UK National Screening Committee

Newborn screening for mitochondrial trifunctional protein (MTP) disorders, including long-chain 3-hydroxyacyl-CoA dehydrogenase (LCHAD) deficiency

28 June 2019

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 LCHAD/MTP deficiency meets the UK NSC criteria for a systematic population screening programme.

Current recommendation

2. In April 2014 the UK NSC recommended extending newborn bloodspot screening to include screening for maple syrup urine disease (MSUD), homocystinuria (HCU), glutaric acidaemia type 1 (GA1) and isovaleric acidaemia (IVA) but not to recommend screening for long-chain 3-hydroxyacyl-CoA dehydrogenase deficiency (LCHADD). The Committee agreed that LCHADD screening should not be implemented nationally because:

    - No cases of asymptomatic LCHADD were identified by screening during the Expanded Newborn Screening Study between July 2012 and July 2013. If clinically presenting cases were removed from the test performance calculations, the PPV would have been 0% over the course of the evaluation.

Evidence Summary

3. The 2018 evidence summary was undertaken by the University of Warwick, in accordance with the triennial review process: https://legacyscreening.phe.org.uk/lchadd

4. The 2018 evidence summary addresses questions relating to birth prevalence of LCHAD/MTP deficiency in the UK, the genotype-phenotype associations in LCHAD/MTP deficiency patients including their clinical prognosis, the accuracy of acylcarnitines measurement in dried blood spots (DBS) using tandem mass-spectrometry (TMS) for LCHAD/MTP deficiency

screening, and whether early treatment with dietary management following screening provides better long-term outcomes than later treatment after the presentation of symptoms. The review aims to assess whether the volume and direction of the evidence produced since the 2013 Expanded Newborn Screening Study is sufficient to reconsider the current UK NSC recommendation on screening for LCHADD.

5. The conclusion of the 2018 evidence summary is that the current recommendation, that whole population screening for LCHADD should not be introduced in the UK, should be retained. This is for the following reasons:

    - There were no studies from the UK on the number of people born with LCHAD/MTP deficiency. Two European studies found that between 0.72 and 0.79 per 100,000 newborns are affected. This is consistent with the results from the last systematic review on the birth prevalence of five inherited metabolic diseases including LCHAD, which estimated approximately 0.67 per 100,000 births. **This element of Criterion 1 met**

    - Evidence from 27 studies identified 95 different genotypes and 76 possible phenotypes. The specific presentation and pathway of the disease appears to vary greatly by individual and could be influenced by a number of other factors such as dietary compliance or the influence of other health problems. Individuals with MTP deficiency may be more likely to be very ill from birth and individuals with LCHAD deficiency may be more likely to present later in infancy but firm conclusions could not be drawn. **This element of Criterion 1 not met**

    - The evidence on the screening test indicates that false positives are common and sensitivity, specificity, and negative predictive values could not be established due to a lack of systematic follow up of newborns who screened negative. Moreover, the included studies used a wide range of markers and thresholds. Test accuracy estimates differ greatly by study, with some suggesting good accuracy albeit on small numbers. However, the results are not presented by marker, so it was not possible to combine data from different studies or determine which combination of markers and thresholds may yield good accuracy. There was no evidence to indicate whether the screening test can distinguish between milder and more severe types. **Criterion 4 not met**

- There is some evidence to suggest that people diagnosed before they have symptoms of LCHAD/MTP deficiency might have better outcomes than those treated once symptoms appear. However, these studies are small and there are biases in all the comparisons, which are mostly in the direction of overestimating any potential benefit of early detection, and the majority of studies are too small to show any statistically significant differences. **Criterion 9 and 11 not met**

Consultation

6. A three-month consultation was hosted on the UK NSC website. Direct emails were sent to 16 stakeholder organisations. **Annex A**

7. Comments were received from the following five stakeholders:

   i. British Inherited Metabolic Disease Group
   ii. Genetic Alliance UK
   iii. Royal College of Midwives
   iv. Royal College of Paediatrics and Child Health
   v. Sheffield Children's Hospital

   (See **Annex B** for comments)

8. The public consultation closed on 17 January 2019. Discussions at the 22 January 2019 FMCH meeting led to further internal work being carried out, with the evidence summary being shared with the Inherited Metabolic Disease (IMD) Screening Advisory Board to comment upon the findings. The additional IMD group's comments are attached after consultation comment no.5. (See **Annex B** for comments)

9. One stakeholder fully supported the review's conclusions

10. The other stakeholders, whilst acknowledging the thoroughness of the review, ultimately disagreed with its conclusion as their overarching opinion is that LCHADD should be added to the newborn bloodspot screening programme. Common themes were:

    - The incidence of isolated LCHADD during the period of the 2013 screening pilot was unusually low and a longer pilot period would have been likely to demonstrate higher number of cases than what was observed. Stakeholders stated that the metabolic centres that manage these conditions have gone on to see clinical cases

presenting with severe symptoms which could have been prevented by newborn screening.

Response: During the 2013 pilot, the expected birth prevalence of LCHADD/MTP deficiency was 1:218,564 with 5 expected screen positive cases (2 true positives and 3 false positives). The pilot reported the following from the screening area:

- 1 screen positive case being treated at the point of testing and before return of the test result
- 1 case diagnosed through cascade testing
- 1 case incorrectly screened negative
- 2 cases which died before screening on day 5

This rate (5:437,000) is consistent with expectations in the pilot screening area. If the two cases which died before screening were MTP cases and were excluded, the rate of 3:437,000 would still be in keeping with the expected rate of isolated LCHADD (2:437,128). Nationally, a total of 7 cases were reported. Again, this is consistent with expectations.

The limitations of the pilot screening strategy might not be primarily related to an unusually low incidence. It might be more properly related to the combination of test cut-off, timing of the test at 5 days, early presentation and mortality, and detection through currently available routes.

- The 2013 pilot did not show any disbenefit in the shape of unacceptable false positive rates. Stakeholders noted that this review suggests that reported studies in the literature have a high false positive rate. However, consultees consider this conclusion to be inapplicable to a UK screening setting because studies included in the review often used low cut-off values and because testing usually occurred before day 5.

  Response: The reviewers have updated the report to clarify that, even removing the non-comparable studies, there are inconsistencies with marker type and thresholds used across studies. Therefore, it is not possible to combine data from different studies or determine which combination of markers and thresholds may yield good accuracy. They also made it clearer in the text that even the UK study has

limitations, as the single true positive case had already been recognised clinically, thus the positive screening result did not offer any additional benefit in that instance. Another case was identified clinically with LCHADD because the screening result was below the cut-off value and, as a consequence, the threshold was re-evaluated and lowered. The reported PPV was 33%; if the clinically presenting cases were removed from the test performance calculations, the PPV would be 0% over the course of the evaluation. The reviewers suggest collaboration between researchers to report scores on a range of relevant markers for both cases of LCHAD, cases of MTP, and in the unaffected population using consistent units.

