UK National Screening Committee

UK National Screening Committee (UK NSC)

Screening for Duchenne Muscular Dystrophy

Date: 04 November 2021

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Aim

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

Current Recommendation

The current UK NSC recommendation is based on an evidence review carried out by Bazian Ltd in 2016. The review aimed to identify evidence on whether there was a reliable, high throughput screening strategy; any additional benefits from early treatment following screen detection or an optimum age for treatment initiation; and demonstration of wider effects or benefits from screening for DMD, such as on reproductive choices. The 2016 found insufficient evidence to recommend the introduction of a systemic neonatal screening for DMD. This was because:

- there was insufficient, high quality evidence of a suitable population screening test in newborns
- of a lack of evidence for a reliable and appropriate screening strategy. The previous review also found a lack of evidence for any additional benefit for early treatment when people with DMD are identified during screening

- there was not enough evidence to demonstrate wider effects or benefits from screening for DMD, such as reproductive choice

Evidence Map/Summary

The 2021 evidence review was undertaken by Costello Medical in accordance to the UK NSC triennial evidence review process.

The scope of the 2021 evidence map is to evaluate the volume and type of evidence in relation to the effectiveness of screening tests for DMD, and to assess whether a more sustained review on screening for DMD should be commissioned at this time. The evidence map looked at the following key question:

Q1: What is the volume and type of evidence on suitable screening tests using dried blood spots to detect DMD?

The conclusion of the 2021 evidence summary is that population screening for DMD should not be recommended. The key reason for this is a lack of evidence for a suitable screening test using dried blood spots. Only one published study with a relatively small sample size (n =1,424) was identified during the search period covered by the evidence map. Therefore, it is unlikely that further work on this topic would lead to a change in the UK NSC's current position because the findings have not yet been replicated in more than one or larger studies. However, evidence from the ongoing pilot studies in the US and China might warrant reconsideration of this topic when such evidence become available**.**

Consultation

A three-month consultation (period of consultation) was hosted on the UK NSC website. Direct emails were sent to 15 stakeholders. (Appendix A)

Comments were received from the following 6 stakeholders (see Appendix B for comments):

- Muscular Dystrophy UK
- The Royal College of Midwives
- The Duchenne Family Support Group
- Genetic Alliance UK
- Royal College of Paediatrics and Child Health
- Royal College of Physicians

Overall, the six above stakeholders all indicated that they were supportive and understood the conclusion of the review.

- Two responses noted that the review doesn't mention Translarna, a Duchenne muscular dystrophy treatment approved by NICE in July 2016 through a managed access agreement for children with a nonsense mutation aged two years and over who are still able to walk 10 steps unaided. Re-evaluation was due by July 2021 but has been delayed due to COVID-19 to January 2023. They suggested inserting this into the evidence map.
- Response: These treatments have been incorporated and mentioned under the treatment options section of the updated evidence map
- Two responses suggested preparing other factors including conversations around ethics, access to testing and genetic counselling rather than waiting for the next review cycle in three years time. This would allow for a quick roll out if screening is approved.
- Response: These other factors are outside of the remit of the UKNSC. Duchenne Muscular Dystrophy will be reviewed again in three years as part of the UK NSC review cycle.
- Language suggestions have been updated in the evidence map these can viewed in Appendix B

Recommendation

The Committee is asked to approve the following recommendation:

A systematic population screening for Duchenne Muscular Dystrophy in newborns is not recommended in the UK.

UK National Screening Committee

Appendix A: List of Organisations Contacted

1. Action Duchenne
2. ArchAngel MLD Trust
3. British Association of Perinatal Medicine
4. Duchenne Family Support Group
5. Faculty of Public Health
6. Genetic Alliance UK
7. Institute of Child Health
8. Metabolic Support UK
9. Muscular Dystrophy UK
10. Royal College of General Practitioners
11. Royal College of Midwives
12. Royal College of Paediatrics and Child Health
13. Royal College of Physicians
14. Royal College of Physicians and Surgeons of Glasgow
15. Royal College of Physicians of Edinburgh

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Appendix B: Consultation Responses

Note: Personally identifiable information has been redacted from certain comments, where individuals have chosen not to have personal details made public

1. Response from Muscular Dystrophy UK

Name: Michaela Regan

Organisation: All Duchenne muscular dystrophy charities

Role: Senior Health Policy Manager

Introduction

We are responding on behalf of the leading Duchenne muscular dystrophy charities in the UK, Action Duchenne, Duchenne Family Support Group, Duchenne UK, Muscular Dystrophy UK, and Pathfinders Alliance.

