] have come to similar conclusions. These criteria include the need for an easy, cheap and accurate screening test, an accurate and available diagnostic test, and an effective treatment. Despite broad consensus in both US and international statements that screening requires parental permission, there is disagreement about whether screening should be opt-in versus opt-out and whether it should require written permission. In the US, NBS is mandatory, although most states allow parents to opt-out.

In the US, NBS is a state function. Historically, states varied in the conditions for which they screened, whether they routinely performed a second screen, and the methodology and cut-offs they used for declaring a screening test to be positive. In 2005, the US Department of Health and Human Services' (HHS) Advisory Committee for Heritable Disorders in Newborns and Children (ACHDNC) was established to promote equity between state newborn screening (NBS) panels, amongst other goals.[20] In 2006, the ACHDNC recommended that all states adopt a uniform screening panel of 29 primary conditions that was developed by the American College of Medical Genetics (now the American College of Medical Genetics and Genomics) in collaboration with the Health Resources and Services Administration.[21] Although adoption of the conditions in the recommended uniform screening panel (RUSP) into state NBS panels is voluntary, all states adopted the initial recommendations and conditions added to the RUSP more recently are being adopted, albeit at different speeds by different states.

Three neuromuscular conditions--Duchenne Muscular Dystrophy (DMD), Pompe Disease, and Spinal Muscular Atrophy (SMA)--have been proposed for the RUSP by advocates in the US, although only Pompe is currently included. In this manuscript, we examine in detail the NBS programs that have existed for these three neuromuscular disorders. These conditions differ in their age of presentation, their symptomatology, and their treatability. We argue that each challenges public health screening criteria and, therefore, should not be included in mandatory screening programs. However, there are clinical, social and reproductive reasons why some parents may want this information early and why some states may be willing to offer it. As such it may be appropriate to offer these conditions but to require parental permission to opt-in to testing in contrast with current mandatory practices that are best described as opt-out. A tiered approach has been supported by the Task Force on Genetic Screening,[5] the American Academy of Pediatrics (AAP) Newborn Screening Task Force,[6] and the President's Council on Bioethics.[8] The main benefit of the tiered approach is its acknowledgment that the clinical benefits and risks provided by screening vary between conditions and that screening that provides great benefit and low risk to the child (tier one) should be highly encouraged whereas greater parental discretion should be given to screening for conditions (tier two) in which 1) treatment is not needed urgently or is not highly effective; or 2) symptoms may not present for months to years. We argue that the three neuromuscular conditions are most appropriately included in the second tier. We further argue that, if second tier screening is offered, a coordinated infrastructure and social support program are needed to support those families who receive a positive diagnosis, particularly for conditions where there may be a significant time delay between recognition through screening and clinical presentation.

Duchenne Muscular Dystrophy (DMD)

DMD is an X-linked neuromuscular disorder characterized by progressive muscle weakness, mainly in boys. A major reason to support screening is to avoid the diagnostic delay that frequently occurs. The mean delay between presentation to a health professional and diagnosis around the globe has consistently been approximately 2 years.[22-25] This diagnostic odyssey is in itself distressing,[25-28] and also prevents parents from accessing genetic counselling and prenatal diagnosis in future pregnancies. More recently, late diagnoses may have inappropriately delayed timely access to steroids that prolong ambulation.[28]

In 1975, Zellweger and Antonik described screening 1,500 male infants for DMD by measuring creatinine kinase (CK) in the newborn blood spots from two Midwestern hospitals in the United States.[29] Having established the proof of principle of CK testing on dried blood spots, the first NBS program for DMD began in New Zealand in 1979.[30] Ten thousand boys were screened and 2 cases of DMD were identified. Programs in Edinburgh, West Germany, Canada, France, Belgium and Cyprus followed.[31] In 1991, Naylor of Pittsburgh PA (US) reported screening approximately 73,000 newborns, including 20,000 specimens from Sao Paulo, Brazil. What was unique to this program was the goal "to provide rapid confirmation of the diagnosis as early as possible," by using "multiplex PCR amplification of DNA from the initial filter paper blood specimens."[32 at p. 23]

But concern about late diagnoses must be balanced by concern about the potential for parental distress and family disruption that might result from identifying pre-symptomatic infants.[33-35] To mitigate the delayed diagnosis/diagnostic odyssey without causing the potentially damaging consequences of screening in the newborn period, a study in Wales attempted to identify boys with DMD by targeting boys not walking when they reached 18

months.[36] Unfortunately, this pilot did not demonstrate any benefits of screening, in part because at least half of affected boys do walk independently by that age.[37] Then, in 1990, with support from the Muscular Dystrophy Group (MDG) of the United Kingdom (UK), Wales began to screen infant boys for DMD by measuring CK on the newborn bloodspot. At that time, the Wales NBS program only tested for phenylketonuria (PKU) and hypothyroidism, both of which require immediate treatment. The decision was to make DMD optional and to require a separate consent "because the disease is untreatable, and there has been uncertainty about the effects on the family of such an early diagnosis."[38 at p. 550]

Although the Wales DMD program was not the first to screen for DMD, it was the longest running program (1990-2011) and it collected both clinical and psychosocial data.[39] In the first 3 years, 34,219 boys were screened and nine affected boys were identified. In their first report, Bradley and colleagues noted that 8 of 9 families were satisfied with the process.[40] Experience with the first few screen-positive families led the program team to modify their protocol that then remained stable for the rest of the duration of the program. The family who was not satisfied had been informed at 2-3 weeks, earlier than in the program that developed subsequently, and their experiences helped the screening team to settle on a program of delayed return of results accompanied by a clear explanation about the purpose of follow-up testing and the provision of psychosocial support during the process. The protocol delayed recontacting the family about a positive screen until 4-6 weeks of age, with discussion in advance between the laboratory, the local pediatrician and the family's primary health care team, especially the health visitor. When contact was established, the parents were informed of the results and the need for a second sample to confirm or refute the risk of neuromuscular disease. If the parent(s) consented to a repeat bloodspot, a system was in place to minimize delays in testing, reporting of results,

and arranging for a medical consultation[38]—all done with provision of on-going support involving the primary care team and (for much of the program) the Muscular Dystrophy Group-supported Family Care Officer or a successor, a National Health Service-employed equivalent.

