UK National Screening Committee

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Newborn Screening for Duchenne Muscular Dystrophy

12 October 2016

Aim

1. To ask the UK National Screening Committee (UK NSC) to make a recommendation, based on the evidence presented in this document, as to whether or not screening for Duchenne Muscular Dystrophy (DMD) in newborns meets the UK NSC criteria to support the introduction of a population screening programme.

Current recommendation

2. The 2012 review of screening for DMD in newborns concluded that screening for DMD should not be recommended.

3. The review highlighted a number of key uncertainties:

    a. around the accuracy of the test. The screening test for DMD, bloodspot measurement of creatine kinase (CK) levels, was reported to have high false negative and false positive rates making it unsuitable for population screening. This is likely to lead to people receiving unnecessary follow up and anxiety following the heel prick test.

    b. about the long term benefits of, and the optimum age for initiating, long term steroid treatment. Whilst it is not possible to cure DMD the management of the condition through the use of genetic therapies was an emerging possibility. A number of novel drugs which aimed to improve the amount of protein the body produces were being studied. However the review found that there was a lack of research in this area to help an assessment of their long term effect and an optimal age of initiation.

    c. There was insufficient evidence as to whether identifying DMD in newborns through screening improved long term outcomes compared to current practice.

d. The review found there to be conflicting evidence about the impact of early diagnosis on parents' subsequent reproductive decisions.

Current review

4. This review was undertaken by Bazian Ltd, in accordance with the triennial review process http://legacy.screening.nhs.uk/musculardystrophy

5. The review was based on the earlier appraisal criteria and focused on the following three areas: of which four key questions were proposed

   i. Whether there was a simple, safe, precise and validated screening test which was suitable for whole population screening
   ii. If any new evidence had emerged, following the 2012 review, relating to treatment which could significantly improve symptoms/ functions
   iii. if there was any benefit of offering newborn screening compared to clinical detection
   iv. whether any evidence been published since the last review to demonstrate the wider effects/ benefits from screening DMD from any high quality trials.

6. The conclusion of this review is that the UK NSC recommendation not to screen for DMD in newborns should be retained. The main conclusions were that:

   - There was insufficient, high quality evidence of a new high volume/rapid throughput test suitable for whole population screening.
     Criterion 5 not met.
   - No studies were identified which assessed the impact of treatment following newborn screening in comparison with existing detection and treatment pathways. Whilst genetic treatments may provide further improvements to the care of DMD patients these have only been tested in boys aged 5 and older, which is the age at which clinical diagnosis occurs. **Criterion 10 not met.**
   - c. 'No new evidence was identified what assessed the wider benefits of screening for DMD for example on the reproductive, or other, choices of the parents. **Criterion 13 not met.**

Consultation

7. A three month consultation was hosted on the UK NSC website. Direct emails were sent to stakeholders of whom 11 organisations were contacted directly. **Annex A**

8. Responses were received from the following four stakeholders: Action Duchenne, Genetic Alliance, Muscular Dystrophy UK, and Royal College of Paediatrics & Child Health. All comments are in **Annex B**, below.

   The Royal College of Paediatrics and Child Health did not submit any comments about the review, nor did they receive any comments about the review.

The remaining three submissions brought together comments from a number of professionals and parents of affected children. All were in favour of screening however there were significant divergences of opinion on some key themes. The following themes were reflected across the individual submissions:

- The situation regarding approaches to testing, management and treatment is evolving and this makes it important that the UK NSC evidence review process should be responsive to evidence published between the regular three yearly updates.

  Response: the UK NSC review process already allows for early updates if significant evidence is published in the period between reviews. As such screening for DMD will be considered again in a maximum of three years.

- Two submissions agreed with the review's conclusion that more research was needed to develop a reliable test. The other submission considered that the review did not pay close enough attention to the improvement in the false positive rate reported in the Ohio pilot of two tier screening which combined CK screening with genetic confirmation in positive cases. In addition the comments suggested that the review's conclusion that a PPV of 38.6% is inadequate was challenged as it was considered appropriate for other tests used in the UK Newborn Screening Programme.

  Response: the review pointed out that the low sensitivity of the test in the Welsh programme was a major limitation on the reliability of CK testing. In addition it was not possible to calculate the sensitivity of the CK cut off used in the Ohio pilot and establish whether it represented an improvement on the false negative rate which was ~20% in the Welsh programme. No studies reporting alternative approaches to screening in a screened population were identified by the review's literature search.

  A paper submitted by one organisation suggested that testing at two years of age might be considered in high risk boys identified through the Child Health Surveillance

Programme. (van Ruiten HJ et al, Improving recognition of Duchenne muscular dystrophy: a retrospective case note review, Arch Dis Child. 2014).

Response: This paper was captured by the literature search but was not included in the review as the review's focus was on newborn screening.

- One submission agreed with the review's conclusion that more research was needed to understand the impact of early treatment. However all three submissions suggested that the development of novel genetic therapies represented a paradigm shift in the treatment of DMD. One drug, Ataluren, had been approved by NICE for use in boys aged 5.5 years and older. Papers published since the literature search and submitted by stakeholders reported further developments in studies of other novel drugs.

  One study of the genetic therapy agent 'eteplirsen' ('Longitudinal effect of eteplirsen versus historical control on ambulation in Duchenne muscular dystrophy') was an update on a paper currently included in the Bazian review. The other paper explored the use of idebenone on respiratory function in patients aged between 10 – 18 years (Efficacy of idebenone on respiratory function in patients with Duchenne muscular dystrophy not using glucocorticoids (DELOS): a double-blind randomised placebo-controlled phase 3 trial).

  One submitted paper was a small observational study reporting on a 14 year follow up of 5 boys aged 2 – 4 years whose ambulatory function remained improved at 16 - 18 years. However this study was very small and the reviewers considered that it did not change the conclusion that the criterion was not met.

  Three submitted papers addressed the natural history of patients receiving steroid treatment. ('DMD genotypes and loss of ambulation in the CINRG Duchenne Natural History Study', 'Categorizing natural history trajectories of ambulatory function measured by the 6-minute walk distance in patients with Duchenne muscular dystrophy' & 'Ricotti, V et al, The NorthStar Ambulatory Assessment in Duchenne muscular dystrophy: considerations for the design of clinical trials'). Two of these papers considered treatment at an earlier age and were submitted to highlight a trend towards treatment at an earlier point than the current mean age of diagnosis (4.5 years) and to link steroid treatment outcomes with genotype. But none studied populations younger than 3 years of age and the emphasis of these was on how the studies could inform the design of future therapeutic trial designs.

- The three submitted responses discussed the diagnostic odyssey and its adverse effects in terms of parental anxiety, missed opportunities to avoid further affected children and planning for the onset of symptoms and long term care of the affected child.

  Two responses suggested that, by focusing on the published evidence, the review did not factor in the views of parents sufficiently given the absence of study evidence. The majority of parents who discussed their experience as part of the responses did

say they were in favour of screening citing early access to treatment, avoidance of anxiety and planning for future care.

Response: across the three submissions there is an indication that parental views vary quite significantly. For example a survey conducted by Muscular Dystrophy UK reported 53 % in favour of detection in the newborn period, 28% in favour of detection closer to the onset of symptoms and 19% didn't know.

One submission suggested that the two papers which addressed this issue in the Bazian review had been incorrectly interpreted by the reviewers as they demonstrated that parents who participated in the studies were in favour of newborn screening. Response: one of the included papers reported that parents were in favour of earlier detection but that this should be at a point much closer to the initiation of treatment. This theme had been raised in a paper submitted by one stakeholder and is reflected in the survey reported by Muscular Dystrophy UK.

- A number of practical steps were suggested. That:

  i) the UK NSC makes contact with the authors of the Ohio pilot screening study. However Stuart Moat is already in contact with this group and has offered to provide feedback on developments,
  ii) the review should be updated to incorporate the suggested papers. The papers are being considered by the reviewers but an initial scan of the papers and comments from stakeholders suggest that they wouldn't alter the conclusions of the review,
  iii) the UK NSC should do more to include patient experience in its reviews to inform discussion on the potential benefits of screening. Response: a UK NSC review of ethical and social issues relating to bloodspot screening highlighted that the imbalance between opinion pieces and empirical studies relating to the diagnostic odyssey was a limiting factor in understanding the impact of screening in those areas. In the absence of formal research it seems unlikely that the acceptability of newborn screening amongst parent will be well understood,
  iv) the UK NSC should begin preparations for a screening programme a) to avoid delays in implementation when a programme is approved and / or b) to identify cohorts for research into the benefits of screening. Response: the first was considered impractical in the discussion on the review of screening for Gaucher Disease. The second was discussed in the recent UK NSC independent review and was not considered a sufficient rationale for the introduction of a screening programme.

Recommendation

9. The committee is asked to approve the following:

Universal screening for Duchenne Muscular Dystrophy is not recommended.

This is because there is an absence of a reliable screening test for the use within a population screening programme and evidence that screening improves outcomes in comparison with current practice.

Based upon the 22 UK NSC criteria to recommend a population screening programme, screening for Duchenne Muscular Dystrophy in newborns did not meet the following primary requisites:

Criteria		Met / Not met
The Test		
5	There should be a simple, safe, precise and validated screening test.	Not met ✗
The Treatment		
10	There should be an effective treatment or intervention for patients identified through early detection, with evidence of early treatment leading to better outcomes than late treatment.	Not met ✗
9	There should be an effective intervention for patients identified through screening, with evidence that intervention at a pre-symptomatic phase leads to better outcomes for the screened individual compared with usual care. Evidence relating to wider benefits of screening, for example those relating to family members, should be taken into account where available. However, where there is no prospect of benefit for the individual screened then the screening programme shouldn't be further considered.	Not met ✗
The Screening Programme		
13	There should be evidence from high quality randomised controlled trials that the screening programme is effective in reducing mortality or morbidity. Where screening is aimed solely at providing information to allow the person being screened to make an "informed choice" (eg. Down's syndrome, cystic fibrosis carrier screening), there must be evidence from high quality trials that the test accurately measures risk. The information that is provided about the test and its outcome must be of value and readily understood by the individual being screened.	Not met ✗

Annex A

List of organisations contacted:

1. Action Duchenne
2. Children Living with Inherited Metabolic Diseases
3. Duchenne Family Support Group
4. Faculty of Public Health
5. Genetic Alliance UK
6. Institute of Child Health
7. Muscular Dystrophy Campaign
8. Royal College of General Practitioners
9. Royal College of Midwives
10. Royal College of Paediatric and Child Health
11. Save Babies Through Screening Foundation UK

Consultation comments: Duchenne Muscular Dystrophy 2016

Comments from:

Comments from RCPCH

Dear UK NSC Evidence Team,

Thank you for inviting the Royal College of Paediatrics and Child Health to comment on the Duchenne Muscular Dystrophy consultation. We have not received any responses for this consultation.

I would be grateful if you could please acknowledge receipt.

