Next steps on newborn screening for Duchenne muscular dystrophy

Summary of Parliamentary roundtable meeting

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 Alex, we can do that before Alex begins to think that we are moving out because of him.

Jeanette George’s son, Alex, was diagnosed with Duchenne muscular dystrophy through newborn screening in Wales.
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Background and context

MDUK called this meeting to discuss next steps on newborn screening for Duchenne muscular dystrophy. This followed the November 2016 announcement by the National Screening Committee that it was continuing not to recommend newborn screening for the condition. The meeting sought to highlight the key barriers to implementing newborn screening – and agree upon next steps to address the NSC’s current concerns.

The roundtable sought the input of the NSC, parents of children and young men with Duchenne, specialist clinicians, researchers developing a revised screening test and protocol and healthcare professionals who had led the former Duchenne newborn screening programme in Wales.

Screening for Duchenne muscular dystrophy has been carried out in 17 countries and states around the world since 1977. However, the majority of these programmes have been pilot studies and a truly national screening programme for Duchenne muscular dystrophy has never been in place.

The test for Duchenne muscular dystrophy looks for the presence of creatine kinase (CK) in dried blood spots collected on Guthrie cards. CK is a protein found in muscle but when the muscles are damaged, owing to disease or injury, it leaks into the bloodstream. Once a positive CK result has been obtained from the original Guthrie card test, it is repeated six to eight weeks later as there is a risk of false positives as a result of the natural trauma associated with some births. If the levels are still high in this repeated test, this could indicate muscle damage. Genetic testing is then used to confirm or reject a diagnosis of Duchenne muscular dystrophy.

In the UK, a screening programme was in place in Wales from 1990 but was withdrawn in 2011 owing to difficulties with the test and the withdrawal of the external quality assurance programme. Following an external review in 2012, the UK National Screening Committee did not recommend the introduction of a UK-wide screening programme for Duchenne muscular dystrophy. The next review in 2016 also didn’t recommend screening for the condition.

Currently, nine conditions are screened for at birth in the UK. These are: cystic fibrosis, phenylketonuria, congenital hypothyroidism, sickle cell disease and medium-chain acyl-CoA dehydrogenase deficiency, Maple syrup urine disease (MSUD), Isovaleric acidaemia (IVA), Glutaric aciduria type 1 (GA1) and Homocystinuria or (HCU).

It is evident that newborn screening for Duchenne muscular dystrophy has been an area fraught with difficulties and challenges. However, with many families reporting that an early diagnosis allows better planning – and with novel treatments now having received regulatory approval - now is the time to address these challenges to ensure newborn screening for the condition can be put in place.
Who attended?

Professor Francesco Muntoni, Director of the Dubowitz Neuromuscular Centre
Dr David Elliman, Clinical Lead for Newborn Bloodspot Screening Programme, National Screening Committee
Sejal Thakrar, Smile with Shiv Family Fund, whose son, Shiv, has Duchenne muscular dystrophy
Phillippa Farrant, Duchenne Family Support Group, whose son, Dan, has Duchenne muscular dystrophy
Dr Juliet Ellis, European Proposal Manager, European Research and Innovation Office, University College London
Dr Stuart Moat, Consultant Biochemist & Director, Wales Newborn Screening Laboratory
Dr Louise Hartley, Consultant Paediatric Neurologist, University Hospital of Wales
Rachel Salmon, Neuromuscular Family Care Advisor, University Hospital of Wales
Dr Vasantha Gowda, Consultant Paediatric Neurologist, Evelina Children’s Hospital
Dr Michaela Guglieri, Honorary Consultant in Human Genetics, John Walton Muscular Dystrophy Research Centre, Newcastle
Dr Elizabeth Wraige, Consultant Paediatric Neurologist, Evelina Children’s Hospital
Dr Arni Majumdar, Consultant Paediatric Neurologist, Bristol Children’s Hospital
Dr Diana Ribeiro, Chief Executive, Action Duchenne
Dr Jenny Versnel, Director of Research and Business Development, Muscular Dystrophy UK
Nic Bungay, Director of Campaigns, Care and Information, Muscular Dystrophy UK
Peter Sutton, Senior Policy and Campaigns Officer, Muscular Dystrophy UK

Next steps

The following next steps and priorities were agreed to:

- An eventual research trial for a revised assay – to gather evidence of effectiveness and of impact of early interventions in a screened population. This would help build evidence in support of a National Screening Committee approved screening programme for Duchenne muscular dystrophy
- The identification within the NorthStar database of a screened population or a child who received an early diagnosis – to monitor any trends in health outcomes or parental choices
- A new survey of families to collect updated data on attitudes to newborn screening
- Muscular Dystrophy UK to work with the paediatric neurosciences Clinical Reference Group at NHS England to push forward service improvements in the provision of psychological support for those affected by Duchenne or other neuromuscular conditions. Provision of psychological support is essential at any stage of diagnosis – and will be a key component to a national newborn screening programme for Duchenne muscular dystrophy
National Screening Committee’s current recommendation on newborn screening for Duchenne muscular dystrophy

The first part of the meeting focused on the NSC’s current recommendation on DMD screening, with a presentation from Dr David Elliman, Clinical Lead for Newborn Bloodspot Screening Programme.