Combined, we support people with Duchenne muscular dystrophy by providing emotional and financial support, funding research and assisting with clinical trial recruitment, and engaging with key policymakers to improve access to and quality of neuromuscular services and treatments across the UK.

We acknowledge the Committee's overall conclusion of a negative recommendation due to the current unavailability of a reliable screening test. It is promising to see the list of on-going pilot Duchenne muscular dystrophy screening programmes in the consultation document to identify a robust screening test. We hope this will lead to identifying a robust test and change the Duchenne muscular dystrophy screening recommendation in the near future.

We feel, however, that more progress has been made in two key areas cited in the Committee's conclusions than is acknowledged in this consultation, namely the best age to start treatment; and evidence that screening and early treatment would improve the long-term health of babies. We would also like to use this opportunity to raise points around the timelines for further reviews and around some of the language and terminology used in the consultation document.

Screening and early treatment

We are pleased the evidence map acknowledges that ‘an early diagnosis and earlier initiation of treatment benefits the duration and quality of life, with evidence that boys who are treated earlier with corticosteroids show better motor function acquisition and maintaining ambulation for longer. Furthermore, an earlier diagnosis allows for informed family planning decisions and participation in potential clinical trials with novel investigational agents. However, there are delays of up to 2 years between the appearance of first symptoms and diagnosis.’

While one of the main aims of testing is to give early access to treatments, the social implications of screening cannot be overemphasised. In fact, one of the big challenges of screening for Duchenne muscular dystrophy would be implementing a process that considers the spread of opinion in the disease community. On one hand, many parents say finding out early allowed (or would have allowed) them to prepare – to move to an adaptable/adapted house in plenty of time, to make informed family planning choices, even to consider the hobbies and activities they would encourage their young child to take part in. On the other hand, some parents whose children were diagnosed in screening programmes tell us they were robbed of the blissful unknown and felt that they bonded very differently to their child and saw no tangible benefit. These issues could easily be compounded if genetic counselling isn’t available to support testing programmes or communication to families about initial screening results is managed poorly – both of which have happened previously.

We appreciate that there isn’t sufficient support for families that receive a positive new-born screening test result without a treatment to target the underlying cause of Duchenne muscular dystrophy. However, until screening is recommended, we urge the importance of increasing awareness of Duchenne muscular dystrophy within primary care. This will go some way to ensuring patients get a faster diagnosis by accelerating referrals for testing and will ensure sooner initiation of treatment by reducing the time between the first symptoms appearing and treatment starting. A faster diagnosis will also help to increase access to clinical trials; to provide families with the opportunity to adapt to the diagnosis; and to enable families to start planning for the longer term.

Timelines for review

Duchenne muscular dystrophy is one of the conditions involved in the Genomics England consultation on new-born sequencing. This approach is to be encouraged; it is a single step, diagnostic test and as such, we hope it would overcome some of the issues with false positives in screening and the false negatives seen in the Welsh and other programmes. However, that programme is still in the early stages and rollout at scale will take time, it is important that

these reviews of new-born screening for Duchenne muscular dystrophy continue.

Rather than simply waiting for three years and checking again to see if a proven test is available, we believe that the complex conversations around ethics, access to testing and genetic counselling, and the processes required could be profitably undertaken while tests are being developed. This would allow the UK to move toward a place where the ethical and practical implications of screening were well understood and where protective processes and procedures were already identified. This could facilitate a quick roll out of the screening programme when tests are available, alongside the provision of appropriate genetic counselling and other support, allowing families to choose whether to use the screening programme.