Kindest regards,

xxxx xxxx

xxxx xxxx

Royal College of Paediatrics and Child Health

xxxx xxxx

xxxx xxxx

Comments from Action Duchenne

FEEDBACK FROM ACTION DUCHENNE

TO THE UK NSC EXTERNAL REVIEW

12th August 2016

Contributors:

Diana Riberio, CEO Action Duchenne

Prof Francesco Muntoni, Primary Investigator/Lead Consultant in Neuromuscular Disorders

Fiona Lawrence, Director of Research & Clinical Development, Duchenne UK

Dr Anirban Majumdar, Consultant Paediatric Neurologist

Alessandra Ferlini, MD PhD, Lead Geneticist, Ferrara University, Italy

Dr Stephen Abbs, Director of Genetics Laboratories, Cambridge University Hospitals NHS Foundation Trust, Addenbrooke's Hospital

Angela Stringer, UK DMD Registry Curator/Action Duchenne & Parent

xxxx xxxx , Trustee Action Duchenne & Parent

Comments from Action Duchenne

Diana Ribeiro, CEO, Action Duchenne

Duchenne Muscular Dystrophy is unusual in the context of rare diseases due to the size of the dystrophin gene (one of the largest in the human body) and therefore the potential of novel mutations and also the absence of specific clinical symptoms to alert medical professionals to the presence of disease in neonates.

The most common recognised first disease sign is ambulatory delay with nearly 50% of DMD boys walking after 18 months (1). Subtle progression of clinical symptoms is responsible for a prolonged diagnostic process, often lasting 2.5 years, giving a mean age of diagnosis of around 4.5 years; a figure which has changed little over the last 3 decades (2). This often means that the optimal Standards of Care are initiated far later than desired (3). In UK the mean age at diagnosis is ~ 5.5 and the mean age at starting steroids well above 6, i.e. when there is already deterioration of function, (see ricotti et al, JNNP 2013). This is against the recommendation of the NICE approved standards of care (4).

There is clear evidence that starting steroids earlier is associated with better outcomes (see Ricotti et al 2015 and Merlini et al, Muscle & Nerve 2014) (5).

Despite this, it is clear that the pervasive of Duchenne has much earlier manifestations than the motor ones; global delay of development, feeding difficulties or failure to thrive and the level of social interaction of affected infants are common early features. These issues cause substantial parental distress as children fail to meet life milestone, but are only rarely identified by medical professionals as early signs of the condition.

These issues cause parental distress as children fail to meet life milestones, but are only rarely identified by medical professionals as early signs of the condition. These parental concerns play a significant impact on family life-quality and on the perceived ability to be good parents. These aspects are important because for many families the time free interval free of concerns for their affected children is in reality limited to the first few months of life. This is considerably shorter time period than commonly acknowledged.

With rational therapies on the horizon, there has been renewed interest in the potential of population newborn screening for Duchenne. The termination of the Wales newborn screening was done because of external quality assurance program a primarily financial reason and the lack of sufficient participants to support a viable scheme. At Action

Comments from Action Duchenne

Duchenne, we urge the UKNSC to reconsider their recommendation of not supporting newborn screening for Duchenne Muscular Dystrophy.

There has been substantial experience generated from at least 17 pilot newborn screening programmes in Duchenne spanning three decades and often protocols were undertaken to fit local-healthcare infrastructure. In Wales, the re-testing of the cut-off of equal to or more than 250U/l and the re-testing of those boys at 6-8 weeks for serum CK following a positive blood spot CK removes the need for genetic studies and/or muscle biopsy in the false-positive group which is not invasive and unethical for the young boys.

The use of serum CK test at 6-8 weeks of age is a good diagnostic test to discriminate those cases of muscular dystrophy from the transient cases (6). Also, from the analysis of the Welsh data, if 50% of the screen positives are transients would suggest the cut-off of more than 250U/l should be increased. Various cut-offs have been utilised more than 300 U/l in Germany, more than 500 in Belgium and more than 750 in Ohio, US, collected between less than 48 hours to less than 4 weeks of age.

The pilot study from Ohio in 37,649 using blood spots collected before 48 hours of life utilised a two-tier approach of blood-spot CK analysis followed by the whole-genome amplification and sequencing of all exons on those samples with increased CK (7).

The development of an immunoassay to detect the CK_MM isoform in blood spots would improve both the sensitivity and specificity and enable robust high-throughput bloodspot screening using standardised reagents and laboratory analysers. Further work and studies are planned standardising the CK cut-off used, collecting a second sample for analysis and including a DNA analysis step. CK not optimal, but current efforts from Perkin Elmer are promising (8).

Each year of a DMD is >70000$. Improved outcomes by early initiation of Standards of Care and novel therapies will result in reduction of morbidity and delay in the onset of complications, or their avoidance (as scoliosis in steroid treated dmd) (9).

The reported incidence of 1:4,046 for DMD in Wales for the birth cohort 1971-1986, before the commencement of this screening program, is higher than the incidence of 1:5136 in the Wales birth cohort 19902011. The avoidance of further affected boys in families where the first affected child is diagnosed early is an important consequence of screening, resulting in the deferral of future pregnancies when a child is found to have a serious illness and in part from parental decisions to use prenatal diagnostic testing to enable the selective termination of unwanted pregnancies (10).There is some evidence from the Wales study that families do re-assess reproductive choices as a result of earlier diagnosis, with 10 out of 12 high-risk families having had prenatal testing in subsequent pregnancies.

Comments from Action Duchenne

They (31) recognized that in the current recommended panel of disorders screened in newborns, there is variability in the manner in which early diagnoses are made and how families are counseled about rare disease management. This variability in early clinical practices has long-lasting effects on later chronic disease follow-up. Because a goal of DMD-NBS is to avoid delays in initiating beneficial treatments, their workgroup wanted to develop consistent recommendations on the clinical care that follows NBS referral. Their vision is to provide "anticipatory guidance" for infants identified as having DMD or other muscle disorders. They have reviewed successful strategies from the cystic fibrosis (CF) NBS programs whose centers follow detailed care guidelines after NBS.

Their recommendations will include information to counsel families whose infants are normal but have a presymptomatic "diagnosis" and to provide psychological support. This guidance will be reflected in a series of encounter templates to be implemented in most specialty care center (SCC) electronic medical record systems, and from which clinical data can be readily extracted and analyzed to ensure ongoing quality improvement. In this way, they hope to incorporate the NBS long-term follow-up goals outlined by the US Secretary for Health and Human Service Advisory Committee on Heritable Disorders in Newborns and Children: care coordination, evidence-based treatment, continuous quality improvement, and new knowledge discovery.

I include the following from Annals of Neurology - Evidence based path to newborn screening for Duchenne Musular Dystrophy

Jerry R Mendell, MD, Chris Shilling, MS, Nancy D. Leslie, MD, Kevin M Flanigan, MD, Roula al-Dahhak, MD, Julie Gastier-Foster, Ph.D., Kelley Kneile BS, Diane M. Dunn, BS , Brett Duval, BS, Alexander Aoyagi, BS, Cindy Hami, Maha Mahmoud, Kandice Roush, R.N., Lauren Bird R.N., Chelsea Rankin BS, Heather Lilly, BS, Natalie Street, MS, CGC, Ram Chandrasekar, Ph.D., Robert B. Weiss, Ph.D. Departments of Pediatrics and Pathology, Ohio State University and Nationwide Children's Hospital; Department of Pediatrics, University of Cincinnati; Department of Human Genetics, University of Utah; National Center on Birth Defects and Developmental Disabilities, Centers for Disease Control and Prevention, Newborn Screening Laboratories of the Ohio Department of Health.

Nevertheless, recent advances in diagnostic testing methods and promising molecular-based therapies for DMD have rekindled interest in establishing a pathway
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Nevertheless, recent advances in diagnostic testing

Comments from Action Duchenne

- *Methods: A fluorometric assay based upon the enzymatic transphosphorylation of ADP to ATP was used to measure CK activity. Preliminary studies established a populationbased range of CK in newborns using 30,547 de-identified anonymous dried blood spot samples. Mutation analysis used genomic DNA extracted from the dried blood spot followed by whole genome amplification with assessment of single/multi-exon deletions/duplications in the DMD gene using multiplex ligation-dependent probe amplification.*

- *Results: DMD gene mutations (all exonic deletions) were found in six of 37,649 newborn male subjects, all of whom had CK levels > 2000 U/L. In three newborns with CK >2000 U/L in whom DMD gene abnormalities were not found, we identified limb-girdle muscular dystrophy gene mutations affecting DYSF, SGCB, and FKRP. Conclusions: A two-tier system of analysis for newborn screening for DMD has been established. This path for newborn screening fits our health care system, minimizes falsepositive testing, and uses predetermined levels of CK on dried blood spots to predict DMD gene mutations.*

- *This margin between documented cases of DMD and those with elevated CK not found to have a DMD mutation provides reasonable assurance for circumventing false positives enabling us to raise the threshold for DNA testing in Phase III of the study to CK ≥750 U/L. This reduced the number of newborns requiring DMD gene testing by about 68%, representing a significant cost saving for a NBS program. With additional confirmation of our findings these initial studies suggest that the threshold for DNA testing could be elevated even higher (e.g., CK ≥ 1000 U/L), improving the potential cost-benefit ratio for NBS.*

- *The program we have introduced differs from past programs and the current Antwerp approach to NBS for DMD that require a three-step process: 1) CK testing on dried blood spots, 2) followed by confirmation of elevated CK levels by venous blood obtained at the Page 16 of 28 John Wiley & Sons Annals of Neurology Newborn screening for Duchenne muscular dystrophy*

- *4-6 week time point, and 3) with a final step that requires an additional blood draw for DNA testing. The approach we have developed is a two-tier approach with all testing done using the original blood obtained from the heel stick within the first 24-48 hours. All testing is done from the same dried blood spot card. A threshold level of CK determines if DNA testing is to be done without additional blood obtained from the neonate. The DNA assay utilizes the most sophisticated technology available 40, (and can be periodically modified if necessary). Whether treatment has advanced to the point of justifying newborn screening for DMD requires assessment through state and federal agencies with appropriate jurisdiction. If and when an early therapy that improves the health outcome for individuals with DMD becomes available, our study serves as a model for implementation of newborn screening for DMD. If the development of promising therapies for DMD continues to proceed at its current pace, newborn screening could be on the horizon for this disease, not only in the USA, but also in other countries of the world. If successful therapy for dystrophinopathies is available for newborns, guidelines will need to be established for referral to an appropriate muscle specialist. In addition, a pathway for referral could be built into the program for those with CK elevations in the absence of DMD*

mutations where there is the potential to identify other causative mutations as we have demonstrated in this report.

Discussion

"DMD-NBS has been controversial because of the lack of early treatments and the perception that early diagnosis did not improve outcome. We now know that significant muscle injury is present in very young DMD boys, and the need to initiate treatment early is supported by promising results from clinical trials of new treatments that improve outcomes, especially if they are given before significant muscle injury has occurred.

Fine and gross motor skills in DMD infants, as assessed by the Bayley III scale, are significantly delayed relative to controls, which confirms the presence of measurable deficits at an early age. This clinical finding is corroborated by the finding of highly elevated CK levels, a biomarker of membrane fragility and active muscle degeneration, in DMD boys at birth and during the first year of life. Histological evidence of dystrophic pathology has been described in DMD foetuses and is evident on muscle biopsies as early as the perinatal period. Furthermore, early pathology of the pelvic girdle musculature can be identified by magnetic resonance imaging in DMD boys in the first 2 years of life. The therapeutic benefit of corticosteroid treatment in prolonging ambulation may be more pronounced in DMD patients treated at an early age.24 This could be the result of having a higher percentage of viable skeletal muscle tissue responsive to treatment, which is seen in emerging therapies that were most beneficial in subjects with a lesser degree of fibrosis as measured by MRI. For many boys with DMD, these observations mean that newer treatments could be considered shortly after birth.