Dr Elliman gave an overview of the role of the NSC, as a body which advises UK Ministers on all aspects of screening and supports the implementation of screening programmes. He highlighted the criteria used to consider a new screening programme. These focus on:

- The condition
- The test
- The intervention
- The screening programme
- Implementation criteria

The routine review of screening for candidate conditions operates on a review cycle. Duchenne was reviewed in 2012 and again in 2016, and the recommendation is currently not to screen for the condition.

The 2012 review highlighted:

- Lack of evidence about long term benefits of treatment
- Lack of evidence that screening would improve outcomes for individuals with DMD and their families (for the latter, in particular in relation to reproductive choice)
- Concerns about the accuracy of the test and the numbers having a two stage process

When DMD screening was reviewed again in 2016, the NSC found that DMD still did not meet a number of important criteria. In particular, the NSC found no new evidence of a high volume/rapid throughput test that is suitable for whole population screening. The poor performance of creatine kinase as a marker was emphasised.

The NSC acknowledged that genetic treatments to restore the normal reading frame of the DMD gene have shown the ability to slow decline in muscle deterioration. Results are promising, and some drugs are in the approvals stage or have recently been approved in the UK. However, they have not yet been tested at earlier ages when boys identified by newborn screening could potentially start treatment. The NSC also found no new evidence that assessed the wider effects of screening on the reproductive or other choices of parents.

Consultation responses from patient groups and other stakeholders recognised the limitations of the current screening test, although it was suggested screening tests for other conditions which are routinely screened for compare less favourably. It was also highlighted that without newborn screening it is not possible to gather evidence of the efficacy of new treatments in a screened population.

Dr Elliman reported that parental views on early screening were mixed. Whilst surveys of families reveal that support for screening – even without treatments – is at 82%, only 53% of families said they would prefer to receive a diagnosis shortly after birth. Muscular Dystrophy UK has agreed to conduct further research in the new year on family’s views on newborn screening.
In summary, the 2016 review argued that:

- the test misses some babies who have DMD. Some babies are also falsely identified as having the condition, when they do not

- currently babies and children are treated once the condition is diagnosed. It is not clear that earlier treatment (such as would be possible following a newborn screening test) would be of benefit to the child’s health

- there is no clear view on whether parents wish for the disease to be diagnosed in the newborn period. Some would like the diagnosis to take place in the newborn period. But others would like this to happen later in childhood to allow time with the child without the knowledge that they would become ill.

During subsequent discussion, the group focused on how evidence in a screened population could be gathered. It was suggested by Dr Elliman that a pilot study could be possible, however he stressed that once a pilot is in place it can be difficult to end it.

Dr Elliman advised that if a good screening test were available, with drugs shown to work in older patients, a research study may be appropriate.

It was felt during the course of the meeting that such a research study – when a revised assay is available – may be the necessary way forward to gather evidence in support of an NSC approved screening programme.
Family perspectives on newborn screening for Duchenne muscular dystrophy

Parents Phillippa Farrant and Sejal Thakrar – who both have sons affected by Duchenne muscular dystrophy – shared perspectives on their own experiences of diagnosis. Sejal’s son, Shiv was diagnosed at the age of three. Phillippa’s son, Dan, was diagnosed at 8 months old. Phillippa and Sejal’s statements are reproduced below:

Sejal Thakrar

My name is Sejal; I have a 5 year old son, Shiv, who was diagnosed with this rare condition shortly after his 3rd birthday by chance. Although a genetic condition we have no family history so was unexpected.

Shiv looks like any other 5 year old boy on the outside; however as we know with this condition all is not fine on the inside.

Shiv started to crawl and walk a little late, but both were just within the time scales of it not being an issue to health professionals. In time, we had noticed that he could not jump, hop or run and always had difficulty with stairs and walking more than 5 minutes, however we had put it down to him being a late developer and were reassured that this was the case, being our only child we did not know any different.