- The phenotypic expression of these disorders can depend upon exposure to environmental factors, such as infections, fasting, environmental temperature, physical activity. According to some stakeholders, even though the review refers to 76 different phenotypes, this is not seen in clinical practice. Hence the clinical and molecular heterogeneity, especially in the MTP group, should not be a bar to screen for the combined conditions (LCHADD and MTP deficiency), particularly since infants with isolated LCHADD represent the majority of patients and the phenotype associated with the common homozygous G1528C mutation is considered to be well established.

  Response: the reviewers noted that 157 out of 301 patients had the G1528C mutation, with the other genotypes distributed among the remaining cases. Thirty-eight out of 49 patients presented with the infant hepatic form. However, there was still a wide variety of presentations (see Appendix 5, table 25 of the evidence summary document). This variation can indeed be linked to environmental factors and because of this, it is still difficult to predict how each case will present.

- While the reviewed studies were too small to reach statistical significance and at high risk of bias, there was some evidence suggesting benefit from early treatment. Stakeholders stated that this should be a worthwhile reason to screen. Stakeholders suggest that the inclusion of LCHADD in the newborn bloodspot screening panel would not lead to an increase in the cost of the laboratory tests and it would align the UK with other countries in the rest of the European Union where screening for LCHADD is available.

Response: The review identified a trend towards benefit from pre-symptomatic treatment. However, there was uncertainty about it as the studies included in the review were too small to reach statistical significance and the risk of bias was high. Additionally, the 2013 pilot shows the potential limitations of screening, given early presentation of some cases (i.e. before day 5) and sibling detection of other cases. Therefore, the benefits of pre-symptomatic treatment may not be dependent on screen detection in a significant proportion of LCHADD cases. The economic evaluation undertaken by the School of Health and Related Research (ScHARR), University of Sheffield in 2013 concluded that screening for LCHADD is predicted to be potentially cost saving when compared to a no screening scenario. However, it is worth noting that the model did not include the cost of managing sequelae of encephalopathic crises and that the marginal QALY gained compared to no screening (0.000114) was extremely small and of the order of hours[1]. The authors themselves noted that the model's conclusion is subject to uncertainties surrounding the fact that the screening test cannot distinguish between LCHADD and generic MTP deficiency, and to uncertainties relating to treatments and outcomes between LCHADD and the range of clinical presentations characterising MTP deficiency, which complicates the screening and diagnostic pathway as well as any potential benefit from screening.

- There were concerns about the methodology used by the review and that, for screening programmes on rare conditions, different standards should be used in their evaluation of the evidence, that the methodology used by the UK NSC is limiting and that the UK NSC's decision should not be based on an analysis of published evidence

  Response: The points made about the difficulty of generating a high quality evidence base in rare diseases are well made. This is acknowledged in the application of the UK NSC criteria. For example, the criterion relating to the need for RCT evidence is not rigorously applied in evaluations of rare diseases. Moreover, the patient voice is considered in UK NSC decision-making. For example, the identification of SCID and Tyrosinaemia type 1 as priorities for consideration as candidate screening

[1] Note: A year of life lived in perfect health is worth 1 QALY. Death is assigned a value of 0 QALYs

programmes was shaped by stakeholder views. This took place through an interaction between review of published evidence and stakeholder engagement. This approach should not be abandoned. Moreover, depending on the nature of specific research questions, published peer-reviewed qualitative evidence has been and would continue to be considered. As for other rare conditions the UK NSC review process was followed in this review. The evidence review process has been developed following the recommendation by the parliamentary Science and Technology Committee in 2014 and it is published on the GOV.UK webpage and is available to the public: https://www.gov.uk/government/publications/uk-nsc-evidence-review-process/uk-nsc-evidence-review-process

UK NSC evidence summaries are developed using rapid review methodologies. They provide an evaluation of the volume and direction of the literature on a single question or set of questions on a given screening topic. They consider whether there have been any significant developments in the evidence base relating to key issues identified from the previous review. Their function is to make a judgement on whether the current recommendation should be retained and whether further work is required. Further work on LCHADD was recommended in the review.

- There was some confusion regarding the initial title of the document "Screening for mitochondrial trifunctional protein disorders, including long-chain 3-hydroxyacylCoA dehydrogenase deficiency". One stakeholder expressed some concerns that this title meant a broadening of scope of the review, which in turn would make it less likely for a screening programme to be recommended because the programme would be retargeted at a population less likely to benefit (infants with MTP).

  Response: The use of the current title is consistent with the pilot report which referred to 'LCHADD/MTP deficiency' because acylcarnitine tests cannot distinguish between the two. Therefore, the title appeared to be a more appropriate way to describe the topic. Going forward, future reviews can focus on screening to reduce adverse outcomes from LCHADD and discuss MTP disorders as a small section linked to incidental findings of the test. This is because MTP will continue to be an output of screening for LCHADD and this fact needs to be taken into account in any evaluation of screening for LCHADD.

Recommendation

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

    Systematic population screening for LCHADD/MTP deficiency is not recommended as a population screening programme 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 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	**Met for Question 1 and not met for Question 2**
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 shouldn't be further considered.	**Not Met**
The Screening Programme	
11. There should be evidence from high quality randomised controlled trials that the screening programme is effective in reducing mortality or morbidity. Where screening is aimed solely at providing information to allow the person being screened to make an "informed choice" (such as Down's syndrome or cystic fibrosis carrier screening), there must be evidence from high quality trials that the test accurately measures risk. The information that is provided about the test and its outcome must be of value and readily understood by the individual being screened.	**Not Met**

UK National Screening Committee

List of organisations contacted

Annex A

1. British Association of Perinatal Medicine
2. British Inherited Metabolic Disease Group
3. Clinical Genetics Society
4. Faculty of Public Health
5. Genetic Alliance UK
6. Institute of Child Health
7. Metabolic Support UK
8. MetBio
9. Royal College of General Practitioners
10. Royal College of Midwives
11. Royal College of Paediatrics and Child Health
12. Royal College of Physicians
13. Royal College of Physicians and Surgeons of Glasgow
14. Royal College of Physicians of Edinburgh
15. Save Babies Through Screening Foundation UK
16. UK Newborn Screening Laboratories Network

Annex B

Newborn screening for MTP disorders, including LCHADD

Consultation comments

1. British Inherited Metabolic Disease Group

Name:	Saikat Santra /Julian Raiman (Q4) / Roshni Vara	**Email address:**	xxxx xxxx
Organisation (if appropriate):	British Inherited Metabolic Disease Group / BIMDG		
Role:	**Member**		

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.*
Key question 1 Page 9	What is the birth prevalence of LCHAD/MTP deficiency in the UK? (UK NSC criterion 1: The epidemiology, incidence, prevalence and natural history of the condition should be understood)	The prevalence of LCHAD deficiency in the Western population is 0.41 per 100,000 (Moorthie et al., J Inherit Metab Dis, 2014; 37: 889-898). The estimated annual incidence of new cases is 3 in the UK. The natural history of the condition is outlined in the response to question 2 below.

