SMA diagnosis via newborn screening: UK treatment pathways

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This document has been written to summarise how clinicians, in consultation with the baby's parents/caregivers, should decide the correct treatment pathway for each individual baby identified by newborn screening for spinal muscular atrophy (SMA).

Patients diagnosed with SMA are historically classified as Type 0, 1, 2, 3 or 4. The SMA type reflects the age of symptom onset and the motor milestones that patients have achieved without treatment.

For babies diagnosed via newborn screening for SMA, clinicians will have to take a different approach to 'classify' the type of SMA in order to define the prognosis and choose the optimal treatment with the parents/caregivers.

The assessment will focus on whether the baby has developed any subtle or more substantial symptoms in the neonatal period, when newborn screening typically occurs. If this is the case, the baby will be classified as type 0 or type 1A SMA, based on the onset of symptoms within the first month of life and on the number of copies of *SMN2* gene they have.

As the vast majority of babies diagnosed via newborn screening are anticipated to be asymptomatic, the number of *SMN2* copies will be crucial in understanding the likely severity of their condition. As a general rule, the higher the number of copies of *SMN2*, the less severe the symptoms of SMA are likely to be in that individual.

Babies who are diagnosed with SMA via newborn screening will follow a clear, well-defined pathway that will provide parents/caregivers with the accurate information they need to understand the baby's condition and the treatment options available.

A baby's positive screening test will be communicated to his/her parents/caregivers by an experienced SMA clinician who will conduct a confirmatory test on an independent blood sample. NHS England's National Genomic Test Directory specifies that the turnaround time for this confirmatory test (MLPA testing for deletions of the *SMN1* gene) is 7-14 days, which was reasonable when no treatments were available.

The current timescale is considerably longer than the timeline achieved in all developed countries where newborn screening is available, where these tests are typically returned within 2-3 days. It is also too long to give patients the best chance of getting optimal efficacy from disease-modifying treatments. The time to genetic confirmation needs to be shortened

to three days if infants are to derive the maximum benefits of treatment. It is well known that starting treatment as early as possible, and before the onset of symptoms, is crucial in SMA to get the best outcome in treated individuals.

The number of *SMN2* copies observed in newborn infants with SMA and the potential symptoms will help the clinician and the family to decide on the most appropriate treatment pathway.

When newborn infants have **severe symptoms at diagnosis**, including contractures, long bone fractures, central nervous system involvement or respiratory distress, they should be offered palliative care; or approved medication in the less severe cases when parents are well informed of the prognosis in terms of disability and dependence on others for all aspects of daily care. In most of these cases, treatment may indeed not be in the baby's best interests – e.g., if there are other significant medical problems such as hypoxic brain injury. National guidelines should be followed (available: https://smareachuk.org/sma-reach-uk-information).

Newborn infants with **mild symptoms or signs at diagnosis** including areflexia, hypotonia or reduced spontaneous movement should be offered any approved medication, after considering specific contra-indications.

Newborn infants with **no symptoms and 2-3 copies of *SMN2*** should be treated as soon as possible with any approved medication after considering specific contra-indications.

Newborn infants with **four copies of SMN2** should be offered either nusinersen, risdiplam (starting at the age of 2 months), or regular follow up every 6 months to decide when treatment initiation is required.

Gene therapy and nusinersen are currently the only approved medications under the age of 2 months in the UK, but risdiplam could potentially also become available for this age range in the future.

Drug-specific contra-indications as well as available data on safety and efficacy of the specific disease-modifying therapy should be discussed in general, and parents/caregivers should be made clearly aware of the realistic effect that treatments might have according to their child's condition and the number of *SMN2* copies.

In all cases, doctors have a professional duty to act in the best interest of the baby. If agreed, disease modifying therapy should ideally be started within 2 weeks after screening identification.

This document should be re-evaluated on a yearly basis, if the availability of any treatment changes, or if new data susceptible to change this strategy become available.