Overall, in the 21 years that the program ran in Wales, approximately 94% of families of male infants agreed to screening, with 145 cases having an initially raised CK activity (at least 250 U/l) and at follow-up, at ~6 weeks of age, this had returned to normal in 79 but remained elevated in the other 66 infants. Of these boys, 56 had DMD, five had Becker muscular dystrophy and the other five had different, rare muscle disorders.[39]

Most parents of children affected with DMD in Wales believed the benefits of early screening outweighed the harms for the child and family, in part because it avoided the diagnostic odyssey.[26,41] Although the Wales data are reassuring, in that most parents expressed satisfaction, the data do not provide proof that it is in an affected boy's best interests for his parents to have this information before he becomes symptomatic. Although 10 NBS programs have screened for DMD over the past 40 years, only one country (Belgium) continues to do so.[31] Despite waning support internationally, surveys of US pregnant women and parents of children affected with DMD, Becker muscular dystrophy and SMA show very strong support for pre-symptomatic screening for DMD, although a significant minority (34.8%) thought NBS for DMD should require parental consent.[42] In 2007, the Centers for Disease Control and Prevention (CDC) funded two studies to evaluate uptake for DMD screening. In Ohio, DMD screening was offered with NBS,[31] and in Georgia, DMD screening was offered at approximately 12 months of life.[43] In both programs, samples with elevated CK measurements had genetic testing done without an additional sample or additional permission sought. Uptake was much higher in newborns when it was done as an add-on test to the neonatal blood spot.

(Ohio). Likewise in Germany, uptake was much lower when parents were offered DMD screening that required a separate blood sample at 6 weeks.[44]

There are significant differences between the Wales program and how NBS for DMD would be conducted in the US.[45] First, NBS bloodspots in Wales are collected at 4-5 days, usually by a community midwife in the family's home, allowing more time for deliberation. In the US, bloodspots are collected between 24-48 hours after birth, before the woman is discharged from the hospital. Average CK levels tend to run higher in the first two days of life, so depending on the cut-off, the US program will have to do follow-up testing on a larger percentage of infants.[30,31] Second, NBS for DMD in Wales was optional and required a separate consent. US advocates seek to incorporate CK measurements into the universal NBS programs which are mandatory and performed without consent (often without explanation[46-48]) despite the fact that symptoms do not usually present in infancy and supportive treatment is not needed then. Third is the timing for addressing a positive screen. In Wales, an elevated CK level was not reported back for four to six weeks which gave parents time to adjust to having a new baby, a practice that is consistent with the optional nature of screening newborns for a condition that will usually not present for years and does not require immediate treatment. In the US, an elevated CK would most likely lead to reflexive genetic mutation analysis, similar to the process used for cystic fibrosis screening where an elevated immunoreactive trypsinogen measurement on the newborn blood spot automatically triggers genetic testing.[31] This reduces parental control over the process which further supports a robust consent process at the time the sample is collected.

Early diagnosis would be less controversial if all agreed that treatment needed to be started before a clinical diagnosis is usually made. Recent data show that boys with DMD do express delays in early childhood as measured by the Bayley III scales of infant and toddler

development,[49] and that the gap increased with time.[50] If treatments were approved in this age group, the arguments that support screening newborns would be significantly strengthened. While some neurologists now support starting steroids earlier, perhaps as young as age 2 based on a single study involving five boys,[51] the guidelines support starting steroid treatment after motor skills plateau at approximately 4-6 years of age.[52-54] The long-term risks of starting corticosteroids in pre-school children have not been well-established. Treatment with Exondys 51 (eteplirsen) to slow the decline in mobility of patients who have a confirmed mutation of the dystrophin gene amenable to exon 51 skipping was approved by the US Food and Drug Administration (FDA) in September 19, 2016.[55] All of the studies reviewed by the FDA involved boys over the age of 7 years,[56] an age at which virtually all boys have been diagnosed, weakening the argument for the need for diagnosis in the newborn period. Further arguments against including DMD in NBS occured on that same day, when Robert Califf, the FDA commissioner, made public a report that he had written on September 16, 2016 in which he argued for retracting the 2013 DMD study by Mendell and colleagues[57] that gave greatest support for the drug's approval.[58] Califf reiterated this position in a letter to the editor in the *Annals of Neurology*.[59] Despite the controversy, the drug is currently approved, although continued approval for this indication is contingent upon verification of a clinical benefit in confirmatory trials. As such, whether there is an effective treatment for the 13% of boys who may benefit from skipping exon 51 remains an open question.

Pompe Disease

Pompe disease is an autosomal recessive neuromuscular disorder that can be identified in newborns by measuring acid alpha-glucosidase (GAA) activity in blood or tissues. One-third of children identified will present with the classic form which has onset in infancy but the remaining two-thirds will present later. The classic or infantile form is characterized by prominent hypotonia, muscle weakness, motor delay, feeding problems, and respiratory and cardiac insufficiency, some of which may be present even at birth.[60] Without treatment, life expectancy is less than one year. Approximately 2/3 of cases are late onset, presenting at variable times from several months of life to several decades. It is characterized by progressive, debilitating, and often life-threatening musculoskeletal, respiratory, and cardiac symptoms. It may be restricted to one organ or may affect all three. Unfortunately, genotype does not fully predict phenotype.