Key Question 2 Page 9	What are the genotype-phenotype associations in LCHAD/MTP deficiency patients, including their clinical prognosis?	The review mentions but does not fully appreciate the difference between LCHADD and MTPD patients. Practitioners in the field are well aware that isolated LCHADD is by a large margin the commoner condition and the vast majority of those patients will be homozygous for the c.1528G>C mutation. This is well established also in the literature. This "common" genotype is well described in the literature and we cannot accept that the genotype-phenotype association is not established for this particular genotype which should, statistically, represent the majority of patients.
		It is true there is more clinical and molecular heterogeneity in the MTPD subgroup but as these generally represent the minority of patients, and this heterogeneity applies equally to the other conditions included in the expanded NBS programme (such as MSUD and IVA), we do not feel that this should be a bar to screening for the combined conditions. Patients identified from screening will benefit provided they were not already diagnosed by the time the screening result was available. If they were already diagnosed, then no dysbenefit will have occurred.
		As was raised by many respondents to the original consultation the majority of (historical) surviving non-screened patients with LCHADD/MTP present acutely unwell, sometimes requiring intensive care and indeed following the cessation of the screening pilot the majority of the UK clinical centres managing these conditions have continued to see patients presenting in this way whose initial severe illness could have been prevented by newborn screening. Indeed, unanimously treating clinical centres feel that the incidence of isolated LCHADD during the period of screening was unusually low, which of course is

		possible when dealing with rare diseases, and a longer pilot period would have been likely to demonstrate considerably further benefit than what was observed.
Subquestion 2 Page 10	What is the incidence of asymptomatic and/or milder phenotype in the neonatal period?	This is a question that is intrinsically difficult to answer with reference to published literature. Published literature, including the single study that was cited, will necessarily come from centres which screen and all such centres will treat all patients identified, because established clinical opinion is that all patients (including attenuated ones) benefit from treatment. Therefore, the natural history of the condition in those patients will necessarily be changed. The cited study says that in 1.2 million screened infants, 9 cases were identified and that these were 7 isolated LCHADD and 2 MTPD. This in itself substantiates the comments made above that 1) The incidence in the UK pilot period was unusually low – in that pilot 800,000 infants were screened and 3 cases were identified which is half the incidence expected from published studies 2) The expectation is that the majority of patients will have isolated LCHADD, of which the majority will be of the common genotype with a proven natural history The cited study states that only 1 of those 9 patients was asymptomatic at the age of 3 implying that all the other 8 patients were truly affected (and by extension would have been more affected were it not for screening). However even the single asymptomatic case may have been symptomatic were it not for the early treatment afforded by screening.
Qn 4 Key question 4: Does early treatment with dietary	General comment	While these responses are based on addressing the specific findings of qn 4, they also build on the document “UK National Screening Committee Expanded Blood Spot Screening

management following screening provide better long-term outcomes than later treatment after the presentation of symptoms?		Consultation comments March 2014" Where the near unanimous response is that the pilot study for LCHADD screening should be continued and/or LCHADD should be added to the other metabolic conditions that are screened for in the newborn period. This review adds nothing to change that overarching opinion. Specific comments relating to key question 4 are summarized below.
Background to LCHADD exclusion from NBS following previous pilot study	General comment	One reason for the exclusion of LCHAD from NBS, was the lack of cases in the one year pilot study. However, the allied reports accompanying this acknowledge "This is a reflection of the fact that these conditions are very rare events; consequently, the expected number of cases is very small. In reality, the number of cases seen annually is likely to fluctuate." In the consultation document to the 2013 report, it is widely stated that the pilot study was too short to reflect a true picture of LCHADD cases in the UK and should have been extended. To highlight this, in the West Midlands since 2015-2018, there have been 4 cases of LCHADD diagnosed (all homozygous for the common mutation). While one of these presented at day 5 and would not have been picked up on time by NBS, the remaining 3 certainly would have – becoming unwell later in infancy with significant illness at presentation that could have been avoided by an earlier diagnosis.
81 Summary of Findings Relevant to Criterion 9 and criterion 11: Not met*	there are biases in all of the comparisons, which are mostly in the direction of overestimating any potential benefit of early detection, and the majority of studies are too small to show any statistically significant differences.	Sample size is an inherent problem in rare disease research, to be able to generate a sample of sufficient size would require a study of a significant duration, which in itself would be unfeasible. In the context of Criterion 11 and need for high quality randomised controlled trials, for LCHADD, would this not

	Criterion 11: There should be evidence from high quality randomised controlled trials that the screening programme is effective in reducing mortality or morbidity)	require that screen positive children be randomised either to standard therapy – ie restricted fat diet, emergency regimens for intercurrent illness and complication surveillance ie cardiac/ophthalmic surveillance, vs no intervention for screen positive control until they were to become unwell – which would be unethical?
64-66	Analysis of the evidence	As the review authors state, while the reviewed studies were too small to reach statistical significance, the overall trend of every clinical feature, suggested an overwhelming trend towards the benefit from early treatment. In its bluntest form if screening can reduce risk of death/significant morbidity of the first presenting illness should this in itself not be a worthwhile reason to screen.
85	The cost effectiveness of screening for LCHAD/MTP. Given that the treatment is dietary management which could be relatively cheap, this may be an important factor to consider.	Using the example of the three cases in the West Midlands that presented after the typical screening timeline in the perinatal period, all required admission to hospital and a spectrum of support at the time of their first presentation which at the most extreme included emergency retrieval from a district general hospital to a regional centre, a prolonged period of intensive care and a total length of stay up to a month. In another case the patient had several admissions to hospital prior to the LCHADD diagnosis with allied clinical symptoms. All of these would have been significantly impacted by a diagnosis in the newborn period and proactive management. The cost of these interventions was likely in excess of the additional whole cost of screening in the region over that time period and would only be amplified when extrapolated at national level.

		The screening laboratories state ‘’The inclusion of LCHADD in the panel of disorders does not increase the cost of the laboratory tests as the internal standards required to test for these conditions are already included in the test kits used to screen for the other disorders.” The lack of recurrent cost/lack of dysbenefit of LCHADD screening is widely reported in the March 2014 comments document. Clearly this factor doesn’t include the extra morbidity these children suffered due to the severity of their illness at presentation. As such we would recommend the UKNSC to reconsider their conclusions and believe the basis of this decision should not be based on an analysis of published literature.