The clinical diagnosis of DMD remains persistently delayed, which not only exacerbates underlying health disparities but also keeps DMD clinical care centers from delivering high quality clinical care that could meaningfully improve outcomes. Currently, among the multidisciplinary clinics that provide high quality neuromuscular care (such as the Muscular Dystrophy Association clinics and Parent Project Muscular Dystrophy Certified Duchenne Care Centers), there is growing awareness of the need for more consistent care driven by registries. However, reducing undesired variability in clinical care and outcomes requires timely DMD diagnosis, which is difficult to accomplish without NBS due to challenges of counselling and disparities in access to health care.

The US National Duchenne Newborn Screening Program Taskforce was formed to systematically address the key issues raised by NBS policy experts who have reviewed the possibility of early diagnosis of DMD by means of NBS. Our workgroup was asked to address the clinical needs of infants and their families identified by

Comments from Action Duchenne

DMD-NBS programs. We assumed that a 2-tier approach, such as modelled in the Ohio pilot program, would be used. Based on their screening outcomes, implementation of DMD-NBS in a large state with 250,000 births annually, will likely result in diagnosis of 20 infant boys with DMD and another 30– 40 infants with highly elevated CK levels who may develop some form of muscle disease. Extrapolating to the entire US, where the annual birth rate is 4 million infants, there will be an estimated 300–350 new DMD diagnoses each year. While costs associated with this screening effort are a relevant concern, addressing them will require costbenefit analyses that extend beyond the scope of our intended discussion. Our goal has been to articulate the components of an effective clinical follow-up program for infants identified as being at risk after DMD-NBS.

We reviewed the evidence for providing high quality short-term and initiating long-term follow-up care to families of infants identified by state NBS programs.

We have taken advantage of our group's own shared history of counselling and managing presymptomatic boys born into families with a history of Duchenne muscular dystrophy. In addition, we reviewed the long-term follow-up strategies used in states, such as California, with a strong history of multidimensional stakeholder involvement in longterm follow-up efforts as well as the successful quality improvement initiatives in cystic fibrosis NBS in developing a prototype of the schedule for following these infants.

Our proposed schedule of follow-up visits as well as the stated goals for each visit lays the foundation for effective lifetime chronic disease care. The earliest visits are made in close consultation with the primary care provider, setting the stage for effective long-term care coordination. While the ideal is for patients to have a medical home that can coordinate their care, the reality is that the SCC must be involved as a medical home partner. For example, neuromuscular SCCs have access to DMD clinical registries that are the basis for continuous quality improvement and evidence-based treatments. It will take partnerships between primary and specialist care providers to move DMD care forward and to realize the goals of NBS long-term follow-up set forth by the federal Advisory Committee and NBS advocates." (31)

Comments from Action Duchenne

Prof Francesco Muntoni, Primary Investigator/Lead Consultant in Neuromuscular Disorders

More formal assessment of whether age at diagnosis could be lowered by improved clinical diagnosis.

- This is an ongoing effort for the last 30 years, it is clearly a waste of time for DMD and all other rare diseases. However, for DMD there are now approved therapies.

Continued research into new treatments for DMD, including long term follow up to assess efficacy and safety.

- Translarna (ataluren) is pursuing these efforts. Translarna is specifically aimed at those with a nonsense mutation and recommended for those aged 5 or older who are able to walk. It is therefore vital that the diagnosis of Duchenne with a clear genetic mutation is established as early as possible to benefit from Translarna.

NICE has published final guidance recommending Translarna for treating children aged 5 and over with Duchenne muscular dystrophy (DMD) caused by a nonsense mutation.
https://www.nice.org.uk/news/article/nice-publishes-final-guidance-recommending-ataluren-for-children-with-duchenne-muscular-dystrophy

Today's guidance follows the announcement on 7 July that NHS England and the company, PTC Therapeutics, have successfully negotiated a 'managed access agreement' that established financial and clinical details surrounding the use of ataluren.

This 'managed access agreement' was a condition for making the drug available imposed by NICE in its April draft guidance
.
As part of the agreement the usual 3-month funding period has been waived by NHS England, meaning ataluren could be available within weeks.

Sir Andrew Dillon, chief executive of NICE, said: "Duchenne muscular dystrophy caused by a nonsense mutation is a cruel disease that currently has few treatment options. Ataluren is an innovative drug that for the first time is aimed at the root cause of the disease and has the potential to offer benefits to people with the condition and their families.

"When we published our draft recommendations in April we acknowledged that ataluren represents a significant cost to the NHS at a time of increased pressure on funding, especially given the uncertainties of the drug's potential long-term benefits.

"We are therefore extremely pleased NHS England and the company have agreed the terms of a 5-year managed access agreement for ataluren. The agreement means children with this condition will now be able to access the drug while at the same time allowing more data to be gathered on its efficacy, before the guidance is reviewed and a further decision made on whether funding should be continued after 5 years."

Comments from Action Duchenne

Robert Meadowcroft, chief executive of Muscular Dystrophy UK, said: "Families in England will deservedly be thrilled by today's news from NICE. Together, we have fought long and hard for this pioneering drug to be made available on the NHS. For all those who campaigned with such determination, today is a very welcome relief.

"Duchenne is a devastating condition and it's almost too much to bear for parents to watch their child's health worsen day by day as it progresses. By keeping these boys mobile, Translarna could also enable them to be eligible for other future drugs on the horizon."

Step change
The drug has been called a 'step change' in the management of the disease which causes progressive muscle wasting and is usually fatal by age 30.

Children with the disease typically become dependent on a wheelchair by age 12 and the NICE committee agreed that ataluren had the potential extend to this by up to seven years, potentially giving children the chance of a normal adolescence and allowing them to continue school for longer.

Patients and their families considered this one of the most important factors for treatment.
Duchenne muscular dystrophy is a severe, progressive muscle-wasting genetic condition caused by the lack of a protein called dystrophin. Usually affecting only boys, there are between 60 and 70 children born with the disease in England each year and in around 6 – 9 children (13%) it is caused by a 'nonsense mutation'.

The standard treatment is corticosteroids which can delay deterioration but can cause unwanted effects such as growth retardation, bone thinning, mood swings and weight gain.

Ataluren works by allowing the body to read over the mutation in the DNA and continue to produce dystrophin.

The committee heard:

- *In a clinical trial, none of the children in the most sensitive group taking the drug lost the ability to walk over the 48 weeks of the trial compared with 8% on the placebo (0 out of 47 compared with 4 of 52).*
- *The research predicted ataluren may delay loss of walking for up to 7 years.*
- *Patient experts said they had seen meaningful stabilisation or improvements in their child's mobility such as being able to get into and out of bed independently and go to school.*
- *Patient experts said once a child loses the ability to walk, greater deterioration follows meaning they need help with self-feeding and personal care such as showering and going to the toilet. If the time to loss of walking could be delayed, their children would have the opportunity to have a more normal adolescence.*

Ataluren is licensed for children with DMD caused by a nonsense mutation aged 5 and over who are able to walk. Its list price is approximately £220,000 per year.

The drug has been considered as part of NICE's Highly Specialised Technologies programme that looks at treatments for very rare diseases that are commissioned nationally by NHS England.

Comments from Action Duchenne

The guidance recommends ataluren be made available under the terms of the MAA and provided the company supplies the drug with the confidential discount agreed in the patient access scheme.
It is thought around 50-60 children could benefit from the drug during the five year managed access agreement.

Is there any new evidence since the last review of a treatment which seeks to alleviate the underlying genetic defect causing DMD or significantly improve symptoms/function?

- Yes ataluren with 'Managed Access Agreement' and early steroids.
- https://www.nice.org.uk/guidance/hst3/resources/managed-access-agreement-july-2016-2553024061

Is there evidence that treatment following newborn screening adds any additional benefit in comparison with existing treatment pathways.

- Currently Standards of Care are initiated later than those agreed by International Standard Guidelines. (3)

Comments from Action Duchenne

Comments on new born screening for DMD external review - version 5 April 2016

Summary of the response from Fiona Lawrence, Director of Research & Clinical Development, Duchenne UK

The internationally recognized criteria for recommendation for a newborn screening programme (NBS) for Duchenne are not currently met according to the latest review of the evidence.

The April 2016 review included studies published between January 2011 and March 2015 and searched for new evidence since the last review in April 2012.

The review focused on only 3 criteria which begs the question of whether that means that all the other criteria were supported by sufficient evidence in the 2012 review.

The two studies that assessed parental attitudes to NBS were both in support of early diagnosis. The survey found that parents of children with DMD and expectant parents were strongly in support of NBS and a mixed methods study found that a delay in diagnosis put families at risk of having a subsequent affected child.

A two stage diagnostic test (CK level with DNA follow up on same blood spot) with high specificity is available. The review rather plays down this evidence

New treatments are on the horizon and many studies with good evidence have been published since the cut-off date for the current review. In addition, understanding of the natural history of Duchenne is advancing rapidly which will allow better trial design and analysis so leading to more effective treatments.

As Duchenne is a degenerative condition it makes logical sense that the sooner an effective treatment or intervention can be started, the more muscle will be preserved and the longer the child will retain the use of their muscles.

The challenge to the Duchenne community is to understand what further evidence is needed to allow an approval of a NBS programme. We need to work out how evidence can be

generated in the most cost-effective, efficient way to allow continuation of the discussion of NBS for Duchenne.

Recommendations on whether to screen for a condition are based on internationally recognised criteria are available online at http://www.screening.nhs.uk/criteria and a rigorous evidence review process.

The latest review of the evidence for newborn screening for Duchenne focused on 3 of the above criteria (numbered as 5, 10 and 13 in the Bazian paper but seem to correspond to numbers 4, 9 and 11 in the updated criteria as laid out in the link) which were areas in the 2012 review that were uncertain or supported by insufficient evidence.

Criterion 5 in document (4 in above) - There should be a simple, safe, precise and validated screening test

Current UKNSC key Q1) Is there any new evidence of a high volume/rapid throughput test that is suitable for whole population screening?

Predictive value is determined by the specificity and sensitivity of the test and the prevalence of the disease in question. When the prevalence of a disease is low (as with Duchenne) the positive predictive value will also be low. Therefore, the comment in the document on page 7 regarding a low positive predictive value of 42% is misleading as it implies that this counts against the fulfillment of the criterion.

The specificity reported in the Moat paper is high (99.97%) i.e. there were few false positives and for a disease such as Duchenne it is very important to have a test that is highly specific. The sensitivity was reported as 81.6%. i.e. around 18% (false negatives) of babies tested were later found to have Duchenne.

Of course it is highly desirable to have a test that is both highly specific and highly sensitive. This is in practice, rarely the case. An alternative is to subject patients who are initially positive to a test with high sensitivity/low specificity, to a second test with low sensitivity/high specificity. In this way, nearly all of the false positives may be correctly identified as disease negative.

