UK NATIONAL SCREENING COMMITTEE

Newborn Screening for Biotinidase Deficiency

6 June 2013

Aim

1. This note provides background to the agenda item addressing the review of newborn screening for biotinidase deficiency.

Current Policy

2. The current policy is that screening for biotinidase deficiency should not be offered. A review document was produced by the UK National Screening Committee's Child Health Subgroup in 2004. This was based on two National Institute for Health Research Health Technology Assessment reports addressing a broad range of inherited metabolic disease:

3. Health Technology Assessment 1997; Vol. 1: No.11. Neonatal screening for inborn errors of metabolism: a systematic review (Seymour *et al*)
Health Technology Assessment 1997 Vol 1: No. 7. Neonatal screening for inborn errors of metabolism: cost, yield and outcome (Pollitt *et al*)

4. The key is issues informing the policy decision in 2004 included:

- the rarity of biotinidase deficiency and varied clinical course
- lack of information on the cost effectiveness of screening
- concern about the test (e.g. its false positive rate and inability to distinguish between severely and mildly affected cases)
- lack of information on the overall benefit of screening

5. A vignette was developed in 2008 by Dr Mike Champion as part of a wider discussion about expanded newborn screening. While drawing attention to the case for screening the vignette highlighted the need for UK prevalence data as a means of addressing the uncertainties about the cost effectiveness of screening. The need for a review was last considered in February 2009 but no document was produced at that time.

Review Process

6. The review addresses the evidence published between January 2004 and May 2012 and the resulting document is attached.

7. The document was considered by the Fetal Maternal and Child Health Co-ordinating Group in November 2012. A three month consultation was hosted on the UK National Screening Committee (UK NSC) website and this closed in 7 May 2013. The following stakeholders were contacted directly: British Inherited Metabolic Disease Group, Children Living with Inherited Metabolic Diseases, Royal College of Paediatrics and Child Health, Royal College of Midwives (RCM) and Saving Babies Through Newborn Screening.

8. Comments were received from the RCM, Saving Babies Through Screening Foundation UK and Dr Mike Champion. The comments are attached at Annex A.

9. The RCM response was content with the review's conclusion that the evidence in the key areas had not changed sufficiently to warrant a change in policy. The response from Saving Babies Through Screening Foundation UK was more critical of the review's conclusions. For example the group focused on the evaluation of the criteria relating to the test which they considered to be met. However, the response from Dr Mike Champion drew attention to ongoing work to develop an approach to screening based on Tandem Mass Spectometry (TMS). The background documents submitted as part of this latter response suggest that current testing methods are time consuming, labour intensive and insensitive. The response proposed a pilot to help develop the evidence base relating to TMS.

10. The response from Saving Babies Through Screening Foundation UK also suggests that, because of the introduction of newborn screening internationally (including Europe), the opportunity to study issues relating to the epidemiology, natural history and the test has passed and the example of other countries should be followed. However a recent EUCERD report noted that there was no European consensus on which conditions should be included in national screening panels. Out of 38 responding countries, 10 screened for biotinidase deficiency.

Continuing areas of uncertainty

11. The review and consultation highlight a number of areas of continuing uncertainty. These relate to the epidemiology and natural history of biotinidase deficiency, the identification of an appropriate test, the varied clinical course of the condition, the overall benefits of screening and its cost effectiveness.

Recommendation

12. The UK NSC is asked to agree the policy position on newborn screening for biotinidase deficiency as follows:-

Newborn screening for biotinidase deficiency is not recommended.

There is insufficient evidence regarding the epidemiology and natural history of biotinidase deficiency in the UK. The clinical course of both profound and partial biotinidase deficiency is varied with some of those affected remaining asymptomatic into adolescence and adulthood. There are concerns about the practicality and reliability of current screening methods and insufficient evidence regarding TMS as an alternative method.

13. The UK NSC is asked to agree that the policy should be reviewed in three years' time unless there is significant new peer reviewed evidence in the meantime.