Treatment for Pompe disease consists of enzyme replacement therapy (ERT). Several ERTs have been tried in patients with Pompe disease since 1967, but it was only in the early 2000s that ERT with recombinant human alpha-glucosidase derived from rabbit milk or Chinese hamster ovary cells was successfully introduced and evaluated.[61] Within a few years, ERT for Pompe disease was approved in Europe, the US, Canada, and Japan.[62]

The first program of NBS for Pompe disease began in Taiwan in 2005 as a research protocol that required parental consent.[63] After showing that screening was feasible and that children with infantile onset Pompe disease benefited from early initiation of ERT, Taiwan incorporated Pompe disease screening into their traditional screening programs in 2008.[64] Because parents must pay for a portion of the test, written parental consent is still required.[64] Over 90% consent. No data about psychosocial outcomes have been reported.

Supporters in the US argued to include Pompe disease in mandatory NBS programs for early screening because ERT reduces morbidity in those with infantile onset Pompe disease. In 2008, Pompe disease was nominated for inclusion in the RUSP. The ACHDNC internal nomination and prioritization workgroup (hereinafter referred to as Workgroup) found its nomination premature.[65] The Workgroup expressed concern about the screening test because Taiwan's pilot data published in 2005 revealed a high false positive rate. It also commented on the lack of prevalence data about infantile versus later onset disease, benefit of early diagnosis, and treatment and cost-effectiveness.[65] In May 2013, with more data from Taiwan, the Discretionary Advisory Committee for Heritable Disorders in Newborns and Children, which temporarily followed the ACHDNC, recommended the addition of Pompe Disease to the RUSP,[66] although it was not approved by the HHS Secretary until March 2015.[67] With HHS approval, one expects US states to add this condition to their NBS panels relatively quickly.

Even before HHS Secretary endorsement, Missouri had already begun NBS for Pompe in 2013 and Illinois in 2014. Pompe screening in Missouri began with a pilot program with IRB approval but without the requirement of getting parental consent. In the first published report from the US to-date, the Missouri public health department described screening 43,701 samples in the first 6 months:

> Among the newborns who screened positive for GAA deficiency (Pompe), 3 were diagnosed with the infantile form of the disease, 3 were classified as late-onset, 2 are currently classified as a genotype of unknown significance/onset, 2 had a pseudodeficiency, and 3 were found to be carriers.[68 at p. 174]

It is not clear how those with late-onset genotypes and those with genotypes of unknown significance will be followed over the long-term.

The decision to include Pompe disease in the RUSP is controversial for several reasons. The main controversy is that most (approximately 2/3) of individuals will be asymptomatic,

often for years or decades, and there is no consensus on when to begin treatment for those with non-infantile forms of the disease. This means that screening for Pompe disease challenges public health screening criteria. It also contradicts US pediatric genetic screening guidelines which strongly discourage testing children for adult onset conditions.[2-5,7-11] Inclusion of Pompe in the RUSP is also controversial because of disagreements about the proper role of ERT. First, ERT for infantile onset Pompe disease, like steroids for DMD, delays morbidity but is not curative, and many affected infants end up ventilator-dependent regardless. Second, ERT may lose effectiveness as patients develop antibodies to the enzyme, and it is relatively ineffective for the 20% with null alleles, who do not produce cross reactive immunological material (that is, CRIM negative status) because those with effectively no protein are more likely to generate antibodies to the ERT, which then block its effectiveness. Third, ERT does not cross the blood brain barrier and so has no impact on preventing or modifying neurological symptoms.[69]).

In August 2016, the ACHDNC heard an update from the Missouri public health department about Pompe screening.[70] As of July 15, 2016, Missouri had screened approximately 276, 000 births and had confirmed 34 cases of Pompe disease with 7 infantile, and the rest late-onset or of unknown status. Six of the 7 infant cases were CRIM positive, but all were started on ERT, even the infant who was CRIM negative. The rest are being followed.[70] Jennifer Kwon, a pediatric neurologist from New York discussed the status of long-term clinical follow-up that is a coordinated effort between the Newborn Screening Translational Research Network and the states in addition to the Genzyme registry.[71] She noted that there are ongoing efforts to clarify genotype-phenotype correlations, but that many questions persist including how frequently to follow these individuals with late-onset pompe disease genotypes and how to

respond to isolated abnormalities like an elevation of CK or complaints of fatigue or weakness in a person with a late onset genotype.[71]

Although the ACHDNC recommended the inclusion of Pompe disease in the RUSP, one might argue that Pompe disease, like DMD, should not be included in the mandatory NBS program (tier 1) but, rather, should require a more robust consent process because 2/3 of individuals will have late onset presentations and we do not have a robust infrastructure to deal with them. Rogers, the Missouri public health department official explained to the ACHDNC that there are no medical management guidelines/practices for the asymptomatic patient. She expressed concern that those individuals at risk of becoming lost to follow-up.[70] There is also the concern of the psychosocial impact of becoming "patients in waiting";[72] that is, patients with a genotypic diagnosis that may present at any time. Moreover, even for the infantile form, more needs to be studied regarding the use of ERT in CRIM negative children and long-term efficacy in CRIM positive children. Other states may want to wait until additional data are available from Missouri.

Spinal muscular atrophy (SMA)

SMA is an autosomal recessive neuromuscular disorder caused by mutation in the survival motor neuron (SMN) gene. There are, in fact, two distinct but virtually identical SMN genes, SMN-1 and SMN-2. In 95% of cases of SMA, there is the homozygous absence of the SMN1 exon 7. SMN2 produces less full-length transcription than SMN1, but the number of copies of SMN2 modifies the clinical course.[73]

SMA is characterized by muscle weakness and atrophy due to loss of anterior horn cells in the spinal cord and brainstem nuclei. It has variability in onset and severity, although 60%

present in the first six months of life with SMA Type 1 (Werdnig-Hoffmann disease). SMA Type

1 is the most severe, and most children are unable to sit or achieve any motor milestones.