While we therefore welcome that there will be a further review of Duchenne muscular dystrophy screening in three years, we would urge the committee to ensure that this timescale can be shortened should significant developments in the diagnosis and treatment of Duchenne muscular dystrophy emerge in the interim period. We have already seen in Spinal Muscular Atrophy (SMA) how quickly treatments can emerge onto the market and the culmination of published evidence supporting the efficacy of screening tests has changed the screening landscape for this disease area. We hope with the on-going Duchenne muscular dystrophy pilot screening sites cited in the consultation document that we may be closer to addressing the outstanding concerns and will be able to implement Duchenne muscular dystrophy screening in the foreseeable future.

We also recommend that the UK Screening Committee should aim to adopt a position of “we will implement a screening programme when a proven test and appropriate processes of support and access to treatments are available” rather than “we will not implement a screening programme until this is the case”. While superficially similar, the first position provides the reason that companies and research funders need to invest in new testing technology and run the evidential studies required. As stated above, we therefore believe the NSC should continue to review Duchenne muscular dystrophy through detailed reviews and conversations around all aspects of the screening programme except the test itself while tests are being developed so that screening can be recommended more quickly when ready.

Accuracy, language and terminology used in the consultation document

There are some areas of the consultation document that contain some inaccuracies or that use language and terminology that we would recommend are reviewed for future documents related to Duchenne muscular dystrophy.

P5, para 3: “as well as heart and lung complications” – The word complication implies that these events are unusual for those living with Duchenne muscular dystrophy. The heart is a muscle and is directly affected by a lack of dystrophin rather than being a complication of muscle wasting. We suggest changing this language throughout the paragraph. We suggest:

as well as heart and lung involvement. As a consequence, OR

as well as circulatory and breathing complications. As a consequence of these complications,
Similarly, wheelchair use is not a complication of Duchenne muscular dystrophy. Progressive muscle wasting means people are unable to walk; using a wheelchair is part of the usual progression of Duchenne muscular dystrophy.

P6, para 1: A confirmed diagnosis of Duchenne muscular dystrophy typically requires blood sample analysis for a deletion or duplication mutation in the Duchenne muscular dystrophy gene – While these mutations are the most common causes of Duchenne muscular dystrophy, they are responsible for approximately 70% of cases. We would suggest adding the following text:

followed by sequencing to identify small insertions/deletions, point mutations and other rare mutations.

P6, para 2: Treatment options – This section generally needs updating. Ataluren (Translarna) was approved by EMA in 2015 and is available on the NHS in the UK. Translarna can treat approximately 10% of Duchenne muscular dystrophy cases caused by a nonsense mutation in the dystrophin gene. This mutation leads to a premature stop codon, which prevents production of a full-length, functional dystrophin protein; Translarna allows readthrough of the premature stop codon to enable production of full-length, functional dystrophin. The latest data from the CINRG network shows that Translarna delays loss of ambulation by approximately five years compared to propensity-score matched control groups. Translarna is currently available to patients aged over 2 who are able to walk.

Other countries have also approved drugs for Duchenne muscular dystrophy. In the US, exon skipping drugs (collectively targeting 3 of the 79 exons of the Duchenne muscular dystrophy gene) are available. Exondys 51, Vyondys 53, Viltepso, and most recently Amondys 45 have all gained approval. Exondys 51

is available to children with no lower age limit. We hope that the confirmatory studies now underway for some of these drugs will provide the evidence needed to support licencing applications in Europe/UK. There are therefore a significant number of treatments in very late-stage clinical development for Duchenne muscular dystrophy that could reach the clinic inside the 3 years suggested for the next review.

P6 para 4: Benefits of early diagnosis – Translarna should be mentioned in this section. While we are not aware of any evidence showing additional benefit of starting treatment with Translarna earlier, it is generally accepted in the Duchenne muscular dystrophy field that muscle wasting starts before symptoms present and that early treatment with agents that restore dystrophin protein may be beneficial. With children diagnosed at around 4-4.5 years, the average child's treatment is currently delayed by 2-2.5 years. Since Translarna is only available to ambulant patients in the UK, a 2.5 year delay potentially represents a significant reduction in how long somebody can receive the drug for.

P6 para 4: informed family planning decisions – This issue is bigger than this text suggests. Many parents have more than one child living with Duchenne muscular dystrophy. For example, the McKell Institute's "Living with Duchenne & Becker in Australia" report (2020) found 23% of survey respondents had more than one child living with Duchenne or Becker muscular dystrophy.

