UK National Screening Committee

Newborn screening for Biotinidase deficiency

28 February 2018

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 screening for biotinidase deficiency in newborns meets the UK NSC criteria for a systematic population screening programme.

Current recommendation

2. The 2013 review of screening for biotinidase deficiency in newborns concluded that systematic population screening is not recommended. This was because:

    a) The screening test involves measuring biotinidase activity in a newborn dried blood spot (DBS) sample, so is relatively simple to perform given that newborn blood spots are already collected as part of the newborn screening programme. However, countries have differed in the enzyme activity cut-off used, and there has been limited test performance data.
    b) The last review found no data on UK prevalence.
    c) There was limited understanding of which screen-detected children with profound or partial biotinidase deficiency would go on to develop symptoms and therefore need treatment.
    d) Oral biotin is considered to be a safe and effective treatment and children with profound deficiency are always treated. However, there was more uncertainty around the management of partial deficiency. Most children are treated, but the dose given has varied between global treatment centres.

Evidence Summary

3. Screening for biotinidase deficiency in newborns was reviewed in accordance with the triennial review process.
   https://legacyscreening.phe.org.uk/biotinidasedeficiency

4. The scope of the current review focused on the criteria addressing prevalence (in the UK population) and natural history of profound and partial biotinidase deficiency, whether a screening test cut-off has been identified, and the treatment outcomes in people with profound and partial deficiency. The review was undertaken by Bazian.

5. The main conclusion of the current review is that population screening for biotinidase deficiency in newborns should not be recommended in the UK. This is because:

   - There is still no UK incidence/prevalence data available. Incidence data available from other countries is highly variable and is difficult to extrapolate this data to the UK. **Criterion 1 not met**
   - The majority of children diagnosed with partial or profound deficiency are treated with biotin. Therefore, there is no data to inform the clinical course of untreated profound or partial deficiency (by enzyme activity or genotype) and explain why some people remain asymptomatic. Consequently, it is still not clear if all screen-detected children need treatment. **Criterion 1 not met**
   - Uncertainties remain around the optimal enzyme activity threshold to use in newborn DBS screening. The optimal screening test threshold and/or timing (such as performing a later repeat DBS for those with partial levels) remain to be clarified. There is no follow-up of screen negatives, so no further test performance data (such as sensitivity and specificity) is available. **Criterion 4 not met**
   - As most children are treated at diagnosis, RCTs or comparative studies comparing treated and untreated populations are not available. Cohorts of children from North American and European screening programmes suggest

that most people remain asymptomatic on biotin. The biotin dose prescribed has been variable. However, it is not known who would have remained asymptomatic without treatment. Reports of symptoms occurring while on treatment have been inconsistent, both for partial and profound deficiency. It is unclear whether all are disease-related. Similarly reported effects of treatment non-compliance both for partial and profound deficiency are inconsistent, with some people developing symptoms and others remaining asymptomatic. The evidence is not available to inform which screen-detected children with partial or profound deficiency would develop symptoms and need biotin treatment, or the optimal dose to give. Neither can the evidence inform whether screen detection improves outcomes compared with clinical detection. **Criterion 9 not met**

Consultation

6. A three month consultation was hosted on the UK NSC website. Direct emails were sent to 12 stakeholder organisations. **Annex A**

7. Responses were received from the following 2 stakeholders;

    - Royal College of Paediatrics and Child Health (RCPCH)
    - Genetic Alliance UK (GAUK)

All comments are in **Annex B**, below.

Recommendation

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

A systematic population screening programme for biotinidase deficiency in newborns is not recommended.

Based upon the UK NSC criteria to recommend a population screening programme, biotinidase deficiency in newborns did not meet the following requisites;

	Criteria	Met / Not met
The condition		
1	The condition should be an important health problem as judged by its frequency and/or severity. The epidemiology, incidence, prevalence and natural history of the condition should be understood, including development from latent to declared disease and/or there should be robust evidence about the association between the risk or disease marker and serious or treatable disease.	Not met ✗
The Test		
4	There should be a simple, safe, precise and validated screening test.	Not met ✗
The intervention		
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 ✗

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Annex A

List of organisations contacted:

1. British Association of Perinatal Medicine
2. British Inherited Metabolic Disease Group
3. Children Living with Inherited Metabolic Diseases
4. Faculty of Public Health
5. Genetic Alliance UK
6. Royal College of General Practitioners
7. Royal College of Midwives
8. Royal College of Paediatrics and Child Health
9. Royal College of Physicians
10. Royal College of Physicians and Surgeons of Glasgow
11. Royal College of Physicians of Edinburgh
12. Save Babies Through Screening Foundation UK

Annex B

UK National Screening Committee
Newborn screening for biotinidase deficiency – an evidence review

