MLD EXPERT STEERING GROUP – RESPONSE TO NSC REJECTION FEB '26

Summary
The NSC's review says there are still unanswered questions about the accuracy of the test, the best cut-offs, whether earlier treatment clearly improves outcomes, and whether screening is cost-effective. We agree these questions matter buta) there have been fundamental flaws in the review process, noting discrepancies in the NSC application of the Drummond Checklist compared to that in an external review, and b) all of the issues can be addressed safely through a UK pilot, using the same approach the NSC is already developing for rare conditions.

Earlier engagement with clinical, methodological, and lived-experience experts would have enabled the inclusion of additional evidence on early diagnosis benefits. This represents a missed opportunity and highlights the need for structured early expert input in future reviews.

The NSC has a moral obligation to problem solve national screening where harm is being caused by inequitable access to an approved treatment in NHS use. Suggested review in 2029/30 is unjustified, unethical and inconsistent with the NSC'shorizon scanning principles.

Key points:

- Countries and pilots using the 3-tier testing approach have to date demonstratedexceptional accuracy, including zero false positives. Thisevidence addresses the main concern about accuracy.
- The UK already has systems to follow babies over time to detect any missed cases. The NSC cites these itself.
- Evidence from treatment centres, including UK clinicians, consistently shows children treated early have significantly improved lives compared to those diagnosed after symptoms begin.
- The NSC has already reclassified the cost-effectiveness criterion as *uncertain,* specifically inviting an external review, which we support.
- 31/37 children have already been denied access to life-changing treatment due to late diagnosis. Evidence review in 2029/30 will potentially condemn another 30-40 children to death and is unethical where treatment is available.

A conditional pilot is the only practical and ethical way to fill the remaining gaps without leaving more children to be diagnosed too late. It is also important to note that, without screening, presymptomatic access to treatment depends onlyon having an already-affected sibling, an inequitable position. A pilot is the only fair route for understanding

1. **Test Accuracy (Criterion 4)**

Comments

The NSC concluded the test isn't fully validated yet.The updated 3-tier test,which adds a simple genetic check at the end, isin use in several countries internationally and been shown to remove almost all false positives. Families do not get recalled unnecessarily, and babies at risk are identified earlier.

The NSC itself states that this third step can be treated as part of the screening process.The NSC are also asking for data on false negatives, which is physically impossible to generate unless screening is in place.

What we propose

- Use the 3-tier version currently in use in several other countries in the UK pilot.
- Follow the NSC's own guidance by checking a sample of screen-negative babies (not every single one), using the UK rare-disease registries already in place.
- Report the results back to the NSC during the pilot.

This approach is practical, proportionate, and already used in other rare disease pilots.

2. Cut-Off Levels (Criterion 5)

Comments

The NSC highlighted one historic case in which an early UK trial missed a baby using an older cut-off. But that event prompted the UK laboratory and other laboratories around the world to update and improve the cut-offs accordingly. The NSC recognises that cut-offs evolve during early implementation, this was exactly the case for another condition, Tyrosinemia, which the UK now screens for.

What we propose

- Start the pilot using today's improved cut-offs.
- Add the early results from Norway's national MLD screening (publication Feb 26), which began in 2025, into a timely NSCreview.
- Use the pilot to confirm cut-offs for UK babies, just as is done for every new screening programme.

We emphasise that relying on sibling-based presymptomatic identification is inherently inequitable and incompatible with population-level responsibility for timely access to treatment. Screening through a conditional ISE pilot is the only mechanism capable of identifying presymptomatic cases fairly and consistently across the entire newborn population.

3. Early Treatment Benefits (Criterion 9)

The NSC says there isn't "direct" evidence comparing screen-detected babies with symptom-detected babies. The NSC's own methodology however, accepts indirect evidence when direct comparisons are not feasible in rare fatal paediatric diseases.Across all published studies, including long-term follow-up, as well as in evidence from hundreds of respondentsto the public consultation, the message is clear:*'Children treated before symptoms do far better than those treated after symptoms appear'*.