P7 para 2: diagnosis of Duchenne muscular dystrophy is only possible via genetic testing – In the absence of a genetic mutation being identified, a muscle biopsy negative for dystrophin can be diagnostic (Lancet Neurol. 2018 Mar; 17(3): 251–267.). However, it is true that Duchenne muscular dystrophy is usually diagnosed via genetic testing.

List of on-going Duchenne Muscular Dystrophy clinical trials

Pharmaceutical Company Name of trial Aim of trial Participant criteria
NS Pharma RACER53 This is a placebo-controlled phase 3 study, designed to investigate the efficacy and safety of NS Pharma's exon skipping drug, Viltolarsen. It will be focusing on patients with mutations amenable to exon 53 skipping and will involve a weekly intravenous infusion over 48 weeks. The dystrophin gene has 79 pieces called exons. These link together to form a code which instructs the body to make dystrophin. If there is a fault, as in Duchenne Muscular Dystrophy, the sequence is broken, and the code cannot be read. Exon skipping drugs complete the sequence and leads to a shortened

dystrophin being produced that still contains the important pieces of this molecule. Age 4-7, mutation specific to exon 53, ambulant.

Pfizer CIFFREO This study is a phase 3 trial testing the safety and efficacy of Pfizer's gene therapy construct, PF-06939926. It is delivered using an adeno-associated virus, AAV, and carries a shortened version of the dystrophin gene (mini-dystrophin). The treatment will be given by an intravenous infusion. Two-thirds of the participants will receive the treatment. One-third will be randomly allocated to the placebo arm but will be able to receive the treatment in the second year, so long as it remains safe to do so. age 4-7, no specific mutation, ambulant

Italfarmaco Givinostat Extension This study is an open label extension, looking at the long-term safety and tolerability of GIVINOSTAT in patients who have already taken part in and completed any of the previous studies. GIVINOSTAT is a drug that may help to promote muscle regeneration and reduce inflammation and fibrosis in Duchenne Muscular Dystrophy patients. age 7+, no specific mutations, ambulant and non-ambulant

Sarepta Therapeutics MOMENTUM This phase 2 study is designed to determine the maximum dose for Sarepta Therapeutics Exon 51 skipping therapy, as well as its safety and tolerability. There will be two arms to the study – in Part A, patients will receive 1 of 5 doses of SRP-5051 monthly by intravenous infusion. Once the maximum dose has been determined, all patients will then roll over into Part B and will receive the maximum dose by intravenous infusion for 24 weeks. In Part B, an additional 15 patients will also be enrolled at the beginning of the study. age 4-21 years old, must be amenable to exon 51 skipping, ambulant and non-ambulant

Sarepta Therapeutics Extension Study for Casimersen or Golodirsen This is an open-label, non-randomized extension trial for patients who have already taken part in the trials testing the drugs, Casimersen or Golodirsen, to evaluate the effects of their long-term use. This trial focuses on patients with Exon 45 and Exon 53 mutations and will involve weekly intravenous infusions of 30mg/kg for up to 2 years.
age 7-23 years old, mutation specific to exon 45 (Casimersen) and exon 53 (Golodirsen), Ambulant and non-ambulant

ReveraGen BioPharma Vamorolone Phase 2b (VISION-DMD) This Phase 2b study is designed to evaluate the efficacy, safety pharmacodynamics and pharmacokinetics of Vamorolone in comparison to corticosteroids and placebo treatments over a 24-week period. The study will also evaluate the persistence of the effect of Vamorolone over a period of 48 weeks. The study is designed to

compare 2 different doses of Vamorolone to a standard dose of corticosteroids (prednisone at 0.75 mg/kg/day) and to a placebo. age 4 to 7 years old, non-mutation specific, ambulant

Italfarmaco Givinostat (EPIDYS) This study will compare the change in stair climb test and other functional tests in patients taking Givinostat and patients taking a placebo. Givinostat has potential anti-inflammatory, antifibrotic and pro-regenerative effects.
aged 6-17 years old, non-mutation specific, ambulant