Comments from Action Duchenne

This was the basis of the Ohio study authored by Jerry Mendell that is reported in the Baxian review. I am not able to access the full paper online so I cannot see whether sensitivity and specificity percentages are quoted. The attached document claims a 0.3% rate of false positives for this study which equates to a specificity of 99.7%. The sensitivity (false negative rate) is not quoted in the article and Baxian maintain that it is not possible to calculate because of incomplete follow up.

DMD_screening_USA_support.pdf

It is also interesting to note from the Moat paper published for the Welsh study that the criteria for the introduction of the Welsh screening programme for cystic fibrosis (CF) were met with similar false negative and false positive rates to those reported by the Ohio group.

A quote from the discussion section of the Moat 2012 paper:

"a very similar, two-tier (protein then DNA) screening programme could be introduced nearly two decades sooner in the case of CF than DMD. The Wales CF protocol has a sensitivity of 94.7%, a PPV of 50% and a FPR of 0.03% – not dissimilar to the current DMD protocol outlined here."

I am not sure whether the comment in this section '*The study population may not be generalisable to a UK population'* refers to the DMD population or the potential different arrangements for midwifery and new-born follow-up in the US vs the UK.

The Bazian report conclusion is that criterion 5 is not met.

The feasibility of a two-tier protocol using CK followed by DNA studies on the new born blood spot collected within the first week of life needs further assessment.

Action: follow up with Jerry Mendell to understand how his research group is building on their pilot study.

Comments from Action Duchenne

Criterion 10 (9 in updated criteria). There should be an effective treatment or intervention for patients identified through early detection, with evidence of early treatment leading to better outcomes than late treatment.

Current UKNSC key Q2a) Is there any new evidence since the last review of a treatment which seeks to alleviate the underlying defect of DMD and/or significantly improve symptoms/function?

The review concludes that there is a small amount of evidence regarding treatments for Duchenne. The review only considers studies published between January 2011 and March 2015. There have been several key developments and many more publications since March 2015 that are relevant to this criterion:

- Ataluren will be available to children aged 5 years and over with DMD caused by a nonsense mutation under a 5 year managed access agreement agreed between NHS England and PTC therapeutics. The agreement includes an outcomes-based incentive for PTC as well as a mechanism to monitor how well Ataluren works in practice before future funding decisions are taken. Therefore, under this agreement more real world data will be collected albeit only on children aged more than 5 years.
- The development of drisapersen has been stopped by the manufacturer BioMarin. It is not yet clear what will happen to the natural history study that BioMarin was also sponsoring. The study enrolled in total 269 boys with confirmed DMD between the ages three and 18 from 10 countries across 16 centers in North & South America and Europe, 80% of whom are ambulatory and 20% non-ambulatory.
- The NDA for eteplirsen is still under review at the FDA. In 2016 a study titled 'Longitudinal effect of eteplirsen versus historical control on ambulation in Duchenne muscular dystrophy' was published (http://www.ncbi.nlm.nih.gov/pubmed/26573217) which provides further data on the 12 boy study that is mentioned in the Bazian report.
- Idebenone reduced the loss of respiratory function in DMD in a double blind randomized placebo controlled phase III study published in the Lancet in May 2015 (http://www.thelancet.com/pdfs/journals/lancet/PIIS0140-6736(15)60025-3.pdf)
- The CINRG study that is collecting data on the natural history of children with DMD has expanded its entry criteria to include children from age 2. This means that there will in time be data available on the effects of starting corticosteroids from an early age and whether it has a beneficial effect on the overall disease trajectory. The CINRG group published a paper titled 'DMD genotypes and loss of ambulation in the CINRG Duchenne Natural History Study' in 2016 (http://www.ncbi.nlm.nih.gov/pubmed/27343068). This study highlights the importance of mutation-specific randomization and selection of placebo groups for clinical trials.
- A study titled 'Categorizing natural history trajectories of ambulatory function measured by the 6-minute walk distance in patients with Duchenne muscular dystrophy' (http://www.nmd-journal.com/article/S0960-8966(16)30076-1/pdf) was

published in 2016. This is important as it is the first paper to propose that the natural history for DMD may be composed of distinct trajectory classes. Knowing what these might be could help in reducing unexplained variation in patient outcomes could help to further improve DMD clinical trial design and analysis and so improve the evidence for new treatments.

Action: update the review to include studies published to July 2016

Current UKNSC key Q2b) Is there evidence that treatment following newborn screen adds any additional benefit in comparison with existing treatment pathways?

'None of the studies identified explicitly assessed participants detected through newborn screening, or compared the effects of treatment in screen detected versus clinically detected boys or treatment given at different ages. Participants included in the studies ranged from 4 to 38 years where reported, i.e., treatments were not initiated in the newborn period, which is when those identified by screening would potentially be able to start treatment if appropriate'

As outlined in the response to question 2a younger children are being recruited to natural history studies in Duchenne so in time it will be possible to assess benefits of starting treatments at younger ages. There is also some data on treatment of very young children with glucocorticoids. It would be useful to collate information on this small group of children with a view to assessing long term outcomes. As most children are diagnosed between the ages of 2 and 4, and there is no national screening programme, it is a bit of a circular argument to state that there is no new evidence that newborn screening adds any additional benefit.

There may be optimal physiotherapy and exercise programmes that could be adopted in newborn and very young children if a diagnosis was in place.

Action: Undertake a review of the evidence from natural history studies published and unpublished (CINRG, AFM, BioMarin, Italian Group) for the long term effects of starting steroids at age 2.

The Bazian paper concludes that criterion 10 was not met. There is growing and emerging evidence for treatment benefit with glucocorticoids, ataluren, idebenone and other drugs. There is also new evidence published from natural history studies that is increasing understanding of the effects of DMD from age 2 onwards. If a newborn screening programme was in place it would be possible to study children from an even younger age allowing for greater treatment optimisation.

Comments from Action Duchenne

Criterion 13b. Where screening is aimed solely at providing information to allow the person being screened to make an "informed choice" (eg. Down's syndrome, cystic fibrosis carrier screening), there must be evidence from high quality trials that the test accurately measures risk. The information that is provided about the test and its outcome must be of value and readily understood by the individual being screened.

Current UKNSC Key Q3) Has any evidence been published since the last review that demonstrates wider effects/benefits from screening for DMD, such as on reproductive choices?

Two studies were identified for this review, a survey and a mixed methods study. In the survey, the level of support for new born screening among parents of children with DMD, BMD and SMA was 95.9% and 92.6% among expectant parents.

A mixed methods study of parents in Australia found that a delay in diagnosis had a negative impact on parents and put families at risk of having a subsequent affected child. Half the respondents felt that their child could have been diagnosed earlier. The median age at diagnosis was 5 years.

The conclusion of the review: *Criterion 13b not met - No new evidence was identified that assessed the wider effects of screening for DMD on the reproductive or other choices of the parents.*

This seems an odd conclusion given the summary of the results from the two studies referenced.

Action: Understand what new evidence is required to meet this criterion. Given advances in diagnostics and promising therapeutic approaches, discussion of inclusion of a new born screening programme should continue.

Comments from Action Duchenne

Dr Anirban Majumdar, Consultant Paediatric Neurologist

With knowledgements to:

Helpful discussions and comments by Professor Angus Clark (Professor of Clinical Genetics, Cardiff, Wales), Dr Mark Rogers (Consultant Clinical Geneticist, Cardiff), Dr Louise Harley (Consultant Paediatric Neurologist, Cardiff) and Dr Juliet Ellis (Clinical Scientist, London).

- The primary purpose of a NBS programme is to detect a potentially curable condition, in the newborn period, before it has had the opportunity to cause irreversible damage.

- a)Although the position in the past has been such that incurable conditions have not been part of a national NBS programme, medical progress has meant that many of these incurable conditions are treatable and therefore should be considered a part of an expanded NBS programme. b)The continued non-inclusion of conditions such as DMD in expanded NBS is an example of inequity and has arisen due to reasons which in themselves are morally problematic. This position therefore should be reconsidered.

- At birth, a male with DMD will be asymptomatic and the manifestations of the disease do not appear till about 18 months. At this stage they show evidence of delayed motor development. The insidious and nonspecific nature of the signs and symptoms of the disease means that there is an inevitable delay in the diagnosis. Often, by the time a diagnosis is confirmed, a family may have already had another child. If this child is male then he will have the same risk of developing DMD.

- It is recognized that there is a mean delay of 23 months from clinical presentation to the diagnosis. An audit by Mohamed (11) showed that even in the presence of modern medicine, there continues to be a delay in diagnosis. A mean age of diagnosis of DMD in England was 4 1/2 years in the 1990's.

- A common complaint from the parents of these boys with DMD was that “no-one listened”. Boys with both learning difficulties and DMD are still being diagnosed in England as late as 7 and 9 yrs.

- There was family frustration at delayed diagnosis of DMD and almost all had to undergo a ‘diagnostic odyssey’. The families expressed anger at missed opportunities for genetic counseling when their second or third affected sons were diagnosed.

- According to Mendell (12), 17 studies in 10 different countries, were subsequently conducted looking specifically at this problem of reducing the diagnostic delay/ odyssey. These early studies highlighted the fact that NBS for DMD was indeed a genuine solution to the problem.

Comments from Action Duchenne

- Of these a German study has looked at a programme which has been ongoing for 34 years and a Welsh study which has looked at a programme which has been ongoing for 21 years. There are currently the only two other ongoing programmes; in Ohio, USA and Antwerp, Belgium. There are plans to introduce expanded NBS to include DMD in Mexico, Taiwan and Sydney (personal communication **xxxx xxxx**).

- In 2004 the UK National Screening Committee rejected a proposal for expanded NBS to include DMD. In 2009, Treat-NMD (Treat-Neuromuscular Disorders) and ENMC (European Neuromuscular Consortium) both made recommendations for DMD to be part of expanded NBS. In 2011, a further application to the UK National Screening Committee was made and subsequently again rejected.

- In the UK, Wales has been the only country to have a NBS programme which has been ongoing since 1990. This programme recently stopped due to funding issues and the outcomes have been published by Moat et al (13). The conclusion of the publication was *"Screening has reduced the diagnostic delay enabling reproductive choice for parents of affected boys and earlier administration of current therapies"***.**

- I have attempted to outline the particular qualities of DMD itself and how it potentially stands to gain much from a NBS screening programme (in terms of early identification). I have also illustrated how the development of NBS programmes is not new and the inclusion of DMD as part of its expansion have actually arisen in an empirical rather than a systematic or evidence based manner. The fact that expanded NBS has not taken off around the world reflects the fact that DMD still remains incurable. I suspect that the policy makers for these programmes are not able to get past the restrictions placed on expansion by the Wilson and Jungner (14) criteria.

- Any screening programme has to be justified. The traditional way of determining if a condition fulfils the requisite for inclusion onto a screening program is to compare it to the ten criteria laid down by Wilson and Jungner (14). The UK NBS programme, for the nine disorders currently screened, fulfil most of these criteria but not all. This particularly refers to the case of CF which will be discussed later.

- The first of the Wilson and Jungner criteria worth examining is Criteria 2 which states that "*The natural history of the condition should be well understood".* On the face of it, the natural history of DMD is well understood. There is a period of being asymptomatic from birth up to 2 years. The condition then progresses in a relentless fashion till ambulation is lost at the age of 10-14 years. With no medical intervention, death is inevitable by the late teens.