However at the age of 2 we continued having concerns about his general health, we suspected he had a food allergy and as a result were referred to a paediatrician who did several blood tests, these did not show any food allergies, however did highlight that Shiv’s liver enzymes were 100X higher than they should have been, this lead to a year of further blood tests. This was a very hard time for us as a family, the effects of all the testing and prodding for this period had an extremely negative impact on Shiv’s confidence and happiness, he changed from being a happy go lucky and sociable toddler to one who was withdrawn, unhappy and very emotional. As parents this was a very anxious time for us, Shiv was tested for many infectious diseases and cancers. Both my husband and I had to continuously take time off from work which meant working through the night on many occasions resulting in little or no sleep, yet at the same time dealing with the uncertainty of our child’s future - to this day, we will never know what real impact this has had on Shiv, but it certainly was a very tough year for us all. As a result of all the blood tests we were eventually diagnosed with Duchenne – but this was by pure chance.

There are some key things which we would have done differently had we been diagnosed at the neo natal stage:

Firstly we would have ensured that Shiv was safeguarded physically and emotionally; we, the family, child minders and nursery would have not encouraged or pushed Shiv to jump,
run or climb stairs, these are things he cannot physically do. It was suggested that a trampoline would help him to learn to jump, so we brought one, now we know harmful this was for him – the damage this has done to his muscles can never be repaired; to this day this haunts me and I know always will.

We also purchased our family home when Shiv was only 6 months old, this property is unsuitable for Shiv’s needs now and for the future, had we known we would not have purchased the property we now live in.

Knowing that my Son has a life limiting condition I personally would have never gone back to work; I constantly battle with the guilt of leaving him with child minders and nursery at the age of 11 months, the time has passed and will never come back.

Having being diagnosed earlier than the average age, we were able to put certain measures into place to safeguard shiv, the benefits of knowing early include-

1) **Early Access to Standards of care**: Shiv has had a multidisciplinary team who monitor and assess him so that appropriate measures are put into place to keep Shiv on his feet longer; this including the start of steroids. Shiv has also been wearing night splints from the age of 4 to ensure he does not develop tightness in his ankles, also has a physio and fine motor skill plan and has had hydrotherapy sessions every 6 months since the age of 3, the therapy is having a clear and positive impact on his mobility and flexibility.

2) **Appropriate school setting to minimise disruption at a later age as the condition progresses**: with the help of MDUK we were able to ensure that Shiv received a place in a school with no stairs, it is a local school but still out of our school catchment area without early diagnosis it would have been possible for him to attend the school.

3) **Put into place appropriate education support**: we were able to put into place an education health care plan for Shiv before he started school; the plan ensures Shiv lawfully receives appropriate care and support at school; the process took a total of one and a half years. Children who are typically diagnosed after the age of 5 have already started school and are not likely to receive the support they require until they are at least 6 or 7, which is far too late.

   - Shiv has had a 1:2:1 full time teaching assistant since he started school at reception level, she ensures he is safe, supported and has put into place measures so that Shiv does not over exert himself; which can lead to a rapid progression of his condition.
   - Shiv has a physiotherapy plan which his teaching assistant carries out on a daily basis at school to ensure he does not develop tightness in his ankles which in turn will keep him walking for longer.

4) **Positive impact on social wellbeing and acceptance at school**: at the age of 4 Shiv started asking questions about his physical capabilities compared to his peers, we were able to explain that his muscles are different to his friends and he has accepted this; this has had a positive impact on his social wellbeing. Shiv’s friends also understand that he has muscles that are different; they support him and play games that shiv can take part him and really look after him.
5) **Positive impact on how the child is perceived:** Shiv is no longer a 'Lazy boy' in the eyes of anyone and is supported with a watchful eye by family & friends at all times.

6) **Early Provisions can be put into place:** such as the blue badge and wheelchair for long distances. This in itself is a long process, it took us over a year to put into place.

7) **Ensure children take part in activities that are beneficial and not detrimental to his condition:** bouncy castles and trampolines are not recommended for children with Duchenne, Shiv is aware that he can only have 10 mins on a bouncy castle and should not use a trampoline. This will minimise damage to muscles. Shiv now attends horse riding lessons on a weekly basis and swimming regularly; both are recommended for Duchenne.

8) **Planning for other children:** during shiv's diagnosis it was confirmed that I am in fact a carrier of Duchenne Muscular Dystrophy, we have no family history, and my mother does not carry the faulty gene, only I do. Finding out earlier is essential when planning a family. We know a few families that have 2 and even 3 children with Duchenne; this was because they like me they were unaware that they are carriers.