Another 20% have SMA Type 2 (Dubowitz disease) which presents between 6-18 months. These

children can sit independently but rarely walk and usually live only until young adulthood. Type

3 (Kugelberg-Welander) presents after 18 months and Type 4 presents in adulthood. Both

Types 3 and 4 have normal life expectancy. While severity does correlate with number of copies

of SMN2, variability has been seen, even between siblings, presumably due to genetic

modifiers.[73]

Respiratory failure is the main cause of mortality in children with SMA Type 1. While

tracheostomy and invasive ventilation can prolong life, it also takes away any chance for oral

communication and there has been a move to promote quality of life with noninvasive

respiratory support. Nutritionally, children with SMA Type 1 often require gastric tube feedings.

They also have orthopedic complications like scoliosis which can worsen respiratory function.

Children with milder forms of SMA also suffer from significant fatigue which can interfere with

walking and quality of life.

When SMA was evaluated by the ACHDNC in 2008, it was determined to be too premature

as no effective treatments existed.[74] There were only supportive treatments like g-tubes and

noninvasive respiratory modalities to preserve the ability to speak. The ACHDNC requested that

educational material be developed and small programs be piloted. The only pilot SMA NBS

program to date was scheduled for Utah and Colorado,[75] but in the end recruited only in Utah

where recruitment was slow. Parental consent was required and led to low uptake (Jeffrey

Botkin, personal communication, April 2016). In December 2016, Nusinersen received global

approval for the treatment of SMA for both children and adults.[76] Nusinersen is an antisense

oligonucleotide drug that must be administered intrathecally. What is not known is whether adverse events become worse over time or more prevalent and what other long-term toxicities may develop.[76,77] Also under development by Avexis is a gene transfer candidate AVXS-101 for the treatment of SMA-1.[77,78] In September 2016, the European Medicines Agency (EMA) granted Avexis access into its PRIority MEdicines (PRIME) program based on data from both preclinical evaluations and the ongoing Phase 1 clinical trial of AVXS-101.[79]

Even before an effective treatment was available, there was strong support for SMA NBS in parents of boys affected with DMD, Becker muscular dystrophy and SMA, although a significant minority supported requiring parental consent.[42] One would expect even greater support now that there is an effective treatment, although there are still good reasons to require parental consent; namely, that 20% will not present until adulthood and that the treatment is quite new so that there are many unknowns regarding how long it will be effective and the risks of intrathecal administration. On March 7, 2017, CureSMA, in partnership with the SMA Newborn Screening Coalition, announced it had re-submitted a request that ACHDNC include SMA in the RUSP.[80] While ACHDNC may vote for its inclusion, ideally it would require parental consent to opt-in to screening (tier 2), pending further study of the therapies.

When and why consent is needed

The debate about whether parents should give permission for newborn screening is as old as newborn screening itself.[2] Those who support seeking parental permission argue that it demonstrates respect and increases parental awareness in the event of a positive test; those who object argue that the benefit-risk ratio justifies a more directive approach, that too much information would have to be given for consent to be "genuine", and that consenting

immediately post-partum is not conducive to a considered decision.[81] However, as states move from screening for a few conditions in which treatment is needed urgently to prevent morbidity and mortality to the use of platform technologies, the conditions now include disorders that do not require emergency treatment and in fact may not even have an effective treatment. Grosse and colleagues persuasively argue that expansion of state newborn-screening panels from public health emergencies to public health services should reopen the question of parental involvement in these decisions.[82] That is, as we move away from conditions that require immediate treatment to prevent serious morbidity and mortality to conditions that may not present immediately or for which treatment is not clearly effective, we should move away from a mandatory model and re-consider what role parents should play in deciding whether or not to test their children.

In the US, there is consensus, albeit not unanimous, that parents should be informed about screening and that provisions should exist for them to opt-out, but that the presumption should be to screen when the condition meets the traditional criteria of a public health emergency.[82] The justification for this is that screening is in the best interest of children.[9-11] For conditions that are not public health emergencies, there is more support for a more robust consent process: parents should be informed about screening and then be empowered to deliberate about whether they are the sort of parent who would want to know if their newborn infant had a serious condition that may or may not present in childhood, and may or may not be effectively treatable. The rationale is that educating parents and promoting deliberation empowers parents to do what they perceive to be best for their child and their family.

In numerous reports, the Wales group spoke of the importance of the informed consent process, even after DMD went from a research pilot (1990-1998) to a program funded by the

health authority (1998-2011). While the Wales researchers justified screening for its potential benefits which include "the avoidance of distressing diagnostic delays, enabling the family to plan for the future in practical ways, including choice in future pregnancies, and the offer of physiotherapy at an early stage",[38 at p 550] they also acknowledged the uncertain effect on the family of an early diagnosis for an incurable disease with the benefit: risk calculation dependent on how the family weighed the value of the early knowledge, the ability to prepare, and the avoidance of a diagnostic odyssey against the value of 'blissful ignorance' until the child developed symptoms that were recognized as requiring investigation. The robust stepwise consent process was designed to empower parents because it was not clear that NBS served the child's best interest.

Despite the steps taken, the Wales team still questioned whether parents were giving an informed and voluntary consent? The 94% consent rate and the detection of a few families very distressed by the diagnosis led the screening team to suspect that the uptake rate was inflated by routinization and, perhaps, parental compliance with what may have been perceived as a professional recommendation. Pilot studies were conducted to look into enhancing the consent process. For example, collecting an additional blood spot card for the DMD test emphasized that this test was different from the others and that it needed to be considered differently. This empowered the midwife to recommend screening for PKU and hypothyroidism without reservation, and to give a more muted recommendation to screening for DMD by emphasizing both risks and benefits. This altered the pattern of communication between professional and parent (usually mother) in a helpful fashion, increasing satisfaction with the process of consent, while reducing uptake to 78%, a level suggesting greater engagement in the decision.[83] Unfortunately it was never adopted into the program, but it does offer insight into how consent

can be performed in a way that promotes greater choice and more informed deliberation. In Germany, when testing was moved to the six-week well child visit and required a new sample be collected, less than 15% of infants were screened.[44] One must question then whether parents truly want testing, despite the surveys,[42] when even small barriers decrease uptake by almost 80% (from 94% in Wales to 15% in Germany). Separating tier one and tier two testing in time and sample may lead to a more considered decision.[84]

The concept of a two-tiered newborn screening system has been supported by several US groups.[5,6,8] When screening for a neuromuscular life-limiting disorder which does not require immediate clinical intervention (DMD) or which identifies many with later onset conditions (Pompe, less so SMA), informing parents, promoting deliberation, ensuring appropriate infrastructure for long-term follow-up, and obtaining their consent is critical to screen ethically. The ACHDNC should seriously consider the benefits of a two-tiered NBS program for these neuromuscular disorders and other conditions that challenge public health screening criteria.