- The aim of modern multidisciplinary care in DMD, is to modify the natural history of the condition and delay its progression for as long as possible. Therefore the natural history of DMD *changes* depending on whether an affected patient is being treated or not. This raises our first issue which is whether leaving a condition, which is incurable but treatable, to follow its natural history (non-treatment) is ethical.

- In essence however the individual choice to select non treatment in cancer, is not deemed unethical.

Comments from Action Duchenne

- These justifications can be drawn from many areas of contemporary ethics namely autonomy and individual choice, ethics of resource allocation and the ethics of suffering and compassion (15).

- Notwithstanding the above statements, in my opinion, criteria 2 has become with the advent of treatments, out of date and irrelevant, when applied to DMD. The known treatments for DMD, such as steroid treatment, early cardiac and respiratory interventions have existed for a number of years and have modified the natural history (16). Despite the aforementioned treatments, it is worth noting that there is still no cure for this condition. Some may consider the treatments for DMD to be almost as good as a cure as treatments can extend life expectancy by up to 15 years and these additional life years can be of very good quality (17,18).

- DMD is considerably different in its natural history, to be treated differently.

- In my opinion, the Wilson and Jungner criteria are very clumsy in their application and they fail to make a distinction in these crucial criteria. Perhaps a mitigating factor is that when the criteria were published 44 years ago, when DMD was both an incurable and untreatable condition

- Clinically detecting DMD, in the first 2 years of life, is possible but very difficult. This inevitably results in a delay in diagnosis and a diagnostic odyssey for the parents (19).

- This can furthermore, be done rapidly and years in advance of when the child will first start to show clinical signs of the condition.

- The counter argument is that DMD , with modern management is treatable. It is precisely because medical treatments for conditions are never static and always in a state of evidence based improvement, one can argue that a fixed and unchanging criteria should not exclusively be used to judge and omit evolving conditions.

- It is well known that starting treatment in a boy with DMD, when they are beginning to lose ambulation (starting at 7 years of age) is more beneficial, then, starting treatment in a teenager with DMD who is beginning to go into end stage respiratory failure, for example. This however is not the point; the question really is about whether it is more beneficial to treat the affected boy in the *asymptomatic or presymptomatic* phase.

- There has always been the concern that a presymptomatic diagnosis of a life limiting condition may affect the parental bonding. The data however does not support this although there may be a degree of increased anxiety which is transient. It may also cause parents to seek alternate and unproven treatments which potentially can be harmful (21).

- This is because of the asymptomatic phase in this condition can last for up to 3 years.

- We have established that treatments in DMD are not curative but merely supportive.

- We have also established that the earlier treatments are gradually improving survival and quality of life in patients with DMD. There is a general trend that suggests that earlier and better care leads to better outcomes. It is precisely because of the trend

in improvement (which may even be accelerated by gene therapy) that we cannot use this point to reject NBS for DMD.

- The purpose of an early detectible phase is precisely so that an early treatment can be instituted, but if we can argue that an early phase detection is irrelevant because a condition is inevitable, then an early treatment consequently does not matter.

- Do these perceived risks actually exist when they are systematically looked for? Analysis of the Welsh data looking at the longer term psychological reactions of parents given a diagnosis by NBS shows that on the whole most parents do not have pathological psychological reactions (personal communication form **xxxx xxxx**) and this has been published by Moat et al (13).

- This is a point echoed by Pollitt (20) who states that the advent of modern and increasingly more sophisticated genetic technologies, such as multiplex genetic sequencing and exon skipping, may also lend support to expanding the Wilson Jungner Criteria enough to allow for conditions such as DMD to be included in a NBS programme.

- The incidence of the condition is 1 in 3500 live births and there are approximately 100 babies born with this condition in the UK per year. The incidence of DMD, at 1: 3500.

- One possible direction is to improve doctors and paediatricians knowledge of this condition. Despite the efforts of the last 20 years, such as improving general awareness of this condition and highlighting the warning signs to GPs and Health Visitors, the delay in diagnosis hasn't improved. Even today, with the advent of free information on the internet, a late diagnosis is still occasionally encountered.

- If we compare this to the contemporary ethics of "what should one do with knowledge of genetic information?" it is generally accepted that people have the right to accept or entirely reject such information, even when it is perceived as beneficial.

- There may be some non-medical practical benefits that NBS in DMD would allow such as life planning and allowing parents time to adjust to the diagnosis. Research shows that parents of children with life limiting conditions want information as early as possible, even when there are no treatments available (21).

- Parsons (21) however did not find long term negative psychological sequelae in parents of boys with false positives.

- I quote from **xxxx xxxx** who states that expanding NBS to include DMD has to be judged by its risk: benefit ratio (22).

- At a practical level, it is the *perception* by individual couples, of this ratio which decides whether to take up the additional screening for DMD.

- The NBS programme in Wales for example uses explicit consent, where the uptake is very high (94 %) (13, 22).

Comments from Action Duchenne

- In Wales virtually all the consent for the opt-in was done at the time of the neonatal blood spot taking which happens at Day 7.

- Consider the situation in Germany, where the DMD screening is done between 1 and 12 months and the uptake is a mere 5%. Is the uptake rate so low because the screening test is done for a fee of 15 Euros? Whether it is appropriate to charge money for an extra test outside the national screening programme is debatable. (23)

- A low uptake may be perceived as a waste of resources and the ramifications of missed diagnosis may be great.

- The bedrock of informed consent is voluntary choice and a discussion about the risks and benefits (amongst other things) ensures that this is achieved.

- If the objective is to promote medical benefit, as defined by avoiding the medical odyssey and being given an early opportunity for medical intervention, then boys should be screened. However there remain several arguments in support of screening females.

- The strongest of these arguments is that screening girls allows the family to have reproductive information on whether the female infant is a carrier [1] and the implications of such a status. The most important piece of information that NBS could provide, if females are screened, is the fact that an identified female carrier will subsequently carry the risk of 50 % of her male offspring will have DMD. Ultimately this information allows for the prevention of the birth of an DMD patient. It also allows for interventions, such as pre-implant diagnosis to occur, again with the aim of preventing a DMD birth.

- Another benefit of screening is that it allows for the manifesting female carrier to be identified and potential manifestations of the condition can be treated. Some manifesting female carriers can have mild cardiac problems but again this is rare and therefore of lesser importance. Screening and identification of a female carrier allows one to be mindful of the potential complications and seek prompt treatment to prevent morbidity.

- Another problem with NBS for DMD carrier status in females is that essentially it is a condition which, were it to manifest, would not do so till adulthood. Therefore the test in females is a predictive test. The consensus guidelines this state that; "...carrier testing and screening for
adult-onset conditions should be delayed until adulthood." (24) (American Society of Human Genetics, American College of Medical Genetics, (25). There have been concerns at the potential negative impact of having such a status may have on the child or the family, these concerns have not really held up to scrutiny or research data (26).

Comments from Action Duchenne

- *So the question of whether to screen only boys or both boys and girls depends upon what the goals of screening are. If the goal is solely to detect children who will become symptomatic in the next decade and for whom early or experimental treatment may need to begin before symptoms develop, then one could argue to screen only boys, admitting that a rare female child will be missed. If the goal of screening is to detect at risk families, then boys and girls should be screened"* (22).

- If the stated aim of NBS in DMD is to provide reproductive information and counselling to at risk women, then surely, screening all women should be the goal. NBS, as practised currently, is too late in one sense, as it only detects affected individuals *after* they are born.

- One such reason is that many women may not seek prenatal care until they have conceived.

- It is important to note that birth often will cause the CPK to be raised and this is related to birth trauma, is transient and usually normalises within 2 weeks. It therefore makes sense to undertake the earliest screening at about 2 weeks of age. Delaying the procedure further than 2 weeks puts an additional burden; paediatricians are often reluctant to have to do another blood draw, the second sample has logistic implications as it is separate from the initial blood draw of the main group in NBS, leading to problems in follow-up and increased potential for missed results.

- The timing of test issue is an important but not the only factor which would inform decisions for expanded national screening programmes.

- There exists one published study of the cost effectiveness of NBS (27) from Canada. This study was a pilot study of newborn males who had CPK tested. The aim of the programme studied was to identify carrier mothers, who could then be offered pregnancy termination in order to avoid a future case of DMD. The programme also sought to give mothers who had a confirmed case of DMD, further care in future pregnancies and offer terminations. The incremental costs of adding the CPK test was calculated in this study was Canadian $4.88 per infant screened (1988 values). The cost of repeat laboratory testing was Canadian $20.01 per infant screened. The overall cost of avoiding one case of DMD, taking into account the models of DMD detection and the willingness of the families to use the information for family planning was estimated to be Canadian $ 172,000.

- If the objective of reproductive knowledge is the prevention of another case of DMD. Such prevention is likely to save hundreds of thousands, if not millions in costs to the health service, when calculated over the lifetime of this one case of DMD.

- The presence of a high enzyme level will lead on to a confirmatory DNA test.

Comments from Action Duchenne

- Knowing that a disorder is manifest within the family allows individuals to consider pre-implantation genetic diagnosis (PGD) and in conjunction with in-vitro fertilisation (IVF), to avoid having further children with serious genetic diseases.

- In DMD this is not achievable as the affected child with DMD will have no choice in the matter, as the disease will have fully manifested itself before the onset of adulthood The whole argument about future autonomy cannot be applied to conditions such as DMD or indeed any condition which leads to death in childhood.

- NBS may expedite this process and it may allow the child to adjust to the circumstances whilst he is young and his plans for the future are not settled or formalized. NBS may foster openness within the family, may resolve some of the parental and family uncertainty. Certainly NBS has the potential to make parental expectations for the child's future more realistic. Eventually it may serve for families and individuals to realise the truth of the following statement: *Recognition that disease is but one part of who we are and the lives we lead, and that we all carry "faulty genes"*(Wertz, 1998) (28).

- Over the last 30 years there has been an enormous amount of research looking at a cure. The prospect of a real genetic cure for DMD has in the last 2-3 years emerged with the advent of gene therapy techniques (29). In addition to this DMD is no longer considered completely untreatable with inevitable death in the late teens. Modern medical therapies, surveillance and interventional techniques now mean that children with DMD are surviving well into adulthood, with a good quality of life. Furthermore, there is increasing evidence that the earlier DMD is treated the better the long term survival and outcome.

- There is no doubt that they will cause a paradigm shift in our current way of thinking about these conditions. Indeed the final point of *'treatment at an early stage should be of more benefit than at a later stage'* would be eminently applicable and thus provide the necessary justification for NBS in DMD.

- The future prospect of curing genetic conditions such as DMD is at a particularly interesting crossroad at this present time. Gene therapy which has been heavily researched over the last 30 years is now beginning to deliver some very encouraging results. The holy grail of finding a cure for DMD, using drugs which alter the fundamental genetic defect is no longer a dream but a tangible reality. Recent research using antisense oligoneucliotides and exon skipping technologies are promising an era of potential genetic cures for such disorders.

- What is very exciting is that there is evidence to suggest that starting treatment earlier on in the course of the disease may reap dividends in terms of survival with good quality of life, in the long run. This can be demonstrated by the use of steroids, scoliosis surgery and non-invasive ventilation (17, 18) in DMD and there is a general trend in the neuromuscular community to use these drugs and interventions earlier in the disease course (16).