EspeRare Foundation RIM4DMD Patients with Duchenne Muscular Dystrophy have imbalanced levels of calcium and sodium in their muscle cells, this is thought to play a key part in the damage which occurs to muscles. This study is evaluating the safety and tolerability of Rimeporide. Rimeporide is a drug which works by inhibiting the movement of sodium and calcium from muscle cells. Inhibition of this mechanism has been proven to be efficient in preventing inflammation and fibrosis (muscle damage) in animal models. In addition to the preventative effect on muscle damage, Rimeporide was also shown to be cardioprotective. Participants: aged 6-14 years old, non-mutation specific, ambulant

PTC Therapeutics Phase 3 Extension study of Ataluren (PTC124) in Patients with Nonsense Mutation Dystrophinopathy

Ataluren is a drug designed to make the body’s machinery less sensitive to nonsense mutations. This phase 3 trial is designed to assess the long-term safety of Ataluren in boys with nonsense dystrophinopathies. The study will also assess changes in clinical measures such as muscle function and pulmonary function.

ages 7-18 years old, nonsense mutations only, ambulant

PTC Therapeutics Patient Registry Translarna (Ataluren) – Long-term observational study of Translarna safety and effectiveness in usual care
This phase 4 clinical study is designed to assess the safety of Translarna, also known at Ataluren. This study will follow patients who are receiving Translarna as part of their usual care for 5 years. At the patients’ usual visits, data will be collected to determine the safety and effectiveness of Translarna.

child, adolescent and adults, nonsense mutation only, ambulant and non-ambulant

Sarepta Therapeutics Sarepta 53 – Phase I/II Study of SRP-4053 in Duchenne Muscular Dystrophy Patients
This study is designed to assess the safety, tolerability, efficacy and pharmacokinetics of Sarepta's exon skipping drug SRP-4053. SRP-4053 is designed to treat patients with Duchenne Muscular Dystrophy with deletions amenable to exon 53 skipping.
ages 6-15 years old, amenable to exon 53 skipping, ambulant

2. Royal College of Paediatrics and Child Health

Name:	Comments received on behalf of Dr Eugen Strehle and Dr Ramla Mohammed	**Email address:**	xxxx xxxx
Organisation (if appropriate):	Royal College of Paediatrics and Child Health		
Role:	**Clinical Guidelines Assistant**		

Do you consent to your name being published on the UK NSC website alongside your response?

Yes

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.*
General	General	The reviewer is happy with the decision regarding DMD screening.
General	General	NBS for DMD has been a controversial matter for several years because of false positives, the lack of effective drugs and the need of more data about screening efficacy.
General	General	The mean age of diagnosis of DMD is reported to be between the ages of 3.5 to 5 years, with a delay up to 2 years between the appearance of first symptoms and the diagnosis. Lab and non-invasive techniques suggest evidence of sub clinical disease in boys younger than this age group. The onset of muscle weakness is typically in early childhood.

General	General	The still high diagnostic delay of DMD and the current availability of newer drugs in addition to gene therapy and forthcoming new drugs, make it appropriate to consider DMD in the NBS programme.
General	General	Moreover, boys diagnosed by NBS and their parents reported a positive impact on their QoL. This was in addition to the decreased morbidity and an increase in lifespan associated with appropriate early interventions and medications. Again, "pre-symptomatic treatment may yield improved outcomes. But that remains an unresolved issue warranting further investigations".
Pages 7,8	NBS - DBS CK in NB male infants	A finding of increased Creatine Kinase (CK - MM), a biomarker of membrane fragility and muscle degeneration, may represent the most frequent finding leading to a suspicion of DMD. Increased CK is a secondary marker for the dystrophic process. Dried Blood Spots test for CK (DBS - CK) in newborn (NB) male infants via the heel prick test is the test that is being considered. It is unclear whether DBS test is sufficiently accurate for affected children to benefit.
Pages 7,8	NBS - DBS CK in NB male infants	The CK test can lead to both false positive and false negative results, with the former often due to birth trauma or other muscular dystrophies. Hence, the need for confirmation by a second CK test. False negatives could be due to the insensitivity of the analytical tests. A two-tiered approach of CK screening followed by DNA testing, could overcome this.
Pages 11,12	UK- NSC currently recommends against screening for DMD	A "wait and see" position adapted earlier were because of 1. Lack of effective drugs 2. Voluntary screening (whose details should yet be evaluated) and 3. The need to have more data about screening efficacy.
Pages 11,12	UK- NSC currently recommends against	Currently, several new medications and novel gene therapies have been approved by the FDA. Deflazacort is the first Gluco Corticoid with a labelled indication for DMD. Studies have shown the long-term clinical benefits in delaying irreversible muscle loss with Nutraceuticals such as Ataluren. (Eteplirsen, Golodiesen) Repurposed drugs such as Rimiporide, Metformin, have shown some benefit.Novel gene therapies, Exon skipping therapies,