2. Genetic Alliance UK

Name:	Jayne Spink	**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 200 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:	Chief Executive		

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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	Title of review	The page on the UK NSC website for this consultation is titled 'Long-Chain 3-Hydroxyacyl CoA Dehydrogenase Deficiency', and the previous consideration of a possible screening programme has been focussed primarily on this condition, though with some mention of mitochondrial trifunctional protein conditions more generally as these are also likely to be detected by the proposed screening test. However, the most recent external review was titled 'Screening for mitochondrial trifunctional protein disorders, including long-chain 3-hydroxyacylCoA dehydrogenase deficiency'. It is not clear from any of the documents available what the reason for this shift is, as it was not suggested in the previous evidence review or consultation. We are concerned about this shift in scope from true LCHAD deficiency to MTP disorders including LCHAD deficiency. This is because, as the external review recognises, a proportion of infants with MTP disorders will be detected clinically prior to screening, and these early presenting patients also respond less well to treatment, reducing their potential to benefit from early detection through screening. Those most likely to benefit from early detection are babies with true LCHAD deficiency and a subset of babies with MTP conditions. Thus this broadening of scope makes it less likely the screening programme will be recommended by retargeting it at a population less likely to benefit. Unless the UKNSC is prepared to examine subgroups within this broadened scope, with the aim of finding a definition for a subgroup where screening is appropriate, then this expansion of scope is a negative step, and we would like to understand the thinking behind it.

p8-9	'A rapid review approach was undertaken for key questions 1 and 2. Full systematic reviews were undertaken for key questions 3 and 4. Two searches were undertaken: a broad search for questions 1, 2 and 4 and a more targeted search for question 3. Key question 1 included studies published since 2013 to build upon understanding from a previous review, and key question 2 was limited to studies published since 2000. No date limit was applied to key questions 3 or 4.'	We question the decision to use different methodology and inclusion criteria for the different questions of the review, rather than maintaining consistency. The limitations applied to key question 1, of only considering evidence since the last review further confounds the chances of a finding in favour of screening given that the scope has broadened since that last review. Previous evidence is therefore only relevant to a subset of the condition being considered in this review. This is therefore an inappropriate choice.
p17 (text is also in both the summary sections)	'The recommendation from the review was that additional focussed training should be provided to neonatal clinicians to raise awareness around the symptoms of LCHAD and MTP deficiencies as clinical management was deemed more effective than systematic population screening'	The reference cited for this recommendation is the previous UK NSC recommendation document which is not available anywhere on the UK NSC website. We question where this suggestion that clinical management would be more effective than screening comes from, as it was not suggested in any of the 2014 evidence review documents nor the compilation of consultation responses. This proposal for additional training to improve clinical management was not suggested or supported by any of the clinical experts who responded to the 2014 consultation.
p18	'Question 2. What are the genotype-phenotype associations in LCHAD/MTP deficiency patients, including their clinical prognosis? Sub-question: What is the incidence of asymptomatic and/or milder phenotype in the neonatal period?'	We note that in requiring this unrealistically high level of epidemiological understanding, LCHADD/MTP is being held to a higher standard than was required, both of this condition and of the others being considered, at the time of the evaluation of the Expanded Newborn Bloodspot pilot.
p19-20	'One systematic literature search was undertaken to cover review questions 1 (incidence), 2 (genotype/phenotype association) and 4 (treatment). A separate literature search was undertaken for key	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

	question 3 (screening test). Searches were conducted in MEDLINE (Ovid), EMBASE (Ovid), MEDLINE In-Process & Other Non-Indexed Citations (Ovid), Web of Science (SCI-EXPANDED, SSCI and ESCI) and Cochrane Library (Cochrane reviews, other reviews, methods studies and technology assessments).'	condition coming from those that either directly manage or are affected by the condition today. NHS England, the National Institute for Health and Care Excellence and the European Medicines Agency all have facility to consider evidence from patients and clinicians that is not sourced from peer reviewed literature. These agencies 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.
p50	'The results of this review support these findings. With no screening in place, no further reviews are likely to provide this information. However, information may be available from UK databases.'	We welcome the recognition from the external review team that only a screening programme is likely to provide the level of evidence on epidemiology being required by the UK NSC. However, we question their suggestion that detailed information on prevalence may be available from UK databases. The nature of the data the reviewers think may be being collected is described on page 14: '*Given the rarity of the diseases, a retrospective review of medical records identifying all people in the UK with LCHAD/MTP deficiency and their genotype, which prospectively follows their outcomes over time may be the most feasible approach to understanding genotype phenotype associations and the relative benefits of early versus late treatment.*' It is highly unlikely data is being collected in the NHS at present with sufficient granularity to provide a more specific answer to question one than has already been established from the ENBS pilot and the literature. Even were such data being collected, it would be unlikely to meet the UK NSC's evidence requirements,

		as it would be unpublished data, and only contact information about patients who had been accurately diagnosed clinically.
p85	'Whilst undertaking the review, the reviewers noticed some key papers for the test accuracy question were not being picked up by the search strategy. Many of the studies were coded using the specific term "inborn errors of metabolism" with no reference to specific disorders. To ensure no studies were missed a new search was undertaken which included this key term and additional screening specific search terms. This means that the test accuracy search may include more recent papers than the search for the other 3 question.'	We are concerned that due to this flawed review strategy, other relevant papers may have been missed.

UK National Screening Committee

3. Royal College of Midwives

Name:	Rachel Scanlan	**Email address:**	xxxx xxxx
Organisation (if appropriate):	Royal College of Midwives		
Role:	**Practice and Standards Advisor**		

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Yes X☐ 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 comment	RCM supports the UK National Screening Committee external review findings that there is not enough high quality evidence to recommend adding this to the newborn blood spot screening programme.

UK National Screening Committee

4. Royal College of Paediatrics and Child Health

Name:	Comments on behalf of Dr Saikat Santra and Eugene Strehle	**Email address:**	xxxx xxxx
Organisation (if appropriate):	Royal College of Paediatrics and Child Health		
Role:	Paediatric Inherited Metabolic Medicine CSAC Chair		

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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.*
		This review was arranged following the original pilot of screening for this condition. That pilot showed no disbenefit from screening but the incidence, particularly of LCHADD, was unusually low and a decision was taken not to include it in the roll out. Respondents from across the field of Paediatric Inherited Metabolic Medicine commented at the time that they felt that this was the wrong decision and their comments remain as true today.
	In response to the 4 key questions that the review looks at:	***1. What is the birth prevalence of LCHAD/MTP deficiency in the UK?*** The birth prevalence of LCHADD/MTPD in the UK is not significantly different from that recorded in Western Europe and which is well published as being in the region of 1:140,000. This is because the majority of patients are homozygous for a

		common mutation prevalent in Caucasian patients. This is similar to many other conditions in the current screening portfolio. That this prevalence was not detected in the period of the original pilot is unusual but not completely unexpected with very rare diseases. All centres that manage these conditions have gone on to see clinical cases presenting with severe symptoms which could have been prevented by newborn screening. In the respondent's centre, they have seen 4 cases of isolated LCHADD in the two years since the end of the screening pilot (of whom 3 would have clearly benefited from screening including the avoidance of 1 PICU and 1 HDU admission) whereas there were no cases seen during the pilot. This pattern has been replicated across the country. The British Inherited Metabolic Diseases Group is attempting to obtain this data from all the UK centres and include them in their reply to this consultation.
	In response to the 4 key questions that the review looks at:	***2. What are the genotype-phenotype associations in LCHAD/MTP deficiency patients, including their clinical prognosis?*** The review mentions but does not fully appreciate the difference between LCHADD and MTPD patients. Practitioners in the field are well aware that isolated LCHADD is by a large margin the most common condition and the vast majority of those patients will be homozygous for the c.1528G>C mutation. This is also well established in the literature. This "common" genotype is well described in the literature and we cannot accept that the genotype-phenotype association is not established for this particular genotype which should, statistically, represent the majority of patients.