Comments from Action Duchenne

- If our ability to cure previously incurable diseases were actually to come to fruition and be translated into actual clinical practice, then this would profoundly transform the ethical landscape.

- The only way of identifying a boy with DMD in the asymptomatic phase would of course be with screening. If this were to happen then I would expect to see that DMD (and many other genetic conditions) becoming part of the NBS programme.

- In DMD there are several skippable exons and the AONs need to be manufactured precisely to match the skippable exon. Of course this will mean that the medicines become prohibitively expensive and the ethical issues of healthcare rationing and cost effectiveness of the medication will play a part in the decision making. All the ethical arguments that have already taken place in the commissioning of expensive cancer drugs and the debate about the role of Quality Adjusted Life Years (QALY) and the role of National Institute of Clinical Excellence (NICE) will have to be revisited.

- The advent of new age of genetic cures is on the horizon and in general these treatments are likely to work better the earlier they are instituted; ideally in the presymptomatic phase, before there is any evidence of damage having been done. NBS for DMD is the only way this is ever likely to be achieved.

- “Since 1993 the Newborn Screening Laboratory in Cardiff has been screening for a sixth condition in Wales - Duchenne muscular dystrophy. This test looks for the presence of creatine kinase (CK) in the blood. Once a positive CK result has been obtained from the original Guthrie card test, it is repeated six to eight weeks later since there is a risk of false positives due to the natural trauma associated with some child births. If the levels are still high in this repeated test, this could indicate several different types of muscular dystrophy but Duchenne muscular dystrophy is the most common cause. Genetic testing is then used to confirm a diagnosis of Duchenne muscular dystrophy. Since the screening programme started in Wales over 300,000 babies have been tested and 50 diagnosed with Duchenne muscular dystrophy.”

- So if CF does not fulfil the Wilson and Jungner criteria but is included in the UK NBS program, then why is DMD not included? Should it be?

- Clearly this situation which has existed for the last 20 years is entirely illogical from an equity perspective.

- It would seem that the UK NBS is taking a logical decision but it should be noted that the reason for stopping screening in Wales is entirely financial and not because of a desire to make NBS equitable. It is an example of the ‘right outcome for the wrong reasons’, which is not, in my opinion, a satisfactory way of dealing with this complex issue.

In conclusion:

Comments from Action Duchenne

- My conclusion is that the current UK stance on NBS for DMD is illogical. Firstly, if there are indeed so many similarities of CF to DMD, it stands to reason that, if CF is part of the National screening programme then so should DMD. Secondly, having a programme in the UK which had screened for DMD in one country (Wales) and not in the other three (England, Scotland and Northern Ireland) was inequitable. Finally, the reason why NBS for DMD was stopped in Wales was one of financial pragmatism and not as a way of redressing inequity.

- DMD achieves this definition in both senses as it leads both to physical impairment and also to a social handicap.

- Any condition with profound physical impairments will inevitably suffer from our imperfect society and therefore it is right that future suffering is prevented by using NBS. NBS may be the means for us to identify those who will be born for such suffering thereby enabling us to do all we can to prevent it.

- Finally, no programme will generate only benefits without some of the burdens and disbenefits. To lump everything together and come up with a 'general good' is somewhat simplistic and ignores the complexities of such screening programmes.

- NBS is a very effective and relatively cheap way of preventing morbidity and mortality. NBS is however limited, in most developed nations, to a few conditions which fulfil the Wilson and Jungner Criteria.

- The current situation in the UK is that CF is being screened whereas DMD is not, despite the large number of similarities CF shares with DMD. This dissertation illustrates the inequity of having two incurable conditions being treated in different manners by a national screening service.

- The mere fact that this programme was in existence and available (albeit in pilot form), in Wales and not in the rest of the UK, is another example of the inequity of the NBS programme. This programme has provided patients in Wales with the potential benefits of early identification of DMD which has not been available to the rest of the UK. It has also exposed them to certain theoretical risks which haven't really come to reality under the scrutiny of evidence. The Welsh experience has been very informative and will no doubt help inform the future of the national NBS programme.

- I do believe that we are however at a cusp of paradigm shift in the way we look at genetic diseases such as DMD and CF because of the advent of gene therapy techniques. For the first time in 30 years there is real hope for a cure rather than just hype (30). In addition to the possibility of a cure, modern treatments have meant that conditions such as DMD and CF now have a life expectancy which is well into the mid 30s to 40s. Effectively they are no longer conditions which are lethal in childhood but ones where survival into adulthood is expected. These two features, better treatments and the prospect of gene therapy, mean that we must look at these diseases in a different way. I believe these two conditions now fulfil one of the crucial

Comments from Action Duchenne

Wilson and Jungner criteria (condition must be treatable) and thereby adds weight to their inclusion onto the NBS programme.

- The final argument I have put forward is to do with genetic conditions and disability in society. Essentially we all have faulty genes but we mostly do not know about them or they do not produce disability. The functional effect of faulty genes can therefore be very variable i.e. some are affected by these genetic conditions more than others. The level of disability experienced by a person can therefore be due to the direct effects of a faulty gene or from the society's reaction to the effects of the gene, in the form of disability.

- DMD is an extreme example of this logic where the large majority of the disability arises perhaps from our imperfect society rather than from the impairment we see in this condition. The point that I make is that if social disadvantage could be eradicated then whether one has or doesn't have a genetic condition will almost become an irrelevance. NBS in this type of society would be able to select those in need of support and whose lives are to be cherished and are worth something rather those whose birth needs to be prevented.

Alessandra Ferlini, MD PhD, Lead Geneticist, Ferrara University, Italy

I carefully read the document. It is very well written well documented and well balanced.

I am a supporter of the newborn screening, since I do believe that its first great benefit is the early diagnosis allowing appropriate care and accurate genetic prevention and reproductive choices, things that would enormously help families and boys, irrespectively from therapies.

Dr Stephen Abbs Director of Genetics Laboratories, Cambridge University Hospitals NHS

Foundation Trust, Addenbrooke's Hospital

I would support the introduction of NBS for DMD, hopefully costs of testing will come down sufficiently in the near future to make it viable.

Comments from Action Duchenne

xxxx xxxx UK DMD Registry Curator/Action Duchenne & Parent

As the Curator of the DMD Registry I come into regular contact with many affected families, especially those who have a son recently diagnosed.

The average age of diagnosis is four and half years old, some are younger if there is a family history or a reason to test and some are older if symptoms are not noticed or diagnosed. Commonly parents will suspect that there is a problem, but GPs/health professionals, due to lack of knowledge about Duchenne, can dismiss it or suggest the parent is overly worried and there is no problem. I had a son with Duchenne and we had four appointments with professionals until one recognized the symptoms. This caused months of uncertainty and anxiety for the extended family.

Without early diagnosis, families like my own can go on to have more children with Duchenne, adding to the family's distress. New born screening can give parents access to the best standards of care and early treatments leading to better outcomes. Early diagnosis gives access to genetic counselling, especially if the mother is a carrier and affecting daughters and sisters.

The diagnosis of Duchenne is traumatising and life-changing for the whole family. If the diagnosis is known earlier, then steps can be taken to see a specialist team to start receiving the best standards of care and to start steroids at an optimal time. Steroids are recognized as a treatment and most effective if started at the right time, but if too late the outcomes can be measurably different. Early diagnosis also gives early and beneficial access to physiotherapy, hydrotherapy and dieticians.

Early diagnosis not only helps with early treatment, but also:

- Housing - like my family we moved before diagnosis and had to move again as house unsuitable for adaptations, adding to the family's finances.
- Schools will have to be investigated.
- Activities – directed to swimming, rather than trampolining.
- Need to avoid the wrong treatment that could be damaging.
- Knowledge of the condition.
- Coming to terms with the condition.
- Counselling and for more children.
- Finances need to be reassessed to cope with the burden of the costs of adaptations and equipment required which is significant. Using the DMD Registry I am acknowledged as a contributor to the published work The Burden of Duchenne

Comments from Action Duchenne

Muscular Dystrophy – An International, cross-sectional study:
http://www.neurology.org/content/83/6/529

*"**Objective:***
The objective of this study was to estimate the total cost of illness and economic burden of Duchenne muscular dystrophy (DMD).

Methods:
Patients with DMD from Germany, Italy, United Kingdom, and United States were identified through Translational Research in Europe–Assessment & Treatment of Neuromuscular Diseases registries and invited to complete a questionnaire online together with a caregiver. Data on health care use, quality of life, work status, informal care, and household expenses were collected to estimate costs of DMD from the perspective of society and caregiver households.

Results:
A total of 770 patients (173 German, 122 Italian, 191 from the United Kingdom, and 284 from the United States) completed the questionnaire. Mean per-patient annual direct cost of illness was estimated at between $23,920 and $54,270 (2012 international dollars), 7 to 16 times higher than the mean per-capita health expenditure in these countries. Indirect and informal care costs were substantial, each constituting between 18% and 43% of total costs. The total societal burden was estimated at between $80,120 and $120,910 per patient and annum, and increased markedly with disease progression. The corresponding household burden was estimated at between $58,440 and $71,900.

Conclusions:
We show that DMD is associated with a substantial economic burden. Our results underscore the many different costs accompanying a rare condition such as DMD and the considerable economic burden carried by affected families. Our description of the previously unknown economic context of a rare disease serves as important intelligence input to health policy evaluations of intervention programs and novel therapies, financial support schemes for patients and their families, and the design of future cost studies.. Neurology. 2014 Aug 5; 83(6): 529–536.

As with the scheme in Wales and despite unreliable testing, I, like many parents would want to know, but this information needs to be comprehensive and the support needs to be there following diagnosis.

I personally would not knowingly bring a child into the world with Duchenne, so having one son with the disease, if I had been offered screening rather than waiting for the disease to show itself I could have made different choices before having a second child. I subsequently had a **xxxx xxxx** three years later and **xxxx xxxx** is now anxiously waiting the results of **xxxx xxxx** genetic testing to see if **xxxx xxxx** is a carrier. **xxxx xxxx** now has choices, but the cycle of Duchenne could carry on.

Comments from Action Duchenne

xxxx xxxx, Trustee Action Duchenne & Parent

- Having a child with Duchenne when you don't have a family history is a huge shock, the early signs are easily dismissed by parents and medics alike. My own experience saw various tests and incorrect diagnosis commencing aged 4 and taking 3 years to get to the right diagnosis. This has resulted in **xxxx xxxx** commencing steroids later and decisions we have made as parents might have been different.
- I would have taken different career decisions and looked at every aspect of our finances, housing needs etc at a much earlier stage.
- Understanding the condition at a much earlier age for me would have been beneficial.
- I started fund raising for research on diagnosis, this perhaps would have started sooner.
- Getting to grips with what damages these kids (trampolines, bouncy castles etc) at an earlier age would be highlighted.
- For parents considering having more children, surely being able to make an informed decision can help each family make a decision – I am devastated for those families that do not expect a diagnosis to then learn that they have more than one child with DMD.
- My son is part of the ForDMD study – perhaps the approach to steroid use may be different once the results are known.

Comments from Action Duchenne

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Comments from Muscular Dystrophy UK

Muscular Dystrophy UK welcomes the opportunity to respond to the National Screening Committee (NSC) review of Newborn Screening for Duchenne Muscular Dystrophy.