9) **Raising awareness, fundraising and campaigning:** Since diagnosis to ensure we have access to treatments for Shiv and others with this condition we have chosen to raise awareness, campaign and fundraise, knowing what we do now this would have most certainly started earlier. Hopefully the outcome of this will have benefits for earlier treatment.

These are the clear benefits, but in terms of disadvantages;

Some people may say 'Ignorance is bliss' and yes, I agree, life certainly was happier before the diagnosis, but it was happier for us as parents, but not for the child. Shiv was being pushed to do things he could not do, once we had the diagnosis we all understood Shiv, overnight it was ok that he could not climb up and walk down the stairs, it was ok that he could not jump or hop and it was certainly ok to be carried when he was tired, very soon after diagnosis we saw a much happier Shiv who was receiving the correct support and attention in all aspects of his life. As a parent it is absolutely heart-breaking to receive such diagnosis whether it’s at 7 years or at neonatal, however it is the child here that is most important and based on personal experience the earlier the diagnosis the better it is for the child in terms of protecting their welfare, happiness, social wellbeing, social acceptance and accessing the standards of care and provisions required to live with this condition.

Duchenne at a very young age is an invisible condition; due to the rarity of the condition GP’s are not likely to come across anyone with the condition, if they are it’s likely to be only one in a lifetime. Based on experience symptoms that cause concern do not appear until the children are much older unless of course a family history exists, screening of this is essential to ensure measures are put into place to safeguard those with Duchenne both physically and mentally as soon as possible, particularly now that evidence shows that the earlier steroids are started the better the outcome and now as the landscape of Duchenne treatment is changing and treatments such as translarna and exon skipping are emerging, evidence suggesting that the earlier a treatment is administered the better the outcome; unfortunately time is not on our side, diagnosis at screening is key.

September 7th 2016 was the 3rd World Duchenne awareness day; this year the campaign was focused on 'Early Diagnosis', as a Global Duchenne Community we strongly believe in
Phillippa Farrant:

Daniel was picked up at eight months old because he was jaundiced as a baby. His liver results wouldn’t go back to normal and the consultant thought he had a damaged liver. They wrote to a consultant at St George’s who suggested testing CK levels for Duchenne muscular dystrophy. So whilst it wasn’t a neo-natal diagnosis, it still came at a very early stage in Dan’s life. The paediatrician did a home visit and told us of the diagnosis. We then went to multi-disciplinary meetings every week with support from OTs and physios, and then because of the early diagnosis his learning difficulties were also picked up at an early stage. He was statemented pre-school, so he has had educational support from the time of nursery right through.

We’re at a promising time with treatments for Duchenne, with Translarna now on the NHS and with other drugs such as the exon-skipping therapies beginning to come through. However, for boys and young men of Dan’s generation, steroid therapy (which is now routinely prescribed) wasn’t even available. So in his younger years, he grew up with what could generally be described as the natural history of the condition.

For us, the early diagnosis was a help because it gave us time to come to terms with the diagnosis and to plan. However, I know that the views of families really vary and that every family will take the news differently, and cope with the news differently.

The key thing in my view – as we move towards potentially screening for this condition – is improving psychological and emotional support at the point of diagnosis. If you are going to diagnose at an early stage you have to have all the right support in place. With psychology support especially, we are really not there yet. There are just a handful of specialist psychological support roles in neuromuscular teams. On the emotional and practical support side of things in my area – the South East Coast – there isn’t even a neuromuscular care advisor in post.

I think we need this screening test – but let’s make sure we have the right support available to go alongside it.
**Previous screening programmes: what technologies were used and what challenges were encountered?**

Dr Juliet Ellis presented to the group on previous screening programmes, the technologies used and the challenges encountered.

Between 1975 and 2011, there have been 10 piloted newborn screening programmes in 11 countries: Wales, Scotland, France, Germany, New Zealand, Belgium, Manitoba (Canada), Brazil, Cyprus, Ohio (USA). 1.8 million newborns were screened – mainly boys – and 344 were diagnosed with Duchenne muscular dystrophy.

Two further pilots are ongoing in China and Australia.

**Dr Ellis explained that the ideal test needs to:**

- Have a high sensitivity
- Have a high specificity
- Have an unequivocal predictive value
- Have a low false positive/negative rate

Tests rely on the measurement of specific molecules released from the diseased muscle into the blood circulation. The current protein of choice is creatine kinase (CK).

Three technologies have been utilised to perform this test:

1. **Fluorimeter.** CK levels are measured in the blood spot collected on the Guthrie card at birth or soon after, using a fluorescence enzymatic assay. This is the oldest method of testing for Duchenne. Positives are rescreened 6 weeks later for serum CK. Second positives were confirmed by muscle biopsy, dystrophin staining or in later studies, by a genetic test.