Consent is necessary but not sufficient

A robust consent process is necessary but, by itself, is not sufficient to achieve an ethically sound NBS program. Tier 2 conditions require an accessible infrastructure to support those families who receive a positive diagnosis and to follow those children even though symptoms may not develop for many years or decades. In Wales, the health system partnered with the MDG (now the Muscular Dystrophy Campaign) to ensure counseling and support, although funding for this became difficult once MDG support was no longer available.

Taiwan has a national health insurance scheme which should simplify Pompe follow-up, although how successful this will be for those who develop symptoms later on in life is

unknown. Internationally, Genzyme, a Sanofi company (Cambridge, MA). started a long-term Pompe disease registry in 2004, but how and whether this will successfully track those who are asymptomatic for years or decades is still to be seen.[85] Imagine a 35-year-old diagnosed with Pompe disease at birth but without symptoms until age 30. The patient might not "remember" his diagnosis as a neonate, or he may never have been told about it, and most primary care physicians will be unaware of the registry. The patient, then, will most likely undergo a diagnostic odyssey before he is re-identified as having Pompe disease. This "lost" time may be detrimental to his health.

Thus, before public health programs can justify screening for a condition in which most patients will be asymptomatic for years or decades, long-term follow-up infrastructure and coordination with the medical home (a team-based health care delivery model led by a primary health care provider) will be necessary.[86] Coordination between NBS and the medical home, proposed back in 2000, is consonant with the mission of NBS programs which have always prided themselves in being more than a test and providing a comprehensive system.[6] Although implementation will be challenging in a fragmented health care system as exists in the US, it is irresponsible to add these conditions without the appropriate resources and infrastructure. One could further argue that these conditions should not be added (even to Tier 2) unless there are research protocols in place to enroll children who screen positive (with parental consent) in order to more quickly advance the science that could justify their inclusion in screening platforms in the first place.

Conclusion

There are many advocates who support expanding NBS to include diseases that do not clearly meet public health screening criteria. Creating a two-tiered NBS program would respect professional ethics and parental autonomy and would promote public trust; disorders can be moved from Tier 2 to Tier 1 as evidence accumulates to establish the overall direct benefit of an early diagnosis through screening. However, screening for second-tier conditions should only be offered if the necessary infrastructure and support services are in place to support those families who receive a positive diagnosis regardless of the time delay from diagnosis to clinical presentation.

REFERENCES

1. Wilson JMG, Jungner G (1968) *Principles of Screening for Disease*. Geneva: World Health Organization, 26-39.

2. National Research Council, Committee for the Study of Inborn Errors of Metabolism. Genetic Screening: Programs, Principles, and Research. Washington, DC : National Academy of Sciences, 1975.

3. Institute of Medicine; Committee on Assessing Genetic Risks. Andrews LB, Fullarton JE, Holtzman NA, Motulsky AG, eds. *Assessing Genetic Risks: Implications for Health and Social Policy.* Washington, DC: National Academy of Sciences; 1994

4. American Society of Human Genetics, American College of Medical Genetics. Points to consider: ethical, legal, and psychosocial implications of genetic testing in children and adolescents. *Am J Hum Genet.*1995;57 :1233– 1441

5. Task Force on Genetic Testing. Holtzman NA, Watson MS, eds. Promoting Safe and Effective Genetic Testing in the United States. Baltimore MD: The John Hopkins University Press, 1998.

6. American Academy of Pediatrics Newborn Screening Task Force. Serving the family from birth to the medical home: a report from the Newborn Screening Task Force convened in Washington, DC, May 10–11, 1999. Pediatrics. 2000;106:383–427

7. American Academy of Pediatrics, Committee on Bioethics. Ethical issues with genetic testing in pediatrics. *Pediatrics.*2001;107 :1451– 1455

8. President's Council on Bioethics (US). The Changing Moral Focus of Newborn Screening: An Ethical Analysis by the President's Council on Bioethics. Washington DC: December 2008. On the web at: https://repository.library.georgetown.edu/bitstream/handle/10822/559367/Newborn%20Screening%20for%20the%20web.pdf?sequence=1&isAllowed=y

9. American Academy of Pediatrics Committee on Bioethics, Committee on Genetics and the American College of Medical Genetics and Genomics Social, Ethical and Legal Issues Committee. Policy Statement: Ethical and Policy Issues in Genetic Testing and Screening of Children. *Pediatrics* 2013; 131(3): 620-622.

10. Ross LF, Saal HM, David KL, Anderson RR and the American Academy of Pediatrics; American College of Medical Genetics and Genomics. Technical Report: Ethical and Policy Issues in Genetic Testing and Screening of Children. *Genet Med* 2013; 15(3): 234-245.

11.   Botkin JR, Belmont JW, Berg JS, et al. ASHG Position Statement: Points to Consider: Ethical, Legal, and Psychosocial Implications of Genetic Testing in Children and Adolescents. Am J Hum Genetics 2015; 97: 6-21.

12.   UK National Screening Committee (UKNSC). First Report of the National Screening Committee. London : Health Departments of the United Kingdom, April 1988. On the web a t: http://aogm.org.mo/assets/Uploads/aogm/Guidelines/NHS/National-Screening-Committee-UK-1998.pdf

13.   Working Party of the Clinical Genetics Society (U.K.). The Genetic Testing of Children. *J Med Genet.* 1994; 31: 785–97.