	screening for DMD	Utrophin modulators ,Myostatin inhibitors and stem cell therapies have found to produce healthy muscle fibres and decrease inflammation.
Pages 11,12	UK- NSC currently recommends against screening for DMD	Most families of an affected boy were in favour of a NBS on the grounds of reproductive choice and time to prepare emotionally and practically. Anxiety levels for the screened groups were slightly above threshold during the process, which soon abated. There was no evidence of any long-term disruption to the mother/ baby relationship. Hence, it is currently appropriate to consider DMD in the NBS programme.
Pages 13-18	Evidence maps	Though the volume and type of evidence related to screening for DMD may appear insufficient; the novel therapies and developments related to DMD if started early on in life are beneficial, therefore, DMD should be considered in the NBS programme.
Page 19	Appropriate thresholds for CK MM	An appropriate threshold has still not been fully identified for the levels of CK. Studies done in the maternity hospitals in Columbus and Cincinnati (Ohio, US) have recommended the following: ○ DBS -CK-NBS test for males ○ 2nd test of Venous blood if CK equal to or more than 600 U/ l ○ DNA screening for DBS in those males with VK equal to or more than 750 U/ l Further studies are needed in this direction.
General	General	Conclusion: ● Culture, social history, religion, beliefs, taboos and shame may influence the opinion of parents towards genetic tests. Adequate education, information sharing, brochures and families' participation can help overcome these. ● In the current scenario, a twostep system of CK, followed by DNA testing should be provided with a rigorous protocol for service delivery ensuring than an adequate infrastructure is in place which can provide continuing support. ● Therefore, an opportunity should be given to test the feasibility of a NBS programme, which in the near future could be applicable to an entire country.

3. Royal College of Midwives

RCM has reviewed the documentation provided on current evidence regarding screening for Duchenne muscular dystrophy and has no comments on the documents, RCM agrees with the conclusion and recommendation.

4. The Duchenne Family Support Group

Duchenne muscular dystrophy is one of the most frequent genetic conditions affecting approximately 1 in 3,500 male births, but is often diagnosed late in the first decade, after parents have established their hopes and expectations for the child, typically enduring a delay of two years from initial worries to diagnosis, by which time younger affected siblings and cousins have been born.
Treatments such as steroids and exon-skipping are becoming increasingly used and earlier in childhood.
Screening would permit earlier diagnosis and treatment and help avert the conception and birth of affected younger siblings and cousins.
As a support charity we are primarily concerned about the care and support of affected children and their families and we frequently assist families working through the shock and distress occurring with new diagnoses. These could be ameliorated by screening and earlier diagnosis.

5. Genetic Alliance UK

Early diagnosis for DMD is vital as many treatments have strict eligibility criteria regarding progression of the condition, such as whether an individual can walk or not. We agree that there hasn't been sufficient improvement in the screening technology. However, the NSC should develop a flexible approach whereby they monitor current trials on suitable screening tests so that when a suitable screening test is found, implementation can happen without delay, rather than waiting a number of years for the next review.

We would also advocate that treatments in long-term managed access agreements, such as translarna in a five year managed access agreement, should be considered in greater detail. With the Innovative Medicines Fund on the horizon, it is likely that a significant portion of treatments for rare conditions will be accessed through these routes. If the UK NSC does not consider these treatments as 'available' they will be missing a large portion of the treatments delivered within the UK national health services.

6. Royal College of Physicians

The RCP is grateful for the opportunity to respond to the above consultation.

We would like to endorse the response submitted by the Royal College of Paediatrics and Child Health (RCPCH).