2. **Two-tiered CK/DNA test.** These 2 tests are conducted on the same blood spot. First the CK test is performed as above, followed by the DNA test to identify any mutations in the dystrophin gene. There is therefore no need for a 6 week delay. It reduces the cases of false positives, and reduces the number of patient recalls. This approach was used in the Ohio screening programme, and is probably the current test of choice. However, there is expense attached. Genetic testing adds at least $150 per patient.

3. **Blood spot CK-MM immunoassay.** CK is an enzyme which exists in different forms in different tissues throughout the body (isozymes). The standard CK test is unable to distinguish between the muscle and other tissue forms. Using an antibody which specifically recognises the MM (muscle) form of the protein will increase the sensitivity of identifying muscle CK.

**Problems:**

1. **CK Threshold value.** Across the 10 programmes this was not standardised (210-1300U/L for fluorescence assay, 750 for two-tiered assay). A two-tiered assay allows for a higher value (reduces false positives) to be chosen given it is performed in conjunction with the DNA test.

2. **Ethnicity variation.** People from different ethnic backgrounds vary in normal CK serum levels.
3. **CK is a secondary biomarker** i.e. its blood level indicates muscle trauma but one cannot make an accurate correlation between the actual CK level and the clinical assessment. This means that patients can be missed (because they happen to not release the CK at sufficient levels when the test is performed), producing false negatives. False positives are also possible, as birth trauma can cause muscle damage not linked to pathology. Screening at 4-6 weeks rather than 1 week after birth reduces the number of false positives from birth trauma. However, only 21 false negatives have been recorded out of a total 1.8million screened newborn babies.

4. **Diagnostic delay.** A wait of six weeks or more can cause significant family anxiety.

5. **Identification of other muscle diseases** (other MD e.g. LGMD, BMD) i.e. this is a non-specific test. 80 individuals from DMD screening programmes had been diagnosed with other MDs in this way. Whilst acknowledging this as a flaw in the test, Dr Ellis suggested this was not necessarily a negative if these individuals could then be offered a positive course of action.
A changing landscape: best standards of clinical care and progressing research for Duchenne muscular dystrophy

Professor Francesco Muntoni shared information on implementation of best standards of care for Duchenne, and new treatments for the condition, some of which are now available to patients not on clinical trials.

Professor Muntoni highlighted that:

- In 1990, the mean age of survival for those with Duchenne was 19 – with therefore no need for transition clinics
- In 2016, the mean age of survival is 29, with a 2% mortality rate in paediatric cases (before transition)

Central to this improvement in life expectancy has been the availability of multi-disciplinary anticipatory care, in particular steroid use, anticipatory respiratory care and cardiac management.

This change in the natural history of the condition has resulted in a much longer ‘walking life’ for patients affected by Duchenne. Loss of ambulation is now at 13 years old, rather than 9 and a half years old. Some patients are still ambulant at the age of transition.

Professor Muntoni went on to share an analysis of diagnosis ages. Whilst there has been some improvement in the age of diagnosis, there continues to be presentational and diagnostic delay. The median age of diagnosis is currently 4.1 years old – however, many children are diagnosed much later, between the ages of 6-10.

This can impact upon the age of beginning steroid treatment, and Professor Muntoni shared evidence that 30-40% of patients are beginning treatment in the decline stage (when it is less likely to have a meaningful impact).

It was acknowledged that published studies on starting steroid treatment early are limited – however, the evidence that is available indicates higher functional abilities for patients who begin treatment at an early stage.

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.

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.

In summary:

- Corticosteroids are started at a median age of 6 years 4 months in the UK, often when patients are deteriorating (later than in NICE-approved standards of care guidelines)
- Starting at a younger age is associated with higher motor function and better preservation of long term ambulatory function
Emerging treatments

Treatments are also now emerging aimed at partially restoring dystrophin production. Professor Muntoni specifically referenced ataluren – for the treatment of some patients with a nonsense mutation – and eteplirsen – for patients with a deletion amenable to the skipping of exon 51.

Whilst these drugs allow the production of some dystrophin protein in the residual muscle fibres, they can’t restore muscle once it is lost to fat and connective tissue.

Clinical trial data for eteplirsen – which has been approved by the Food and Drug Administration - showed that after 4 years of treatment, the difference of the 6MWT between boys treated with eteplirsen and the external control group was 162 metres.

After four years of treatment, the age at which ambulation was lost was compared. 10 of the 12 boys with Duchenne muscular dystrophy that were treated with eteplirsen, could still walk compared to two out of ten boys that could still walk at the same age in the control group.