14.   Health Council of the Netherlands: Committee Genetic Screening. Genetic Screening. The Hague: Health Council, 1994; publication no. 1994/22E. ISBN 90-5549-073-3 On the web at: : https://www.gezondheidsraad.nl/sites/default/files/9422e.pdf.

15.   British Society for Human Genetics (BSHG). *Report on the Genetic Testing of Children*. Edgbaston Birmingham UK: British Society of Human Genetics, 2010. On the web at: http://www.bsgm.org.uk/media/678741/gtoc_booklet_final_new.pdf.

16.   Ministry of Health [New Zealand].   Newborn Metabolic Screening: Policy framework. Wellington, New Zealand: Ministry of Health, 2011. On the web at: https://www.nsu.govt.nz/system/files/page/newborn_metabolic_screening_programme_policy_framework_june_2011.pdf

17.   Cornel M, Rigter T, Weinreich S, Bugard P, Hoffmann GF, Lindner M, Loeber JG, Rupp K, Taruscio D, Vittozzi L. A framework to start the debate on neonatal screening policies in the EU: an Expert Opinion Document. *Eur J Hum Genet*. 2014; 22: 12–17.

18.   Royal Australasian College of Physicians. Newborn Screening in Australia. Position statement May 2015. On the web at: https://www.racp.edu.au/docs/default-source/advocacy-library/newbornscreeninginaustraliapositionstatement.pdf

19.   UK National Screening Committee. Criteria for appraising the viability, effectiveness and appropriateness of a screening programme. Last updated 23 October 2015. On the web at: https://www.gov.uk/government/publications/evidence-review-criteria-national-screening-programmes/criteria-for-appraising-the-viability-effectiveness-and-appropriateness-of-a-screening-programme.

20.   Howell RR. Advisory Committee on Heritable Disorders and Genetic Diseases in Newborns and Children. *Ment. Retard. Dev. Disabil. Res. Rev.* 2006;12:313-5.

21.   Watson AS, Mann MY, Lloyd-Puryear MA, Rinaldo P, Howell RR. Newborn screening: toward a uniform panel and system. *Genet Med* 2006;8(Suppl 1):1S–11S.

22.   Appleton RE, Nicolaides P. Early diagnosis of Duchenne muscular dystrophy. *Lancet.* 1994;345:1243–4.

23.   Bushby KMD, Hill A, Steele JG. Failure of early diagnosis in symptomatic Duchenne muscular dystrophy. *Lancet.* 1999;353:557-8

24.   Mohamed K, Appleton R, Nicolaides P. Delayed diagnosis of Duchenne muscular dystrophy. *Eur J Paediatr Neurol.* 2000;4:219-23.

25.   Ciafaloni E, Fox DJ, Pandya S, Westfield CP, Puzhankara S, Romitti PA, et al. Delayed diagnosis in duchenne muscular dystrophy: data from the Muscular Dystrophy Surveillance, Tracking, and Research Network (MD STARnet). *J Pediatr.* 2009;155(3):380-5.

26. Firth M. Diagnosis of Duchenne muscular dystrophy: experiences of parents of sufferers. *Br Med J (Clin Res Ed).* 1983;286(6366):700-701.

27. Firth M, Gardner-Medwin D, Hosking G, and Wilkinson E. Interviews with parents of boys suffering from Duchenne muscular dystrophy. *Dev Med Child Neurol.* 1983;25:466–71.

28. Wong SH, McClaren BJ, Archibald AD, Weeks A, Langmaid T, Ryan MM et al. A mixed methods study of age at diagnosis and diagnostic odyssey for Duchenne muscular dystrophy. *Eur J Hum Genet.* 2015;23:1294-300.

29. Zellweger H, Antonik A. Newborn screening for Duchenne muscular dystrophy. *Pediatrics*. 1975;55:30-4.

30. Drummond LM. Creatine phosphokinase levels in the newborn and their use in screening for Duchenne muscular dystrophy. *Arch Dis Child* 1979;54:362-366.

31. Mendell JR, Shilling C, Leslie ND, Flanigan KM, al-Dahhak R, Gastier-Foster J et al. Evidence-based path to newborn screening for Duchenne muscular dystrophy. *Ann Neurol*. 2012;71:304-13.

32. Naylor EW. New technologies in newborn screening. *Yale J Biol Med*. 1991;64(1):21–24

33. Gardner-Medwin D, Bundey S, Green S. Early diagnosis of Duchenne muscular dystrophy. *Lancet* 1978;311 (8073):1102

34. Gardner-Medwin D. Recognising and preventing Duchenne muscular dystrophy. *Br Med J (Clin Res Ed).* 1983;287(6399):1083-84.

35. O'Brien T, Sibert JR, Harper PS. Implications of diagnostic delay in Duchenne muscular dystrophy. *Br Med J (Clin Res Ed).* 1983;287(6399):1106-07

36. Smith RA, Rogers M, Bradley DM, Sibert JR, Harper PS: Screening for Duchenne muscular dystrophy. *Arch Dis Child.* 1989;64:1017–1021

37. Parsons EP, Clarke AJ, Bradley DM.   Developmental progress in Duchenne muscular dystrophy: lessons for earlier detection. *Eur J Paediatr Neurol.* 2004;8:145-153

38. Parsons EP, Bradley D, Clarke A: Disclosure of Duchenne muscular dystrophy after newborn screening. *Arch Dis Child.* 1996,74:550-553

39. Moat SJ, Bradley DM, Salmon R, Clarke A, Hartley L. Newborn bloodspot screening for Duchenne muscular dystrophy: 21 years' experience in Wales (UK). *Eur J Hum Genet.* 2013;21:1049-53

40. Bradley DM, Parsons EP, Clarke AJ. Experience with screening newborns for Duchenne muscular dystrophy in Wales. *BMJ.* 1993;306(6874):357-60.

