UK National Screening Committee

Newborn Screening for Mucopolysaccharidosis Type I

26 February 2020

Aim

1. To ask the UK National Screening Committee (UK NSC) to make a recommendation, based on the evidence presented in this document, whether or not newborn screening for mucopolysaccharidosis type I (MPS I) meets the UK NSC criteria for a systematic population screening programme.

Current recommendation

2. The UK NSC currently does not recommend systematic population screening for MPS I in newborns. The Committee based this recommendation on the evidence provided by the 2015 review carried out by Bazian Ltd.

Evidence Summary

3. The 2019 evidence summary was undertaken by Costello Medical, in accordance with the triennial review process: https://www.gov.uk/government/publications/uk-nsc-evidence-review-process/uk-nsc-evidence-review-process

4. The 2019 evidence summary assesses the quality and volume of evidence published since 2014 on the accuracy of available tests and the potential benefit of early treatment following screening compared to later treatment following clinical detection.

5. The conclusion of the 2019 evidence summary is that the current recommendation, that whole population screening for MPS I in newborns should not be introduced in the UK, should be retained. This is for the following reasons:

    - There is limited evidence to support that newborn screening tests for MPS I in dried blood spots (DBS) are sufficiently accurate for use in a national screening programme. Four studies were identified: three measured α-L-iduronidase (IDUA) enzymatic activity by tandem mass spectrometry (MSMS), and one study evaluated a fluorometric assay in combination with a pattern recognition software. There was

substantial heterogeneity in screening test methods and only screen-positive cases received the reference standard. This in turn increased the risk of bias and limited the reporting of test accuracy parameters, with positive predictive values (PPVs) being the only measure of test performance reported. For the three studies which evaluated MSMS as a screening test for MPS I, the PPV were 7.7%, 26.7% and 50.0%, whilst the fluorometric enzyme assay achieved a PPV of 11%. Two studies also reported a relatively high incidence of pseudodeficiency* with 5/44,411 newborns identified in one study and 7/43,701 newborns in another. The review acknowledged that assessment of test accuracy parameters, such as sensitivity and specificity, is difficult to achieve in studies of screening for rare diseases. Additional studies with improved methodological consistency (in terms of index test cut-offs, repeat testing and the reference standard used) may be achievable and would allow for an informative evaluation of a putative test to be used in screening for MPS I in newborn babies, particularly given the potential for identification of carriers and pseudodeficiency in MPS I screening. Overall, at present there was insufficient evidence to determine whether newborn DBS screening using MSMS or fluorometric assays is sufficiently accurate to identify all patients with MPS I. **Criterion 4 not met**

- Thirteen studies evaluated the relationship between age at initiation of haematopoietic stem cell transplantation (HSCT) or enzyme replacement therapy (ERT) and clinical outcomes for MPS I patients. The quality of the included studies was generally low, and the risk of bias was high. Although some studies indicated a statistically significant association, the effect was small. It is therefore unclear whether early diagnosis of MPS I would lead to a clinically significant improvement in patients' symptoms. Other studies did not demonstrate any effect of age of treatment initiation on clinical outcomes. The majority of studies focussed solely on Hurler patients, while the effect of early initiation of treatment for patients with attenuated MPS I was rarely investigated. The median age of treatment in these studies was also more aligned with clinical detection of MPS I rather than earlier initiation of treatment following detection through screening. Overall, there is insufficient evidence to determine whether early initiation of HSCT or ERT improves

* Pseudodeficiency results in reduced enzymatic activity of IDUA *in vitro* but it is not known to lead to any disease or clinical symptoms, and therefore treatment is not required.

clinical outcomes for MPS I patients compared to current practice. **Criterion 9 not met**

Consultation

6. A three-month consultation was hosted on the UK NSC website. Direct emails were sent to 21 stakeholders. **Annex A**

7. Comments were received from the following stakeholders:

    i. MPS Society
    ii. Royal College of Paediatrics and Child Health

    (See **Annex B** for comments)

8. The public consultation closed on 14 January 2020. The total number of consultation responses received was 2.

9. The consultation comments received are presented below in **Annex B**.

10. The MPS Society acknowledged the findings of the review and will be working closely with key stakeholders in the near future to address the concerns outlined in the review. The Royal College of Paediatrics and Child Health agreed with the conclusions of the review.

Recommendation

11. The Committee is asked to approve the following recommendation:

A population screening programme for MPS I in newborns is not recommended in the UK

Criteria (only include criteria included in the review)	Met/Not Met
Section 1 - Criteria for appraising the viability, effectiveness and appropriateness of a screening programme	
The Test	
4. There should be a simple, safe, precise and validated screening test.	**Not Met**
The Screening Programme	
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 should not be further considered.	**Not Met**

List of organisations and individuals contacted Annex A

1. British Association of Perinatal Medicine
2. British Inherited Metabolic Disease Group
3. Clinical Genetics Society
4. Colin Pavelin - DH rare diseases
5. Faculty of Public Health
6. Genetic Alliance UK
7. Institute of Child Health
8. Mark Bale - DH rare diseases
9. Metabolic Support UK
10. MetBio
11. MPS Society
12. PHE ANNB Screening Programmes
13. Royal College of General Practitioners
14. Royal College of Midwives
15. Royal College of Paediatrics and Child Health
16. Royal College of Physicians
17. Royal College of Physicians and Surgeons of Glasgow
18. Royal College of Physicians of Edinburgh
19. Save Babies Through Screening Foundation UK
20. Tom Fowler - Genomics England/ PHE
21. UK Newborn Screening Laboratories Network

Annex B

Newborn screening for mucopolysaccharidosis type I (MPS I)

Consultation comments

1. **MPS Society**

Name:	Bob Stevens	**Email address:**	xxxx xxxx
Organisation (if appropriate):	MPS Society		
Role:	**CEO**		

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

Yes 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.*
		Overall Comments: The MPS Society acknowledges the findings of the committee and will be working closely with all key stakeholders in the near future to address these concerns with the intention for a resubmission in due course

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2. Royal College of Paediatrics and Child Health

Name:	Comments received on behalf of Dr Eugen Strehle	**Email address:**	XXXX XXXX
Organisation (if appropriate):	Royal College of Paediatrics and Child Health		
Role:			

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.*
General	General	The reviewer agrees with the conclusion of this review.