The Phase III study for ataluren - ACT DMD - was a double-blind, placebo controlled trial carried out over a period of 48 weeks involving 228 participants aged between seven and 16 years old. It takes place in 53 sites across 18 countries.

In the overall study population, a 15 metre benefit in 6MWD was observed. However, in a pre-specified sub-group of 300-400 metres at baseline, a 48 metre benefit was observed.

The drug has recently had its conditional licence renewed by the EMA, and is the subject of a 5 year Managed Access Agreement in England, approved by NICE.

The terms of the licence for ataluren (aged five an over and still ambulant) reflects the population studied to date, rather than an indication of the drug’s likely efficacy in a younger population.

Professor Muntoni stressed that:

- It is logical to expect these dystrophin restoration therapies to work better in younger children and infants, before there is significant loss of muscle mass
- At an EMA meeting on translational research development for DMD, the full rationale and expected advantage for starting therapies as early as possible understood by regulators
- Sarepta will start an infant study in 2017

Professor Muntoni also went on to address some recent criticisms of the FDA’s accelerated approval for eteplirsen, which have appeared in a number of journal articles.

Whilst acknowledging his own role in the clinical trials, he stressed that FDA reviewers (who have subsequently voiced disagreement with the approval) ignored important elements of the trial data which indicated dystrophin production. Professor Muntoni stressed that – like a Principle Investigator – FDA reviewers should engage with the totality of the data, and not solely those which support their arguments.

A rebuttal to this published criticism is currently being prepared.
Newborn screening for Duchenne muscular dystrophy: past experiences and future challenges

Dr Stuart Moat is leading work, in collaboration with PerkinElmer, to develop an immunoassay for bloodspot CK-MM isoform.

Dr Moat began his presentation by outlining arguments both for and against newborn screening for Duchenne muscular dystrophy. Benefits include the avoidance of diagnostic delay, informed family planning choices and the identification of a pre-symptomatic cohort in anticipation of effective, available treatments. However, Dr Moat acknowledged that such treatments are not curative – and an early diagnosis can in some cases affect family stability.

Along with clinical colleagues in the Cardiff neuromuscular team, Dr Moat led the former newborn screening programme in Wales. This was an ‘opt-in’ test and Dr Moat stressed that – due to a lack of education and training for midwives – tests were not always properly described and consented for. As a result, consent from families was often shallow and not properly informed – which in some cases caused significant difficulty once a diagnosis was received, as families did not feel they had properly consented.

The screening programme in Wales ran from 1990-2011:

- 343,170 newborn boys were screened (PPV 38.6%)
- 16 false negatives were recorded
- Newborn screening in Wales was terminated because of the withdrawal of the external quality assurance programme from the Centre of Disease Control in America. Therefore the test results could no longer reliably be validated.

The Wales DMD screening protocol, and 6 week follow up for CK positive bloodspots are detailed below:

Wales DMD Screening Protocol
Developing a new assay

As Dr Moat explained, there is now renewed interest in newborn screening for Duchenne since the cessation of the Wales programme. This is because:

- Molecular and gene therapies are on the horizon
- Current therapies started earlier improve outcomes
- Some national screening policies have been amended to reflect the ‘diagnostic odyssey’.

However, a central challenge faced in screening for Duchenne are the limitations of the CK enzyme test as a first line screening test. Dr Moat outlined that:

- There are issues with reagent stability
- It is difficult to automate for high throughput screening
- There is a lack of assay standardisation
- Poor stability of enzyme activity in DBS
- There is no External Quality Assurance Scheme

Dr Moat and his team in Cardiff have now worked to develop a two-site chemiluminescent immunoassay to detect CK-MM in DBS. The team are now collaborating with PerkinElmer. The assay has a 100% cross reactivity with CK-MM isoenzymes, and an analytical run time of 4 hours 50 minutes (26 plates/13 hours on GSP).

Details of the CK-MM analytical performance and population study are shared below:
Perkin Elmer GSP® CK-MM
analytical performance

LOB - <1 ng/mL
LOD - 3.1 ng/mL
LOQ - 8 ng/mL

Perkin Elmer GSP® CK-MM

Precision studies – Inter-assay (n=40)

• C1 - 123 ng/mL (CV 5.2%)
• C2 – 410 ng/mL (CV 6.5%)
• C3 – 1780 ng/mL (CV 5.1%)
CK-MM patient study

Population study
(n=8,741 newborn boys)
Population study (n=8,741 boys)
10 cases >688 ng/ml (703-5490ng/ml)

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<td>Not affected</td>
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Population study (n=8,741 boys)
**Next steps**