Response from Dr Mike Champion

Dear Adrian,

I have spoken with Neil Dalton and Charles Turner , who work in the WellChild Research Lab here at the Evelina who developed the TMS screening techniques for underivatised MCADD screening and haemoglobinopathies, for references/further information regarding the TMS method for biotinidase screening: .

There have been several abstracts going back 10 years (2 attached) along with a patent for a novel method for doing both biotinidase deficiency and type 1 tyrosinaemia screening simultaneously with metabolite screening or haemoglobinopathy screening. The latter is preferred and a kit is available which has been supplied to colleagues in the Czech Republic to gather real time data, but this has yet to start. It requires no more machine time and minimal extra sample preparation.

Within our hospital, our formal clinical assay for biotinidase deficiency has been stable isotope dilution electrospray MSMS for over 10years . More than 1,000 plasma samples have been analysed in the past 2 years alone.

Neil Dalton comments, 'Given that 3 newborn screening labs in England are now piloting haemoglobinpathy screening by MSMS, with a 4th lab to be introduced later in the summer, it would appear to make sense to pilot the biotinidase and type 1 tyr screening, using PBG synthase activity, now'.

The UK has the opportunity to be creating rather than waiting for an evidence base for these newer techniques that continue to be developed in the UK that can then be exported to overseas providers.

Regards,

Mike

Dr Mike Champion
Consultant in Paediatric Inherited Metabolic Disease
[redacted]

Annex A

Consultation Responses

Organisation:	Royal College of Midwives		
Name:	Mervi Jokinen	**Email address:**	[redacted]
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.*	
In General		RCM has no comments re detailed issues. We agree on the conclusion that the evidence published since the last policy update has not changed significantly in the key areas of concern identified in previous, and therefore does not suggest the needs to review the UK NSC's policy position on newborn biotinidase deficiency screening. In taking into consideration how many of the criteria are not met and where the evidence is lacking RCM would not perceive that the programme would not be seen cost-effective due to its rarity. It would be most probable that it would increase the burden of resources.	

Organisation:	Save Babies Through Screening Foundation UK & the UK Patient Advocates for Newborn Screening (PANS) Group		
Name:	Pat Roberts	**Email address:**	[redacted]

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 Comments	We have shared this review document with some of our expert colleagues overseas. They have read all the review evidence within the document, anticipating a final conclusion that it will be recommended that NBS for Biotinidase Deficiency be included in the UK screening programme. To be really honest with you I have to say they were fairly staggered that, having read your own evidence, a conclusion was reached not to recommend it. A comment was made that it is pretty unbelievable that in terms of general medical and scientific advances and achievement in the UK, that there is such a lethargy in terms of the right decisions on NBS. Many of the not met or unclear if met are fairly standard areas that you would look at, develop and test as part of the introduction of the pilot screening programme. *Can we please suggest that a specific meeting of experts is convened to discuss this review evidence to help reach a consensus on how this can be sensibly moved forward.*
Criteria 1	The condition should be an important health problem.	Individuals with untreated biotinidase deficiency usually develop neurological symptoms, including seizures, hypotonia, feeding problems, ataxia, cognitive defects, atrophy and hearing loss. Biotin therapy can alleviate and, if initiated early, prevent many of these symptoms. Some symptoms e.g. hearing loss, cognitive development are usually irreversible if they occur before treatment is initiated. Symptoms are particularly severe and painful for children. Seizures often cannot be controlled by most anticonvulsive medications. The argument for newborn screening is strong