The charity's response can be summarised as follows:

- Duchenne muscular dystrophy is a progressive muscle wasting condition. Progressive weakness is the result of the progressive loss of muscle mass.
- With approved drugs for Duchenne muscular dystrophy (Translarna) - and others in late stage clinical trial.- the need to prepare a screening programme that will enable early detection is crucial. As treatments are aimed at protecting muscle from further degeneration, their use in patients is anticipated to be much more beneficial the earlier the age at which they are administered.
- Muscular Dystrophy UK supports screening for Duchenne muscular dystrophy, but recognises that important preparatory work must be completed to enable NSC approval, particularly on the creatine-kinase assay
- Muscular Dystrophy UK acknowledges concerns around the reliability of the current screening test. However, it is important to note that a new more sensitive and specific test has been developed by Dr Stuart Moat at the University Hospital of Wales/Cardiff University in collaboration with PerkinElmer and this new test is undergoing an extensive evaluation. Furthermore, a partnership between PerkinElmer and the California Department of Health Newborn Screening Programme is currently underway to develop a more refined screening protocol.
- Given the rapid developments in testing protocol and the fact that there are approved drugs for the treatment of Duchenne, the NSC should be prepared to bring any future reviews for Duchenne forward. This would avoid a position where Duchenne screening is ready for approval, but the next NSC evidence review is some years away.
- There is widespread support amongst parents for a newborn screening programme, and most families whose children have been screened report that it was helpful in allowing them to plan ahead and make adjustments to their lives at an earlier stage. This lived experience should be better acknowledged and captured by the NSC.
- Diagnostic delay is still prevalent for Duchenne muscular dystrophy. This means children diagnosed late miss out on best standards of care, leading to worse outcomes than those children who are diagnosed early. Newborn screening would play an important role in addressing the 'diagnostic odyssey' and allow timely introduction of standards of care.
- Recent published evidence indicates that in the UK the age at starting steroids (recognised standard of care) is later than optimal, due to the delay in the diagnostic process for families.
- Recent peer reviewed publications suggest that treatment with steroids at an earlier age than the average age of diagnosis is associated with better outcomes, and a clinical consensus is emerging around this.

Comments from Muscular Dystrophy UK

Implementation of best standards of care and treatment

Without any treatment, the natural history of Duchenne muscular dystrophy suggests that patients typically lose the ability to walk before the age of 13 and average life expectancy is in the late teens to early twenties. However, with the right management and best standards of care a child diagnosed with Duchenne in 2016 could live well into their 30s.[2]

For newly diagnosed children, treatment will usually include commencement of a corticosteroid regime, which has been shown to prolong ambulation. Given that earlier loss of ambulation is associated with a faster progression of the disease, access to steroids at an early stage is an essential method of treatment and could play a role in prolonging life expectancy.

Professor Francesco Muntoni of the Dubowitz Neuromuscular Centre, says:

> *"In a child at around the age of five, already one third of the muscle mass has been lost. At the age of 18, normal individuals will have approximately 30 kilograms of muscle; an individual with Duchenne muscular dystrophy will have 1.5 kilograms of muscle. Avoiding progressive muscle loss is of paramount importance for this condition. Anticipatory care is necessary to retain as much function and muscle mass as possible. You don't wait until there is a big problem and then start finding a way to patch it. When children are diagnosed, they already have been symptomatic. They really have lost a lot of ground…the later you start steroid treatment the less [likely] the steroid will have an effect. So if you start the steroid the day before, for example, or a week before children are going to stop walking, it will have no effect. If you start much earlier, they will prolong the ability to walk for four to five years, which makes a huge difference to subsequent life-expectancy."*

There is a growing amount of evidence in favour of commencing steroids an earlier stage, which Muscular Dystrophy UK does not believe has been properly captured in the NSC's review.

For example, standardised clinical data analysed through the NorthStar Network found that starting corticosteroids between 3 and 5 years 'conferred an additional gain in motor function of 3 units/year (in the North Star functional assessment tool) up to age 7'[3] . There is a clear correlation in Duchenne between the level of function and the subsequent loss of motor activities and ultimately respiratory insufficiency and death. Therefore, initiating treatment at an early age – when function is at a higher level – can be expected to confer significant longer term advantage in terms of health outcomes.

Another independent recent study showed that initiation of corticosteroids between 2-4 years showed good long term outcomes after a 14 year observational study. [4] There is therefore strong evidence favouring the commencement of steroids at a significantly earlier age than the mean age of diagnosis. Clinical consensus is coalescing around this viewpoint.

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Comments from Muscular Dystrophy UK

It must also be noted that treatments targeting the underlying genetic cause of the disease – such as ataluren – would be expected to be more effective the earlier they are implemented. Licensing restricting use to those aged five and over is an indication of the population who took part in the clinical trials, not because such treatments would be ineffective in younger children, and indeed this point was discussed at a recent EMA workshop on standards of care and experimental therapies for DMD (Lancet Neurology), while PTC therapeutics is planning limited safety studies in infants, to confirm the safety and pharmacokinetics of the drug.

Given the probability that more drugs will come 'on stream' in the future, ensuring preparedness for newborn screening is essential (see also P.4 'revising the testing protocol). The NSC must therefore be prepared to bring any future review for Duchenne forward should further treatments become available and a revised and commercially available test be in place.

Diagnostic delay

Diagnostic delay is a crucial issue affecting the diagnosis and management of Duchenne muscular dystrophy.

Parents and early years professionals are usually the first to spot developmental delay, such as difficulties in getting up off the floor or an inability to keep up with friends or siblings. This is typically between the ages of 2-3 years old although in some instances symptoms may become apparent earlier.

Average age of diagnosis is 4.5 years old, and diagnosis later than this age is prevalent, indicating a significant delay from first reported parental concerns to diagnosis. This is primarily due to a lack of awareness of the disease amongst professionals involved in primary care, who may make an incorrect referral or initially misdiagnose the condition.

The diagnosis of Duchenne muscular dystrophy is devastating for families, and can be made all the worse if it follows months and years of such uncertainty.

Diagnostic delay affects subsequent access to the care pathway and implementation of best standards of care. This means there is delayed access to specialist physiotherapy, regular monitoring by specialists and often boys start steroids later than recommended, or in some instances are unable to begin steroid treatment if they have been diagnosed too late.

Lack of diagnosis can also lead to a lack of appropriate support at school, and in other aspects of day to day life. This can have an impact on cognitive and behavioural development.

xxxx xxxx, whose son, xxxx xxxx, was diagnosed with Duchenne muscular dystrophy aged 7 and a half, said:
xxxx xxxx

"My son, when he was diagnosed, was seven and a half years old. Therefore he missed out on essential steroid treatment– not really bringing into it the enormous distress that was caused by the lack of diagnosis within his schooling and everything else… I can only speak from my own point of view, and having a son diagnosed at seven and a half is horrific. We didn't know why he couldn't walk down the stairs fast enough; the dyslexic problems; the behavioural problems…it was unutterably awful."

Comments from Muscular Dystrophy UK

Muscular Dystrophy UK believes that neo-natal screening would play a central role to addressing the 'diagnostic odyssey' in Duchenne muscular dystrophy, and allow children to access best standards of care at an earlier stage of the process.

Revising the testing protocol

Muscular Dystrophy UK fully recognises the concerns around the reliability of the current assay for Duchenne newborn screening. The creatine-kinase test is prone to a relatively high rate of 'false positives', and in Wales the number of 'false negatives' the test produced was close to 20%.

This represents a significant barrier to NSC approval for newborn screening for Duchenne, and it is essential that the assay is revised in order to enable screening to move forward.

We strongly support the work being led by PerkinElmer[1] in partnership with the California Department of Health Newborn Screening program to refine the screening protocol for Duchenne muscular dystrophy

We also recognise the work that Parent Project Muscular Dystrophy [2]are undertaking in this area. Muscular Dystrophy UK is committed to supporting this work and to ensuring that steps can be taken to ensure screening can be implemented in the UK.

Further information on the new skeletal muscle specific creatine kinase screening test is available here.

The family experience

Whilst there has never been a UK-wide programme of newborn screening for Duchenne muscular dystrophy, a screening programme was in place in Wales between 1990 and 2011 before it was withdrawn.

This means there are a number of children and young adults in Wales who were diagnosed through newborn screening, and whose parents are able to comment on the effects this very early diagnosis had on the family. For many of these families, the choice to screen and the early diagnosis was helpful in enabling them to plan ahead and make important adjustments to their lives, even in the absence of now approved drugs, such as ataluren.

xxxx xxxx, **xxxx xxxx**, was diagnosed via newborn screening in Cardiff and the family are supportive of neo-natal testing for the condition.

xxxx xxxx says:

xxxx xxxx

> *Having a very early diagnosis was a positive … because it has allowed us to plan. We can take holidays that we wouldn't be able to take with an older boy. We can move into accommodation. We have a nice family home with plenty of space, but if we want to have a purpose-built area for* **xxxx xxxx***, we can do that before* **xxxx xxxx** *begins to think that we are moving out because of him. We can plan and put things in place; I changed my career. I*

Comments from Muscular Dystrophy UK

think with an early diagnosis, we can try and spend more time at home, taking the positive out of it. **xxxx xxxx** *gets assessed every six months, so any change in his wellness will be picked up immediately. He has taken steroids from the age of four."*

xxxx xxxx says:

"The positive result and the immediacy of having to face up to the diagnosis of a little boy who appeared to be physically fine was initially traumatic, but we cannot emphasise enough how the early diagnosis has helped us cope, plan and nurture **xxxx xxxx** *in the knowledge of his condition".*

Other families working with Muscular Dystrophy UK – whose children were not screened - also feel that they would have preferred to have received a diagnosis through newborn screening.

xxxx xxxx, whose son, xxxx xxxx, was diagnosed aged 3, says:

"Speaking as a mum who has a boy with Duchenne muscular dystrophy, there's never going to be a 'good' time to find out. But I strongly believe that once you have a diagnosis, you can take positive steps to help your child. I feel that it is in the boys' best interests to be diagnosed as soon as possible, so that they can receive the support they need - as soon as they need it.

Giving parents the opportunity to screen their child can give them precious extra time to think about the implications of trying for another child, where to live, and where their son should go to school. It is devastating to find out that your longed-for and loved child has a condition like Duchenne, but I think we need to accept that the benefits of an early diagnosis are well worth having. "

xxxx xxxx, whose son, xxxx xxxx, was diagnosed with Duchenne aged seven-and-a-half, says:

"The diagnosis was devastating, the loss of the healthy child we thought we had. If we had known earlier we would have had more time to plan housing and think about **xxxx xxxx** *education. We would have moved earlier. We still would have been devastated and grieved, but would have found out how to manage the condition and would have made the best of those early years. Given there have been so many advances in research and management of the condition, the outlook for boys with Duchenne muscular dystrophy has improved tremendously. Even without a treatment available right now, having the choice to screen your child could make a profound difference to their quality of life, as early management is so important."*

However, it must be acknowledged that not all families have the same point of view, including those who experienced newborn screening in Wales.

xxxx xxxx son, xxxx xxxx, was diagnosed via newborn screening. He strongly feels that in the absence of effective treatments administered in early life, a neonatal diagnosis was the wrong time at which to be told his child has Duchenne.