Dr Moat, PerkinElmer and colleagues will now be following a series of next steps to evidence the new assay’s efficacy as a reliable and specific screening test for Duchenne. These include:

- The retrieval and analysis of 200 DBS from Duchenne cases and 750 matched controls. This will be through a study in California funded by Parent Project Muscular Dystrophy.
- Retrieval and analysis of DBS from the false negative cases from the Wales newborn screening programme
- Developing an External Quality Assurance Scheme – Centres for Disease Control and Prevention in the United States
- Assess utility of the CK-MMM assay as part of a single-tier or two-tiered (CK-MM-DNA) protocol
- Pilot studies in China, the United States (California and New York State) and Australia

In conclusion:

- The development of molecular therapies to treat Duchenne has renewed interest in newborn screening for the condition
- There are limitations to the DBS CK enzyme test
- There is ongoing development and evaluation of an immuno-assay for DBS CK-MM on a routine analyser
- Assessment of a two-tier screening protocol (CK-MM – DNA) is required
Newborn screening for Duchenne: Welsh experience 1990-2011

Dr Louise Hartley and Rachel Salmon from the Cardiff neuromuscular service gave a detailed overview of the Wales Programme – outlining the challenges faced and learning to inform any future Duchenne newborn screening programmes.

The programme was introduced in Wales with aims to:

- Reduce diagnostic delay
- Permit reproductive choice
- Allow better planning of care for the affected boy

Whilst the programme was introduced as a pilot in July 1990, it was endorsed and funded by the Welsh Office in April 1998.

The protocol was designed to fit in with existing healthcare infrastructure in Wales. Bloodspots were collected routinely as part of the Wales newborn screening programme between days 5-8. Re-testing was done at 6-8 weeks to remove the need for genetic testing in the false positive group.

Families had to give specific consent to be tested for Duchenne. The information they were presented with is reproduced below:

*We also offer baby boys a screening test for a muscle disease called Duchenne Muscular Dystrophy. This test will identify most, but not all, affected boys. In Wales 4 boys a year are born with this disease.*

*Duchenne Muscular Dystrophy* is a progressive muscular disease that only affects boys. They show no symptoms at birth but their muscles gradually become weaker. At about the age of 10 they become unable to walk and do not often live beyond 20 years.

There are arguments for and against having the screening test. At the present time there is no cure for the disease and you may feel that you would rather not have the earlier diagnosis.

We are however offering the screening test because you or a relative could have another affected boy before your first boy was diagnosed and we can now offer you choices in future pregnancies. In addition, if your son has Duchenne, it provides you with information so that you can plan for the future and we can offer him early support.

We would like to emphasise that this is a screening test and, as with all such tests, there can be other reasons for an abnormal result and occasionally an affected boy will not show up on the test.

The midwife will ask you whether you want this extra test done and ask you to give your consent by signing the back of the sample card – *it is your choice.*
During 21 years of screening, 76 boys were identified as having Duchenne muscular dystrophy. In that period, there were:

- 16 false negatives
- 2 children whose parents declined screening
- 1 card marked as female diagnosed at 7.5 years
- An incidence of 1:5282 male births in Wales

**What impact did newborn screening have?**

27 boys in south-east Wales are currently on the NorthStar database:

- 15 of these are true positives
- 7 are false negatives
- 2 had a family history (so were not screened)
- 2 were born post-screening
- 1 was born outside Wales.

Of the true positives:

- 4 mothers were found to be carriers
- 5 of these families had younger siblings
- The mean age of loss of ambulation was 11.5 years old

Of the false negatives:

- 3 mothers were found to be carriers
- 4 of these families had younger siblings
- The mean age of loss of ambulation was 9.8 years old

There is therefore some suggestion – although based on a small patient population – that diagnosis via neo-natal screening was associated with a later loss of ambulation.

No second cases of Duchenne in a family have been diagnosed to date.

**How did parents react to diagnosis?**

Dr Hartley and Rachel Salmon conveyed that parents were devastated upon receiving their son’s diagnosis. Most were unaware of Duchenne, had not been aware that they had consented to screening and many had not been planning future children.