Consultation comments pro-forma

Name:	xxxx xxxx	**Email address:**	xxxx xxxx
Organisation (if appropriate):	Genetic Alliance UK is the national charity working to improve the lives of patients and families affected by all types of genetic conditions. We are an alliance of over 180 patient organisations. Our aim is to ensure that high quality services, information and support are provided to all who need them. We actively support research and innovation across the field of genetic medicine. Rare Disease UK is a multi-stakeholder campaign run by Genetic Alliance UK, working towards the delivery and implementation of a national strategy for rare diseases in the UK. The UK Strategy for Rare Diseases was published in November 2013. Pertinent to this consultation, the Strategy includes a commitment from all four Governments of the UK to: "Continue to work with the UK National Screening Committee to ensure that the potential role of screening in achieving earlier diagnosis is appropriately considered in the assessment of all potential new national screening programmes and proposed extensions to existing programmes." Commitment 9, The UK Strategy for Rare Diseases, November 2013. This commitment recognises the value that the rare disease community places on early diagnosis, not only for the benefits it can bring to an affected individual but because of the impact it can have on improving the quality of life for their whole family.		
Role:	xxxx xxxx		

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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.*
p26	'Natural history of profound and partial deficiency: no studies described the clinical course of profound or partial deficiency (by enzyme activity or genotype) in untreated populations.'	Given that the majority of children diagnosed with partial or profound deficiency are treated with biotin, and this has been the case both in the UK and elsewhere for many years, it is difficult to imagine how natural history of the untreated conditions would be studied at this point. Biotin is a highly effective treatment, with (as the review recognises) no known side effects. Furthermore, the experience of patients detected clinically suggests that once certain symptoms (including vision problems, hearing loss and developmental delay) occur, they are irreversible even with biotin therapy. It would be highly unethical to withhold or withdraw treatment in order to better understand untreated natural history. This being the case, it is unreasonable to regard the lack of natural history data as a reason not to recommend screening for biotinidase deficiency. Where a criterion cannot realistically be met, it is unreasonable, and potentially unethical, for this to be required.
p32	'A clear consensus on enzyme activity cut-off and other characteristics of the biotinidase deficiency screening test has not been established. Several aspects of test performance remain uncertain.'	Shortly after the literature search was carried out, the American College of Medical Genetics and Genomics published their updated Standards and Guidelines on laboratory diagnosis of biotinidase deficiency (https://www.nature.com/articles/gim201784) which addresses many of these issues. We note that several of the journal articles considered in the review discuss screening tests and reference thresholds and

		how, since these are based on a percentage of normal activity, they must be adapted to suit the local population. The evidence review team dismisses these as of uncertain applicability to the UK without explanation or discussion. By this standard any evidence would be of limited applicability to the UK until a proper pilot screening programme is carried out here. The review recognises that while half of false positives may be explained by prematurity, the others could be due to mishandling of samples and possible exposure to excessive heat or humidity. The ACMG Standards and Guidelines recommend that screen positives be confirmed by testing the enzyme activity in the parents, as well as discussing the option of genotyping, since for most of the pathogenic variants so far identified it is possible to state whether they are associated with profound or partial deficiency. We suggest the UK NSC consider these newer approaches to confirmatory testing which were not addressed in the evidence review.

p40	'This was a rapid evidence review process. Searching was limited to 3 bibliographic databases and did not include grey literature sources.'	The current methodology used by the UKNSC when making decisions about whether the benefits of introducing a newborn screening programme for a condition outweighs the risks places a premium on peer reviewed literature to the exclusion of all other forms of evidence. Relying solely on peer reviewed literature excludes the direct contribution of the patient voice to the process. While information from clinicians and patients may not be published, it represents the most recent and relevant information on a condition coming from those that either directly manage or are affected by the condition today. Not taking this type of information into account during a review of the evidence is out of step both with other institutions with

		responsibility for decisions regarding public health, such as NHS England, the National Institute for Health and Care Excellence and the European Medicines Agency, and with accepted practice in dealing with rare disease issues. All three of these agencies, and more, have accepted that evidence will always be scarce in the area of rare disease, and is likely to be of weaker statistical significance than that expected from more common conditions. They have resolved to fill this gap by accepting qualitative evidence from the patient community. We believe the UK NSC should take steps to do the same. The last four conditions that were added to the newborn screening programme (homocystinuria, maple syrup urine disease, glutaric aciduria type 1 and isovaleric acidaemia) were included following a pilot where these conditions were screened for routinely at birth in a small number of centres. Without the evidence gathered by such pilots, it would not have been possible for the UK NSC to satisfy their evidence requirements and positively recommend newborn screening for these conditions. It is now proposed that a pilot also take place for SCID, even though that evidence base is much more advanced and sufficient to warrant implementation of a full screening programme. We would encourage the UK NSC to consider establishing a similar pilot for biotinidase deficiency and related conditions in order to address this. As biotinidase deficiency is already part of newborn screening programmes in the US and several European countries, it is likely that the pilots would be successful and provide the UK NSC with sufficient evidence to support the introduction of newborn screening for biotinidase deficiency in the UK.

Please return to the Evidence Team at screening.evidence@nhs.net **by Tuesday 9th January 2018.**