The NSC questions whether results from cascade testing would differ to those from population testing. This evidence cannot be generated without a pilot study. Implied uncertainty over genotype/phenotype correlation has been addressed in evidence which has been overlooked.

The consultation also records that multiple children in the UK have already missed treatment eligibility because they were diagnosed too late.

What we propose

- We ask that Criterion 9 be set to "provisionally met" within a conditional pilot, with prospective outcomes monitoring to address residual uncertainty.
- Re-examine existing evidence on genotype/phenotype correlation
- Track real outcomes using the UK registries the NSC already works with.

This is the fairest and safest path.

We note that the review does not clearly explain how it treated differences between the cohorts being compared—screen-eligible infants versus clinically detected cases. Without clear adjustment for age at treatment, phenotype and pathway delays, conclusions based on generalising between these cohorts risk under-representing the true benefits of earlier detection. Clarifying this would strengthen the evidential presentation.

4. Cost-Effectiveness (Criterion 14)

The NSC has already changed this criterion from "not met" to "uncertain", specifically because an independent review is needed. We welcome this.

What we propose

- Conduct the independent economic review with full transparency.
- Combine its findings with real-world cost data from the pilot.
- Let the NSC make a final value-for-money judgement on this combined evidence.

This gives the public complete clarity.Given that new international data (including national pilots such as Norwayresults due to be published Feb 26) and UK registry linkageswhich are expected within 12–24 months, scheduling the next review for 2029–30 is neither justified nor consistent with NSC horizon-scanning principles. An interim evidence checkpoint—no later than 2027—is necessary to prevent the topic being deprioritised or delayed due to workload pressures.

Given that horizon scanning already anticipates major publications and pilot outputs within the review cycle, delaying formal reassessment until 2029–30 is inconsistent with the principle of responsive evidence integration. Emerging data should automatically trigger earlier review.

5. Why a Conditional Pilot Is the Right Approach

The NSC's own consultation responses confirm:

- Cut-offs often need refinement in early implementation, this is normal.
- Following every negative baby is not feasible, so sampling is the recommended approach.
- MLD has already been identified as a strong candidate for the NSC's new EquipoISE evaluation model.
- New data from Norway and ongoing international pilots are expected soon.
- The biggest harm happening today is late diagnosis, which screening directly prevents.

A UK pilot is the safest and most balanced solution.

Additional points

We also highlight the NSC's historic pattern of delayed review cycles, as reflected on its own website. To ensure timeliness, clear milestones and trigger criteria should be established so that evidence—when published—cannot be deferred due to competing internal priorities.

Despite this, several important elements remain unaddressed, including the performance of the modern 3-tier test, the feasibility of sampling screen-negatives through existing registries, and the imminent availability of international pilot data. Incorporating these factors would provide a more complete and balanced assessment.

Although personal accounts are mentioned throughout the NSC documents, their evidential value has not been meaningfully weighted. For rare paediatric conditions where direct comparative evidence cannot exist, structured lived-experience evidence—such as diagnostic timelines, missed eligibility cases, and observed treatment benefits—should contribute to contextual analysis in line with NSC methodology for rare diseases.

Key Issues

This annex summarises the main areas where the NSC's statements can be approached differently *without* technical detail.

1. No method to identify false negatives

The NSC itself notes that it is not feasible to check every negative baby. Instead, it recommends following a sample, which is exactly what we propose.

2. PPV was only 15%

This figure comes from an older 2-step version of the test. Using the modern 3-step version, pilots have found almost no false positives.

3. A UK case fell below the cut-off

That happened before laboratories updated the cut-offs. The new dual-marker method would have detected that baby.

4. No direct evidence early treatment improves outcomes

There cannot be direct evidence without screening in place. But all indirect evidence shows better results when treatment is early, and the NSC accepts indirect evidence for rare diseases.

5. Cost-effectiveness uncertain

That's exactly why an external review is needed and why we support it.

6. No relevant stakeholder engagement

Relevant experts should be engaged as per the NSC's published strategy in order to problem solve the evidence gaps with the greatest possible accuracy and efficiency.