UK National Screening Committee

Newborn screening for the Organic acid oxidation disorders propionic acidaemia and methylmalonic acidaemia

12 February 2016

Aim

1. To ask the UK National Screening Committee (UK NSC) to make a recommendation, based upon the evidence presented in this document, on whether newborn screening for the Organic acid oxidation disorders (OAODs) propionic acidaemia (PA) and methylmalonic acidaemia (MMA) meets the UK NSC criteria to support the introduction of a population screening programme.

2. This document provides background on newborn screening for PA and MMA.

Current recommendation and background

3. The current recommendation, published in 2009, is that a systematic population screening programme for the organic acid oxidation disorders PA and MMA is not recommended.

4. The 2009 recommendation also included two additional conditions, isovaleric acidaemia and maple syrup urine disease. Both these OAODs have subsequently been recommended for screening and implemented as part of the newborn blood spot screening programme following a 14 month evaluation of screening for five inborn inherited metabolic disorders. So are not included in this update

Review

5. The two conditions are being reviewed as part of the UK NSC's cycle of reviews and have been undertaken by Bazian Ltd. Separate reviews have been produced for PA and MMA but both reviews focus on:

    i. the understanding of the epidemiology and natural history of the conditions
    ii. the implications of having a single copy of the gene (carrier) found as a result of screening

iii. whether there is a precise and validated screening test
iv. whether there is additional benefit of treatment following screen detection
v. treatment guidelines and
vi. the wider ethical, legal and social implications of screening for these two conditions

6. The conclusion of this review reaffirms the existing recommendation not to offer universal screen newborn for PA and MMA.

7. The key reasons for these conclusions are:

    a. For MMA, evidence based guidelines suggest a reasonable understanding of the relationship between being screen positive result and actually having symptoms of the disease (enzymatic subtype-phenotype correlation). For PA there is no clear understanding of genotype-phenotype or enzyme activity and phenotype correlation. While some forms of MMA are better understood, current evidence is insufficient to accurately predict prognosis from other forms of MMA and for PA. **Criterion 2 is not met**

    b. The current screening test has a poor predictive value (usually less than 20% for MMA and 11% and lower for PA). This means that there will be many more families worried by results than actually have the diseases. The initial screening test cannot distinguish between PA and MMA due to them utilising the same chemicals in the blood (mainly C3 and ratios involving C3). The timing of the test is also of concern, with many babies presenting with clinical symptoms before screening results. **Criterion 5 is not met**

    c. No studies, allowing for comparison of treatment outcomes from screened and unscreened populations were identified. **Criterion 10 is not met**

    d. The identified treatment guidelines did not give explicit recommendations about management of asymptomatic individuals identified through screening, or use specific genotype or level of PCC enzyme activity to guide management. **Criterion 11 is not met**

    e. Despite parents of the affected newborns being carriers of the mutation, no studies were identified in the update search which explored the implications of the carrier state identified as a result of screening. Additionally, no direct evidence was

identified that explored the impact of newborn bloodspot screening for PA or MMA on wider ethical, legal, or social issues. **Criterion 14 is not met**

f. Given the rarity of both MMA and PA, it is likely a prospectively constructed international study or registry would be needed to gain sufficient evidence to compare the impact of treatment following screening versus treatment following clinical detection. **Criterion 17 is not met**

Consultation

8. A three month consultation was hosted on the UK NSC website. Direct emails were sent to stakeholders of whom 16 organisations and individuals were contacted directly. **Annex A**

9. One joint response was received from Save Babies Through Screening Foundation and the Patient Advocates for NBS, UK Group (PANS)

10. The response from PANS acknowledged that more work is needed in terms of evidence gathering before these two conditions can be recommended. Limitations in the test and early identification of the conditions were highlighted. However, the response from PANS did note the potential for both PA and MMA to be good candidates for screening, based on the benefit gained from treatment.

Recommendation

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

A systematic population screening programme for the organic acid oxidation disorders PA and MMA are not currently recommended.

This is because:

- For PA, there is not a good enough understanding of the condition to accurately predict prognosis
- The screening test has poor PPV and cannot distinguish between PA and MMA
- Many babies with the two conditions die before the results of the screening test have been reported
- There is not enough evidence to be clear that early identification through screening is of benefit

- There are no guidelines on the management of asymptomatic individuals identified through screening
- There are wider ethical, legal and social implications, such as; the screening test identifying parents as unaffected carriers of the conditions that remain unexplored

Based upon the 22 UK NSC criteria to recommend a population screening programme, screening for the OAODs PA and MMA in newborns did not meet the following primary requisites:

	Criteria	**Met / Not met**
The Condition		
2	The epidemiology and natural history of the condition, including development from latent to declared disease, should be adequately understood and there should be a detectable risk factor, disease marker, latent period or early symptomatic stage	Not Met ✗
The Test		
5	There should be a simple, safe, precise and validated screening test.	Not met ✗
The Treatment		
10	There should be an effective treatment or intervention for patients identified through early detection, with evidence of early treatment leading to better outcomes than late treatment.	Not met ✗
11	There should be agreed evidence based policies covering which individuals should be offered treatment and the appropriate treatment to be offered.	Not met ✗
The Screening Programme		
14	There should be evidence that the complete screening programme (test, diagnostic procedures, treatment/ intervention) is clinically, socially and ethically acceptable to health professionals and the public.	Not met ✗

Annex A

List of organisations/ individuals contacted:

1. NHS England
2. British Inherited Metabolic Disease Group
3. Children Living with Inherited Metabolic Diseases
4. Clinical Genetics Society
5. Two Department of Health rare disease team contacts
6. Genetic Alliance UK
7. Institute of Child Health
8. Organic Acidaemias UK
9. Rare Disease UK
10. Royal College of General Practitioners
11. Royal College of Midwives
12. Royal College of Paediatrics and Child Health
13. Save Babies Through Screening Foundation UK
14. Genomics England/ Public Health England contact
15. UK Newborn Screening Laboratories Network

UK National Screening Committee Screening for the organic-acid oxidisation disorders MMA and PA in newborns- an evidence review

Annex B

1.

Consultation comments pro-forma

Name:	Pat Roberts	**Email address:**	**xxxx xxxx**
Organisation (if appropriate):	Save Babies Through Screening Foundation UK on behalf of the Patient Advocates for NBS UK Group PANS		
Role:	**Chair of PANS**		
Do you consent to your name being published on the UK NSC website alongside your response? **Yes** x☐ **No** ☐			

Section and / or page number	Text or issue to which comments relate	
General Comments on the review documents	This response covers both Methylmalonic Acidaemia and Propionic Acidaemia	PANS recognises that both Methylmalonic Acidaemia and Propionic Acidaemia are good candidates for consideration of newborn screening in that these are fairly straightforward conditions, i.e. in terms of responding well to treatment. However in terms of screening tests they are quite complicated e.g. MA separating out the different types is not without problems. Also the argument that early diagnosis may not always make a significant difference to outcomes. Unfortunately we have been unable to obtain further input/observations from UK clinicians on these 2 disorders. In light of this we would not totally reject these 2 disorders for consideration but suggest that more work is done in terms of evidence gathering.
		We therefore suggest that there is an opportunity here to do more work on reviewing what has happened in both Australia and the Netherlands in terms of screening for these disorders.