However, in time, these families divided into three groups characterised by their reactions to the situation:

1. ‘Resolution’ – this group is characterised by an acceptance that an early knowledge was helpful in planning for the future and making informed choices

2. ‘Denial’ – these parents refused a DNA analysis and antenatal testing in subsequent pregnancies

3. Occasional extreme reaction – in some cases, the diagnosis had a significant impact on mother/baby bonding and caused an extreme adverse reaction in the mother with had implications for their psychological wellbeing
Dr Hartley outlined the lessons learned from the programme – and the practical considerations for any future programmes:

- The training of staff obtaining consent for screening programmes needs to be kept up to date and a focus maintained even when the results processed are mostly negative.
- The timing of screening needs to be discussed – as consent is often sort from tired, overwhelmed new parents at appointments where there are also many other topics to be discussed.
- Screening needs to be joined up with clinical follow up, with planned capacity in the care system. This includes adequate provision of neuromuscular care advisor time, psychology and physiotherapy support and sufficient staffing and training for testing, diagnosis, treatment and ongoing care.
- The diagnosis must be disclosed in the right environment, with counselling and psychology support available.
- The risk of false negative cases should be better highlighted to paediatricians.
**Newborn screening: clinicians’ perspectives**

Clinicians from the NorthStar network attended from across the UK and were invited to share their own perspectives, priorities and potential concerns in relation to newborn screening for Duchenne.

Dr Vasantha Gowda from Evelina Children’s Hospital highlighted that – regardless of age – the right support needs to be available to patients. Central to this is robust psychology support – which is unfortunately often lacking for some patients, and would need to be an essential component of a newborn screening programme.

Dr Gowda’s colleague, Dr Elizabeth Wraige, voiced concerns on the other conditions that could inadvertently be diagnosed through Duchenne newborn screening. Some of these other muscular dystrophies would usually only be diagnosed in the teenage years and early adulthood. She stressed that giving an individual a diagnosis which for many years they could not act upon is hugely problematic.

This was discussed in more detail – and Dr David Elliman advised that withholding such information would be considered unethical. Further consideration of this issue and the ethical implications will be necessary in preparing and finalising the implementation of any newborn screening programme for Duchenne.

Dr Michaela Guglieri from the John Walton Muscular Dystrophy Centre, Newcastle, emphasised that the mean age of diagnosis has improved in recent years, but not significantly so: it remains at just over 4 years of age.

She outlined that clinically a diagnosis at the neo-natal stage or at 2 years of age is not significantly different – but the impact on a family may be. However, Dr Guglieri felt that in order to achieve a diagnosis at 2 years of age (at which stage treatment could potentially be commenced) it may be necessary to have a neo-natal screening programme.

Dr Guglieri and Dr Arni Majumdar from Bristol Children’s Hospital referenced adverse parental reactions to a neo-natal diagnosis. Both clinicians highlighted that it is currently unclear whether parents reacting in an extreme adverse way to a neo-natal diagnosis would have the same reaction if the diagnosis came following the presentation of clinical symptoms.

Dr Majumbar raised the similarly of Duchenne to cystic fibrosis – a condition which is currently the subject of an NSC approved newborn screening programme. Both are severe genetic conditions.

Cystic fibrosis was originally not recommended for screening by the NSC, but was implemented because of a Ministerial intervention.

Dr Elliman from the NSC acknowledged that if cystic fibrosis were reviewed now there would still be discussion on whether approval should go ahead, but there is now more evidence on the benefits of early treatment.

Dr Majumbar also raised the case of families under his care in Bristol – who until screening was discontinued in Wales were faced with not having the option to screen their child, whereas families a few miles away were able to exercise that choice. Any future screening programme would need to be UK-wide, to ensure no regional variations, which would have ethical implications for the families denied the choice to screen.
Dr Diana Ribeiro, Chief Executive at Action Duchenne, highlighted newborn screening in the context of access to emerging treatments. He specifically referenced access to ataluren in the context of diagnostic delay – where if boys are diagnosed later than average, they would miss out on access treatment from the age of 5.

Dr Jenny Versnel, Director of Research at Muscular Dystrophy UK, stressed that the test would only be offered to boys. There may be ethical implications therefore if girls or manifesting carriers of Duchenne are not offered the possibility of an early diagnosis.

**Next steps**

The following next steps and priorities were agreed to:

- An eventual research trial for the revised assay – to gather evidence of effectiveness and of impact of early interventions in a screened population
- The identification within the NorthStar database of a screened population or a child who received an early diagnosis – to monitor any trends in health outcomes or parental choices
- A new survey of families to collect updated data on attitudes to newborn screening
- Muscular Dystrophy UK to work with the paediatric neurosciences Clinical Reference Group at NHS England to push forward service improvements in the provision of psychological support for those affected by Duchenne or other neuromuscular conditions. Provision of psychological support is essential at any stage of diagnosis—and will be a key component to a national newborn screening programme for Duchenne muscular dystrophy

For more information on newborn screening for Duchenne muscular dystrophy, please contact Peter Sutton on p.sutton@musculardystrophyuk.org