41. Parsons EP, Clarke AJ, Bradley DM. Newborn screening for DMD: a psychosocial study. *Arch Dis Child Fetal Neonatal Ed*. 2002;86:F91-95.

42. Wood MF, Hughes SC, Hache LP, Naylor EW, Abdel-Hamid HZ, Barmada M et al. Parental Attitudes toward Newborn Screening for Duchenne/Becker Muscular Dystrophy and Spinal Muscular Atrophy. *Muscle Nerve.* 2014; 49: 822-8.

43. Cyrus A, Street N, Quary S, Kable J, Kenneson A, Fernhoff P. Clinic-based infant screening for Duchenne muscular dystrophy: a feasibility study. *PLoS Curr.* 2012:e4f99c5654147a.

44. Scheuerbrandt G, Lundin A, Lövgren T, Mortier W. Screening for Duchenne muscular dystrophy: an improved screening test for creatine kinase and its application in an infant screening program. *Muscle Nerve.* 1986; 9(1):11-23.

45.   Mendell JR, Lloyd-Puryear M. Report of MDA muscle disease symposium on newborn screening for Duchenne muscular dystrophy. *Muscle Nerve.* 2013;48:21-26.

46.   Kusyk D, Acharya K, Garvey K, Ross LF. A Pilot Study to Evaluate Awareness of and Attitudes about Prenatal and Neonatal Genetic Testing in Post-Partum African American Women. *J Natl Med Assoc.* 2013;105:85-91.

47.   Newcomb P, True B, Walsh J, Dyson M, Lockwood S, Douglas B. Maternal attitudes and knowledge about newborn screening. *MCN, Am J Matern Child Nurs.* 2013;38:289-94.

48.   Lang CW, Stark AP, Acharya K, Ross LF. Maternal knowledge and attitudes about newborn screening for sickle cell disease and cystic fibrosis. *Am J Med Genet.* 2009;149A:2424-9.

49.   Connolly AM, Florence JM, Cradock MM, Malkus EC, Shierbecker JR, Siener CA, et al. for the MDA DMD Clinical Research Network. Motor and cognitive assessment of infants and young boys with Duchenne Muscular Dystrophy: results from the Muscular Dystrophy Association DMD Clinical Research Network. *Neuormuscul Disord.* 2013; 23: 529-539.

50.   Connolly AM, Florence JM, Cradock MM, Eagle M, Flanigan KM, McDonald CM et al. for the MDA DMD Clinical Research Network. One Year outcome of boys with Duchenne muscular dystrophy using the Bayley-III scales of infant and toddler development. *Pediatr Neurol.* 2014; 50: 557-63.

51.   Merlini L, Cicognani A, Malaspina E, Gennari M, Gnudi S, Talim B et al. Early prednisone treatment in Duchenne muscular dystrophy. *Muscle Nerve*. 2003;27:222-7.

52.   Moxley RT 3rd, Ashwal S, Pandya S, Connolly A, Florence J, Mathews K et al, for the Quality Standards Subcommittee of the American Academy of Neurology; Practice

Committee of the Child Neurology Society. Practice parameter: corticosteroid treatment of Duchenne dystrophy: report of the Quality Standards Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society. *Neurology.* 2005;64:13-20.

53.   Gloss D, Moxley RT, 3rd, Ashwal S, Oskoui M. Practice guideline update summary: Corticosteroid treatment of Duchenne muscular dystrophy: Report of the Guideline Development Subcommittee of the American Academy of Neurology. *Neurology.* 2016;86:465-72.

54.   Bushby K, Finkel R, Birnkrant DJ, Case LE, Clemens PR, Cripe L et al. for DMD Care Considerations Working Group. Diagnosis and management of Duchenne muscular dystrophy, part 1: diagnosis, and pharmacological and psychosocial management. *Lancet Neurol.* 2010;9:77-93.

55.   US Food and Drug Administration. Press release: "FDA grants accelerated approval to first drug for Duchenne muscular dystrophy? September 19, 2016. On the web at: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm521263.htm.

56.   US Food and Drug Administration. Drug Trials Snapshots: EXONDYS 51. On the web at: http://www.fda.gov/Drugs/InformationOnDrugs/ucm525048.htm

57.   Mendell JR, Rodino-Klapac LR, Sahenk Z, Roush K, Bird L, Lowes LP et al. for the Eteplirsen Study Group. Eteplirsen for the treatment of Duchenne muscular dystrophy. *Ann Neurol.* 2013; 74(5): 637-47.

58.   Retraction Watch: Amid controversial Sarepta approval decision, FDA head calls for key study retraction.   On the web at: http://retractionwatch.com/2016/09/21/amid-controversial-sarepta-approval-decision-fda-head-calls-for-key-study-retraction/.

59.   Unger EF, Califf RM. Regarding "Eteplirsen for the Treatment of Duchenne Muscular
        Dystrophy" Annals of Neurology. 2017; 81(1): 162-164.

60.   Chien YH, Hwu WL. A review of treatment of Pompe disease in infants. *Biologics.*
        2007;1:195-201.

61.   Angelini C, Semplicini C. Enzyme replacement therapy for Pompe disease. *Curr Neurol
        Neurosci Rep*. 2012;12:70-5.

62.   McVie-Wylie AJ, Lee KL, Qiu H, Jin X, Do H, Gotschall R et al. Biochemical and
        pharmacological characterization of different recombinant acid alpha-glucosidase
        preparations evaluated for the treatment of Pompe disease. *Mol Genet Metab*.
        2008;94:448-55.

63.   Chien YH, Chiang SC, Zhang XK, Keutzer J, Lee NC, Huang AC, et al. Early detection
        of Pompe disease by newborn screening is feasible: results from the Taiwan screening
        program. *Pediatrics*. 2008;122:e39–e45.

64.   Yang CF, Liu HC, Hsu TR, Tsai FC, Chiang SF, Chiang CC et al. A large-scale
        nationwide newborn screening program for Pompe disease in Taiwan: towards effective
        diagnosis and treatment. *Am J Med Genet.* 2014;164A:54-61.