"My son was picked up as part of the newborn screening testing in Wales. We had no information about the screening process before the test being done. We were in hospital for one day; it was our first child and we were offered it under the premise that it

Comments from Muscular Dystrophy UK

always comes back negative ... It is the worst thing that we have done to sign the consent form for the test. It is a cruel and unusual torture. The test has no backbone to it; it is performed by one professional, early diagnosis is given by a different set of professionals; there is no overriding person who sees you through the process … You get an early diagnosis at six weeks but we can only get an appointment with a neuromuscular consultant once Seth starts to become symptomatic. We have a diagnosis but we can't do anything with it."

The **xxxx xxxx** family's experience also highlights the need to ensure that sufficient numbers of neuromuscular care advisors are in place to support parents whose infant son has just been diagnosed. Families face huge challenges coming to terms with a diagnosis and will need to know what support is available and where to find it. Appropriate and robust support for families will be a crucial component of any newborn screening programme in the UK.

Surveying family views on newborn screening

During the previous NSC consultation period on newborn screening, Muscular Dystrophy UK, in partnership with the Duchenne Family Support Group and Action Duchenne, conducted a survey to ask the opinion of families affected by Duchenne muscular dystrophy.

In total, 255 people from the UK participated in the survey, 17 of whom were from Wales and had participated in the newborn screening programme for Duchenne muscular dystrophy.

We sought to find out if people supported the introduction of a newborn screening programme now, in the absence of effective or curative treatments. We also wished to see what effect the introduction of such treatments for Duchenne muscular dystrophy might have on support for a newborn screening programme.

The survey results showed that:

- 82 percent were in favour of a newborn screening programme even without an effective treatment to prevent the development of symptoms
- 97 percent of people were in favour of newborn screening if effective treatments were available.

Comments from respondents included:

"[I would support it] wholeheartedly. Currently knowing there is no treatment for Duchenne muscular dystrophy is similar to telling parents their child has an incurable cancer. Whereas if there is a known treatment then the sooner diagnosis is made the quicker treatment can start."

"I would support it regardless of current available treatments. Newborn screening would prevent boys from falling through the net and [would] ensure that they could get the help they need as soon as possible."

When to screen?

Current steroid treatment for Duchenne muscular dystrophy is not administered before the age of two and new treatments may not be given to babies. Therefore, the survey looked to find out parents' views on the time at which they would have preferred to learn of their child's diagnosis:

Comments from Muscular Dystrophy UK

- 53 percent of parents said they would prefer to know soon after birth
- 28 percent of parents said they would prefer to know once their child started showing symptoms
- 19 percent of respondents didn't know when a preferred time would be.

Those in favour of knowing soon after birth felt it would have helped them to plan for the future, plan future pregnancies and access the full range of therapies. Comments included:

"As soon as possible would be best because you can be prepared for what changes you will have to make for your family life."

Some felt they could have been better parents had they known earlier:

"Speaking to other mums who did not have the diagnosis early, they felt guilty, thinking their child was lazy when they were tired due to their condition and sorry that they reprimanded him at times when he was not at fault."

Others would have liked to have known at birth because they found getting a diagnosis later on very stressful:

"I personally would have liked to have known soon after birth because for me, feeling something was wrong and always pressuring my GP and health visitor for a referral was a very difficult time."

"If screening had been available when my son was born, an early diagnosis could have been made. I could have made better choices about health and education. I could also have found a more suitable home location and secured better support from social services."

For those who would have preferred a diagnosis when symptoms arose, their view was largely informed by the stress-free time they would have had prior to diagnosis:

"We had six wonderful years of blissful ignorance in which to enjoy our two young boys."

Several people commented that they felt the timing of newborn screening was wrong:

"I feel newborn is too early and at signs of symptoms is too late, if steroid treatment can be given as early as two to three years old, then testing may be better around then," and *"knowing soon after birth could rob a child of some 'normal' interaction and bonding with family."*

Informed consent and post-diagnosis support

Parents reiterated their concerns about the necessary support being available at diagnosis. This was mirrored in the responses from families in Wales who participated in newborn screening for Duchenne muscular dystrophy, many of whom said there was a lack of support and information throughout the diagnostic process:

- only two in five respondents felt they received enough information about the heel prick test when making a decision to participate in the screening
- nearly a third of respondents were unaware their baby had been screened for Duchenne muscular dystrophy
- half of respondents said the consent process could be improved

Comments from Muscular Dystrophy UK

- only one in three parents felt they received enough professional support during the diagnosis process, with many being left to seek out information themselves on the Internet and from charities.

Several respondents, however, praised the help they received:

"I cannot fault the support that we had at the time, or the support since."

To follow up on this, we asked families from all over the UK what information they thought should be provided to parents to help them make the decision to take part in Duchenne muscular dystrophy newborn screening programme if it were offered, and by whom, when and how. Almost all respondents wanted a full and comprehensive description of the effects of Duchenne muscular dystrophy and of which treatments could be administered if their child were diagnosed shortly after birth. Respondents differed in their view of who should deliver this information, but common responses included specialists on Duchenne muscular dystrophy, as well as neuromuscular care advisors.

Name:	Alastair Kent OBE	**Email address:**	xxxx xxxx
Organisation (if appropriate):	Genetic Alliance UK is the national charity working to improve the lives of patients and families affected by all types of genetic conditions. We are an alliance of over 180 patient organisations. Our aim is to ensure that high quality services, information and support are provided to all who need them. We actively support research and innovation across the field of genetic medicine. Rare Disease UK is a multi-stakeholder campaign run by Genetic Alliance UK, working towards the delivery and implementation of a national strategy for rare diseases in the UK. The UK Strategy for Rare Diseases was published in November 2013. Pertinent to this consultation, the Strategy includes a commitment from all four Governments of the UK to: "Continue to work with the UK National Screening Committee to ensure that the potential role of screening in achieving earlier diagnosis is appropriately considered in the assessment of all potential new national screening programmes and proposed extensions to existing programmes." Commitment 9, The UK Strategy for Rare Diseases, November 2013. This commitment recognises the value that the rare disease community places on early diagnosis, not only for the benefits it can bring to an affected individual but because of the impact it can have on improving the quality of life for their whole family.		
Role:	Director		

Do you consent to your name being published on the UK NSC website alongside your response? Yes ☒ No ☐		
Section and / or page number	**Text or issue to which comments relate**	**Comment** *Please use a new row for each comment and add extra rows as required.*
4	"The UKNSC does not recommend screening for Duchenne muscular dystrophy. There remain uncertainties across key criteria and the evidence suggests that the recommendation not to screen for Duchenne muscular dystrophy should be retained."	We support the submissions of our member organisations Action Duchenne and Muscular Dystrophy UK, both of whom support DMD screening but recognise that the accuracy of the test needs to be addressed. We understand that there is work currently underway looking at a revised testing protocol which may avoid the high false positive and negative rates seen in the standard CK test. However, this evidence would not be available until after the UK NSC's scheduled review is complete in November.
19	"Overall there was a small amount of evidence regarding treatments which seek to alleviate the underlying genetic defect causing DMD or significantly improve symptoms or function."	An accurate newborn screening programme for Duchenne muscular dystrophy has the potential to positively impact the lives of patients and their families quite substantially, and we are concerned that the review document downplays this. While it is not possible to completely cure DMD there are new medicines which have been licensed since the previous review or are in the pipeline which directly act to increase the amount of functional dystrophin protein produced and available in the body, for patients with amenable mutations. The first of these, ataluren, has now been recommended for use in England by NICE, and a second, eteplirsen is currently being scoped. These represent a step change in the management of the condition, as the first medicines which

		treat the underlying cause of the disease in these subpopulations of DMD patients. Though neither of these medicines would be appropriate for all patients with Duchenne, as they are targeted to specific mutations, nonetheless they represent a substantial step forward in the treatment of the condition. The review focuses on the uncertainties of evidence relating to treatment rather than the implications of what is known. We have previously repeatedly expressed concerns about the UK NSC's current methodology, which places a premium on peer reviewed literature to the exclusion of all other forms of evidence. Relying solely on peer reviewed literature excludes the direct contribution of the patient voice to the process. This is out of step both with other institutions with responsibility for decisions regarding public health, such as NHS England, the National Institute for Health and Care Excellence and the European Medicines Agency, and with accepted practice in dealing with rare disease issues. All three of these agencies, and more, have accepted that evidence will always be scarce in the area of rare disease, and is likely to be of weaker statistical significance than that expected from more common conditions. They have resolved to fill this gap by accepting qualitative evidence from the patient community. We believe the UK NSC should take steps to do the same. This is particularly concerning in this case, as NICE's Highly Specialised Technologies committee has extensively reviewed the evidence on the effectiveness of ataluren for treating

		Duchenne caused by a nonsense mutation. NICE determined that not only did the research suggest that ataluren may delay loss of walking for up to 7 years, it judged the treatment as likely to be cost effective. Thus the UK NSC is holding evidence on the effectiveness of a treatment to a stricter standard of proof than NICE.
20-21	"No studies were identified which assessed the impact of treatment following newborn screening in comparison with existing detection and treatment pathways. The identified studies provided no direct assessment of potential treatment benefits following screening as none described participants as being detected through screening."	Although, as the review suggests, DMD is typically diagnosed at around 5 years of age, there are frequently missed opportunities for diagnosis much earlier because of delays in attainment of developmental milestones, such as independent walking or language. Screening could play an important role in preventing diagnostic delay, and an increasing possibility of improving patient outcomes by slowing muscle deterioration before it reaches the point of clinically detectable weakness. Research on the new disease-modifying treatments suggests that even in the case of patients who respond to the medicine, disease progression appears to be largely irreversible. In addition, an emerging body of evidence suggests that even for current standards of care for Duchenne like steroids, the earlier they are administered the more likely the benefit. Early diagnosis and treatment are therefore vital. While we understand that there is a need for further research to investigate the impact of early management of the condition, widespread diagnostic delay means it is not clear how this information is likely to be generated within a reasonable time frame without either substantial improvements in early clinical identification of affected boys or a screening programme.

		Separate from the potential benefits of early treatment, there are other benefits to a newborn screening programme for the family of affected boys. Diagnosis in infancy allows families to also have more time to plan and deal with all the hurdles and obstacles they face, and a lot of families who were identified through screening in Wales did feel it was helpful in terms of enabling them to plan ahead and make adjustments to housing, work etc.
22	"No new evidence was identified that assessed the wider effects of screening for DMD on the reproductive or other choices of the parents."	The review accepts unchanged the previous NSC report's suggestion that parents' reproductive behaviour may not be largely influenced by the results of newborn screening. However, information about whether an individual is affected by a genetic condition with childhood onset like Duchenne can be immensely valuable for the future reproductive choices of their parents and families. There are well known cases in which the family have had three affected children before the eldest child began to show symptoms, where newborn screening could have allowed the parents to consider their reproductive options at an earlier stage. In addition, since the review was carried out in 2012 there have been major advances in reproductive techniques to enable couples at risk of having a child with Duchenne to make an informed choice. Pre-implantation genetic diagnosis is now widely available for families with a history of Duchenne muscular dystrophy or other serious genetic conditions, and families in the UK have been able to access non-invasive prenatal genetic testing for Duchenne privately or in research studies. However, these techniques rely on couples knowing that they are at risk of having an affected child, and so depend on early diagnosis. We suggest that the review should be
		updated to reflect these developments.