		There is more clinical and molecular heterogeneity in the MTPD subgroup but as these generally represent the minority of patients, and this heterogeneity applies equally to the other conditions included in the expanded NBS programme (such as MSUD and IVA), we do not feel that this should be a bar to screening for the combined conditions. Patients identified from screening will benefit provided they were not already diagnosed by the time the screening result was available. If they were already diagnosed, then no disbenefit will have occurred. As was raised by many respondents to the original consultation the majority of (historical) surviving non-screened patients with LCHADD/MTP present acutely unwell, sometimes requiring intensive care and indeed following the cessation of the screening pilot the majority of the UK clinical centres managing these conditions have continued to see patients presenting in this way whose initial severe illness could have been prevented by newborn screening. Indeed, unanimously treating clinical centres feel that the incidence of isolated LCHADD during the period of screening was unusually low, which of course is possible when dealing with rare diseases, and a longer pilot period would have been likely to demonstrate considerably further benefit than what was observed.
	In response to the 4 key questions that the review looks at:	***Sub question 2: What is the incidence of asymptomatic and/or milder phenotype in the neonatal period?*** This is a question that is intrinsically difficult to answer with reference to published literature. Published literature, including the single study that was cited, will necessarily come from centres which screen and all such centres will treat all patients

		identified, because established clinical opinion is that all patients (including attenuated ones) benefit from treatment. Therefore, the natural history of the condition in those patients will necessarily be changed. The cited study says that in 1.2 million screened infants, 9 cases were identified and that these were 7 isolated LCHADD and 2 MTPD. This in itself substantiates the comments made above that 1) The incidence in the UK pilot period was unusually low – in that pilot 800,000 infants were screened and 3 cases were identified which is half the incidence expected from published studies 2) The expectation is that the majority of patients will have isolated LCHADD, of which the majority will be of the common genotype with a proven natural history The cited study states that only 1 of those 9 patients was asymptomatic at the age of 3 implying that all the other 8 patients were truly affected (and by extension would have been more affected were it not for screening). However, even the single asymptomatic case may have been symptomatic were it not for the early treatment afforded by screening.
	In response to the 4 key questions that the review looks at:	***3. What is the test accuracy (sensitivity, specificity, and predictive values applicable to UK prevalence) of acylcarnitines measurement in dried blood spots (DBS) using TMS for LCHAD/MTP deficiency screening?*** The response from Newborn screening laboratories to the original conclusion was overwhelming that the test accuracy was good for this condition and in keeping with many other conditions on the screening portfolio. The following quote is representative of this view (and from the Manchester laboratory):

		"The decision not to include LCHADD/MTPD seemed to be largely on the basis that a benefit of screening (in the shape of a patient identified through screening who was not already diagnosed or dead prior to screening) was not shown during the 1-year term of the pilot project. However, the pilot project was intended to demonstrate that it was possible and practical to undertake expanded screening, it was not set up to prove benefit. When dealing with such rare disorders 1 year is far too short a period of time in which to reach such conclusions. It will be entirely due to chance that a patient with classic LCHADD (with common 1528G>C mutation), who typically do not present in the neonatal period but often present in a critical state at a few months of age, did not occur during the 1-year period. All metabolic centres have had experience of diagnosing these patients and we have no doubt that they would benefit from screening. It is unfortunate that the picture is confused by the severe MTP type patients, whom it is very hard to demonstrate could ever benefit from screening even if the day of screening was brought forward. However, this should not be a reason not to screen, it should be done for the sake of the milder MTP and classic LCHADD patients, especially since the ***pilot did not show any disbenefit in the shape of unacceptable false positive rates."*** The original pilot did not show unacceptable false positive rates, in fact it showed an unusually low number of true positive rates. This review makes the claim that reported studies in the literature have a "high false positive rate" but this is **NOT APPLICABLE** to the UK where screening is currently done at day 5 rather than early. Our pilot clearly showed that false positives

		are NOT an issue with this test. A longer pilot, or indeed a recommendation to implement screening, would demonstrate considerable benefit over a number of years. In addition, the cost of expanded screening varies very little with the number of disorders being screened for, therefore any saving made by not screening for LCHADD would be absolutely marginal, so long as false positives are minimal. Therefore, there would need to be a very concrete reason to continue to exclude LCHADD from the panel that was unrelated to cost. Indeed, their inclusion could help to make the whole programme more cost effective by increasing the number of pickups for the same amount of money spent.
	In response to the 4 key questions that the review looks at:	***4. Does early treatment with dietary management following screening provide better long-term outcomes than later treatment after the presentation of symptoms?*** The clinical centres managing these patients, and European guidelines and consensus, agree that early diagnosis clearly leads to positive outcomes for patients with isolated LCHADD and attenuated MTPD. Severe MTPD patients are likely to present (and indeed succumb) before screening but this is seen in MCADD also and is not in itself a reason not to screen. The following are all paediatric clinical outcomes that can be expected with early institution of dietary management: • Prevention of Critical Care Unit Stays • Resolution of cardiomyopathy and prevention of cardiomyopathy related complications

		• Prevention of and shortening of rhabdomyolysis episodes • Prevention of hypoglycaemic episodes • Prevention of death (albeit in a small number of patients) • Prevention of avoidable neurological disability due to a critical initial decompensation There are long term outcomes such as retinopathy and neuropathy which appear to progress despite dietary therapy but these are rarely clinical problems in childhood and not in themselves acceptable reasons not to screen.
	Scope	The original scope did not really take into account the clinical opinion that clinical centres feel that the incidence in the period of the pilot was unusually low and this is not reflected in the review. Clinical centres feel that the decision not to continue screening was taken purely on the basis of prevalence and not due to issues with the test and this appears to be flawed.
	Equality issues	Equality across the rest of the EU remains a significant issue as these are conditions which have been screened for on the continent for a long time.
		The BIMDG and ICH are compiling a joint response to this consultation which the CSAC unanimously supports and has contributed to.