65.   Secretary's Advisory Committee on Heritable Disorders in Newborns and Children
        Summary of 15th Meeting October 1-2, 2008 Washington, DC, p. 17. On the web at:
        http://www.hrsa.gov/advisorycommittees/mchbadvisory/heritabledisorders/meetings/fifte
        enth/minutes.pdf.

66.   Discretionary Advisory Committee on Heritable Disorders in Newborns and Children
        Summary of 1st Meeting May 16-17, 2013 Webinar P. 18. On the web at:

http://www.hrsa.gov/advisorycommittees/mchbadvisory/heritabledisorders/meetings/2013/first/meetingminutes.pdf.

67. Letter to Joseph A Bocchini, Jr, Committee Chairperson Discretionary Advisory Committee on Heritable Disorders in Newborns and Children from Sylvia Burwell, Secretary of Health and Human Services, March 2, 2015. On the web at: http://www.hrsa.gov/advisorycommittees/mchbadvisory/heritabledisorders/recommendations/correspondence/secretaryfinalresponse.pdf.

68. Hopkins PV, Campbell C, Klug T, Rogers S, Raburn-Miller J, Kiesling J. Lysosomal storage disorder screening implementation: findings from the first six months of full population pilot testing in Missouri. *J Pediatr.* 2015;166:172-7

69. Kishnani PS, Goldenberg PC, DeArmey SL, Heller J, Benjamin D, Young S et al. Crossreactive immunologic material status affects treatment outcomes in Pompe disease infants. *Mol Genet Metab.* 2010; 99:26–33.

70. Rogers SV. Missouri's Experience Implementing Lysosomal Storage Disorders Screening and Follow-up for Pompe, Gaucher, Fabry, and MPS-1 and Krabbe Disorders. Presentation to the Advisory Committee on Heritable Disorders in Newborns and Children. August 26, 2016. On the web at: https://www.hrsa.gov/advisorycommittees/mchbadvisory/heritabledisorders/meetings/2016/twelfth/pompegaucherfabrymps1krabbe.pdf.

71. Kwon JM. Newborn Screening for Pompe Disease: Status of Long-term Clinical Follow-up Efforts. Presentation to the Advisory Committee on Heritable Disorders in Newborns and Children. August 26, 2016. On the web at:

https://www.hrsa.gov/advisorycommittees/mchbadvisory/heritabledisorders/meetings/201 6/twelfth/pompediseasescreening.pdf.

72.   Timmermans S, Buchbinder M. Patients-in-waiting: Living between sickness and health in the genomics era. *J Health Soc Behav.* 2010;51:408-23.

73.   Phan HC, Taylor JL, Hannon H, Howell R. Newborn screening for spinal muscular atrophy: Anticipating an imminent need. *Semin Perinatol.* 2015;39:217-29.

74.   Secretary's Advisory Committee on Heritable Disorders in Newborns and Children Summary of 16th Meeting, November 24, 2008, Washington DC, Pp 6-7. On the web at: http://www.hrsa.gov/advisorycommittees/mchbadvisory/heritabledisorders/meetings/sixte enth/minutes.pdf.

75.   Rothwell E, Anderson RA, Swoboda KJ, Stark L, Botkin JR. Public attitudes regarding a pilot study of newborn screening for spinal muscular atrophy. *Am J Med Genet.* 2013;161A:679-86.

76.   Hoy SM. Nusinersen: First Global Approval. Drugs. 2017;77(4):473-479.

77.   Farrar MA, Park SB, Vucic S, Carey KA, Turner BJ, Gillingwater TH et al. Emerging Therapies and Challenges in Spinal Muscular Atrophy. *Ann Neurol*. Published on-line 17 February 2017. 10.1002/ana.24864

78.   ClinicalTrials.gov identifier NCT02122952. Gene Transfer Clinical Trial for Spinal Muscular Atrophy Type 1. Sponosr AveXis. First registered April 23, 2014; last updated, may 24, 2016. On the web at: https://clinicaltrials.gov/ct2/show/study/NCT02122952?term=avxs+101&rank=1

79.   Almeida MJ. AVXS-101. *SMA News Today.* September 8, 2016. On the web at: https://smanewstoday.com/avxs-101-avexis/.

80.   Spinal Muscular Atrophy Submitted to the Recommended Uniform Screening Panel. Amzeal News/10222605. March 6, 2017. On the web at: http://amzeal.com/doc/10222605.

81.   Ross LF. Mandatory versus Voluntary Consent for Newborn Screening? *Kennedy Inst Ethics J.* 2010; 20: 299–328.

82.   Grosse SD, Boyle CA, Kenneson A, Khoury MJ, Wilfond BS. From Public Health Emergency to Public Health Service: The Implications of Evolving Criteria for Newborn Screening Panels. *Pediatrics.* 2006;117: 923-9.

83.   Parsons EP, Clarke AJ, Hood K, Bradley DM. Feasibility of a change in service delivery: the case of optional newborn screening for Duchenne muscular dystrophy. *Community Genet.* 2000;3:17–23.

84.   Ross LF. Screening for Conditions that Do Not Meet the Wilson and Jungner Criteria: The Case of Duchenne Muscular Dystrophy. *Amer J Med Genet.* 2006, 140A: 914-922.

85.   Kishnani PS, Amartino HM, Lindberg C, Miller TM, Wilson A, Keutzer J and the Pompe Registry Boards of Advisors. Timing of Diagnosis of Patients With Pompe Disease: Data From the Pompe Registry. *Am J Med Genet.* 2013;161A:2431-43.

86.   American Academy of Family Physicians (AAFP) American Academy of Pediatrics (AAP) American College of Physicians (ACP) American Osteopathic Association (AOA) Joint Principles of the Patient-Centered Medical Home March 2007. On the web at: http://www.aafp.org/dam/AAFP/documents/practice_management/pcmh/initiatives/PCMHJoint.pdf.