		which is why many countries across the world, including Europe, already screen for this disorder.
Criteria 2. Page 6	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	With the advent of newborn screening for this disorder and the adoption of newborn screening by many countries, including European countries, the window of opportunity to characterize the consequences of untreated disease and to collection of date is now gone. In any decision making we need to apply to the information that is already known. There is significant data from across the world and Europe. We need to start saving children's lives in the UK now instead of introducing further research for the UK only. See The neurology of biotinidase deficiency: Barry Wolf 3rd June 2011 - Journal of Molecular Genetics and Metabolism
Criteria 4 Page 12	If the carriers of a mutation are identified as a result of screening the natural history of people with this status should be understood, including the psychological implications.	It is not clear why the summary shows that this criteria is not met. The summary does not accord with the statements made in the paragraphs. Can I suggest that you contact Dr Barry Wold the world expert on Biotinidase deficiency to discuss this criteria. His e mail is: BWOLF1@hfhs.org
Criteria 5 Page 13	There should be a simple, safe, precise and validated screening test	It is difficult to understand why this is only assessed as partly met. We have stringent guidelines and laboratory standards in the UK. The screening test is currently being done across the world. Whatever disorder we introduce on the screening programme we have careful analysis in place on detection of false positives or false negatives. We have to be sensible in considering these things however examining the European position we should not be putting lives at risk.
Criteria 6 Page 19 Summary	The distribution of test values in the target population should be known and a suitable cut-off level defined and agreed. Summary - Not Met	There is sufficient evidence from around the world (and indeed quoted in your review paper) for our expert laboratory scientists in the UK to determine which method is appropriate for our UK population. We have been involved in newborn screening for 50 years. Our laboratory scientists have significant expertise. We have links with scientists in Europe. We try to be always objective however it defeats us how you can possibly say in this review that we are unable to overcome the challenges in obtaining a reasonable cut off rate

		for the UK population.
Criteria 7 Page 19 Summary. Also Criteria 14 summary is relevant here.	The test should be acceptable to the population. Not clear if it is met!	We have been doing NBS for 50 years. This question arises for every new disorder that goes onto the screening programme. There is no evidence to demonstrate that screening for Biotinidase deficiency is unacceptable. With our current processes and procedures parents have a choice. It is clear from the current NBS pilot of the 5 disorders that declines are reducing (presumably as the pilot becomes better known and bedded in, the staff are more familiar and the parents are becoming more knowledgeable.
Criteria 8 Page 20 Summary Also Criteria 18, page	There should be an agreed policy on the further diagnostic investigation of individuals with a positive test result and on the choices available to those Individuals. Summary - Not met	The UK develops a policy on all other disorders being screened for consequently it is not insurmountable that a policy for this is not part of putting in place screening for this disorder. We have sufficient expertise in the UK to do this.
Criteria 11 Page 26 Summary	There should be agreed evidence based policies covering which individuals should be offered treatment and the appropriate treatment to be offered. Summary - Not Met	See The neurology of biotinidase deficiency: Barry Wolf 3rd June 2011 - Journal of Molecular Genetics and Metabolism. This research report covers the neurological findings of symptomatic individuals, characteristic features of the disorder, consequences of biotin treatment.
Criteria 16 Pages 28 and 29 Summary	The opportunity cost of the screening programme (including testing, diagnosis and treatment, administration, training and quality assurance) should be economically balanced in relation to expenditure on medical care as a whole (i.e. value for money). Assessment against this criteria should have regard to evidence from cost benefit and/or cost effectiveness analyses and have regard to the effective use of available resource Not Clear if met	This is always going to be a difficulty until you actually introduce screening for a disorder and unfortunately PANS members did not have the financial resource (over £2000) to attend recent training on economic evaluation for the NHS which would have assisted us in trying to help with this knotty problem. However what we do know is that the symptoms of biotinidase deficiency are particularly severe and painful for children and the seizures cannot always be controlled by most anticonvulsive medications. This is quite apart from quality of life issues such as developmental delay, deafness which blights a child's life. Biotinidase deficiency requires life long and costly medical intervention and even if the disorder is rare it must be economically viable to diagnose it early with associated treatment rather than cause significant suffering for a lifetime.

		See The neurology of biotinidase deficiency: Barry Wolf 3rd June 2011 - Journal of Molecular Genetics and Metabolism. Paragraph 10 of the neurological and biochemical features of profound biotinidase deficiency.
Page 33 Implications for research	Assessment of the long term effects of biotin treatment in children identified by newborn screening and in children identified clinically	See The neurology of biotinidase deficiency: Barry Wolf 3rd June 2011 - Journal of Molecular Genetics and Metabolism.