UK National Screening Committee

5. Sheffield Children's Hospital

Name:	xxxx xxxx	**Email address:**	xxxx xxxx
Organisation (if appropriate):	Sheffield Children's Hospital		
Role:	xxxx xxxx		

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

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.*
	Please see attached document for comments	

Newborn screening for long chain 3-hydroxyacyl-CoA dehydrogenase and mitochondrial trifunctional protein deficiencies using acylcarnitines measurement in dried blood spots

Thank you for the consultation document. We do have some significant disagreement with the final conclusions however. Overall we would congratulate the review team on a thorough review of the available literature. We do understand also that analysis & conclusions were restricted by inclusion/exclusion criteria /QUADAS-2 & lack of available surveillance data on follow up. Reading through the report there are a number of observations to comment upon. Firstly with reference to manuscript 1 [published 2002] which sites evidence that 38% of affected babies die within 3 months of diagnosis - the important caveat on this "good" manuscript is that it reported data on many of the earlier patients to be diagnosed with LCHAD/MTP when knowledge & treatment regimens for this condition were not well developed and it is unfortunate that it was not possible to find more contemporary data on screened patients as we feel it would almost certainly be significantly different now with regards to mortality & morbidity. There is reference to the study [in Spanish] of Einoder-Moreno et al who reviewed 6 manuscripts on LCHAD/MTP screening & concluded

that the sensitivity, specificity & negative predictive value for LCHAD/MTP was close to 100% & PPV ranged from 9-100%. It is apparent that this latter study had missed these 3 papers which were additionally evaluatd in this review. These 3 papers are referenced (2, 6, 7). Manuscript (Zytkovicz 2001) was a relatively small USA study (164,000) which found no cases (US incidence of LCHAD you cite as 1:363,738) & 5 false positives (PPV = 0). However the weakness of this latter study is that they only looked at 16(OH) which would be a significant weakness of protocol. Manuscript 6 was a large German study of >1,000,000 with 6 TP cases & no FP (PPV = 100%). Manuscript 7 was another small (Spanish) study 210,000 with 2 TP & no FP, PPV = 100%. So addition of these 3 studies would (all other considerations being equal) tend to strengthen the conclusions of Einoder-Moreno et al. This review evaluated 10 manuscripts which fitted the eligibility criteria. It is worth noting here that the common LCHAD mutation appears to be predominantly of European/Caucasian distribution. Of note, studies 2, 3, 4 & 8 - three European studies, one USA, - 2,037824 screened, 13 TP no FP, PPV 100%. Manuscript 5 a large German study (1,200,000) found 9TP, 10FP, PPV 47%. However it is highly likely that the screening cut offs set for this study are significantly too low (i.e. C16(OH) >0.08, C18:1(OH) >0.06) and that the relatively increased FP rate is at least partly due to this. Manuscript 9 is a very small Slovenian study (10,048) with no cases & 8 FP but again the cut offs (0.009-0.042) & numbers screened are clearly too low. The two Asian studies manuscript 10 & 11 where the incidence of LCHAD/MTP would look to be very much lower, found no cases. Manuscript 10 was a tiny study (2,440) with 2 FP but with no clear information on the cut off used - a significant problem for objective evaluation. While manuscript 11 covered a bigger study (still only 100,077), it had a high FP rate but with a clearly unrealistic cut off set at >0.03 - >0.05. The UK pilot study (436,969) found 1 TP & 2 FP, PPV = 33%.

The conclusions of the review indicate that currently there are significant concerns regarding the high number of false positives. This we believe is not the case if you critically evaluate the methods/cut-offs, total numbers screened & locations evaluated. Generally, although opinions will differ somewhat between individual screeners/clinicians a PPV of 33% or above is pretty good and indeed in practice many newborn screening programs for other metabolic disorders have significantly lower PPV. If you evaluate the evidence there is clearly in virtually all cases where the PPV is <33% a logical scientific reason for this. Indeed the bulk of evidence using the larger European studies (most applicable to our UK population) with a realistic screening cut off gives a PPV closer to 100% rather than 33%. Such PPV are exceptionally good. Implementation of a NBS screening program in the UK would be at very low cost as already the method used in DBS covers the acylcarnitines required for screening.

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Comments submitted by the IMD Screening Advisory Board on the 2018/19 review on LCHADD/MTP deficiency

Responses from IMD Screening Advisory Board as of 07 March 2019

Dr Anupam Chakrapani
Consultant in Metabolic Medicine
Great Ormond Street Hospital
Chair, IMD Screening Advisory Board

25 February 2019
Comments on NBS review re LCHADD (clinical criteria):

Criterion 1, Question 2 (Genotype-phenotype correlation):
It is important to note the following background in interpreting genotype-phenotype correlations in LCHADD/MTP:

1. LCHAD/MTP deficiency affects all body tissues and organs, as these enzymes are fundamental to energy production and survival of all cells. Potentially, any organ can be affected.
2. Apart from the very severe neonatal form, the phenotypic expression of these disorders largely depends upon exposure to environmental factors – such as infections, fasting, environmental temperature, physical activity. Two children with the same genotype are not expected to have the same phenotype, if, for example, they are not subjected to infections of the same severity in infancy.
3. Individual organ expression is age-dependent, and the manifestations evolve over time. For example, the tendency to develop hypoketotic hypoglycaemia in infancy improves over time, and the main manifestation of decompensation in the same infants when they become teenagers and adults is rhabdomyolysis.
4. The review refers to 76 different phenotypes. This is not seen in practice, as the manifestations occur simultaneously in the same patient and are not seen in isolation. To re-emphasize point 2, this condition affects every organ in the body and the manifestations largely depend upon exposure to environmental factors.

5. The distinction between clinical manifestations and clinical presentation is very important, and the review does not seem to take this into account. In clinical practice, only 3 clinical presentations are relevant: neonatal, childhood, and late-onset (adult).

The answer to Key question 2 relating to genotype-phenotype correlations is therefore yes, there is correlation but the manifestations condition are largely determined by environmental factors.

Criterion 9 and 11, key question 4:

In interpreting outcome data, there are many different parameters that have been assessed. There are a number of problems in drawing conclusions from the data presented:

1. Equal weightage has been given to the different outcome parameters. This is not correct, as the outcomes depend on a number of environmental factors, as above. The only truly "irreversible" outcomes are mortality and neurological damage. Mortality was much lower in the early treated and the asymptomatic screened population. Neurological outcome was likewise very different in the early and late treated groups. Other parameters, such as rhabdomyolysis and cardiomyopathy are potentially reversible with treatment. Yet others, such as visual problems, are not considered treatable.
2. The natural history of the various outcome parameters should be taken into account. For example, cardiomyopathy and hypoglycaemia tend to improve with age, whereas visual disturbances worsen with age, regardless of treatment.
3. Some of the parameters are not well defined: for example, "Motor and muscular problems" relates to psychomotor development, myopathy, rhabdomyolysis, and myoglobinuria. Each of these are separate entities and should be interpreted as such: rhabdomyolysis is a reversible manifestation of acute decompensation, whereas delayed psychomotor development may be irreversible and related to neurological problems; likewise, myopathy is a chronic problem and may be related to neuropathy or muscle disease.
4. Most of the outcome measures, in any case, report beneficial effects of early dietary treatment – reductions in mortality, cardiac, neurological, motor and muscular problems, hypoglycaemia, failure to thrive, brain damage, acute metabolic encephalopathy, liver related problems, and developmental delay (page 12 and section on criteria 9 and 11, pages 63-80). The studies are necessarily small because of the rarity of the condition, and in the context of rare metabolic conditions, the total sample size of >180 patients is quite reasonable. All the data presented suggest that the answer to the question, "Does early treatment with dietary management following screening provide better long-term outcomes than later treatment after the presentation of symptoms" should be "Yes", so I disagree with the conclusion that criteria 9 and 11 are not met.

5. The only RCT available relates to a modification of dietary intervention (conventional MCT versus odd-chain MCT supplementation). This is because it would not be ethical to withhold treatment from patients to conduct a treatment v no treatment trial – in view of the outcome as in point no. 4.

Final comment: thorough review of the literature, but disagree with the final conclusions.

Dr Mark Sharrard
Consultant Paediatrician with an Interest in Metabolic Disease
Sheffield Children's Hospital
Member, IMD Screening Advisory Board

12 February 2019

Dear Anupam

I think it is important that the report is read critically especially considering the relevence to the English population in the 2010's. Some of the literature cited is quite old and some may relate to other, non-European population countries with a different distribution of disease types, ie fewer 1528G>C. Also studies cited concerned with LCHAD screening from other countries may not have had a screening programme like ours where the cut-off avoided many false positives.

I believe xxxx xxxx 's letter raises important concerns about the report and that it should be read by the IMD screening board members as a companion document to assist the committee members in reaching their own conclusions.

Regards
Mark

UK National Screening Committee

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28 February 2019

Dear xxxx xxxx

Thank you for circulating xxxx xxxx's and Anupam's comments regarding the LCHAD/MTP newborn screening review.

I would wholeheartedly agree with their comments and Anupam's final comment that he disagrees with the final conclusions of the review (that there is insufficient evidence that the benefits of screening for LCHADD/MTP outweigh the harms). With such a rare condition, it would be virtually impossible to undertake a study to generate sufficient high quality data to answer this question. However those working in the field of this disorder are presented with the consequences of a clinically presenting previously undiagnosed case which may be as a fatal cardiac arrest or sever cardiomyopathy from which there is no recovery, or as a crisis episode including hypoglycaemia from which there is recovery with permanent neurological damage. These event are relatively rare in those who have been diagnosed and started on treatment while asymptomatic. Whilst treated patients may experience metabolic decompensation due to intercurrent illness, prompt instigation of emergency treatment would usually lead to recovery without deficit. There is much anecdotal evidence of the benefits of early treatment while asymptomatic, in addition to that cited in the review.

The review of Moorthie et al J Inherit Metab Dis 2014; 37: 889-898 concludes that the prevalence of clinically presenting LCHADD/MTP in Western populations (presumably with a similar genotype distribution to the UK) is 0.4/100,000 whilst the screening prevalence is 0.65/100,00. The implication is that that most of those detected by screening would present clinically at some time, and this is in contrast to some of the IMDs for which there is current NBS in the UK.

The review indicates the high false positive rates and low PPV values for LCHADD/MTP screening world wide in some studies. It is recognised that the UK pilot appears to have not detected many true positives (3) which was unexpectedly low, which would have a negative impact on the PPV.

Some of the studies quoted in the review site a high false positive rate and low PPV, but these may have different methodologies and cuts to those used in the UK pilot. The UK pilot screened on day 5, later than many other countries, and had a relatively high cut-off thus tending to reduce the false positive rate. Anecdotally it would appear that most of those LCHADD/MTP cases presenting clinically after the end of the pilot would have been detected by the UK criteria ie would have had a C16-OH level above cut-off. My own experience of those presenting clinically before the pilot was similar in that they would have been detected by the NBS pilot study criteria. It would appear that the high cut would not result in non-detection of cases.

I strongly feel that the benefits of screening for LCHADD/MTP outweigh the harms. The harm of false positives is minimised by screening on day 5 with a high cut-off. There appears to be little description in the literature of dysbenefit from treating affected individuals.

Kind regards
Mark

J R Bonham
National Blood Spot Programme Laboratory Lead and Director, Division of Pharmacy, Diagnostics and Genetics
Sheffield Children's NHS FT
NBS Programme Laboratory Lead, IMD Screening Advisory Board

25 February 2019

Dear All,

I think that the results of the studies cited in relation to PPV% for LCHADD are very variable.

NSC UK National Screening Committee

In practice of course the PPV% achieved can be "set" by the programme depending upon the metabolite monitored, the cut-off used and any secondary or corroborative testing used as part of the screening algorithm.

In the UK our PPV%, particularly for fat oxidation defects such as MCADD, is higher than most other countries because the cut-offs used are relatively high and the lipolytic stress of birth, which can generate false positive results in some cases, has passed by day 5 of life. This will also apply to LCHADD.

It would therefore be reasonable, based on experience, if we were to assume that in the UK we could match if not better the highest PPV% recorded elsewhere in the literature, provided that it were a sufficiently large study to make comparison valid.

I am not sure that this is made clear in the report or taken into account when drawing conclusions for future policy.

Kind regards
Jim

Professor Stuart J Moat PhD FRCPath EuSpLM HonMFPH
Consultant Clinical Biochemist
Director - Wales Newborn Screening Laboratory

05 March 2019

Dear xxxx xxxx

Many thanks for accepting this late response!

I have several issues/concerns with the conclusions made in this review.

In particular Criterion 4 – “accuracy of acylcarnitines measurement in dried blood spots for LCHAD/MTP deficiency screening”

The review highlights concerns regarding the PPV of the test – The number of infants screened, the biomarkers used/cut-offs employed and the day of life when screened all impact on the PPV. The screening test for LCHADD using C16-OH has a high PPV and a low false positive rate when appropriate cut-offs are used. Many of the studies quoted where the PPV was low used lower screening action values and were relatively small studies.

Prior to the implementation of English pilot expanded screening programme it was predicted that PPV for the LCHADD test (based upon published EU studies and UK data) would be 40%. The observed PPV was 33% based upon the screening of 436K births (results of the 1 year study submitted to UK NSC).

However, it is important to point out that the final data set of 730K babies screened as part of the English expanded screening pilot, the actual PPV of the test was 71%. Interestingly, these data were not included in the consultation document. This additional data set (July 2012 to March 2014) was presented at both the UK IMD Screening board and BSAG in 2014/15.

The cost of adding the LCHAD to the current screening programme would be minimal in terms of laboratory costs as the internal standard for the C16-OH acylcarnitine is already included in the commercial preparations for the newborn screening panel.

Finally, international experience indicates that there is significant clinical benefit from the early detection of LCHAD cases through screening as opposed to diagnosing clinically presenting cases.

Kind regards

Stuart

Dr Helena Kemp
Consultant Chemical Pathologist
North Bristol NHS Trust

07 March 2019

Hi xxxx xxxx,

Many apologies for the delay in responding to this consultation.

The authors are to be congratulated on their thorough literature review, I would however echo my metabolic colleagues comments in the following areas:

1. NSC Criterion 1. Question 2.
   Genotype/phenotype correlation. As Anupam has highlighted this is a simplistic concept in a metabolic condition such as LCHADD when clinical manifestations are so dependent on environmental influences, are multi-systemic in nature and develop over time. In practical terms there are 3 phenotypes recognised which do demonstrate a correlation with genotype. I'm not sure I understand the meaning of statement 'Further analysis of the current evidence base to determine whether type rather than location of the defect is linked to phenotypic presentation is needed'. The implication is that there is a need to demonstrate a genotype/phenotype correlation to be a pre-requisite to introducing a screening programme – such evidence has never been sort/required for e.g. CHT screening.
2. NSC Criterion 4. Question 3.
   Positive predictive value. The authors suggest 'There is currently insufficient evidence about acylcarnitine measurement in DBS using TMS to screen for LCHAD/MTP deficiency from which to draw conclusions about its usefulness'. Clearly interpreting the current literature in the context of the UK screening programme is challenging due to differences in screening test, cut-offs and time of sampling, I would support xxxx xxxx's views however that a detailed consideration of the most applicable studies, taking into account the use of the optimal acylcarnitine to test, and more appropriate cut-offs, would suggest that acylcarnitine measurement in DBS using TMS is indeed acceptable methodology to screen for LCHAD/MTP deficiency. In particular the positive predictive value is likely to be at least 33% and most likely significantly higher and consequently a low positive predictive value should not be held up as a reason not to implement screening.
3. NSC Criterion 9 & 11

There would seem to be consistent evidence presented in this review to indicate clear benefit from early dietary treatment in the majority of studies. I agree with Anupam that some form of weighting of outcomes is appropriate to consider.

Overall therefore I disagree with the conclusions of this review and consider that there is further evidence now available to support the view that screening for LCHADD does meet the NSC criteria. I would highlight that implementation would be straight forward and low cost as the analytical basis for the test is already in place along with the clinical referral pathways.

With best wishes.

Helena

Appendix [Please note that the following is a repeat of comment no.5 already submitted during public consultation, with the addition of the second to last sentence]

Sheffield metabolic laboratory

Newborn screening for long chain 3-hydroxyacyl-CoA dehydrogenase and mitochondrial trifunctional protein deficiencies using acylcarnitines measurement in dried blood spots

Thank you for the consultation document. We do have some significant disagreement with the final conclusions however. Overall we would congratulate the review team on a thorough review of the available literature. We do understand also that analysis & conclusions were restricted by inclusion/exclusion criteria /QUADAS-2 & lack of available surveillance data on follow up. Reading through the report there are a number of observations to comment upon. Firstly with reference to manuscript 1 [published 2002] which cites evidence that 38% of affected babies die within 3 months of diagnosis - the important caveat on this "good" manuscript is that it reported data on many of the earlier patients to be diagnosed with LCHAD/MTP when knowledge & treatment regimens for this condition were not well developed and it is unfortunate that it was not possible to find more contemporary data on screened patients as we feel it would almost certainly be significantly different now with regards to mortality &

morbidity. There is reference to the study [in Spanish] of Einoder-Moreno et al who reviewed 6 manuscripts on LCHAD/MTP screening & concluded that the sensitivity, specificity & negative predictive value for LCHAD/MTP was close to 100% & PPV ranged from 9-100%. It is apparent that this latter study had missed these 3 papers which were additionally evaluated in this review. These 3 papers are referenced (2, 6, 7). Manuscript (Zytkovicz 2001) was a relatively small USA study (164,000) which found no cases (US incidence of LCHAD cited as 1:363,738) & 5 false positives (PPV = 0). However the weakness of this latter study is that they only looked at 16(OH) which would be a significant weakness of protocol. Manuscript 6 was a large German study of >1,000,000 with 6 TP cases & no FP (PPV = 100%). Manuscript 7 was another small (Spanish) study 210,000 with 2 TP & no FP, PPV = 100%. So addition of these 3 studies would (all other considerations being equal) tend to strengthen the conclusions of Einoder-Moreno et al. This review evaluated 10 manuscripts which fitted the eligibility criteria. It is worth noting here that the common LCHAD mutation appears to be predominantly of European/Caucasian distribution. Of note, studies 2, 3, 4 & 8 - three European studies, one USA, - 2,037824 screened, 13 TP no FP, PPV 100%. Manuscript 5 a large German study (1,200,000) found 9TP, 10FP, PPV 47%. However it is highly likely that the screening cut offs set for this study are significantly too low (i.e. C16 (OH) >0.08, C18:1(OH) >0.06) and that the relatively increased FP rate is at least partly due to this. Manuscript 9 is a very small Slovenian study (10,048) with no cases & 8 FP but again the cut offs (0.009-0.042) & numbers screened are clearly too low. The two Asian studies manuscript 10 & 11 where the incidence of LCHAD/MTP would look to be very much lower, found no cases. Manuscript 10 was a tiny study (2,440) with 2 FP but with no clear information on the cut off used - a significant problem for objective evaluation. While manuscript 11 covered a bigger study (still only 100,077), it had a high FP rate but with a clearly unrealistic cut off set at >0.03 - >0.05. The UK pilot study (436,969) found 1 TP & 2 FP, PPV = 33%.

The conclusions of the review indicate that currently there are significant concerns regarding the high number of false positives. This we believe is not the case if you critically evaluate the methods/cut-offs, total numbers screened & locations evaluated. Generally, although opinions will differ somewhat between individual screeners/clinicians a PPV of 33% or above is pretty good and indeed in practice many newborn screening programs for other metabolic disorders have significantly lower PPV. If you evaluate the evidence there is clearly in virtually all cases where the PPV is <33% a logical scientific reason for this. Indeed the bulk of evidence using the larger European studies (most applicable to our UK population) with a realistic screening cut off gives a PPV closer to 100% rather than 33%. Such PPV's are exceptionally good. With regards to "false negatives" we are not aware from our experiences over the past 30 years that our metabolic physicians in the UK are reporting significant numbers of late presenting "mild" cases that would likely have evaded screening. Implementation of a NBS screening program in the UK would be at very low cost as already the method used in DBS covers the acylcarnitines required for screening.

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